Innovation, Sciences et Développement économique Canada
Office de la Propriété Intellectuelle du Canada

Innovation, Science and Economic Development Canada
Canadian Intellectual Property Office

CA 3083000 A1 2019/05/02

(21) 3 083 000

(12) DEMANDE DE BREVET CANADIEN
CANADIAN PATENT APPLICATION

(13) A1

(86) Date de dépôt PCT/PCT Filing Date: 2018/10/24
(87) Date publication PCT/PCT Publication Date: 2019/05/02
(85) Entrée phase nationale/National Entry: 2020/04/23
(86) N° demande PCT/PCT Application No.: US 2018/057339
(87) N° publication PCT/PCT Publication No.: 2019/084157
(30) Priorités/Priorities: 2017/10/24 (US62/576,591); 2018/04/25 (US62/662,424)

(51) Cl.Int./Int.Cl. *C07K 16/28* (2006.01), *G01N 33/574* (2006.01)

(71) Demandeur/Applicant:
YUMANITY THERAPEUTICS, INC., US

(72) Inventeurs/Inventors:
LUCAS, MATTHEW, US;
LE BOURDONNEC, BERTRAND, US;
WRONA, IWONA, US;
PANDYA, BHAUMIK, US;
TIVITMAHAISOON, PARCHAREE, US;
OZBOYA, KEREM, US;
VINCENT, BENJAMIN, US;
...

(74) Agent: BORDEN LADNER GERVAIS LLP

(54) Titre : COMPOSES ET UTILISATIONS DE CES COMPOSES
(54) Title: COMPOUNDS AND USES THEREOF

(57) Abrégé/Abstract:
The present invention features compounds useful in the treatment of neurological disorders. The compounds of the invention, alone or in combination with other pharmaceutically active agents, can be used for treating or preventing neurological disorders.

(21) 3 083 000

(13) A1

(72) **Inventeurs(suite)/Inventors(continued):** TARDIFF, DANIEL, US; PIOTROWSKI, JEFF, US; SOLIS, ERIC, US; SCANNEVIN, ROBERT, US; CHUNG, CHEE-YEUN, US; ARON, REBECCA, US; RHODES, KENNETH, US

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
02 May 2019 (02.05.2019)

WIPO | PCT

(10) International Publication Number
WO 2019/084157 A1

(51) International Patent Classification:
C07K 16/28 (2006.01) *G01N 33/574* (2006.01)

(21) International Application Number:
PCT/US2018/057339

(22) International Filing Date:
24 October 2018 (24.10.2018)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/576,591 24 October 2017 (24.10.2017) US
62/662,424 25 April 2018 (25.04.2018) US

(71) Applicant: **YUMANITY THERAPEUTICS, INC.** [US/US]; 790 Memorial Drive, Suite 2C, Cambridge, MA 02139 (US).

(72) Inventors: **LUCAS, Matthew**; 48 Parker St, Lexington, MA 02421 (US). **LE BOURDONNEC, Bertrand**; 2 Mohican Avenue, Northborough, MA 01532 (US). **WRONA, Iwona**; 17 Harding Street, Sharon, MA 02067 (US). **PANDYA, Bhaumik**; 325 Springs Rd, Bedford, MA 01730 (US). **TIVITMAHAISOON, Parcharee**; 580 Commonwealth Ave. #606, Boston, MA 02215 (US). **OZBOYA, Kerem**; 11 Ellery St. Apt #1, Cambridge, MA 02138 (US). **VINCENT, Benjamin**; 9 Locke Street Apt 2, Cambridge, MA 02140 (US). **TARDIFF, Daniel**; 48 Newland Road, Arlington, MA 02474 (US). **PIOTROWSKI, Jeff**; 171 Walnut Street #3, Somerville, MA 02145 (US). **SOLIS, Eric**; 29 Princess Pine Lane, Milford, MA 01757 (US). **SCANNEVIN, Robert**; 26 Huckleberry Road, Hopkinton, MA 01748 (US). **CHUNG, Chee-Yeun**; 416 Clinton Road, Brookline, MA 02445 (US). **ARON, Rebecca**; 1 Whittemore Avenue #104, Cambridge, MA 02140 (US). **RHODES, Kenneth**; 86 Juniper Road, Belmont, MA 02478 (US).

(74) Agent: **BELLIVEAU, Michael, J.**; Clark & Elbing LLP, 101 Federal Street, 15th Floor, Boston, MA 02110 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report (Art. 21(3))*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*
— *with sequence listing part of description (Rule 5.2(a))*

(54) Title: COMPOUNDS AND USES THEREOF

(57) Abstract: The present invention features compounds useful in the treatment of neurological disorders. The compounds of the invention, alone or in combination with other pharmaceutically active agents, can be used for treating or preventing neurological disorders.

WO 2019/084157 A1

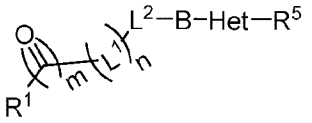
COMPOUNDS AND USES THEREOF

Background

An incomplete understanding of the molecular perturbations that cause disease, as well as a limited arsenal of robust model systems, has contributed to a failure to generate successful disease-modifying therapies against common and progressive neurological disorders, such as Parkinson's Disease (PD) and Alzheimer's Disease (AD). Progress is being made on many fronts to find agents that can arrest the progress of these disorders. However, the present therapies for most, if not all, of these diseases provide very little relief. Accordingly, a need exists to develop therapies that can alter the course of neurodegenerative diseases. More generally, a need exists for better methods and compositions for the treatment of neurodegenerative diseases in order to improve the quality of the lives of those afflicted by such diseases.

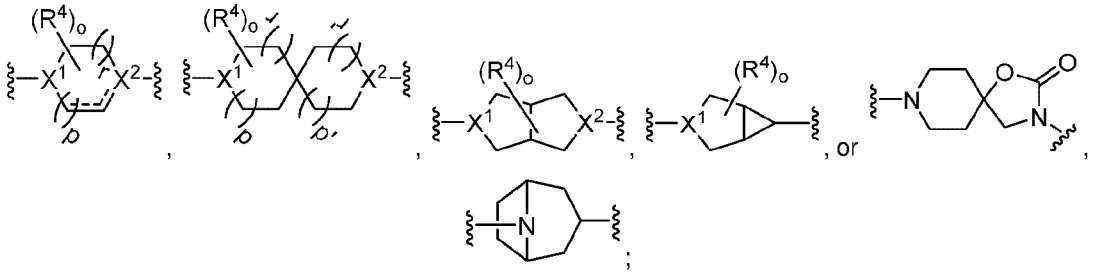
Summary of the Invention

This disclosure provides a compound, or a pharmaceutically acceptable salt thereof, having the structure of Formula I:



Formula Ia

wherein B is absent or has the structure:



Formula Ib **Formula Ic** **Formula Id** **Formula Ie** **Formula If**

the dashed lines represent an optional double bond;

Het is –C(O)NH- or an optionally substituted C_2-C_9 heteroaryl;

m is 0 or 1;

n is 0, 1, or 2;

o is 0, 1, 2, 3, 4, 5, 6, 7, or 8;

p, p', r, and r' are, independently, 0 or 1;

X^1 and X^2 are each, independently, N or CR^6;

L^1 is -O-, -SO_2-, NR^2, optionally substituted C_1-C_6 alkylene, optionally substituted C_1-C_6 alkenylene, optionally substituted C_1-C_6 heteroalkylene, optionally substituted C_3-C_7 cycloalkyl, optionally substituted C_2-C_9 heteroaryl, an optionally substituted C_6-C_{10} aryl, or optionally substituted C_2-C_9 heterocycle;

L^2 is absent, -O-, -SO_2-, NR^2, or -CR^2R^3-;

R^1 is hydrogen, amino, hydroxy, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_6-C_{10} aryl C_1-C_6 alkyl, optionally substituted C_3-C_7 cycloalkyl, optionally substituted C_3-C_7 cycloalkyl C_1-C_6 alkyl, optionally substituted C_2-C_9 heteroaryl, optionally substituted C_2-C_9 heteroaryl C_1-C_6 alkyl, optionally substituted C_2-C_9 heterocycle, or optionally substituted C_2-C_9 heterocycle C_1-C_6 alkyl;

R^2 and R^3 are each, independently, hydrogen, halogen, hydroxyl, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, or combine with the carbon to which they are attached to form a carbonyl or an optionally substituted C_3-C_7 cycloalkyl;

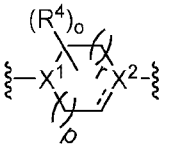
each R^4 is, independently, halogen, hydroxyl, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, or two R^4 combine with the carbon two which they are attached to form a carbonyl or optionally substituted C_3-C_7 cycloalkyl;

R^5 is optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_1-C_6 alkyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, optionally substituted C_2-C_9 heterocycle, optionally substituted C_6-C_{10} aryl C_1-C_6 alkyl, optionally substituted C_2-C_9 heterocycle C_1-C_6 alkyl, or optionally substituted C_2-C_9 heteroaryl C_1-C_6 alkyl; and

each R^6 is, independently, hydrogen, halogen, hydroxy, optionally substituted C_1-C_6 heteroalkyl, or optionally substituted C_1-C_6 alkyl.

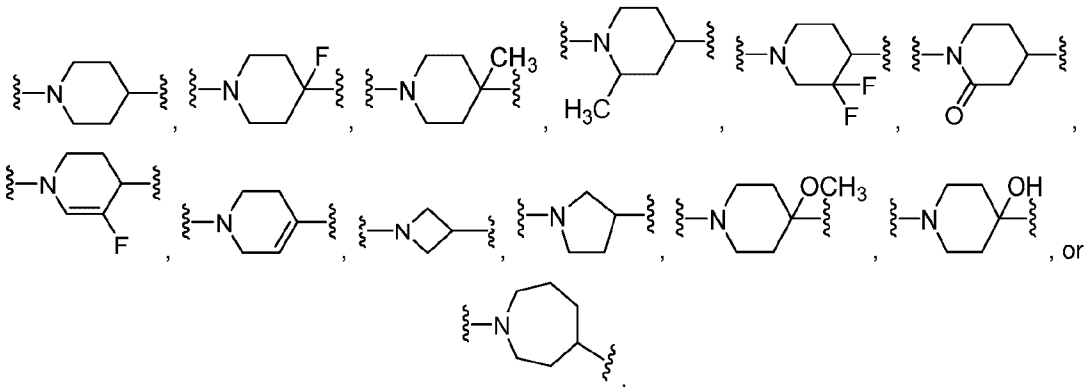
In some embodiments, B is absent.

In some embodiments, B has the structure of Formula Ib:



.

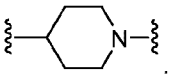
In some embodiments, X^1 is N and X^2 is CR^6. In some embodiments, o is 0, 1, or 2. In some embodiments, R^4 is halogen (e.g., fluoro), optionally substituted C_1-C_6 alkyl (e.g., methyl), or two R^4 combine with the carbon two which they are attached to form a carbonyl. In some embodiments, R^6 is hydrogen. In some embodiments, R^6 is halogen (e.g., fluoro). In some embodiments, R^6 is optionally substituted C_1-C_6 alkyl (e.g., methyl). In some embodiments, the dashed line represents a double bond. In some embodiments, both dashed lines represent a single bond. In some embodiments, p is 1 and r is 1. In some embodiments, p is 1 and r is 0. In some embodiments, p is 0 and r is 0. In some embodiments, B has the structure:



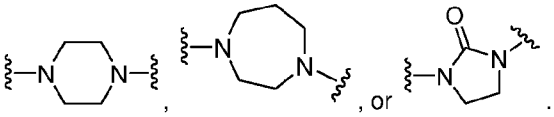
, or

.

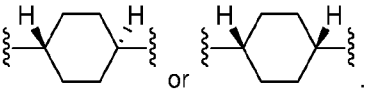
In some embodiments, X^1 is CR^6 and X^2 is N. In some embodiments, o is 0, 1, or 2. In some embodiments, R^4 is halogen (e.g., fluoro), optionally substituted C_1-C_6 alkyl (e.g., methyl), or two R^4 combine with the carbon two which they are attached to form a carbonyl. In some embodiments, R^6 is hydrogen. In some embodiments, R^6 is halogen (e.g., fluoro). In some embodiments, R^6 is optionally substituted C_1-C_6 alkyl (e.g., methyl). In some embodiments, the dashed line represents a double bond. In some embodiments, the dashed line represents a single bond. In some embodiments, p is 1 and r is 1. In some embodiments, p is 1 and r is 0. In some embodiments, p is 0 and r is 0. In some embodiments, B has the structure:



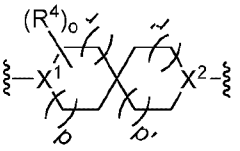
In some embodiments, X^1 is N and X^2 is N. In some embodiments, o is 0, 1, or 2. In some embodiments, R^4 is halogen (e.g., fluoro), optionally substituted C_1-C_6 alkyl (e.g., methyl), or two R^4 combine with the carbon two which they are attached to form a carbonyl. In some embodiments, the dashed line represents a double bond. In some embodiments, the dashed line represents a single bond. In some embodiments, p is 1 and r is 1. In some embodiments, p is 1 and r is 0. In some embodiments, p is 0 and r is 0. In some embodiments, p is 1 and r is 2. In some embodiments, B has the structure:



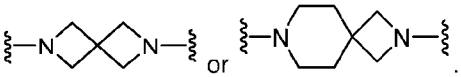
In some embodiments, X^1 is CR^6 and X^2 is CR^6. In some embodiments, o is 0, 1, or 2. In some embodiments, R^4 is halogen (e.g., fluoro), optionally substituted C_1-C_6 alkyl (e.g., methyl), or two R^4 combine with the carbon two which they are attached to form a carbonyl. In some embodiments, the dashed line represents a double bond. In some embodiments, the dashed line represents a single bond. In some embodiments, p is 1 and r is 1. In some embodiments, p is 1 and r is 0. In some embodiments, p is 0 and r is 0. In some embodiments, B has the structure:



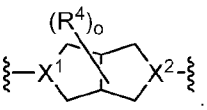
In some embodiments, B has the structure of Formula Ic:



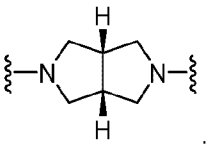
In some embodiments, X^1 is N and X^2 is N. In some embodiments, o is 0. In some embodiments, p, p', r, and r' are 0. In some embodiments, p and r are each 1 and p' and r' are 0. In some embodiments, B has the structure:



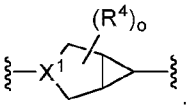
In some embodiments, B has the structure of Formula Id:



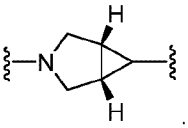
In some embodiments, X^1 is N and X^2 is N. In some embodiments, o is 0. In some embodiments, B has the structure:



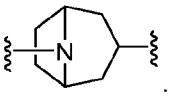
In some embodiments, B has the structure of Formula Ie:



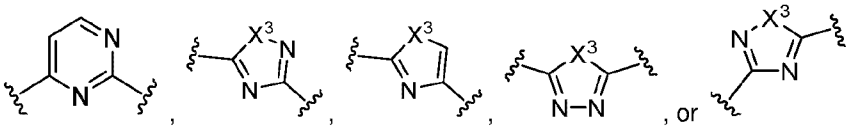
In some embodiments, X^1 is N and X^2 is N. In some embodiments, o is 0. In some embodiments, B has the structure:



In some embodiments, B has the structure of Formula If:

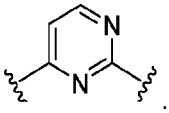


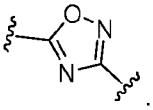
In some embodiments of any of the foregoing compounds, Het is –C(O)NH- or:

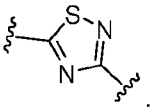


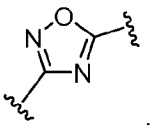
wherein X^3 is O or S.

In some embodiments, Het is –C(O)NH-.

In some embodiments, Het is  .

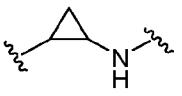
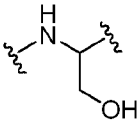
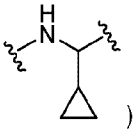
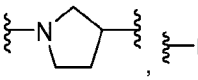
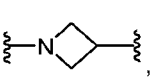
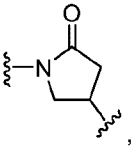
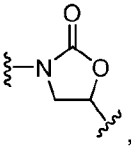
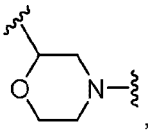
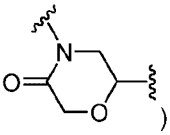
In some embodiments, Het is  .

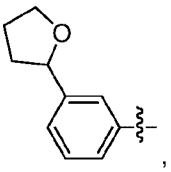
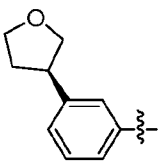
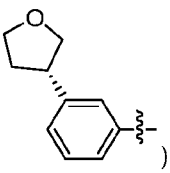
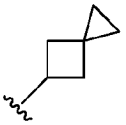
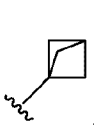
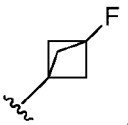
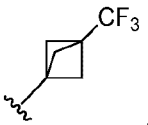
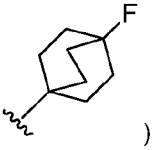
In some embodiments, Het is  .

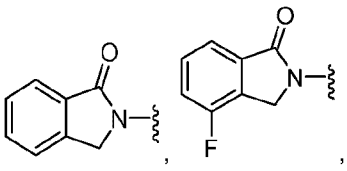
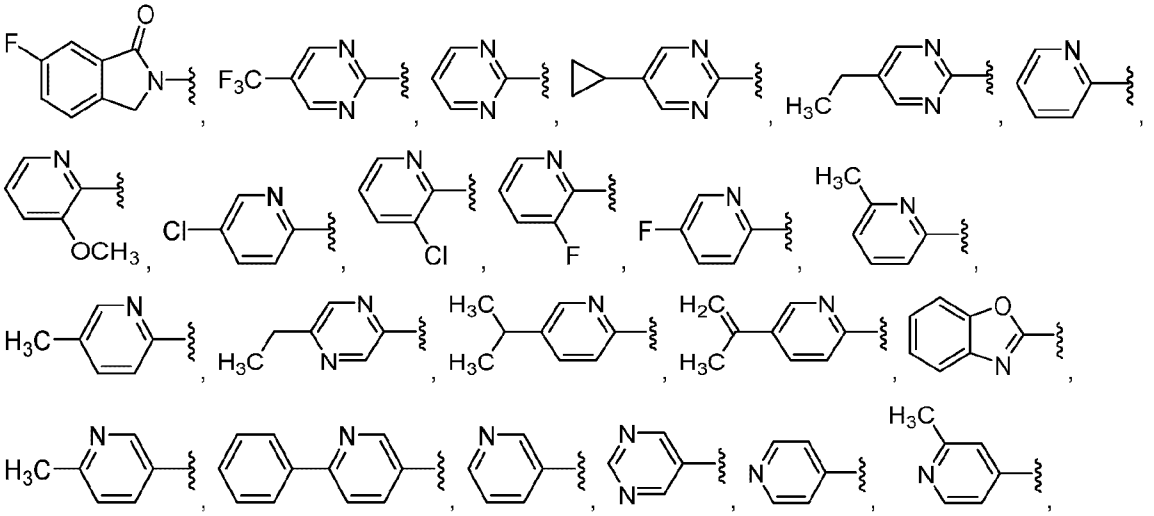
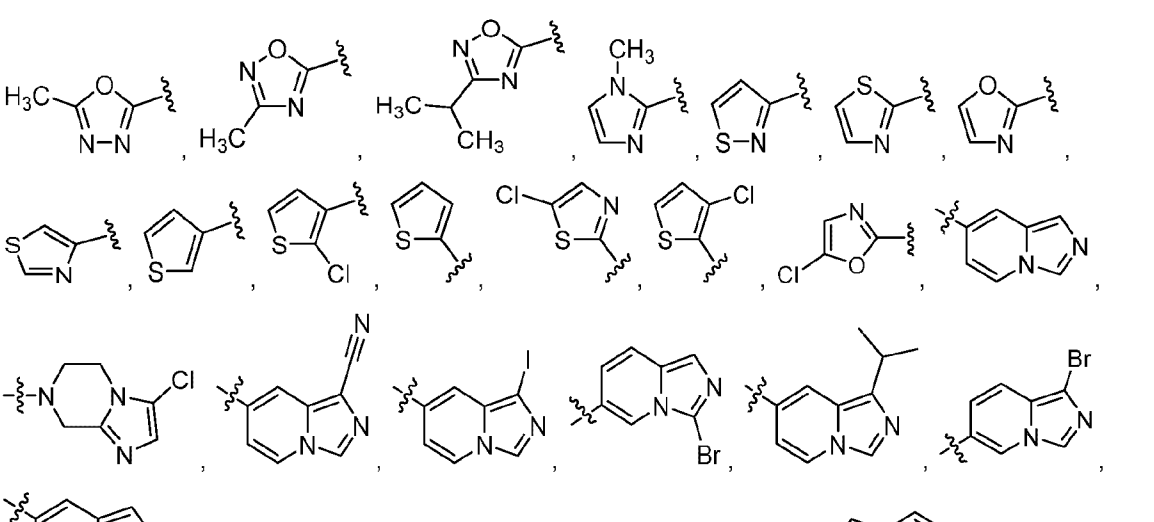
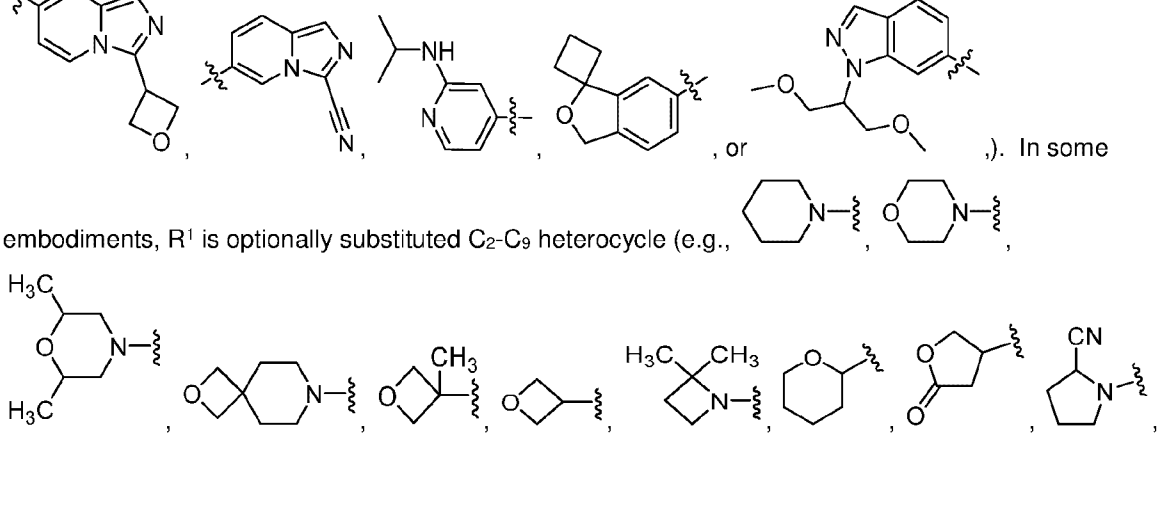
In some embodiments, Het is  .

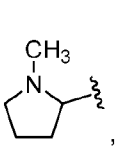
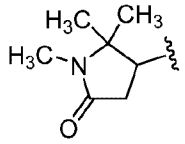
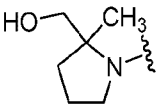
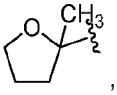
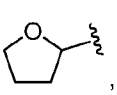
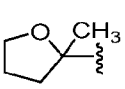
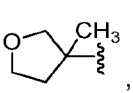
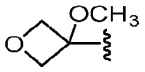
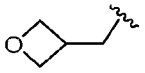
In some embodiments, L^2 is absent. In some embodiments, L^2 is $–NR^2-$ (e.g., -NH-). In some embodiments, L^2 is –O-. In some embodiments, L^2 is $–SO_2-$. In some embodiments, L^2 is $–CR^2R^3-$. In some embodiments, R^2 and R^3 combine with the carbon to which they are attached to form a carbonyl. In some embodiments, R^2 and R^3 combine with the carbon to which they are attached to form an optionally

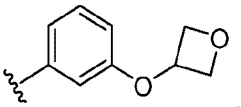
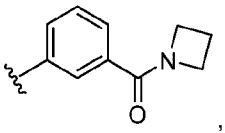
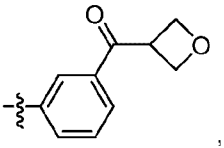
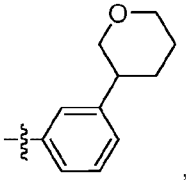
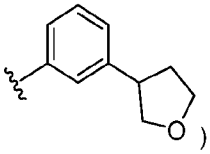
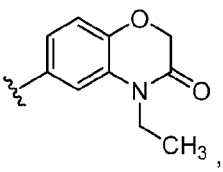
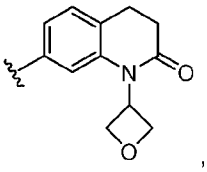
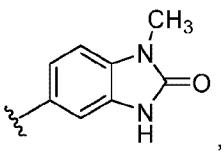
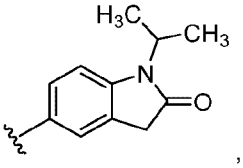
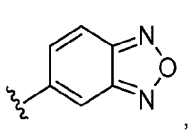
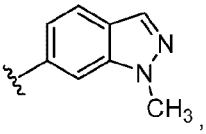
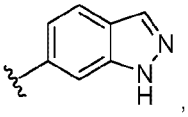
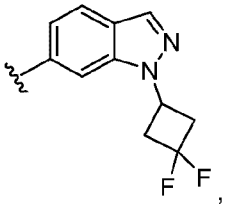
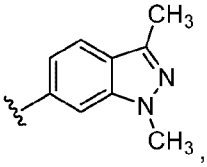
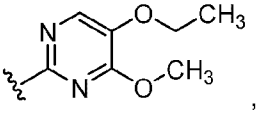
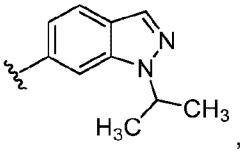
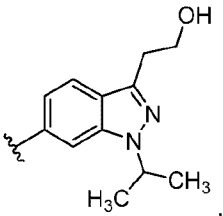
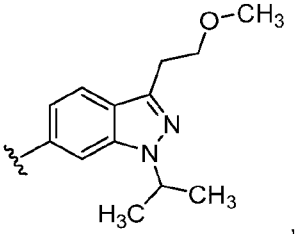
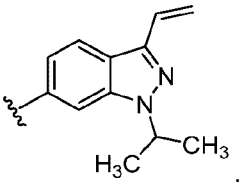
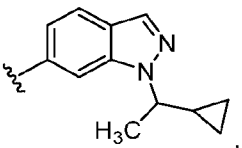
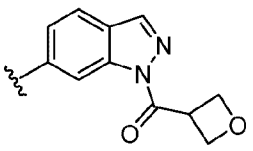
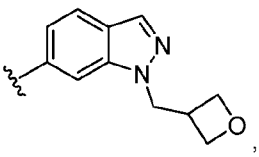
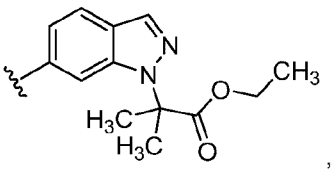
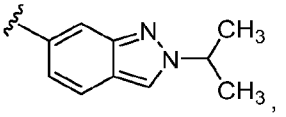
substituted C_3-C_7 cycloalkyl (e.g., cyclopropyl). In some embodiments, R^2 and R^3 are both hydrogen. In some embodiments, R^2 is hydrogen and R^3 is optionally substituted C_1-C_6 alkylene (e.g., methylene).

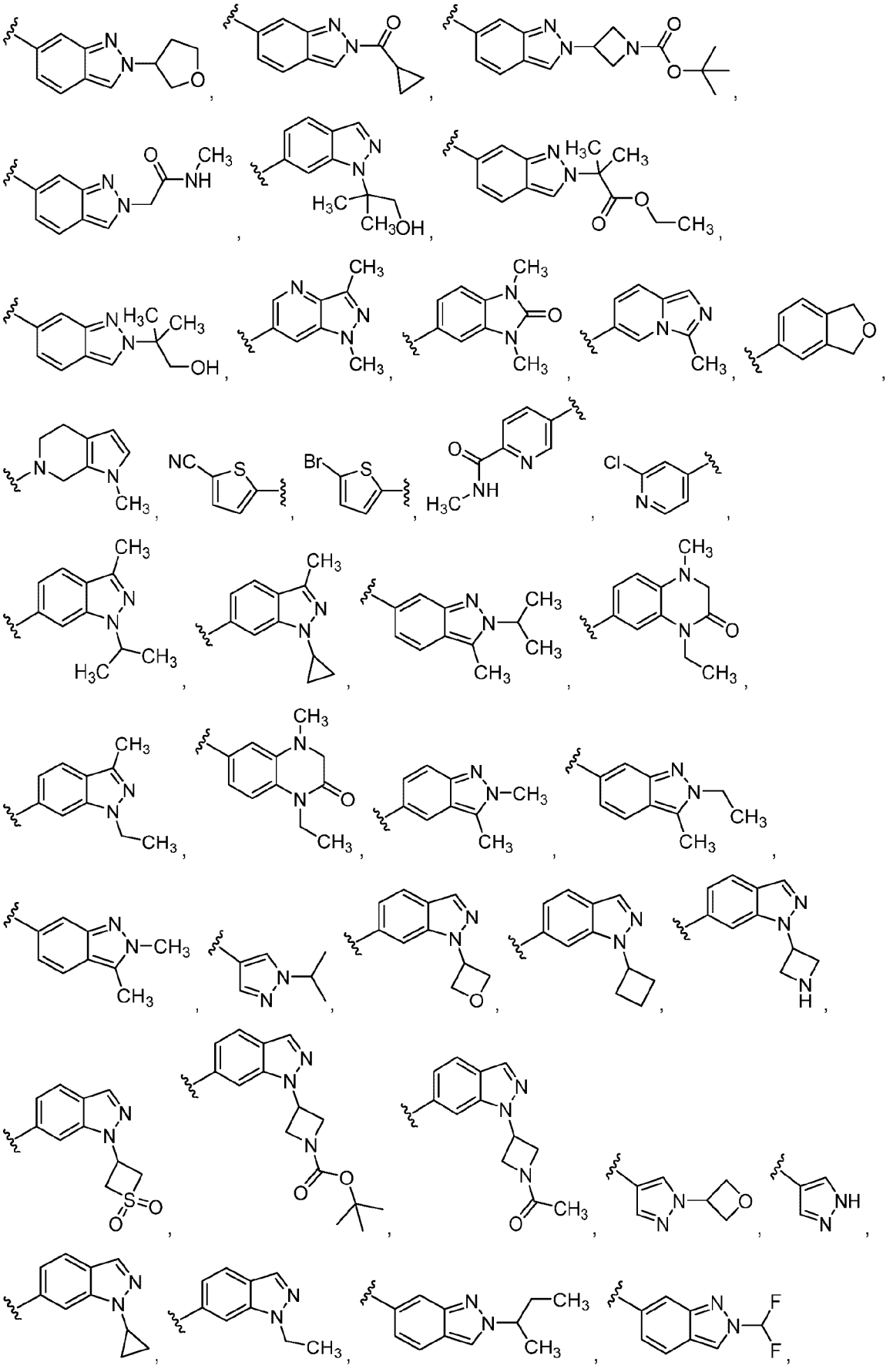
In some embodiments, n is 0. In some embodiments, n is 1. In some embodiments, L^1 is $-NR^2$- (e.g., -NH- or –N(Et)-). In some embodiments, L^1 is –O-. In some embodiments, L^1 is $-SO_2$-. In some embodiments, L^1 is optionally substituted C_1-C_6 alkylene (e.g., methylene or hydroxy-methylene). In some embodiments, L^1 is optionally substituted C_1-C_6 heteroalkylene (e.g., -NH-CH_2-, -O-CH_2-, -O-CH_2-CH_2-, -CH_2-O-CH_2-, -CH_2-O-,  ,  , or ). In some embodiments, L^1 is optionally substituted C_2-C_9 heterocycle (e.g.,  ,  ,  ,  ,  , or ).

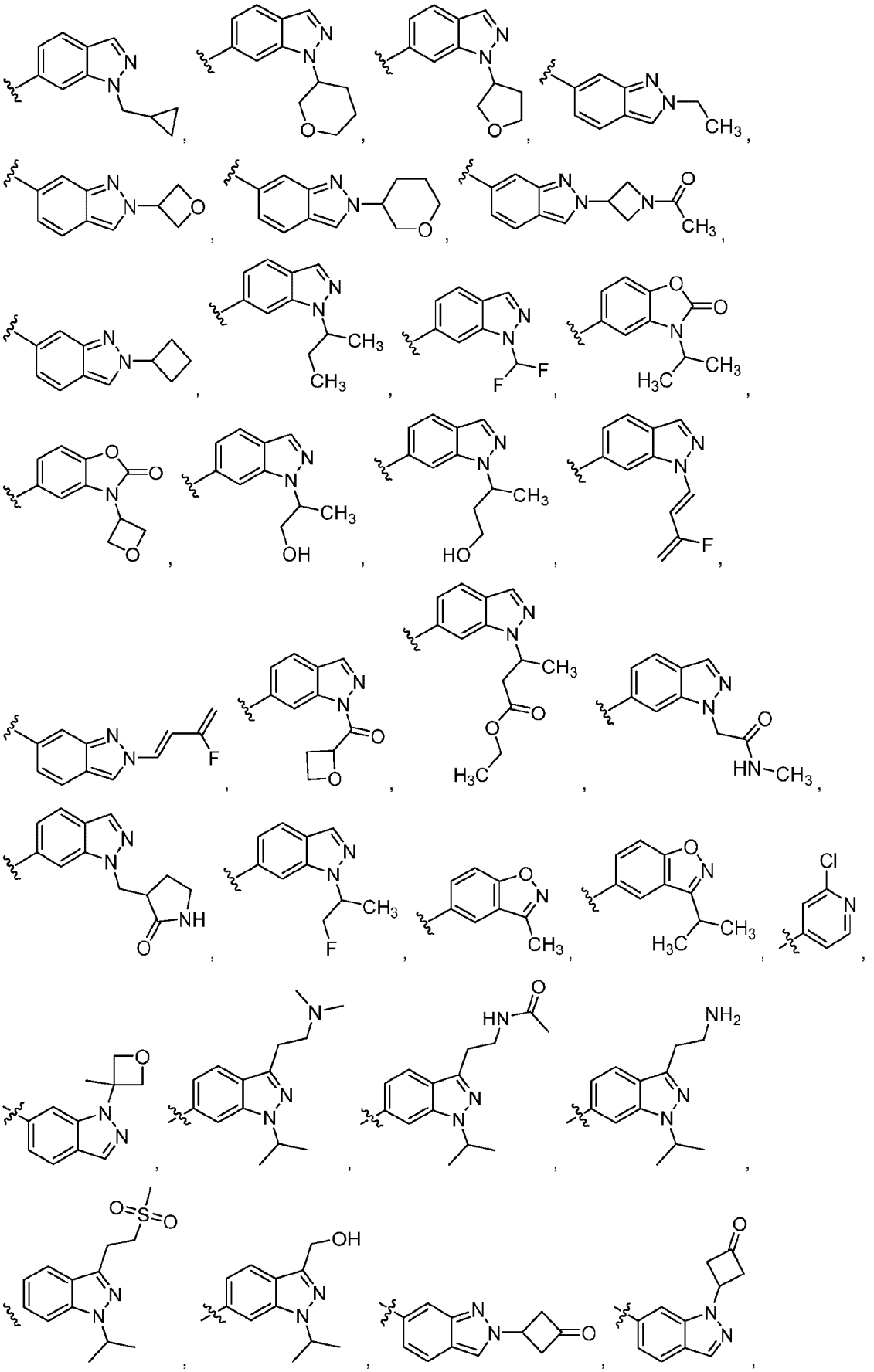
In some embodiments, R^1 is cyano, optionally substituted C_1-C_6 alkyl (e.g., methyl, ethyl, isopropyl, tert-butyl, trifluoromethyl, trifluoroethyl, pentafluoro-ethyl, 2-chloro-ethyl, 1-chloro-3-hydroxy-isopropyl, 2-methoxy-ethyl, or hexafluoro-isopropyl). In some embodiments, R^1 is optionally substituted C_6-C_{10} aryl (e.g., phenyl, 2-chloro-phenyl, 3-chloro-phenyl, 4-chloro-phenyl, 2-trifluoromethyl-phenyl, 3-trifluoromethyl-phenyl, 4- trifluoromethyl–phenyl, 2-cyano-phenyl, 3-cyano-phenyl, 4-cyano-phenyl, 3-isopropyl-phenyl, 4-isopropyl-phenyl, 2-fluoro-phenyl, 3-fluoro-phenyl, 4-fluoro-phenyl, 4-methoxy-phenyl, 4-difluoromethoxy-phenyl, 4-trifluoromethoxy-phenyl, 2-chloro-5-fluoro-phenyl, 2-fluoro-4-chloro-phenyl, 3-fluoro-4-chloro-phenyl, 2-bromo-4-methoxy-phenyl, 2-trifluoromethyl-5-fluoro-phenyl, 2-trifluoromethyl-5-chloro-phenyl, ,  ,  , or ). In some embodiments, R^1 is optionally substituted C_6-C_{10} aryl C_1-C_6 alkyl (e.g., naphthylmethyl). In some embodiments, R^1 is optionally substituted C_3-C_7 cycloalkyl (e.g., cyclopropyl, cyclohexyl, 6-methoxy-cyclohexyl, 1-cyano-cyclopropyl, bicycle[1.1.1]pentane, 1-methyl-cyclopropyl, 1-ethyl-cyclopropyl, 1-fluoro-cyclopropyl, 1-methoxy-cyclopropyl, 1-hydroxy-cyclopropyl, 2,2-dimethyl-cyclopropyl, 2,2-difluoro-cyclopropyl, cyclobutyl,  ,  ,  ,  , or ). In some embodiments, R^1 is optionally substituted C_3-C_7 cycloalkyl C_1-C_6 alkyl (cyclopropylmethyl). In some embodiments, R^1 is

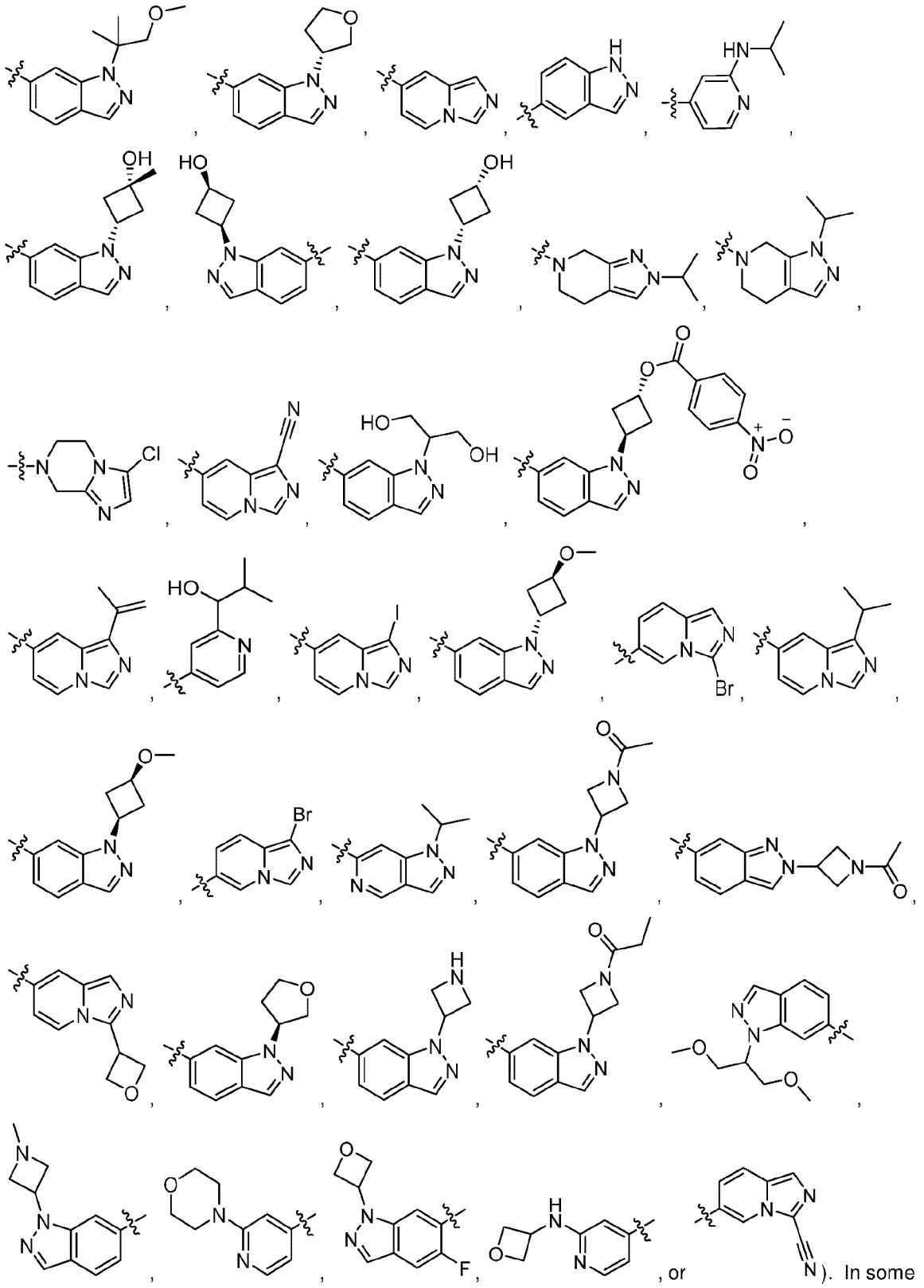
optionally substituted C_2-C_9 heteroaryl (e.g.,  ,  ,  ,  , ). In some embodiments, R^1 is optionally substituted C_2-C_9 heterocycle (e.g., ,).

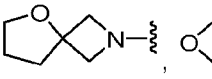







, or

,). In some embodiments, R^1 is optionally substituted C_2-C_9 heterocycle C_1-C_6 alkyl (e.g.,

).

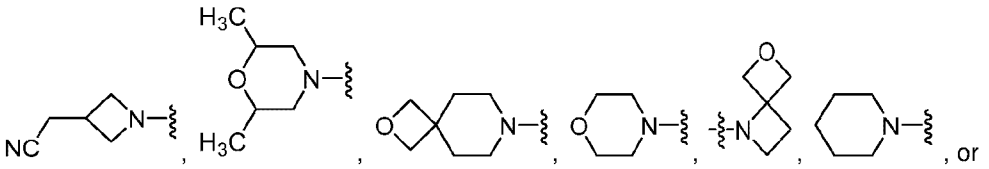
In some embodiments, R^5 is optionally substituted C_6-C_{10} aryl (e.g., phenyl, 3,4-dimethoxy-phenyl, 3-methoxy-4-ethoxy-phenyl, 3,5-dimethoxy-phenyl, 3-methoxy-4-cyclopropoxy-phenyl, 3-methoxy-4-trifluoromethoxy-phenyl, 3-isopropoxy-4-methoxy-phenyl,

,



, or

). In some embodiments,


R^5 is optionally substituted C_2-C_9 heteroaryl (e.g.,


















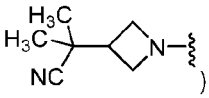


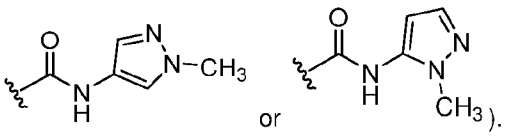




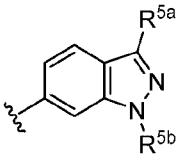
embodiments, R^5 is an optionally substituted indazole. In some embodiments, R^5 is optionally substituted C_2-C_9 heterocycle (e.g., a nitrogen containing heterocycle such as  ,


, or


). In some embodiments, R^5 is optionally substituted C_2-C_9 heteroaryl C_1-C_6 alkyl (e.g.,

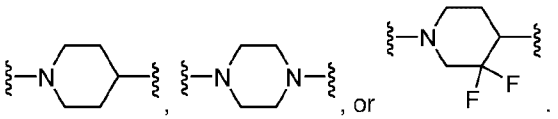

).

In some embodiments, R^5 is a bicyclic heterocyle. For example, a bicyclic heterocycle such as an indazole. In some embodiments, R^5 is an indazole having the structure:

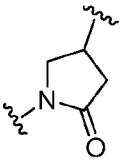
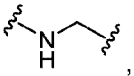


wherein R^{5a} is hydrogen or optionally substituted C_1-C_6 alkyl (e.g., methyl) and R^{5b} is optionally substituted C_1-C_6 alkyl (e.g., methyl or iso-propyl), optionally substituted C_2-C_9 heterocyclyl (e.g., oxetane), or optionally substituted C_3-C_7 cycloalkyl (e.g., cyclopropyl).

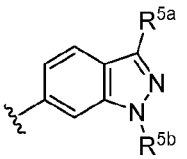
In some embodiments, B has the sturucture:



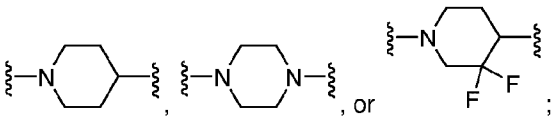
In some embodiments, R^1 is optionally substituted C_1-C_6 alkyl (e.g., methyl, ethyl, iso-propyl, or tert-butyl), optionally substituted C_6-C_{10} aryl, or optionally substituted C_2-C_9 heteroaryl.

In some embodiments, m is 0, n is 1, L^1 is –O-, and L^2 is –C(O)-. In some embodiments, m is 0, n is 0, and L^2 is –C(O)-. In some embodiments, m is 0, n is 1, L^1 is  , and L^2 is –C(O)-. In some embodiments, m is 1, n is 1, L^1 is  , and L^2 is –C(O)-.

In some embodiments, R^5 is an indazole having the structure:

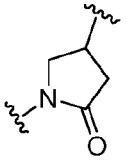


wherein R^{5a} is hydrogen or optionally substituted C_1-C_6 alkyl (e.g., methyl) and R^{5b} is optionally substituted C_1-C_6 alkyl (e.g., methyl or iso-propyl), optionally substituted C_2-C_9 heterocyclyl (e.g., oxetane), or optionally substituted C_3-C_7 cycloalkyl (e.g., cyclopropyl); B has the sturucture:

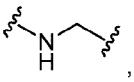


R^1 is optionally substituted C_1-C_6 alkyl (e.g., methyl, ethyl, iso-propyl, or tert-butyl), optionally substituted C_6-C_{10} aryl, or optionally substituted C_2-C_9 heteroaryl; and

m is 0, n is 1, L^1 is –O-, and L^2 is –C(O)-, m is 0, n is 0, and L^2 is –C(O)-, m is 0, n is 1, L^1 is



, and L^2 is –C(O)-, or m is 1, n is 1, L^1 is

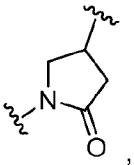


, and L^2 is –C(O)-.

In some embodiments, m is 0, n is 1, L^1 is –O-, L^2 is –C(O)- and R^1 is optionally substituted C_1-C_6 alkyl (e.g., methyl, ethyl, iso-propyl, or tert-butyl).

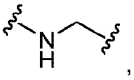
In some embodiments, m is 0, n is 0, L^2 is –C(O)-, and R^1 is optionally substituted C_6-C_{10} aryl.

In some embodiments, m is 0, n is 1, L^1 is



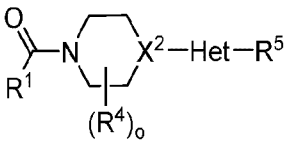
, L^2 is –C(O)-, and R^1 is optionally substituted C_6-C_{10} aryl, or optionally substituted C_2-C_9 heteroaryl.

In some embodiments, m is 1, n is 1, L^1 is



, L^2 is –C(O)-, and R^1 is optionally substituted C_6-C_{10} aryl.

In some embodiments, the compound has the structure of Formula Ig:



Formula Ig

wherein Het is an optionally substituted oxadiazole;

o is 0, 1, 2, 3, 4, 5, 6, 7, or 8;

X^2 is N or CR^6;

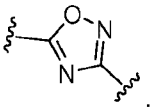
R^1 is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_6-C_{10} aryl C_1-C_6 alkyl, optionally substituted C_3-C_7 cycloalkyl, optionally substituted C_3-C_7 cycloalkyl C_1-C_6 alkyl, optionally substituted C_2-C_9 heteroaryl, optionally substituted C_2-C_9 heteroaryl C_1-C_6 alkyl, optionally substituted C_2-C_9 heterocycle, or optionally substituted C_2-C_9 heterocycle C_1-C_6 alkyl;

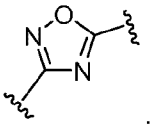
each R^4 is, independently, halogen, hydroxyl, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, or two R^4 combine with the carbon two which they are attached to form a carbonyl or optionally substituted C_3-C_7 cycloalkyl;

R^5 is optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_1-C_6 alkyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_2-C_9 heteroaryl, optionally substituted C_2-C_9 heterocycle,

optionally substituted C_6-C_{10} aryl C_1-C_6 alkyl, optionally substituted C_2-C_9 heterocycle C_1-C_6 alkyl, or optionally substituted C_2-C_9 heteroaryl C_1-C_6 alkyl; and

each R^6 is, independently, hydrogen, halogen, optionally substituted C_1-C_6 heteroalkyl, or optionally substituted C_1-C_6 alkyl.

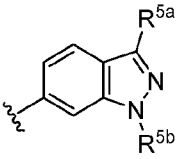
In some embodiments, Het is  .

In some embodiments, Het is  .

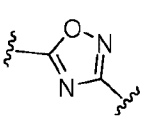
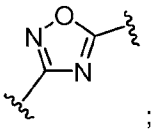
In some embodiments, X^2 is N or CH. In some embodiments, X^2 is N. In some embodiments, X^2 is CH.

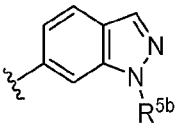
In some embodiments, R^1 is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, or optionally substituted C_6-C_{10} aryl.

In some embodiments, R^5 is optionally substituted C_6-C_{10} aryl or optionally substituted C_2-C_9 heteroaryl (e.g., bicyclic heteroaryl such as an indazole). In some embodiments, R^5 has the structure:



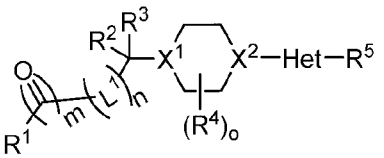
wherein R^{5a} is hydrogen or optionally substituted C_1-C_6 alkyl (e.g., methyl) and R^{5b} is optionally substituted C_1-C_6 alkyl (e.g., methyl or iso-propyl), optionally substituted C_2-C_9 heterocyclyl (e.g., oxetane), or optionally substituted C_3-C_7 cycloalkyl (e.g., cyclopropyl). In some embodiments, R^{5a} is hydrogen.

In some embodiments, Het is  or  ; o is 0; X^2 is N or CH; R^1 is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl (e.g., C_1-C_6 alkoxy or C_1-C_6 alkylamino), or optionally substituted C_6-C_{10} aryl; and R^5 has the structure:



wherein R^{5b} is optionally substituted C_1-C_6 alkyl (e.g., methyl or iso-propyl), optionally substituted C_2-C_9 heterocyclyl (e.g., oxetane), or optionally substituted C_3-C_7 cycloalkyl (e.g., cyclopropyl).

In some embodiments the compound has the structure of Formula I:



Formula I

wherein Het is an optionally substituted optionally substituted C_2-C_9 heteroaryl;

m is 0 or 1;

n is 0, 1, or 2;

o is 0, 1, 2, 3, 4, 5, 6, 7, or 8;

X^1 and X^2 are each, independently, N or CR^6;

L^1 is optionally substituted C_1-C_6 alkylene, optionally substituted C_1-C_6 alkenylene, optionally substituted C_1-C_6 heteroalkylene, optionally substituted C_3-C_7 cycloalkyl, optionally substituted C_2-C_9 heteroaryl, or optionally substituted C_2-C_9 heterocycle;

R^1 is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_6-C_{10} aryl, optionally substituted C_3-C_7 cycloalkyl, optionally substituted C_2-C_9 heteroaryl, or optionally substituted C_2-C_9 heterocycle;

R^2 and R^3 are each, independently, hydrogen, optionally substituted C_1-C_6 alkyl, or combine with the carbon to which they are attached to form a carbonyl;

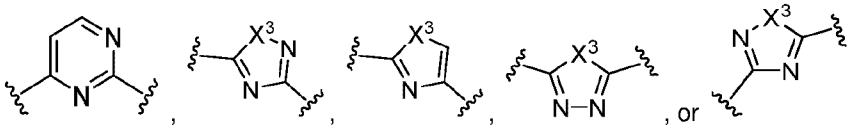
each R^4 is, independently, halogen, hydroxyl, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, or two R^4 combine with the carbon two which they are attached to form a carbonyl;

R^5 is optionally substituted C_6-C_{10} aryl or optionally substituted C_2-C_9 heteroaryl; and

each R^6 is, independently, hydrogen or optionally substituted C_1-C_6 alkyl.

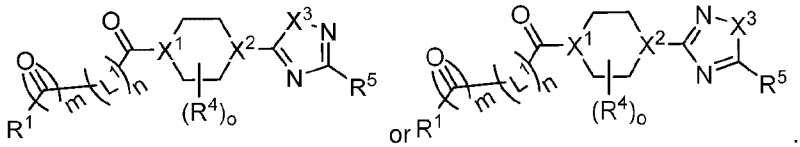
In some embodiments of any of the foregoing compounds, R^2 and R^3 combine with the carbon to which they are attached to form a carbonyl. In some embodiments of any of the foregoing compounds, R^2 and R^3 are both hydrogen.

In some embodiments of any of the foregoing compounds, Het is:



wherein X^3 is O or S.

In some embodiments, the compound has the structure of Formula II or IIa:



Formula II **Formula IIa**

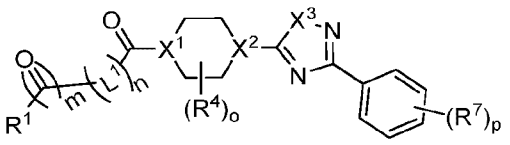
In some embodiments of any of the foregoing compounds, X^3 is O. In some embodiments of any of the foregoing compounds, X^3 is S.

In some embodiments of any of the foregoing compounds, X^1 is N and X^2 is CR^6. In some embodiments of any of the foregoing compounds, X^1 is N and X^2 is N. In some embodiments of any of the foregoing compounds, X^1 is CR^6 and X^2 is N. In some embodiments of any of the foregoing compounds, R^6 is hydrogen.

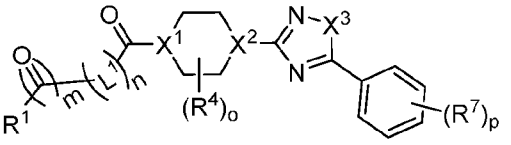
In some embodiments of any of the foregoing compounds, R^5 is optionally substituted C_6-C_{10} aryl. For example, in some embodiments, R^5 is a C_6-C_{10} aryl substituted with 1, 2, 3, or 4 substituents independently selected from C_1-C_6 alkyl (e.g., methyl), halogen (e.g., fluoro, chloro, or bromo), C_1-C_6

alkoxy (e.g., methoxy or ethoxy), nitrile, or two substituents combine to form a 5 or 6-membered heterocycle (e.g., 2,2-difluoro-1,3-benzodioxole). In some embodiments of any of the foregoing compounds, R^5 is phenyl, 2-methyl-phenyl, 3-methyl-phenyl, 4-methyl-phenyl, 3,4-dimethyl-phenyl, 2-methoxy-phenyl, 3-methoxy-phenyl, 4-methoxy-phenyl, 3,4-dimethoxy-phenyl, 2-fluoro-phenyl, 3- fluoro - phenyl, 4- fluoro -phenyl, 3,4-di fluoro –phenyl, 3,4-dichloro-phenyl, 3-methoxy-4-ethoxy-phenyl, 3-chloro-4-ethoxy-phenyl, 3-fluoro-4-ethoxy-phenyl, 3-bromo-4-ethoxy-phenyl, 3-cyano-4-ethoxy-phenyl, or 2,2-difluoro-1,3-benzodioxole.

In some embodiments, the compound has the structure of Formula III or IIIa:



Formula III



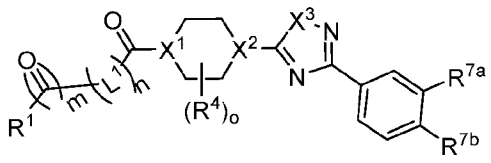
Formula IIIa

wherein p is 1, 2, 3, 4, or 5;

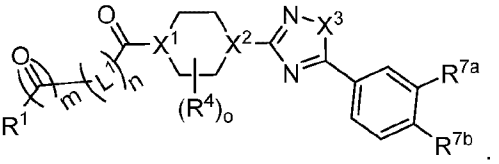
each R^7 is, independently, halogen, nitrile, OR^8, or optionally substituted C_1-C_6 alkyl; and

each R^8 is, independently, hydrogen or optionally substituted C_1-C_6 alkyl.

In some embodiments, the compound has the structure of Formula IV or IVa:



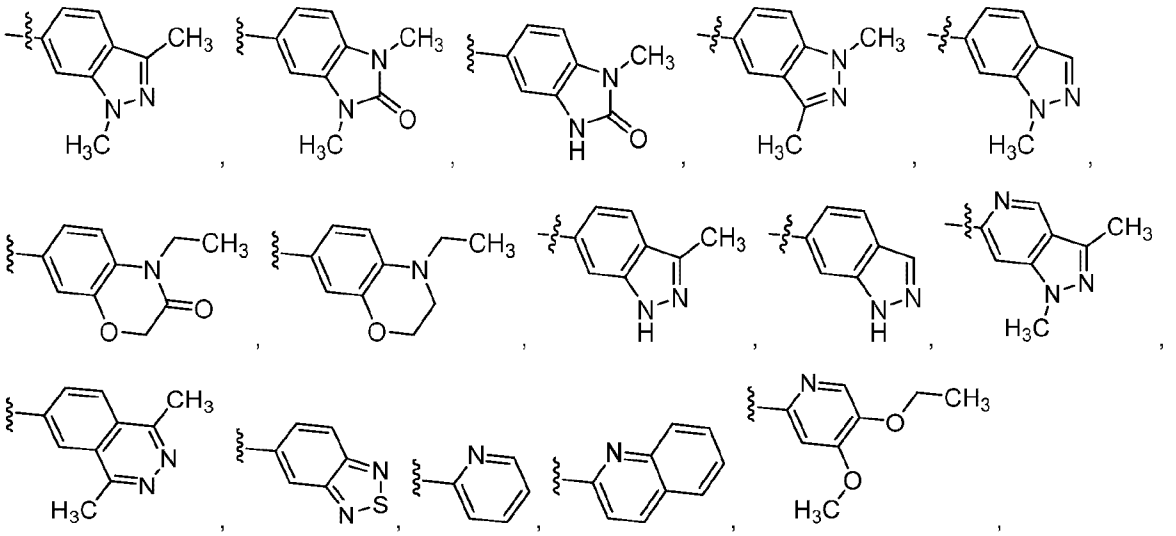
Formula IV

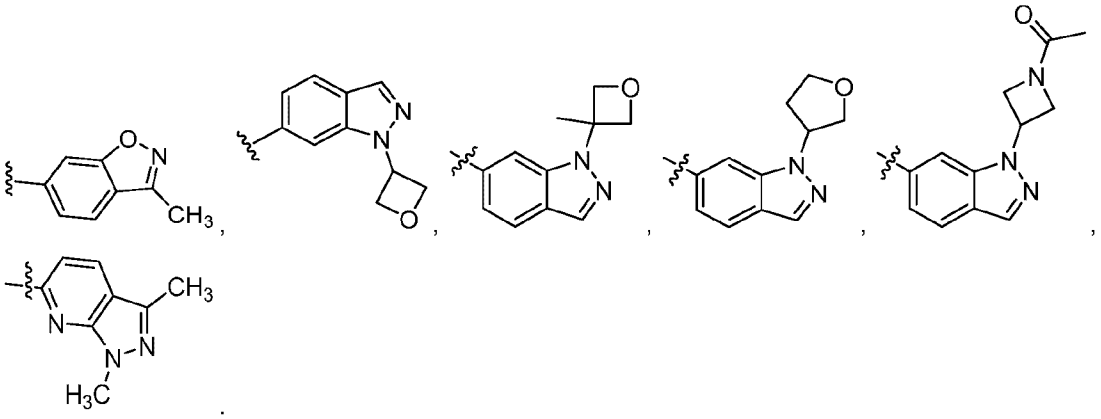


Formula IVa

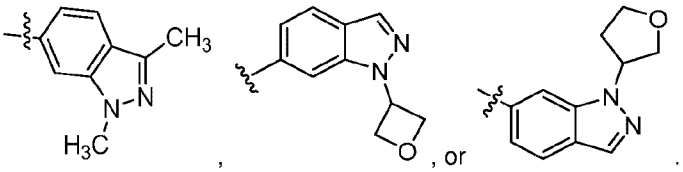
In some embodiments, each R^7 is OR^8. In some embodiments, each R^8 is optionally substituted C_1-C_6 alkyl (e.g., methyl or ethyl).

In some embodiments of any of the foregoing compounds, R^5 is optionally substituted C_2-C_9 heteroaryl (e.g., bicyclic heteroaryl). In some embodiments of any of the foregoing compounds, R^5 is:

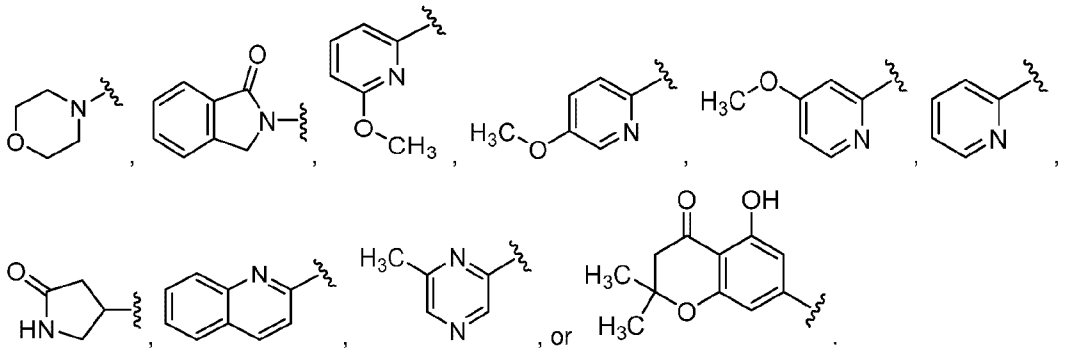




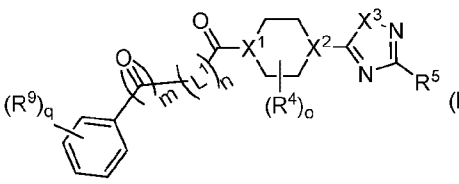
In some embodiments of any of the foregoing compounds, R^5 is:



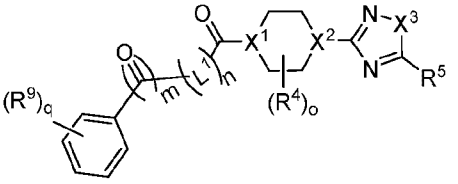
In some embodiments of any of the foregoing compounds, R^1 is optionally substituted C_6-C_{10} aryl or optionally substituted C_2-C_9 heteroaryl. In some embodiments, R^1 is optionally substituted C_6-C_{10} aryl. For example, phenyl or a C_6-C_{10} aryl substituted with 1, 2, 3, 4, or 5 substituents independently selected from C_1-C_6 alkyl (e.g., methyl or iso-propyl), C_1-C_6 alkoxy (e.g., methoxy), or halogen (e.g., chloro). In some embodiments of any of the foregoing compounds R^1 is 2-methoxy-phenyl, 3-methoxy-phenyl, 4-methoxy-phenyl, 3,4-dimethoxy-phenyl, phenyl, 3-methyl-phenyl, 4-methyl-phenyl, 3,4-methyl-phenyl, 4-iso-propyl-phenyl, 2-chloro-phenyl, 3-chloro-phenyl, or 4-chloro-phenyl. In some embodiments of any of the foregoing compounds, R^1 is a bicyclic C_6-C_{10} aryl (e.g., naphthalene). In some embodiments of any of the foregoing compounds, R^1 is C_3-C_7 cycloalkyl (e.g., cyclohexyl). In some embodiments of any of the foregoing compounds, R^1 is optionally substituted C_2-C_9 heteroaryl or optionally substituted C_2-C_9 heterocycle. For example, in some embodiments, R^1 is:



In some embodiments of any of the foregoing compounds, the compound has the structure of Formula V or Va:



Formula V

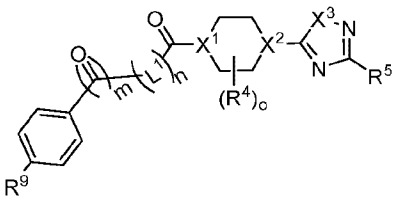


Formula Va

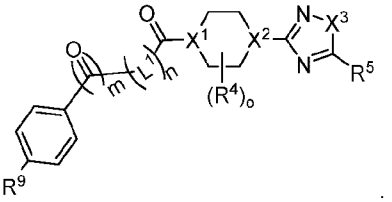
wherein q is 1, 2, 3, 4, or 5; and

R^9 is halogen or optionally substituted C_1-C_6 alkyl.

In some embodiments of any of the foregoing compounds, the compound has the structure of Formula VI or VIa:



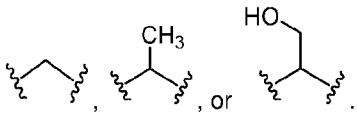
Formula VI



Formula VIa

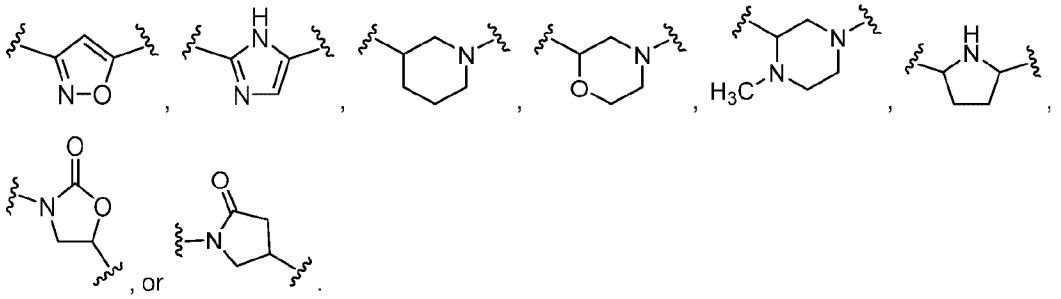
In some embodiments of any of the foregoing compounds, n is 1. In some embodiments of any of the foregoing compounds, n is 0.

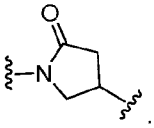
In some embodiments of any of the foregoing compounds, L^1 is optionally substituted C_1-C_6 alkyl. For example, L^1 has the structure:



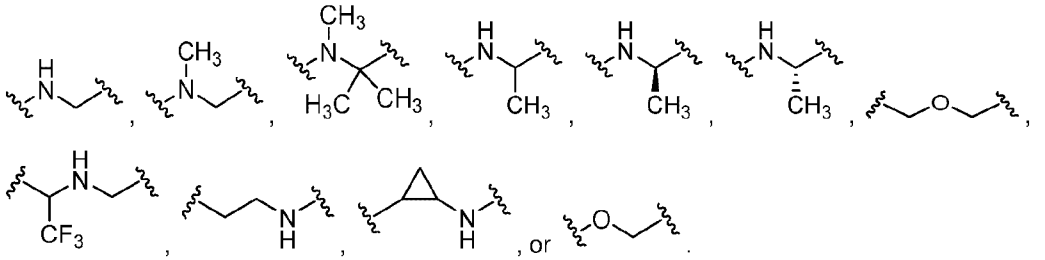
In some embodiments of any of the foregoing compounds, L^1 is optionally substituted C_1-C_6 alkenylene (e.g., ethenylene).

In some embodiments of any of the foregoing compounds, L^1 is optionally substituted C_2-C_9 heterocyclene or optionally substituted C_2-C_9 heteroarylene. For example,



In some embodiments, L^1 is  .

In some embodiments of any of the foregoing compounds, L^1 is optionally substituted C_1-C_6 heteroalkylene. For example, in some embodiments, L^1 is:



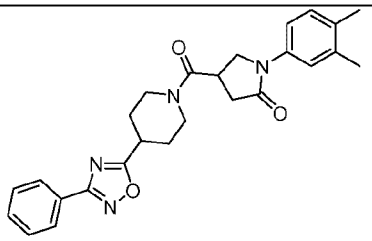
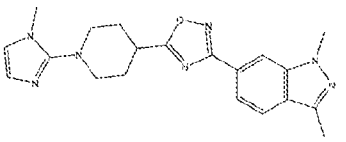
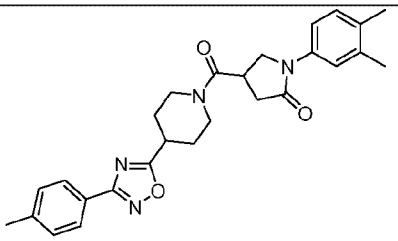
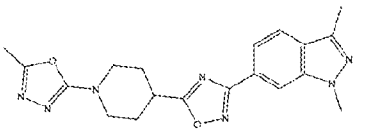
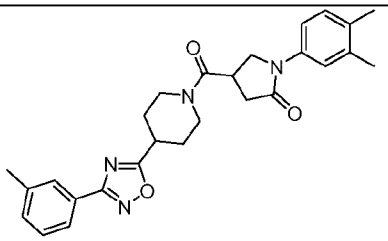
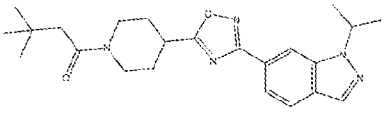
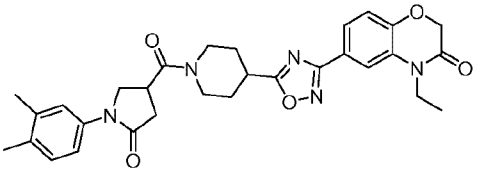
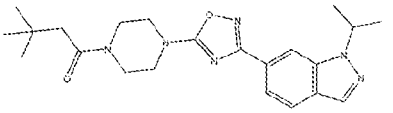
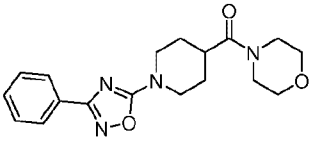
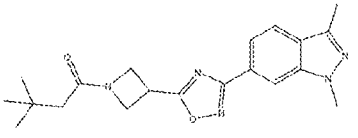
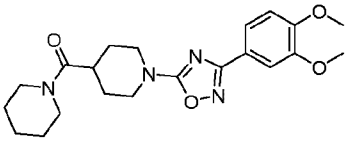
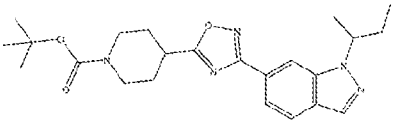
In some embodiments of any of the foregoing compounds, L^1 is -NH-$(CR^{10}R^{11})_r$-, wherein r is 1, 2, 3, 4, 5, or 6, and each R^{10} and R^{11} is, independently, hydrogen or optionally substituted C_1-C_6 alkyl. For example, in some embodiments, L^1 is -NH-CH_2-, –NH-$CR^{10}R^{11}$-, wherein each of R^{10} and R^{11} is methyl, or –NH-CHR^{11}-, wherein R^{11} is methyl.

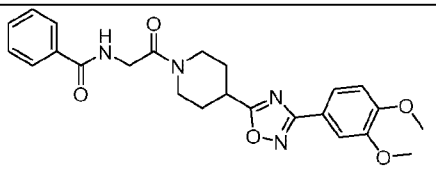
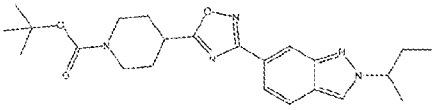
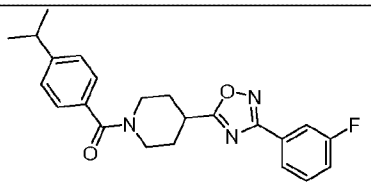
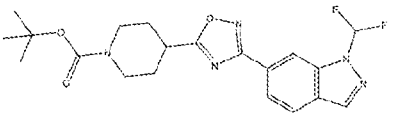
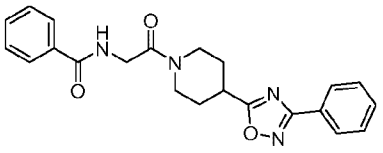
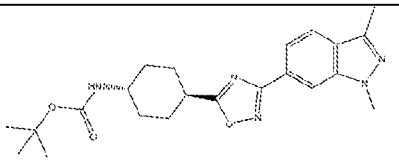
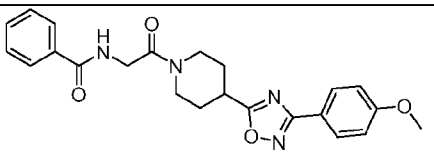
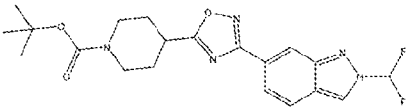
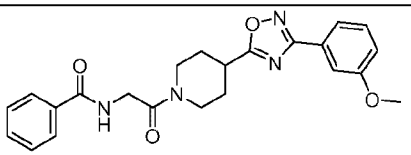
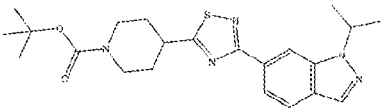
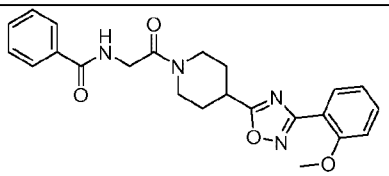
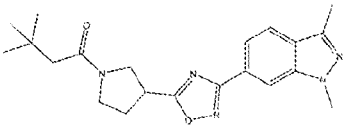
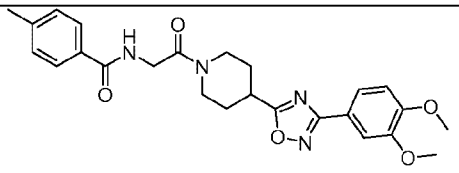
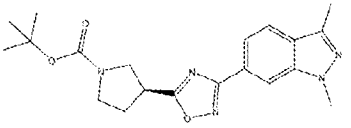
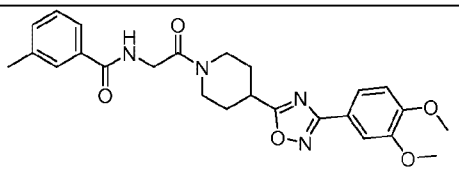
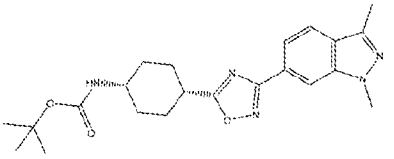
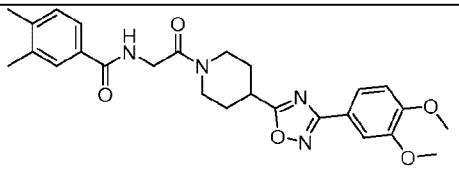
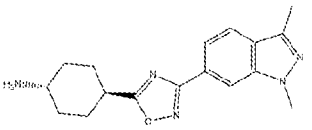
In some embodiments of any of the foregoing compounds, m is 1. In some embodiments of any of the foregoing compounds, m is 0.

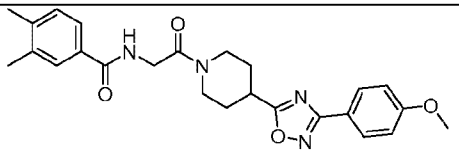
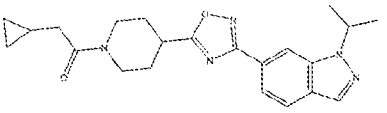
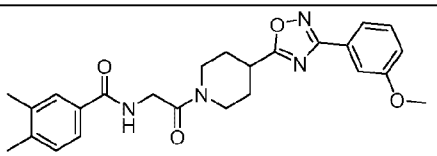
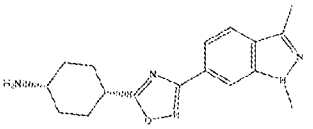
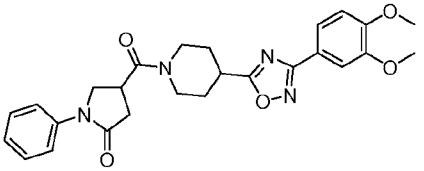
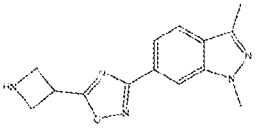
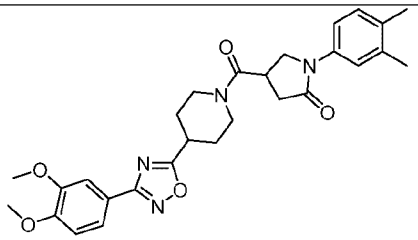
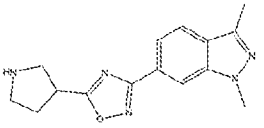
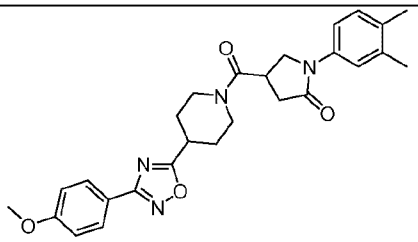
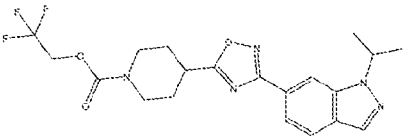
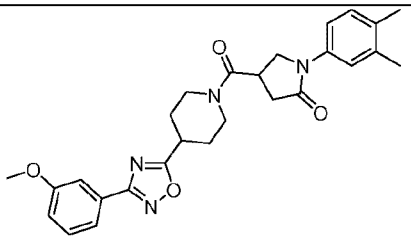
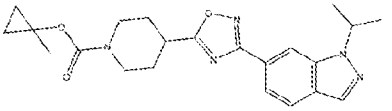
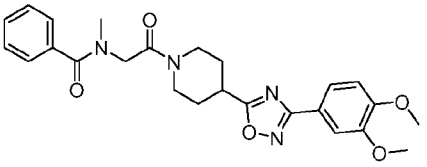
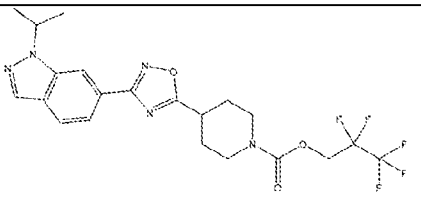
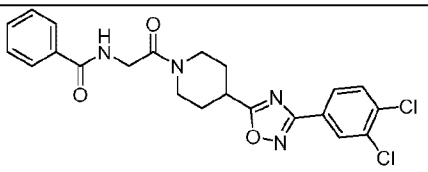
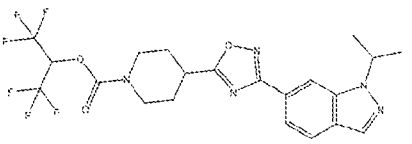
In another aspect, the disclosure provides a compound, or pharmaceutically acceptable salt thereof, having the structure of any one of compounds 1-1313 in Table 1, Table 2A, Table 2B, and Table 2C. In some embodiments, the compound is any one of compounds 1-264, 266-271, 274-276, 278-299, 302-318, 320-329, 331-340, 344-354, 358, 362-364, 367, 369, 371-378, 385, 388-392, 396, 397, 399-401, 403, 406-411, 414, 418-420, 422, 425-432, 434-436, 438, 440-444, 446, 450-454, 456, 458, 460, 461, 464, 466, 470, 472-474, 476, 477, or 481-746 in Table 1. In some embodiments, the compound is any one of compounds 1-347, 349, 350, or 354-746 in Table 1. In some embodiments, the compound is any one of compounds 1-387, 389, 393-405, 407-430, 432-439, 441-449, 452, 454-457, 459-472, 475, 477-480, 482-487, or 489-746 in Table 1, In some embodiments, the compound is any one of compounds 1-483 or 491-746 in Table 1. In some embodiments, the compound is any one of compounds 747-966. In some embodiments, the compound is any one of compounds 27, 40, 96, 128, 140, 168, 184, 204, 226, 244, 265, 268, 269, 284, 286 291, 294, 302, 305, 306, 308, 317, 319, 343, 344, 345, 346, 349, 355-357, or 359-364. In some embodiments, the compound is any one of compounds 244, 265, 269, 319, 345, 349, 355-357, 361, or 364. In some embodiments, the compound is any one of compounds 750, 767, 775-778, 780, 784, 785, 789-792, 795, 799, 812, 813, 817, 828, 838, 839, 842-844, 846, 848, 850, 851, 853, 854, 861, 862, 865, 874-881, 884-888, 890-898, 902, 903, 907, 910, 916, 928, 932, 934, 953, 957, 960, 964, or 965. In some embodiments, the compound is any one of compounds 967-1195. In some embodiments, the compound is any one of compounds 970, 971, 974, 975, 979-982, 986, 988, 990, 992, 997, 999, 1000, 1003-1006, 1010, 1012, 1013, 1015-1026, 1028, 1029, 1031, 1034-1037, 1039-1050, 1052-1062, 1065-1073, 1075-1080, 1082-1087, 1090, 1092, 1093, 1096-1098, 1100, 1104, 1105, 1107, 1109-1114, 1125, 1131, 1134-1141, 1144, 1146, 1149, 1151-1154, 1156, 1161, 1162, 1164, 1170, 1171, 1175-1182, 1190, or 1192. In some embodiments, the compound is any one of compounds 970, 971, 974, 975, 979, 981, 982, 986, 988, 990, 992, 997, 999, 1005, 1012, 1016-1020, 1022, 1024, 1025, 1028, 1029, 1036, 1039, 1041-1043, 1046-1050, 1053-1062, 1065-1073, 1075, 1078, 1082-1084, 1086, 1087, 1092, 1093, 1096-1098, 1104, 1107, 1109-1112, 1114, 1134-1137, 1139, 1140, 1144, 1149, 1152, 1154, 1161, 1162, 1171, 1176, 1180, 1190, or 1192. In some embodiments, the compound is any one of compounds 970, 971, 974, 975, 986, 988, 990, 997, 999, 1005, 1012, 1016-1019, 1022, 1024, 1025, 1028, 1029, 1036, 1039, 1041, 1043, 1046-1050, 1053-1059, 1061, 1062, 1065-1073, 1075, 1078, 1083, 1084, 1086, 1087, 1092, 1093, 1096, 1097, 1104, 1107, 1109, 1110, 1134, 1136, 1137, 1139, 1140,

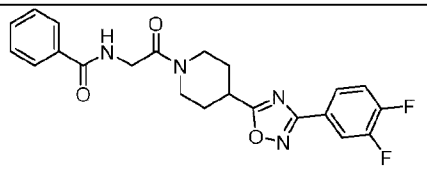
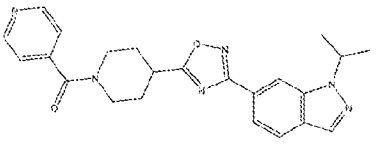
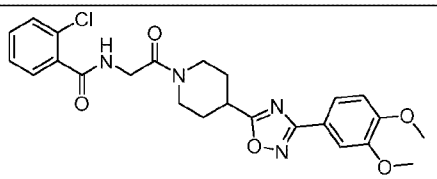
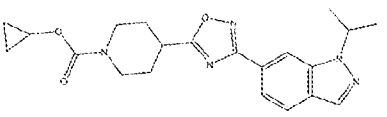
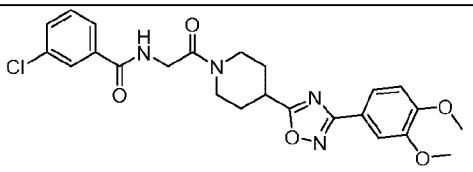
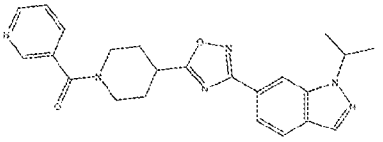
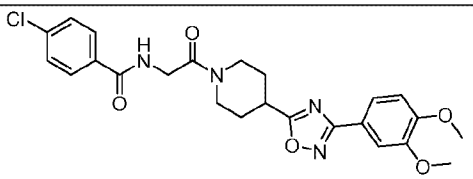
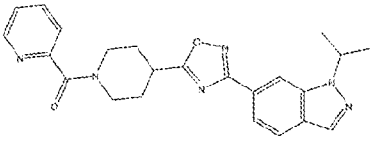
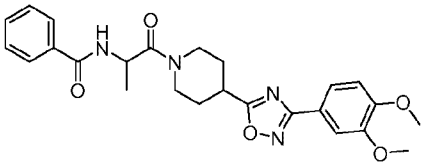
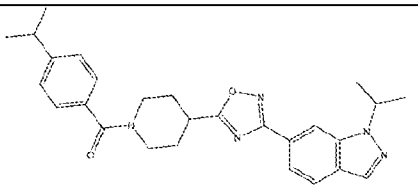
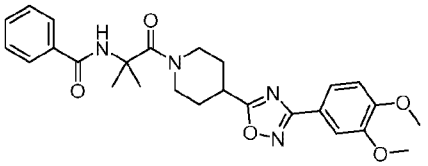
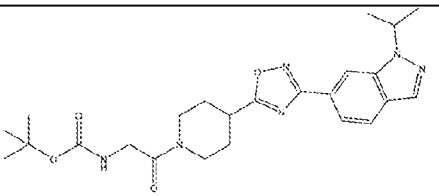
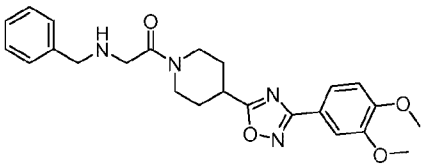
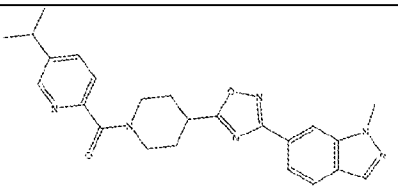
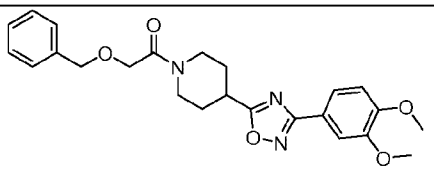
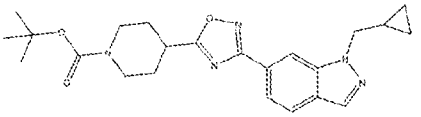
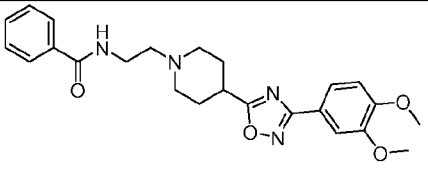
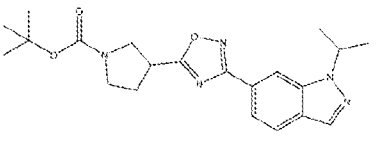
1144, 1149, 1152, 1154, 1161, 1162, 1171, 1180, 1190, or 1192. In some embodiments, the compound is any one of compounds 970, 1053-1056, 1058, 1059, 1065-1069, 1071-1073, 1093, or 1096. In some embodiments, the compound is any one of compounds 1196-1131. In some embodiments, the compound is any one of compounds 1201, 1202, 1206, 1207, 1209, 1210, 1211, 1213, 1214, 1215, 1217, 1218, 1219, 1220, 1221, 1225, 1226, 1227, 1237, 1238, 1240, 1241, 1242, 1243, 1247, 1252, 1253, 1259, 1260, 1261, 1267, 1271, 1272, 1274, 1275, 1276, 1280, 1283, 1284, 1285, 1288, 1294, 1295, 1297, 1298, 1299, 1301, 1304, 1311, or 1313.

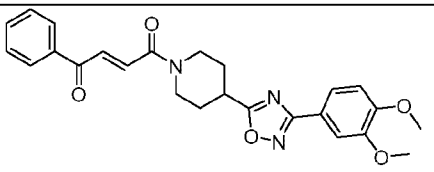
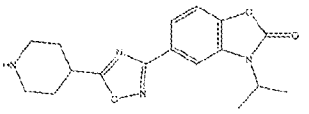
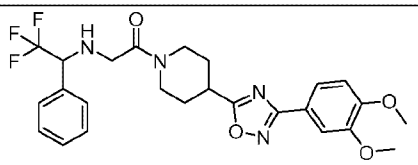
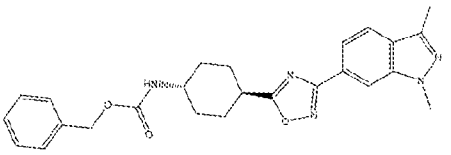
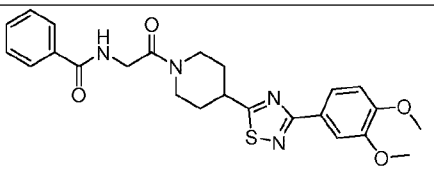
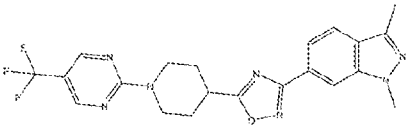
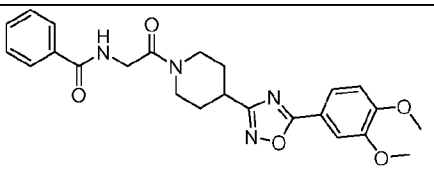
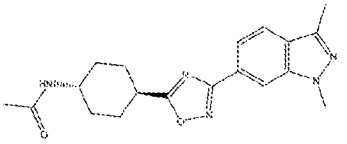
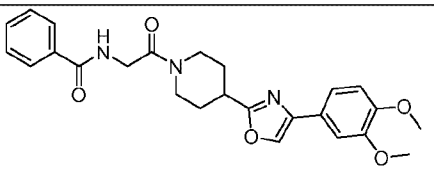
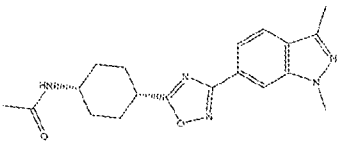
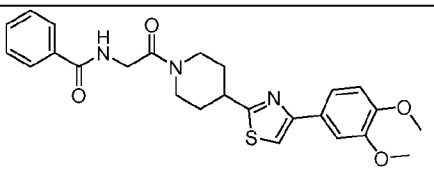
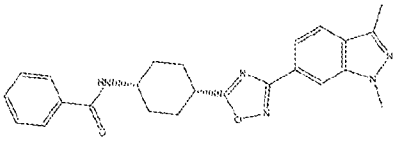
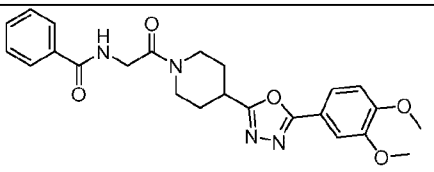
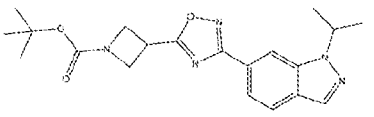
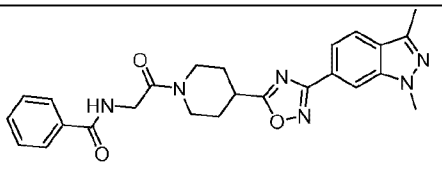
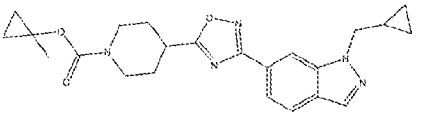
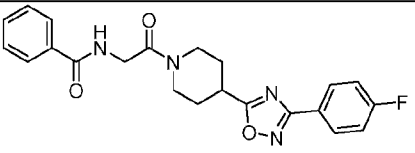
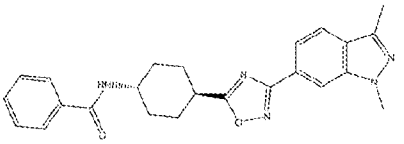
Table 1. Compounds of the Invention

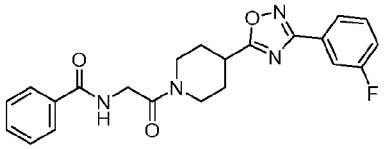
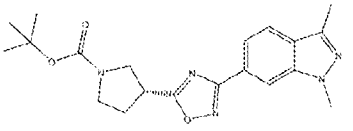
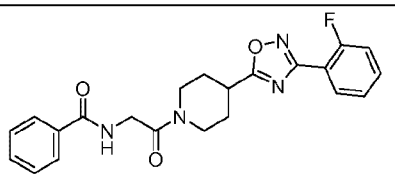
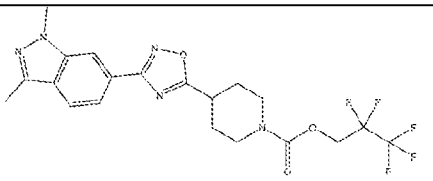
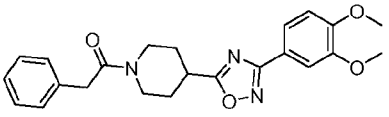
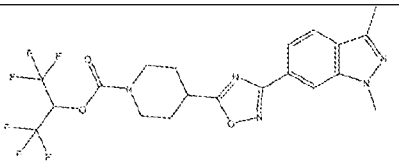
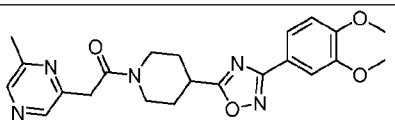
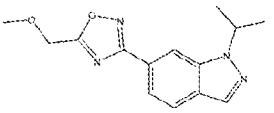
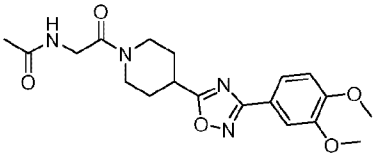
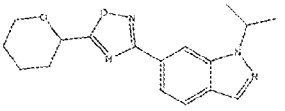
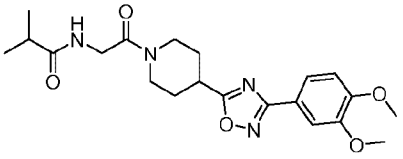
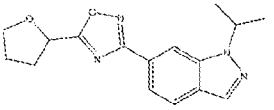
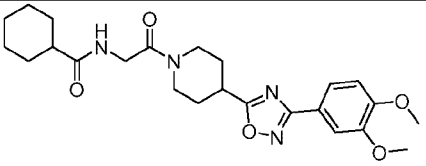
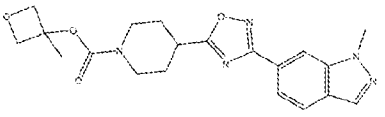
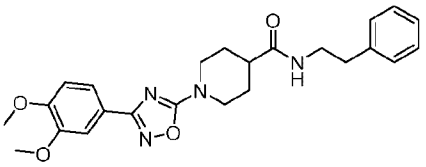
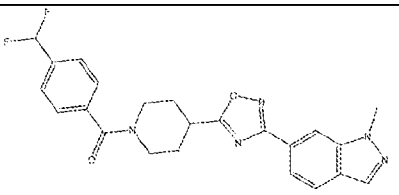
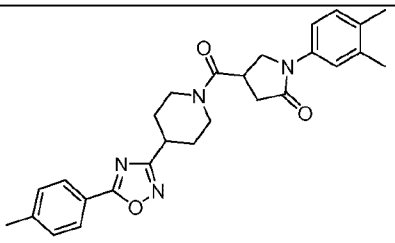
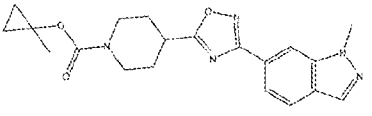
#	Structure	#	Structure
1		374	
2		375	
3		376	
4		377	
5		378	
6		379	

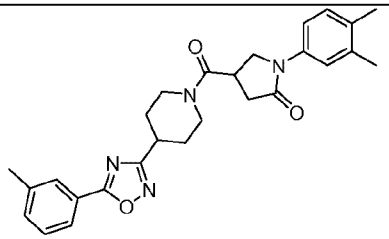
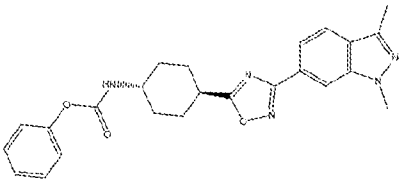
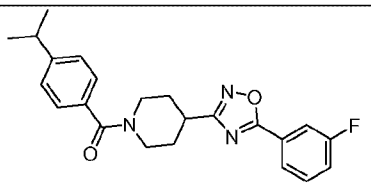
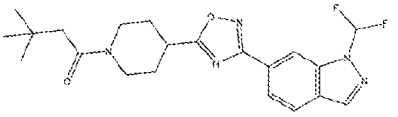
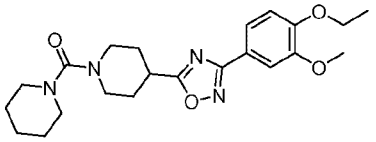
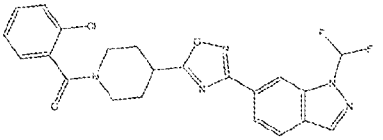
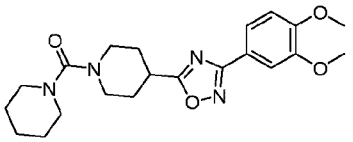
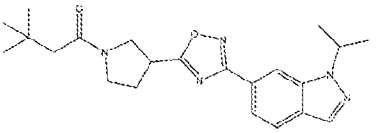
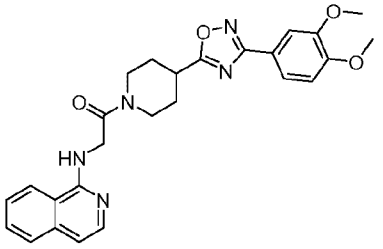
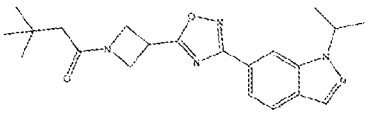
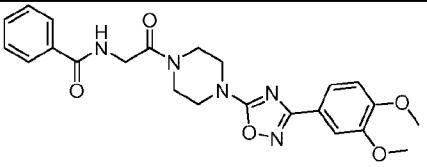
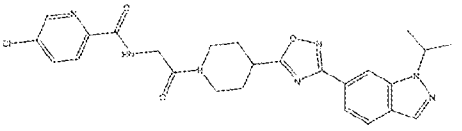
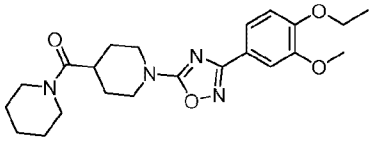
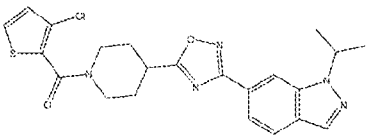
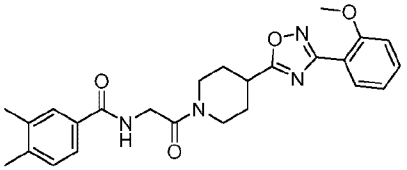
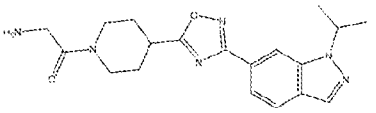
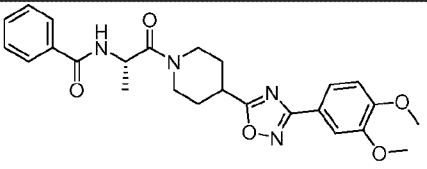
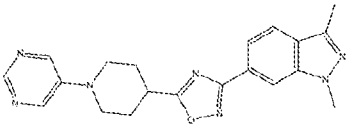
#	Structure	#	Structure
7		380	
8		381	
9		382	
10		383	
11		384	
12		385	
13		386	
14		387	
15		388	

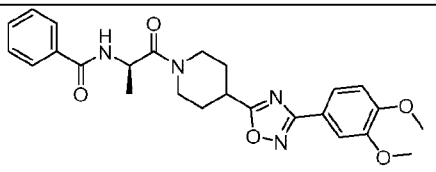
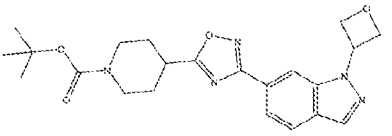
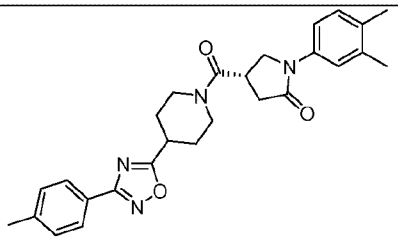
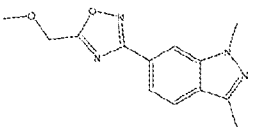
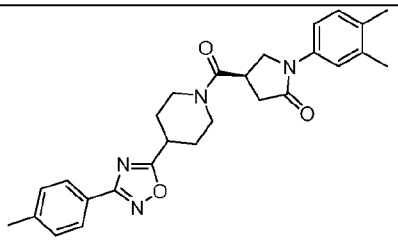
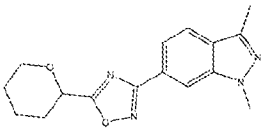
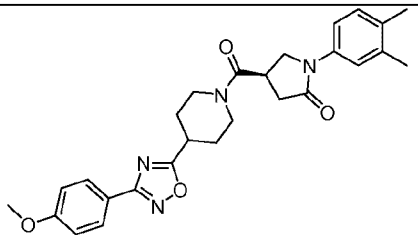
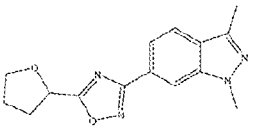
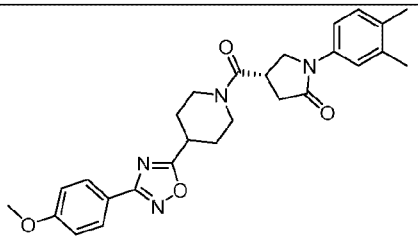
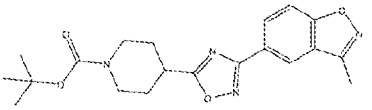
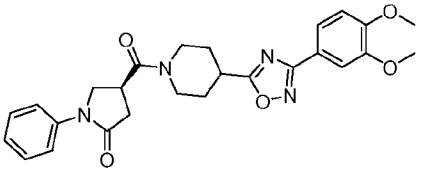
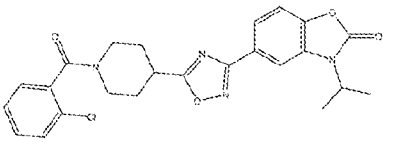
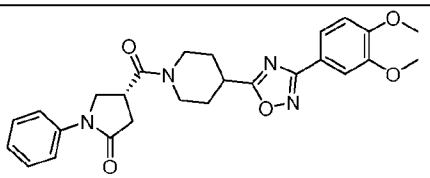
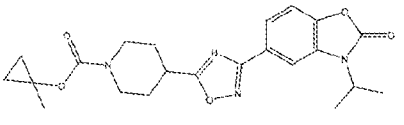
#	Structure	#	Structure
16		389	
17		390	
18		391	
19		392	
20		393	
21		394	
22		395	
23		396	

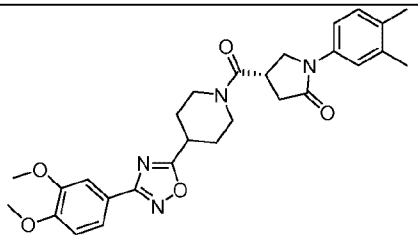
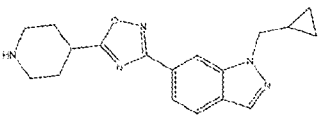
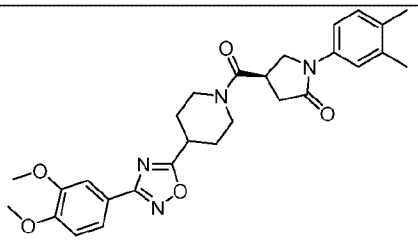
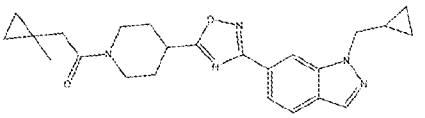
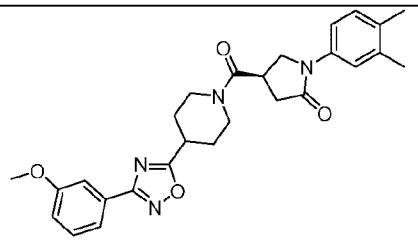
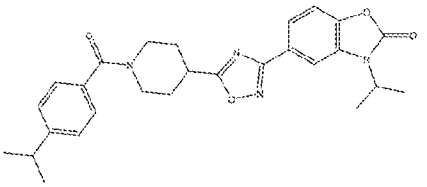
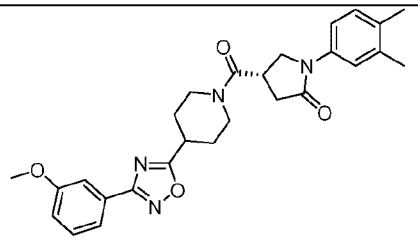
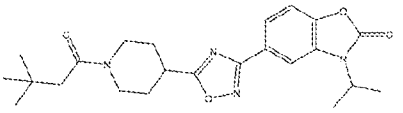
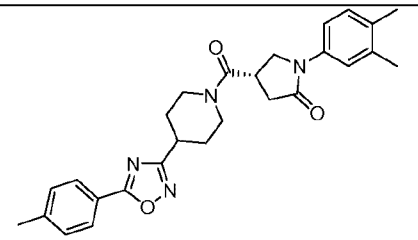
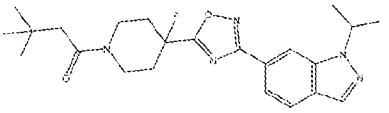
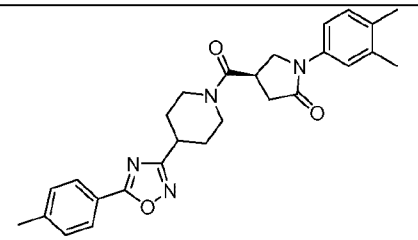
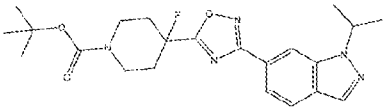
#	Structure	#	Structure
24		397	
25		398	
26		399	
27		400	
28		401	
29		402	
30		403	
31		404	
32		405	

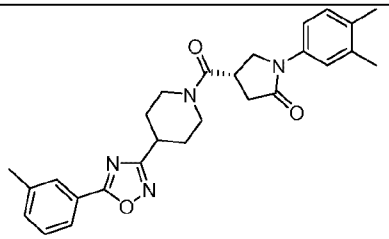
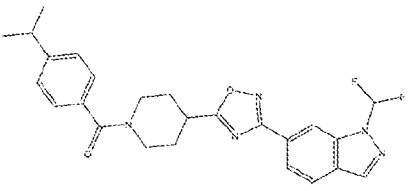
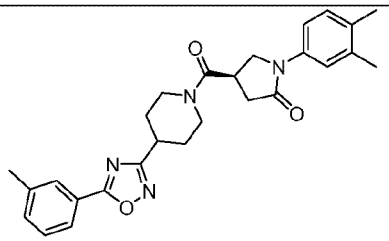
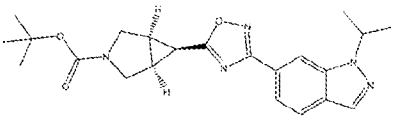
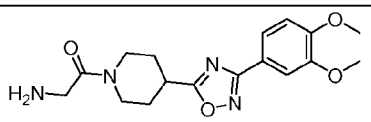
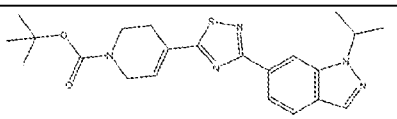
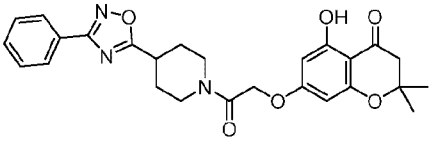
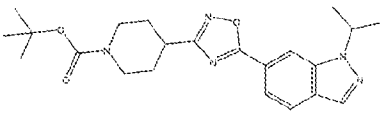
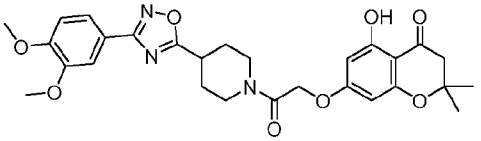
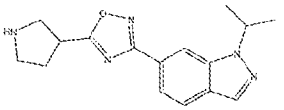
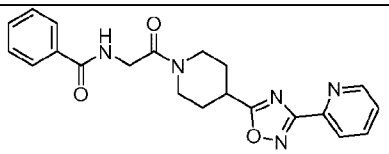
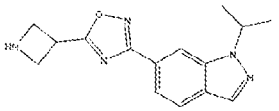
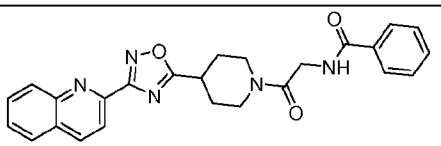
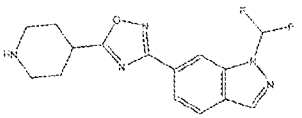
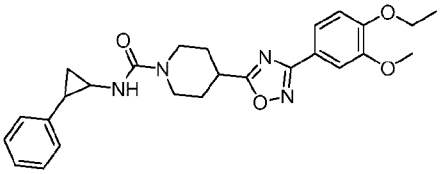
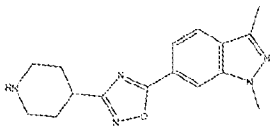
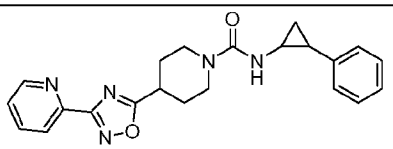
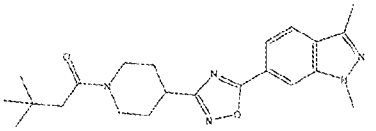
#	Structure	#	Structure
33		406	
34		407	
35		408	
36		409	
37		410	
38		411	
39		412	
40		413	
41		414	

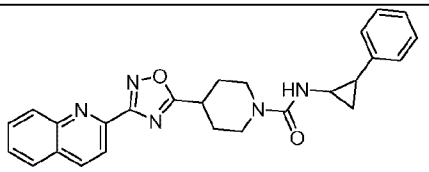
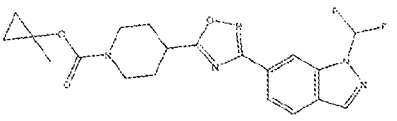
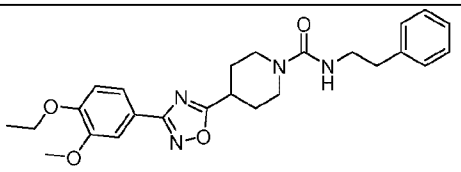
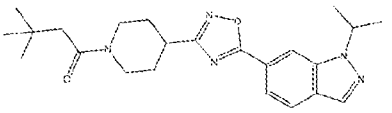
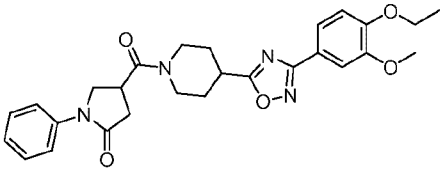
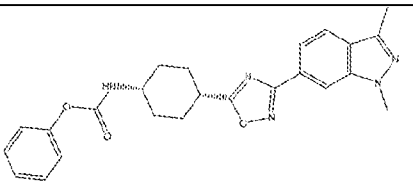
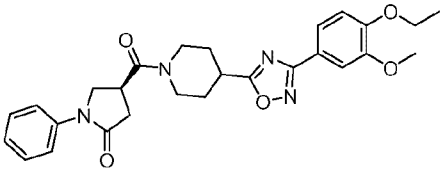
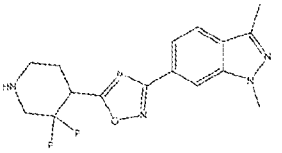
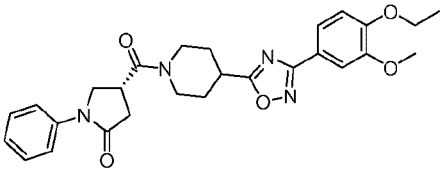
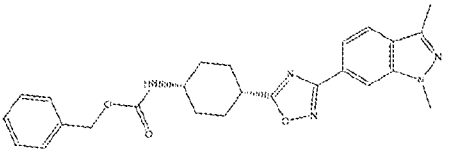
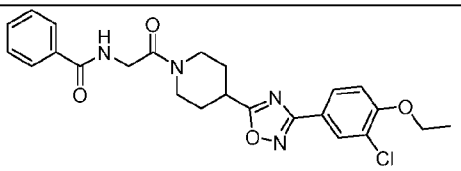
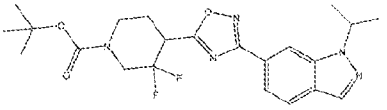
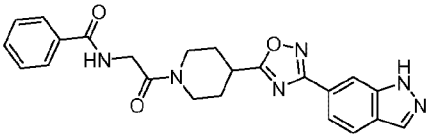
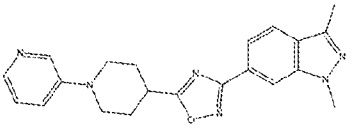
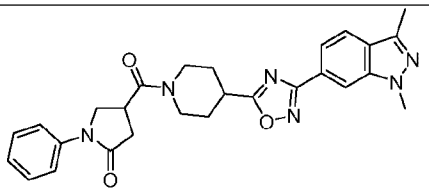
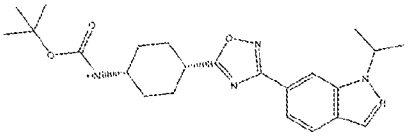
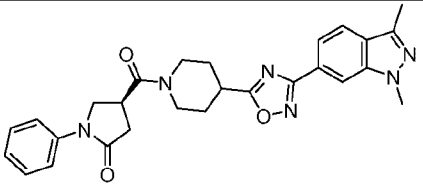
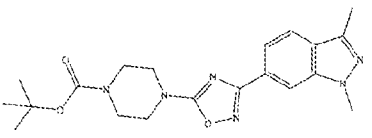
#	Structure	#	Structure
42		415	
43		416	
44		417	
45		418	
46		419	
47		420	
48		421	
49		422	
50		423	

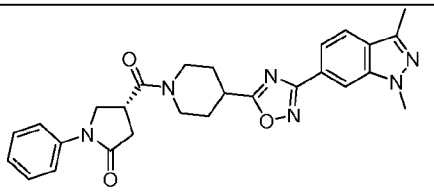
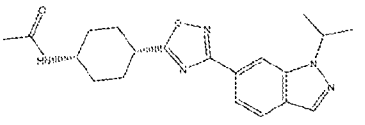
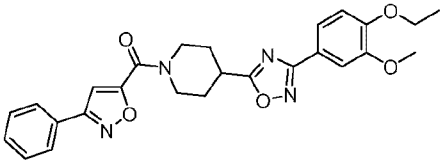
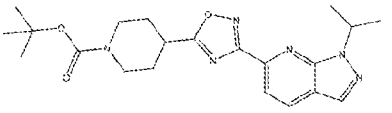
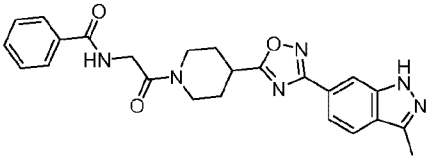
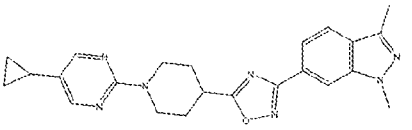
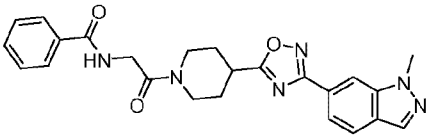
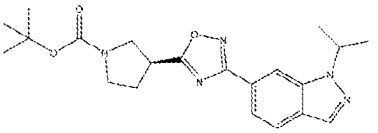
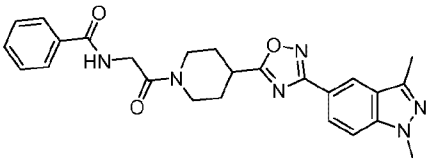
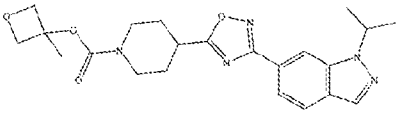
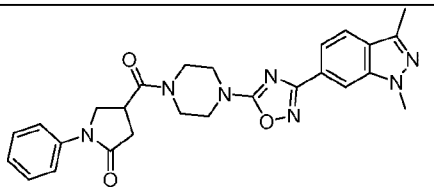
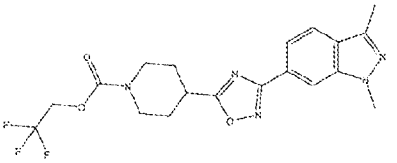
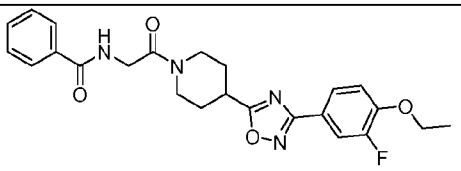
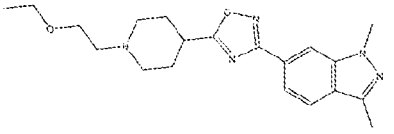
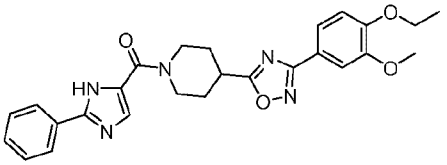
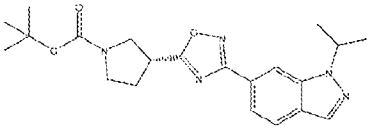
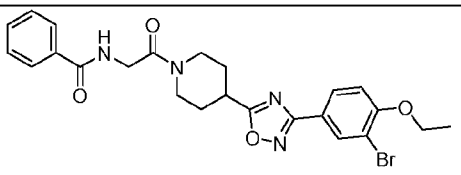
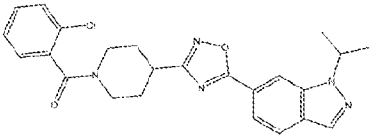
#	Structure	#	Structure
51		424	
52		425	
53		426	
54		427	
55		428	
56		429	
57		430	
58		431	
59		432	

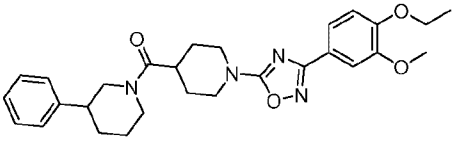
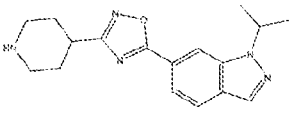
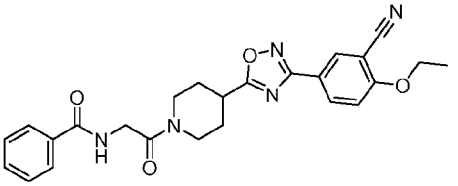
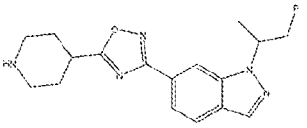
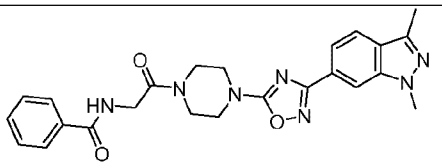
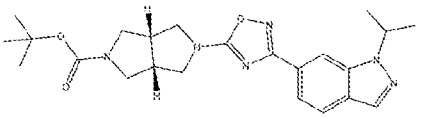
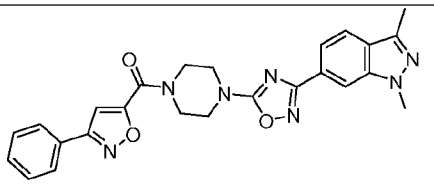
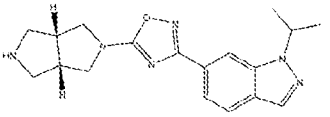
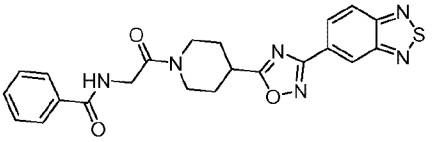
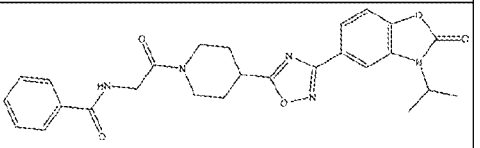
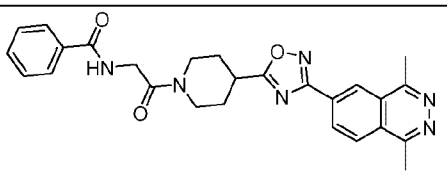
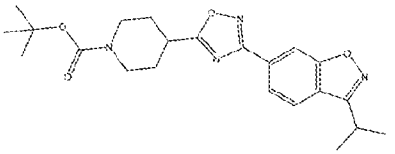
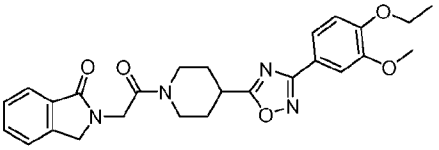
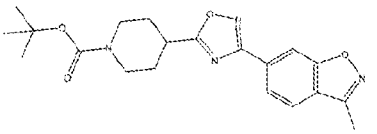
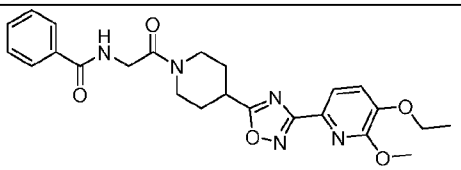
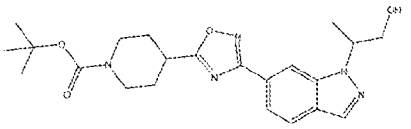
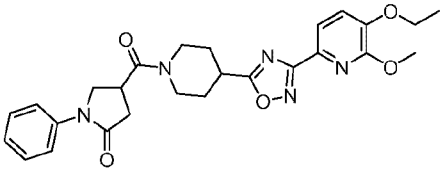
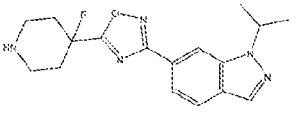
#	Structure	#	Structure
60		433	
61		434	
62		435	
63		436	
64		437	
65		438	
66		439	

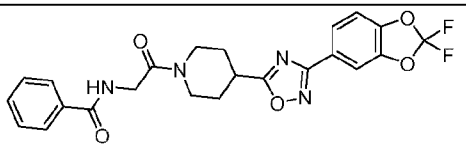
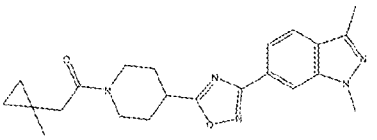
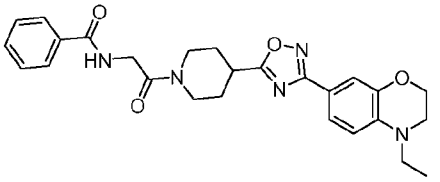
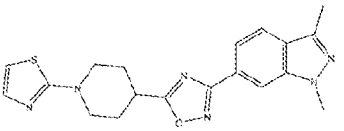
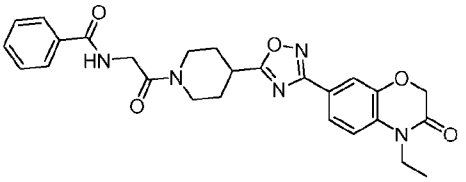
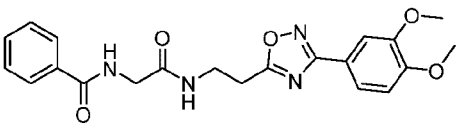
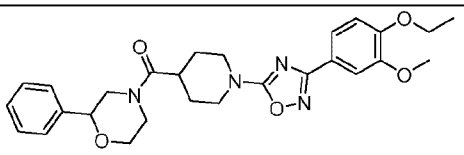
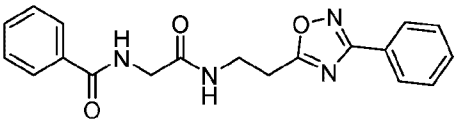
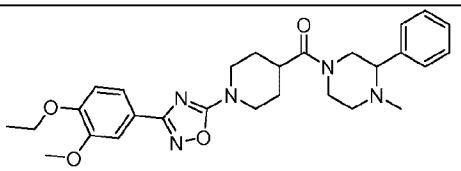
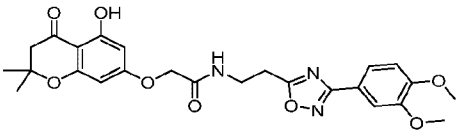
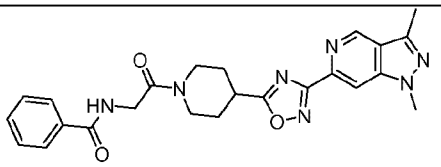
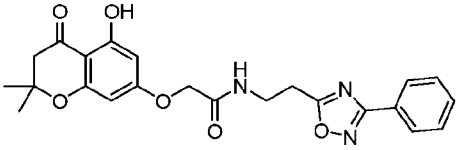
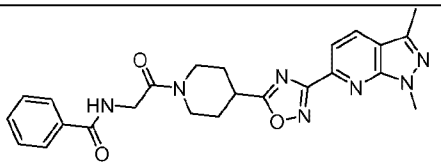
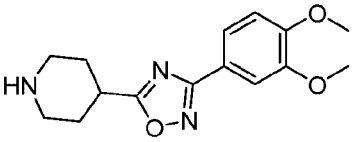
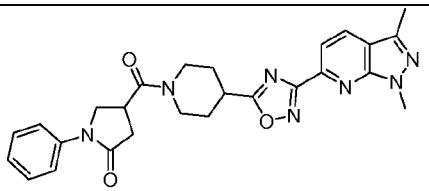
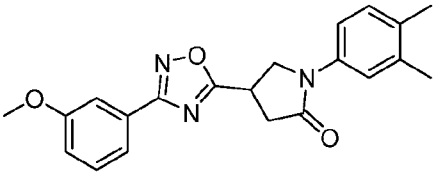
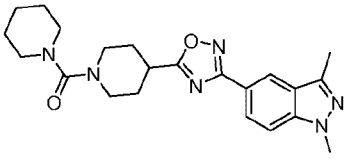
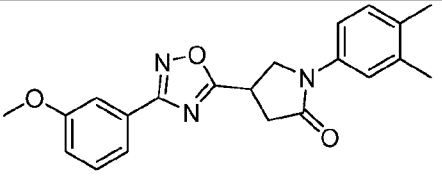
#	Structure	#	Structure
67		440	
68		441	
69		442	
70		443	
71		444	
72		445	

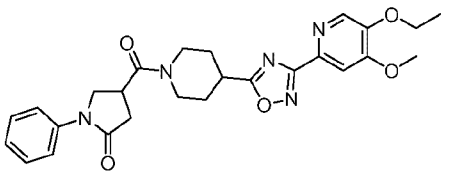
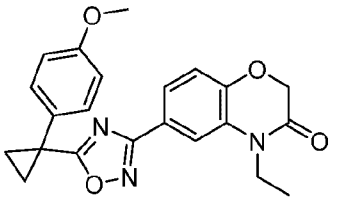
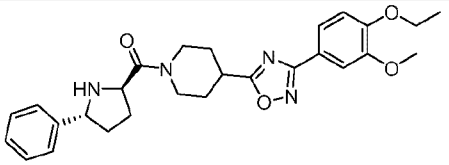
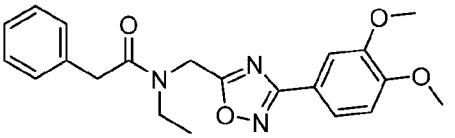
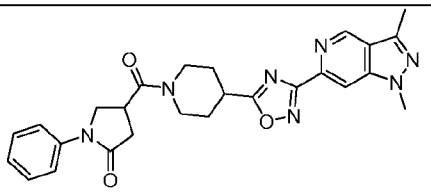
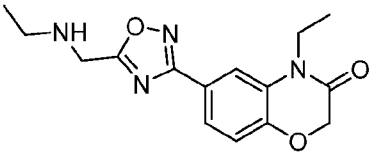
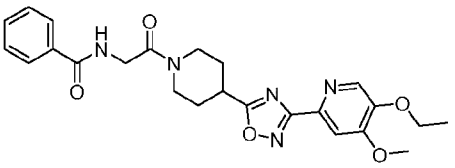
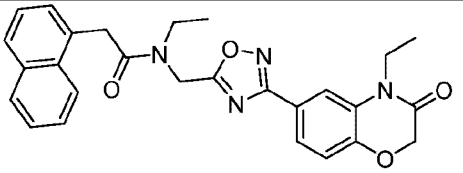
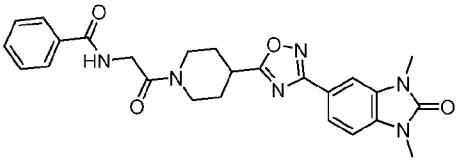
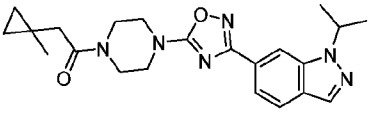
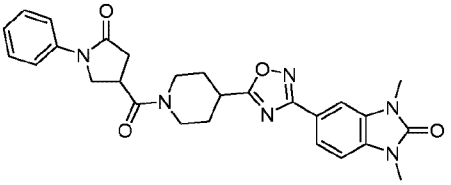
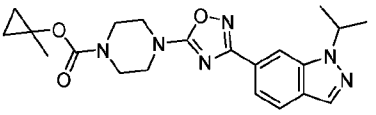
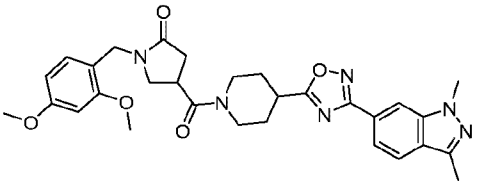
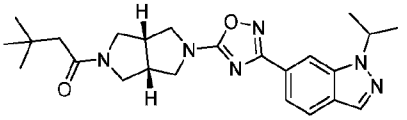
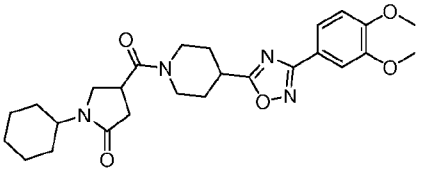
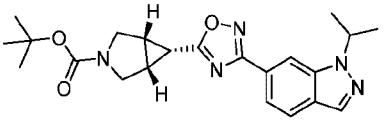
#	Structure	#	Structure
73		446	
74		447	
75		448	
76		449	
77		450	
78		451	
79		452	
80		453	
81		454	

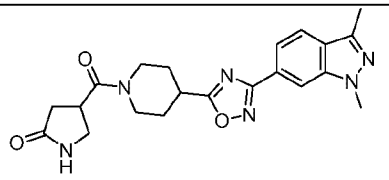
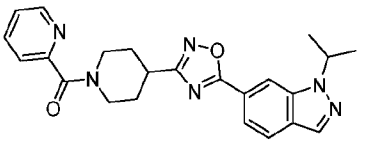
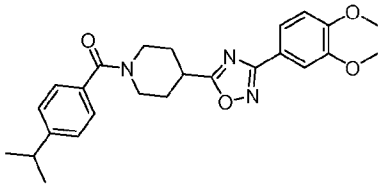
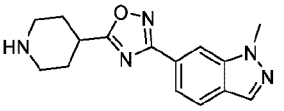
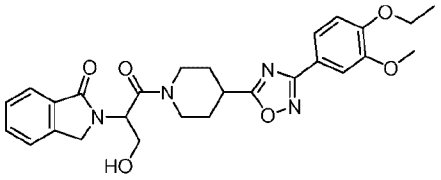
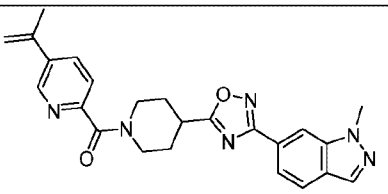
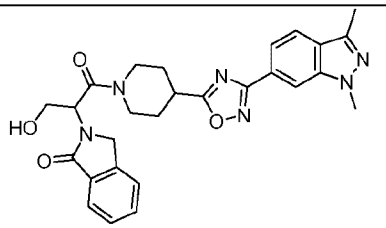
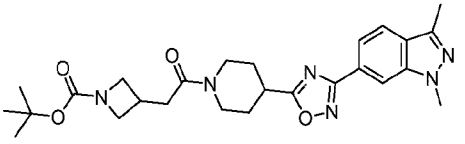
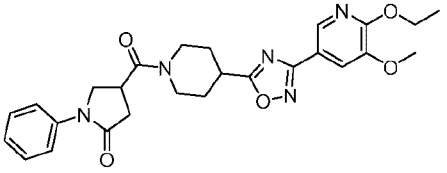
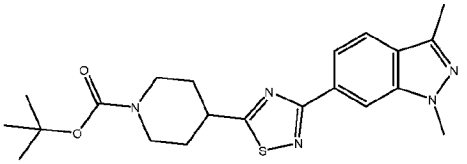
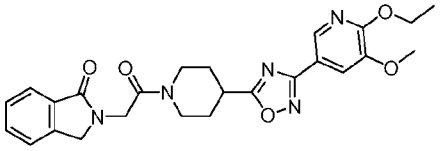
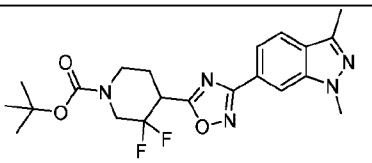
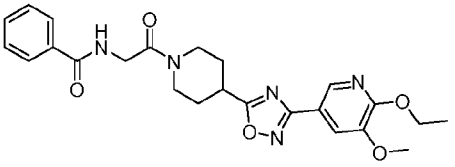
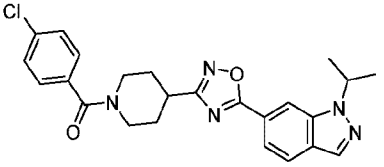
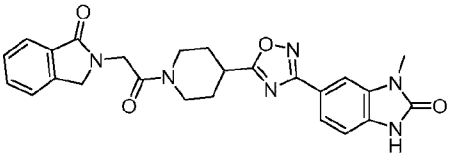
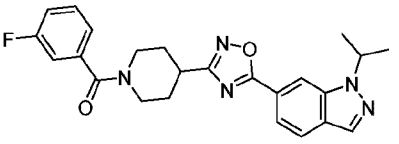
#	Structure	#	Structure
82		455	
83		456	
84		457	
85		458	
86		459	
87		460	
88		461	
89		462	
90		463	

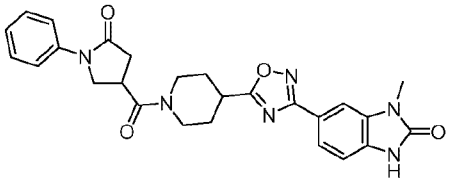
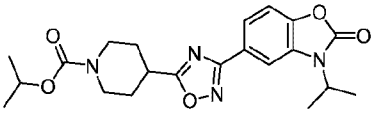
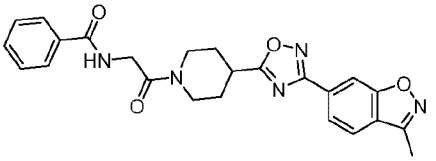
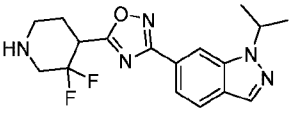
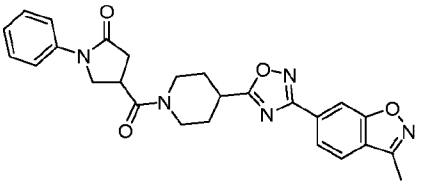
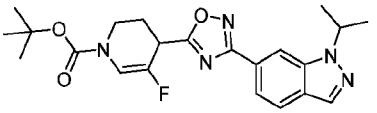
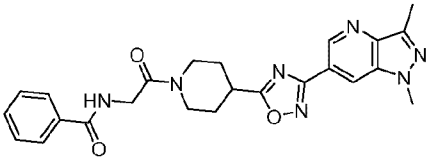
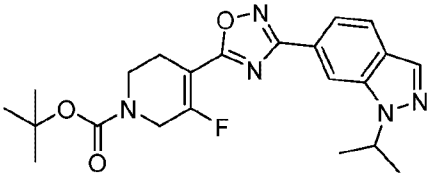
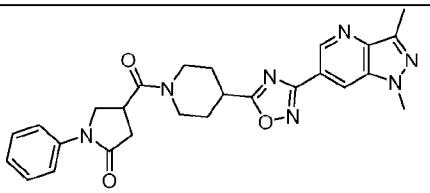
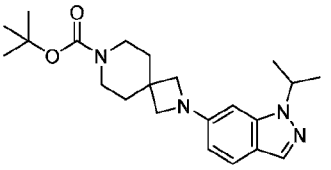
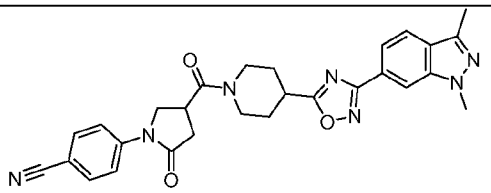
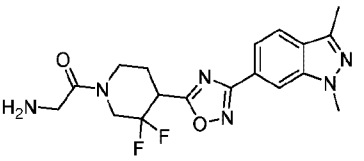
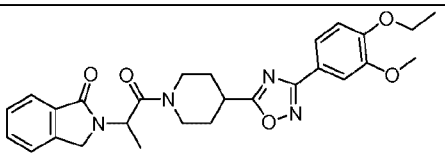
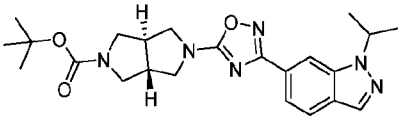
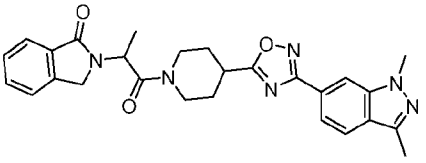
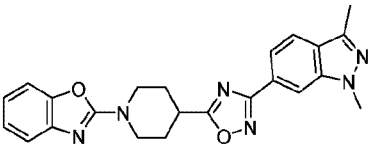
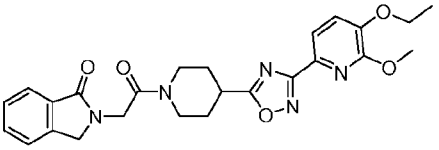
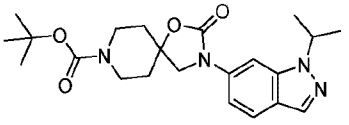
#	Structure	#	Structure
91		464	
92		465	
93		466	
94		467	
95		468	
96		469	
97		470	
98		471	
99		472	

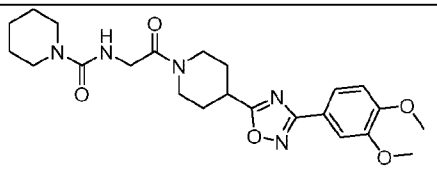
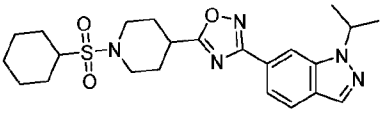
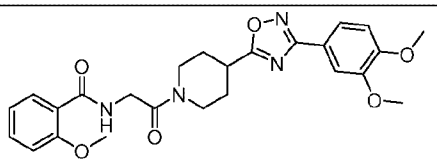
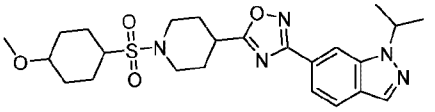
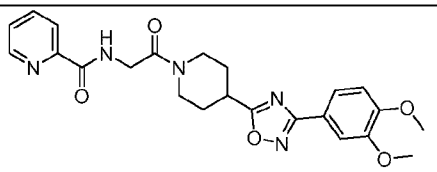
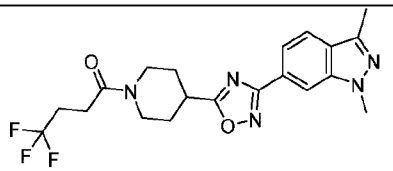
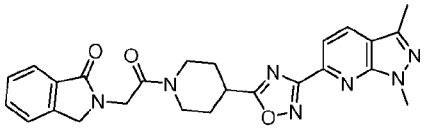
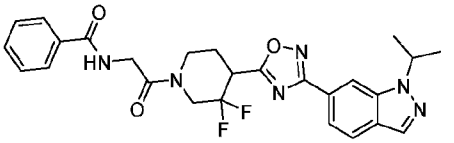
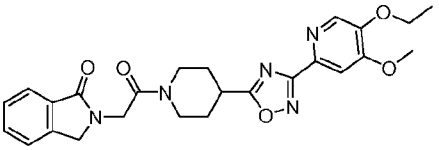
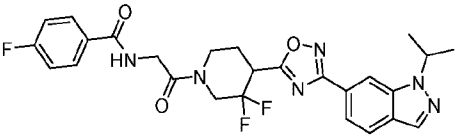
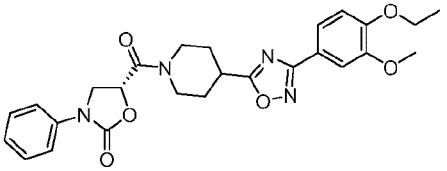
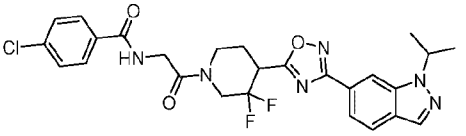
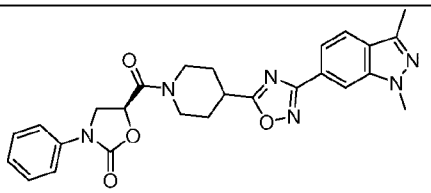
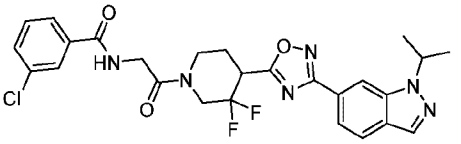
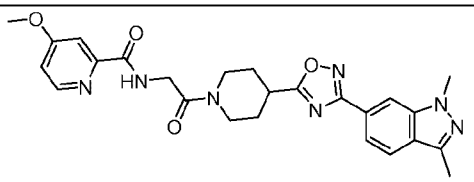
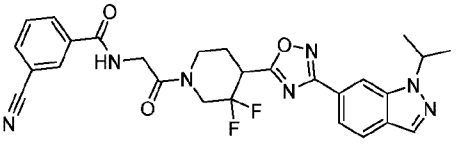
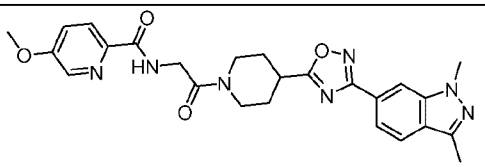
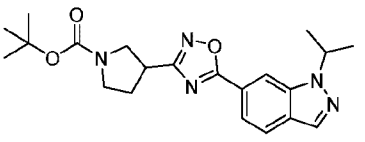
#	Structure	#	Structure
100		473	
101		474	
102		475	
103		476	
104		477	
105		478	
106		479	
107		480	
108		481	

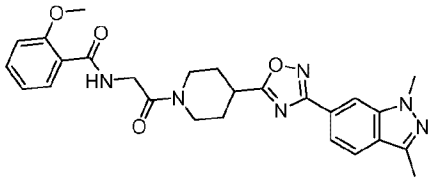
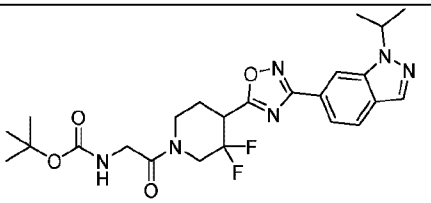
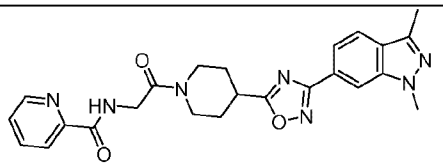
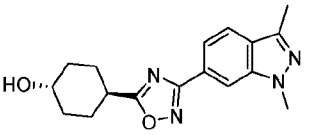
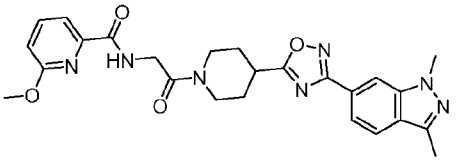
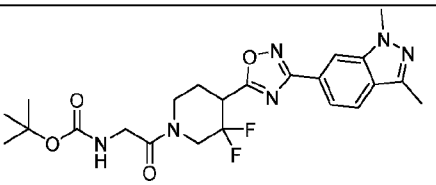
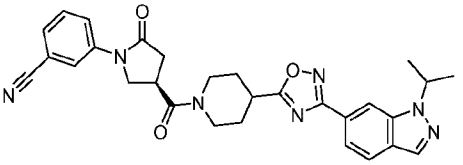
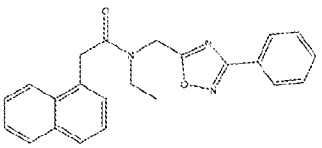
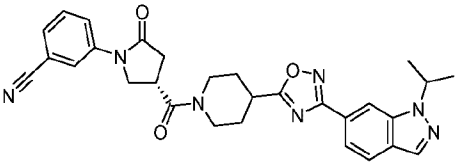
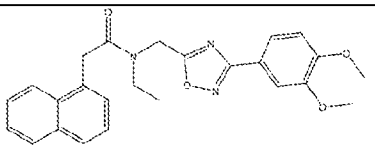
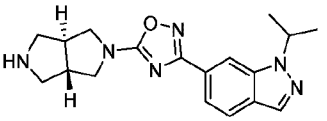
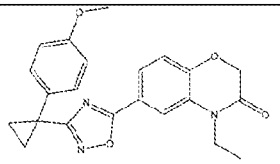
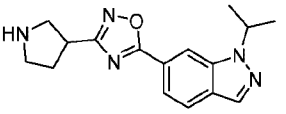
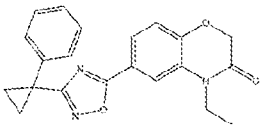
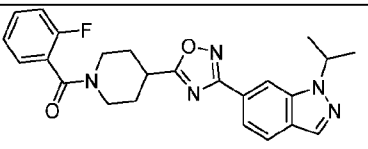
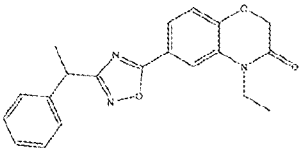
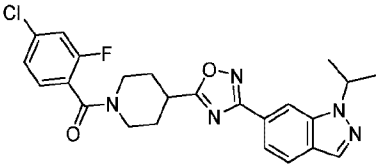
#	Structure	#	Structure
109		482	
110		483	
111		484	
112		485	
113		486	
114		487	
115		488	
116		489	
117		490	

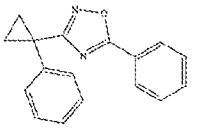
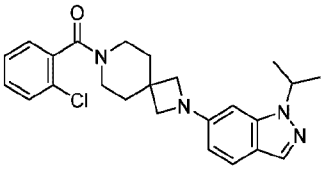
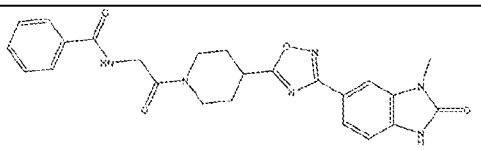
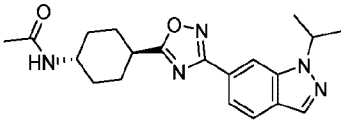
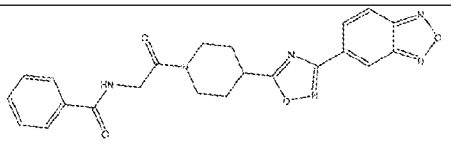
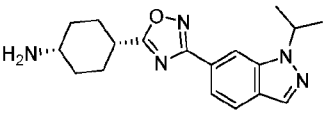
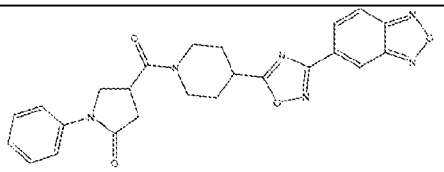
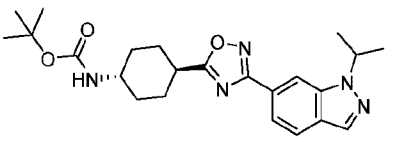
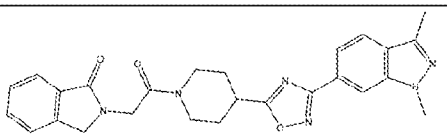
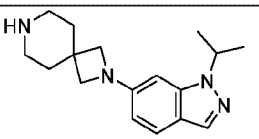
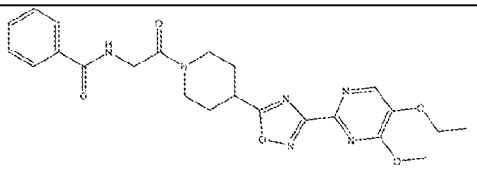
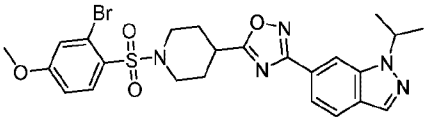
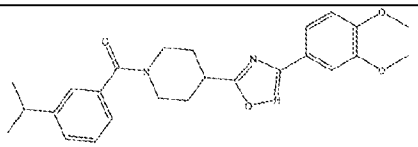
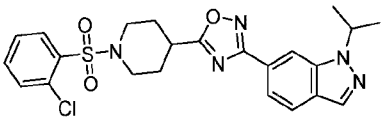
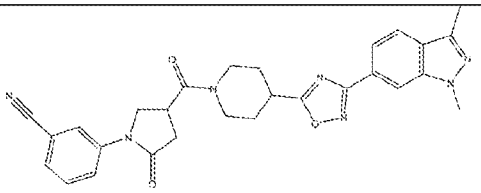
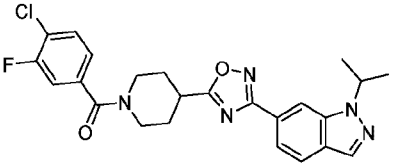
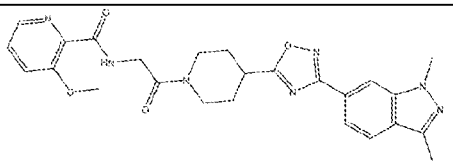
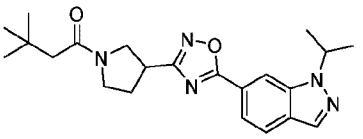
#	Structure	#	Structure
118		491	
119		492	
120		493	
121		494	
122		495	
123		496	
124		497	
125		498	

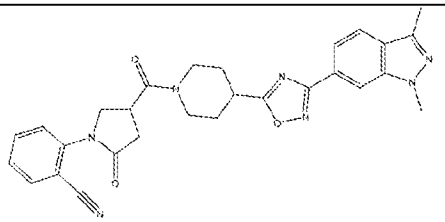
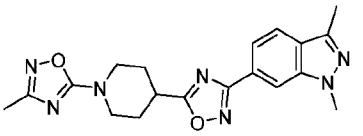
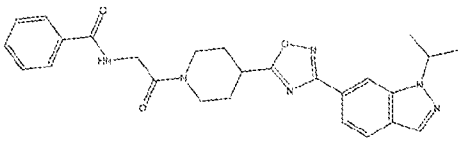
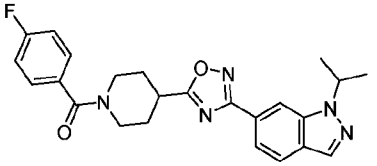
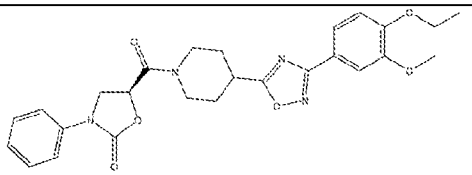
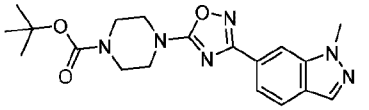
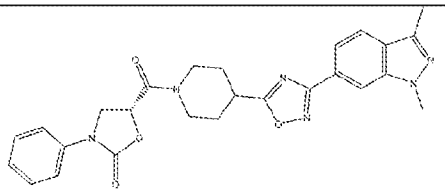
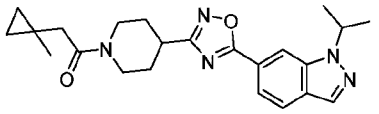
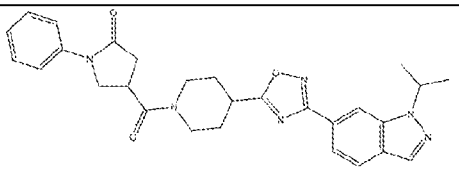
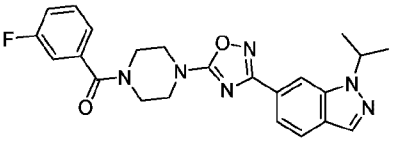
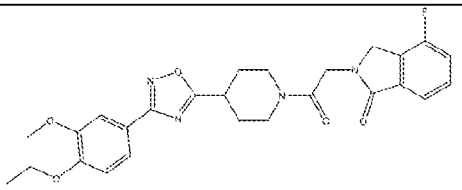
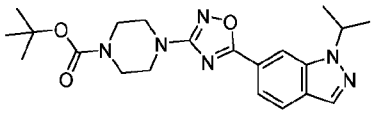
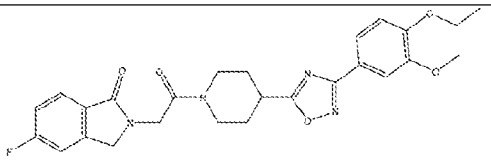
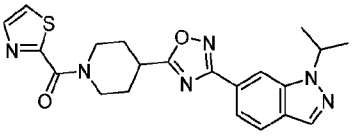
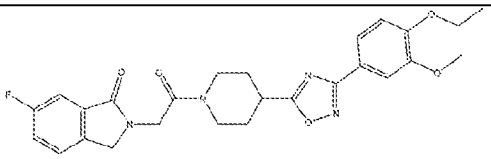
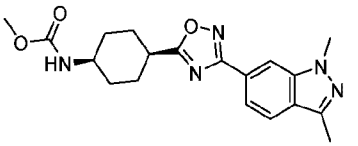
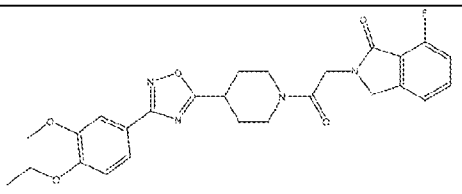
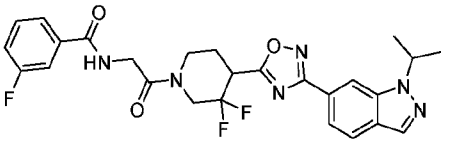
#	Structure	#	Structure
126		499	
127		500	
128		501	
129		502	
130		503	
131		504	
132		505	
133		506	

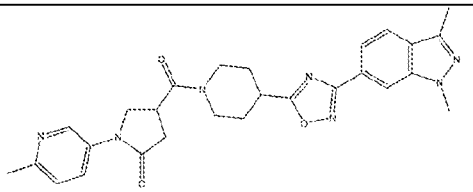
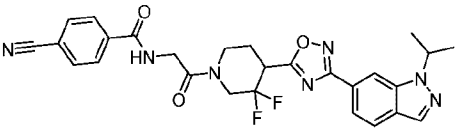
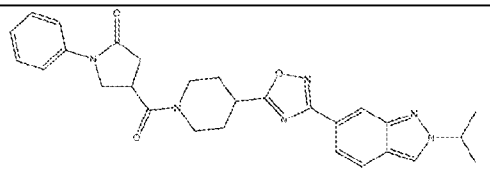
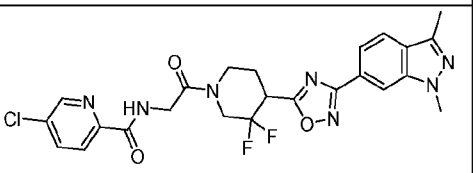
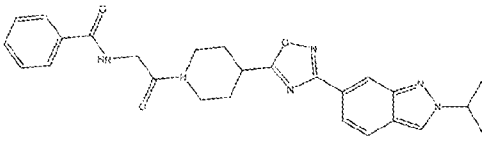
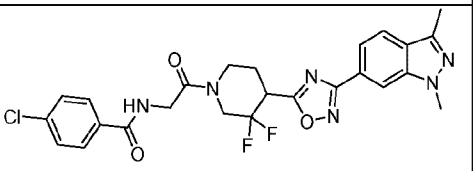
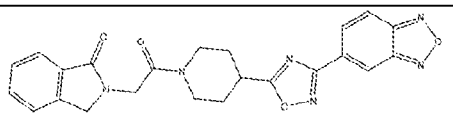
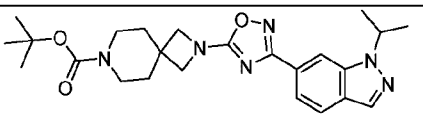
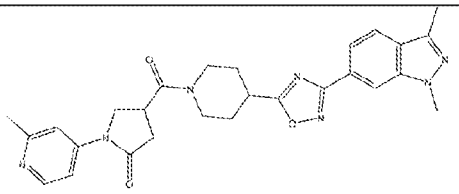
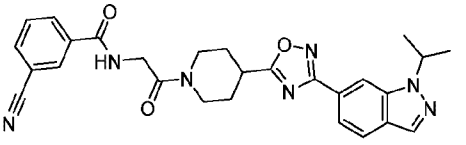
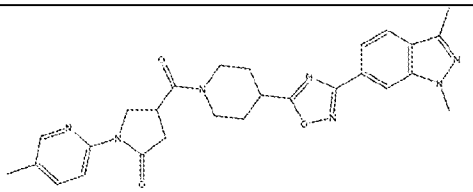
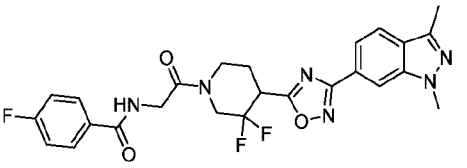
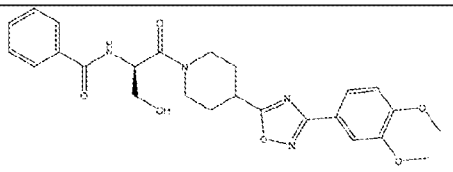
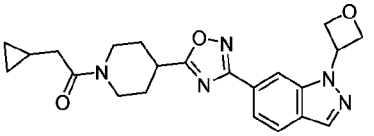
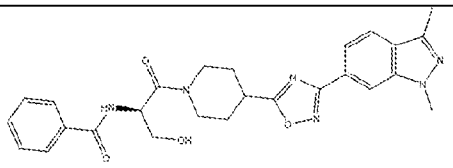
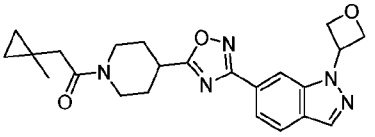
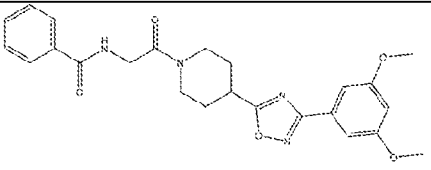
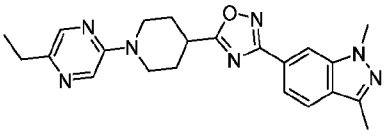
#	Structure	#	Structure
134		507	
135		508	
136		509	
137		510	
138		511	
139		512	
140		513	
141		514	
142		515	

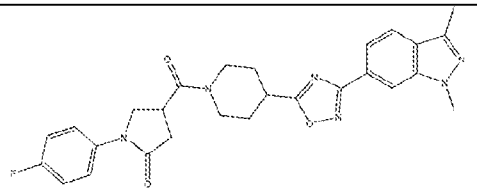
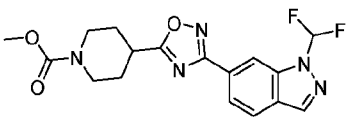
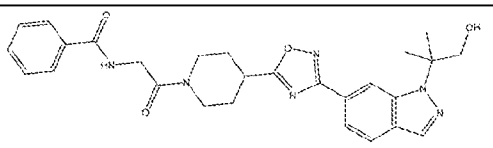
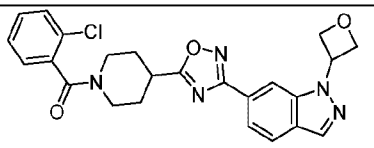
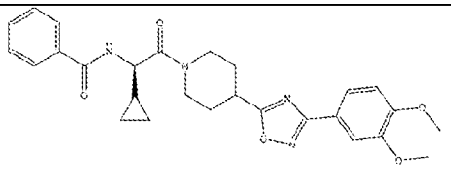
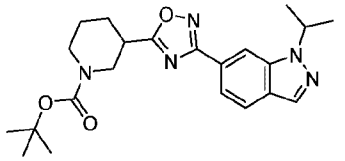
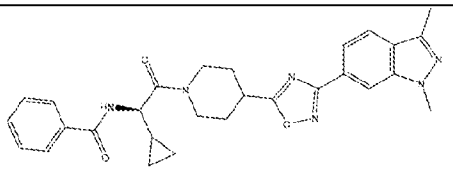
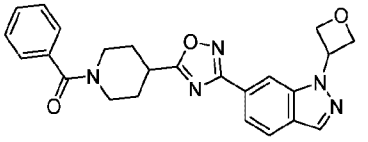
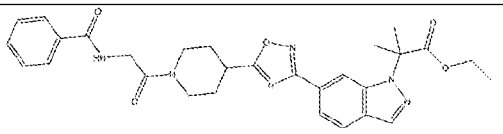
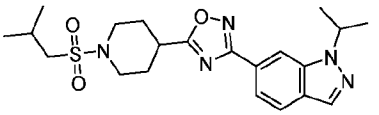
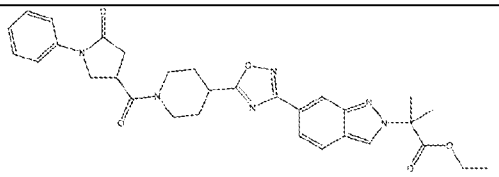
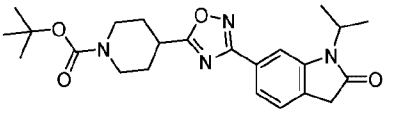
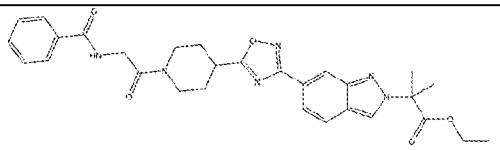
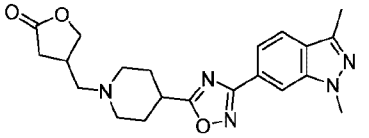
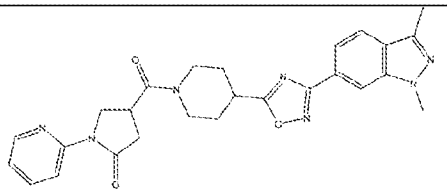
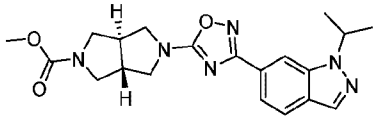
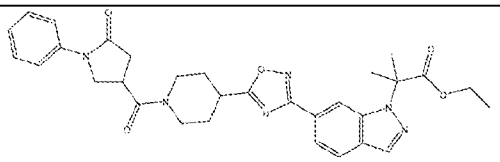
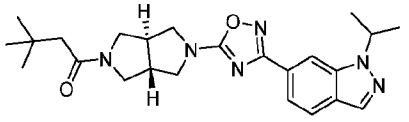
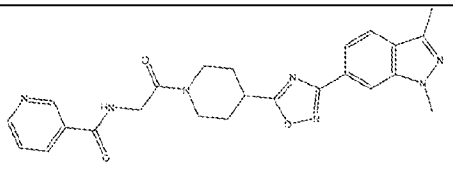
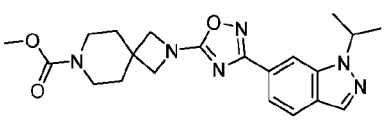
#	Structure	#	Structure
143		516	
144		517	
145		518	
146		519	
147		520	
148		521	
149		522	
150		523	
151		524	

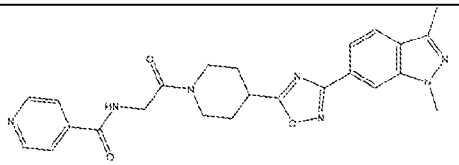
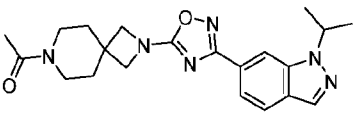
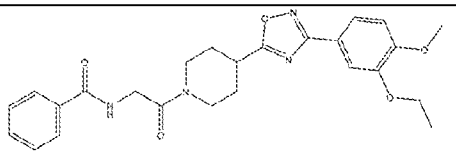
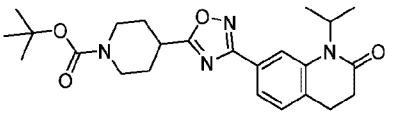
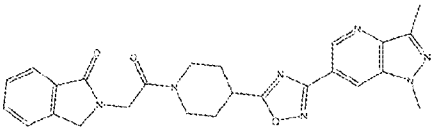
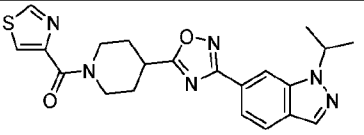
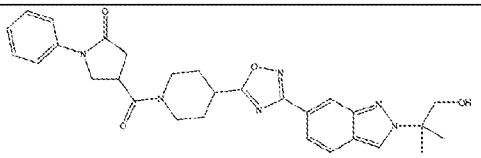
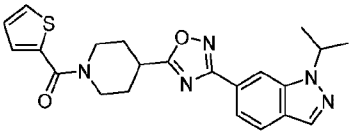
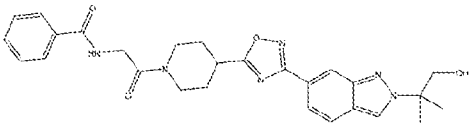
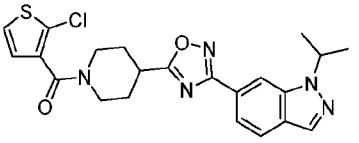
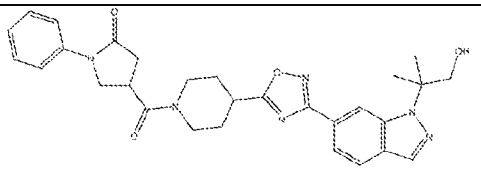
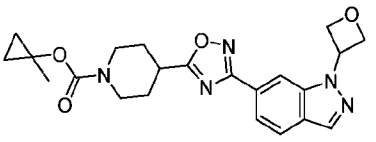
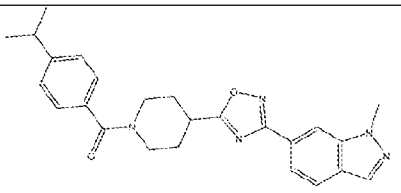
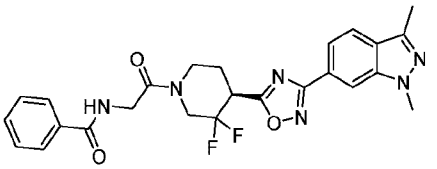
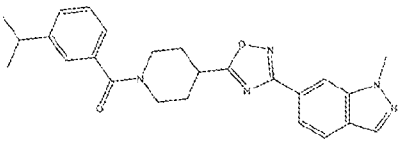
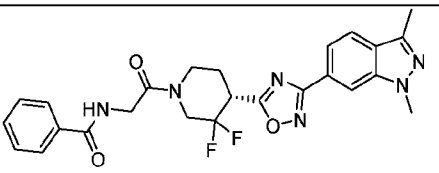
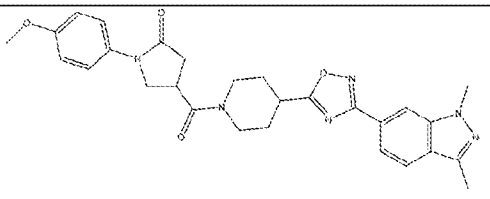
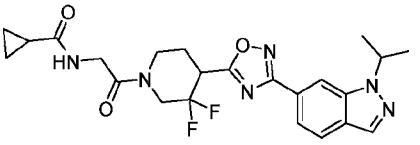
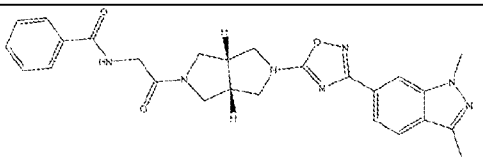
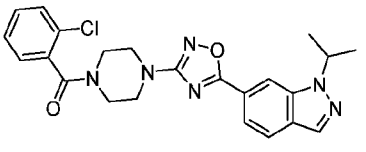
#	Structure	#	Structure
152		525	
153		526	
154		527	
155		528	
156		529	
157		530	
158		531	
159		532	
160		533	

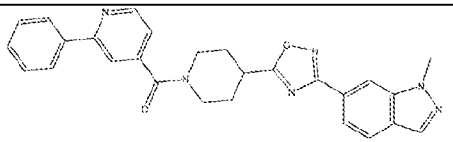
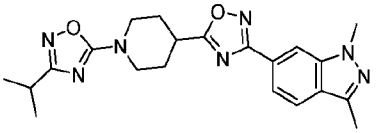
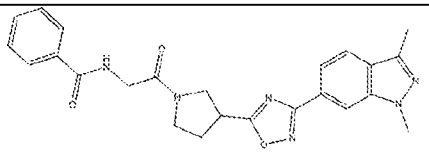
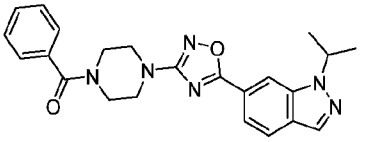
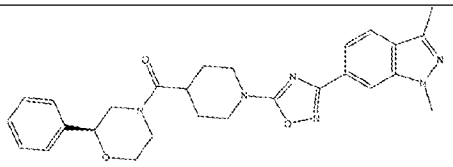
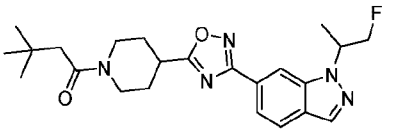
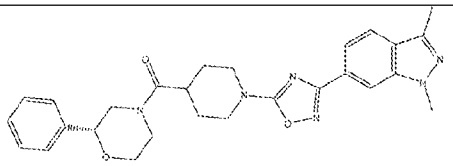
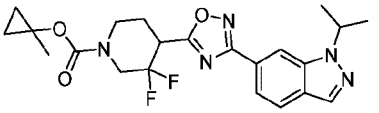
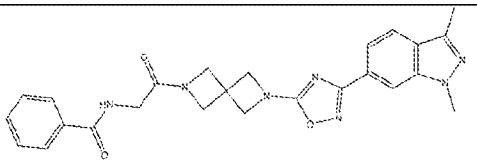
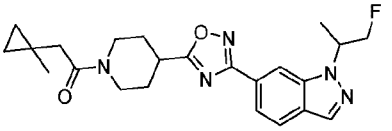
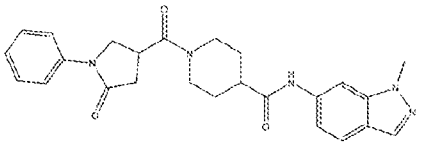
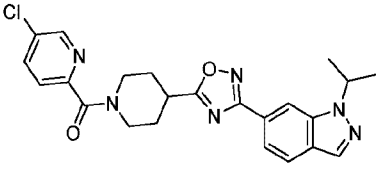
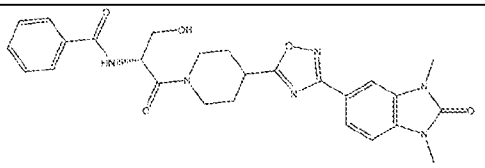
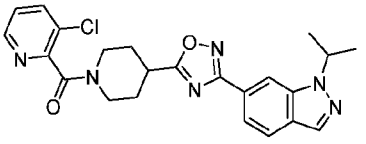
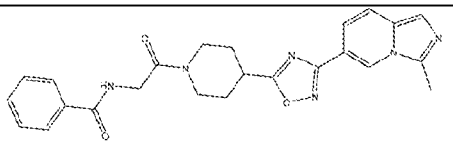
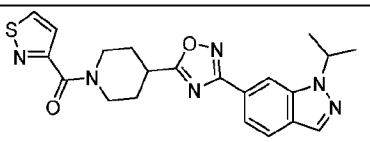
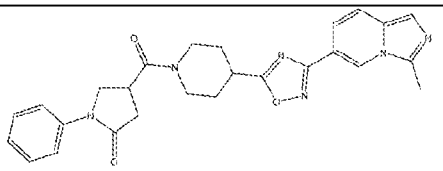
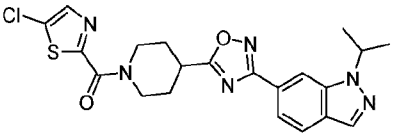
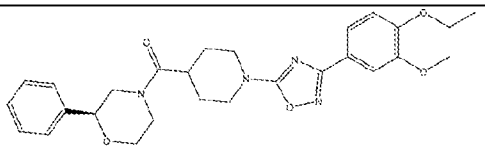
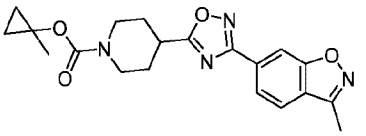
#	Structure	#	Structure
161		534	
162		535	
163		536	
164		537	
165		538	
166		539	
167		540	
168		541	
169		542	

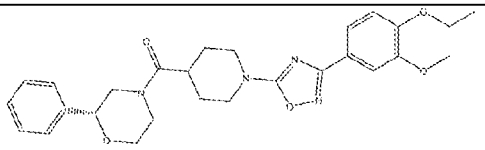
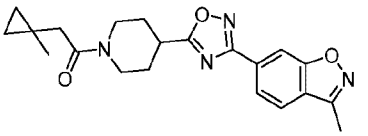
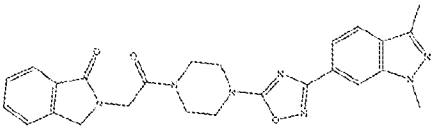
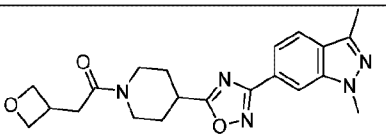
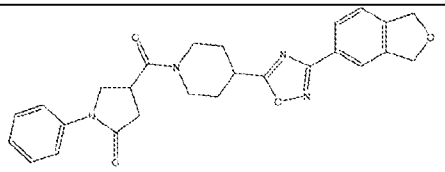
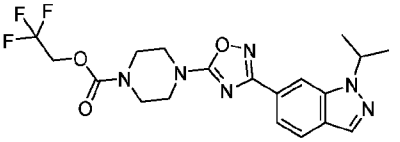
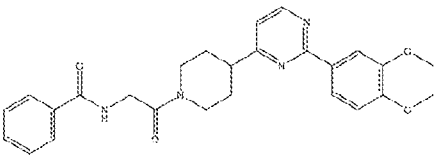
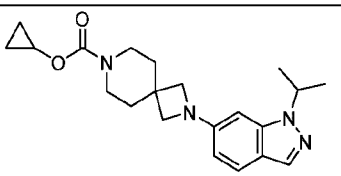
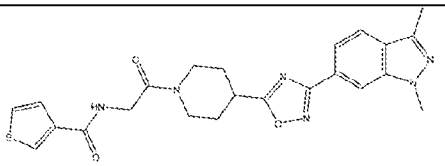
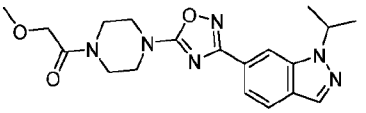
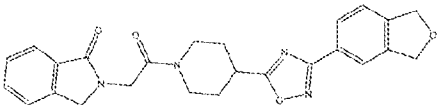
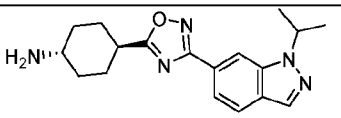
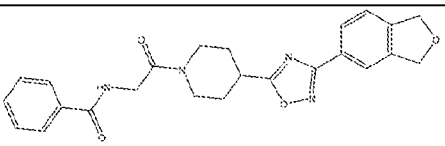
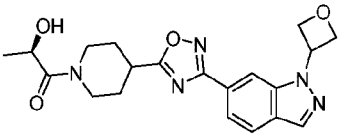
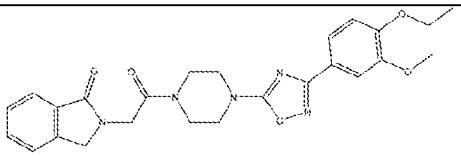
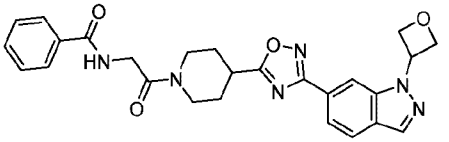
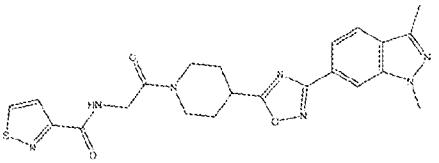
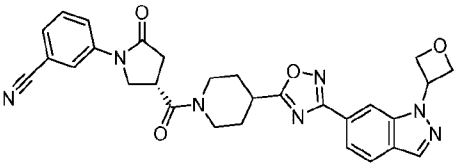
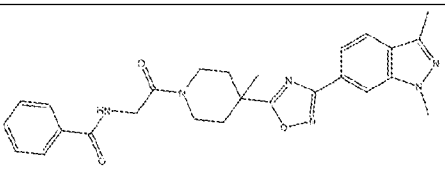
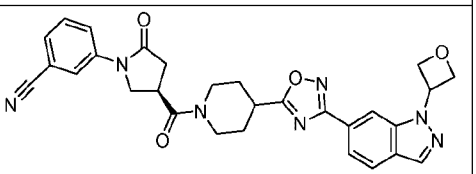
#	Structure	#	Structure
170		543	
171		544	
172		545	
173		546	
174		547	
175		548	
176		549	
177		550	
178		551	

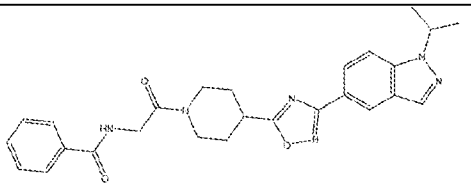
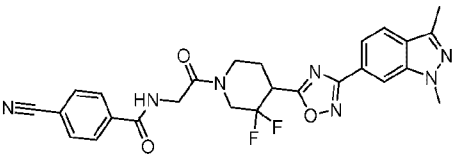
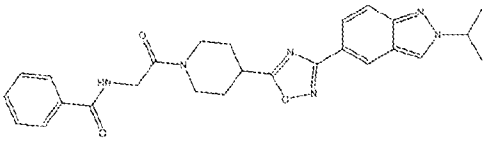
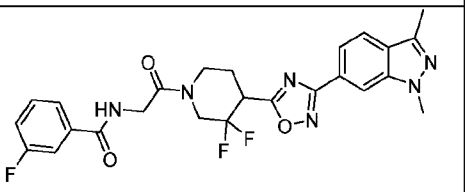
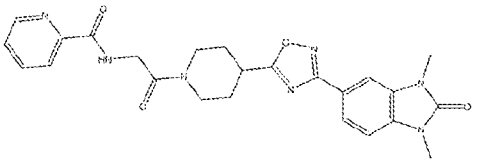
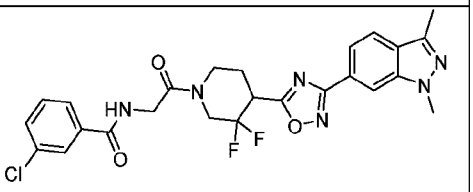
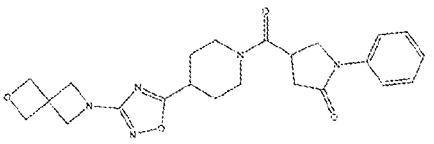
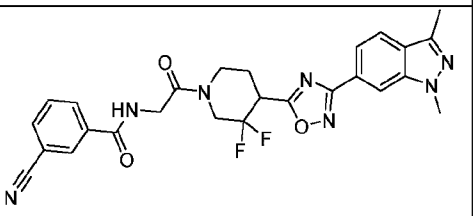
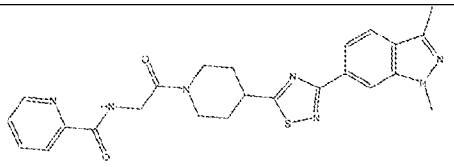
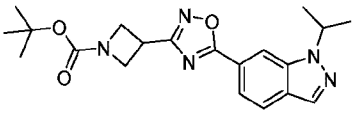
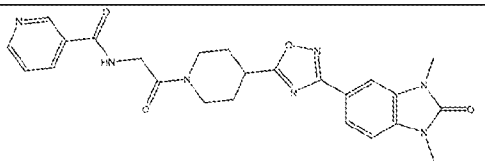
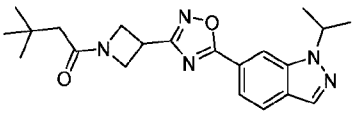
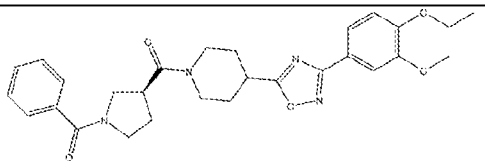
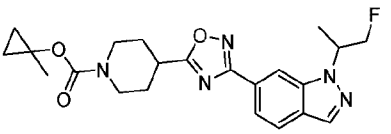
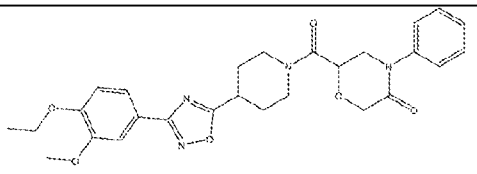
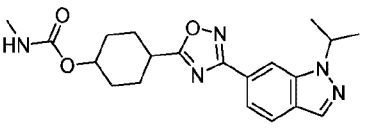
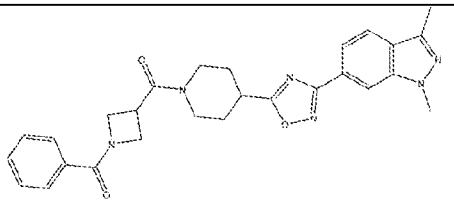
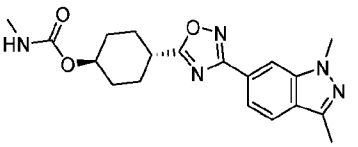
#	Structure	#	Structure
179		552	
180		553	
181		554	
182		555	
183		556	
184		557	
185		558	
186		559	
187		560	

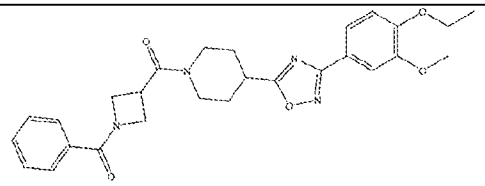
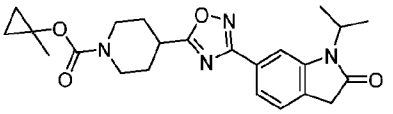
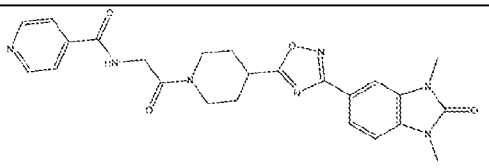
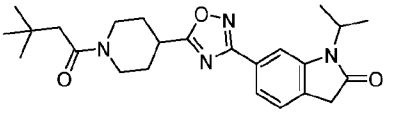
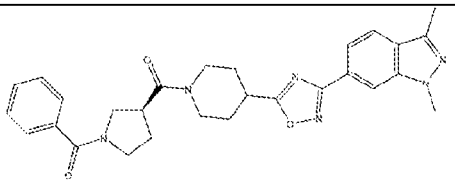
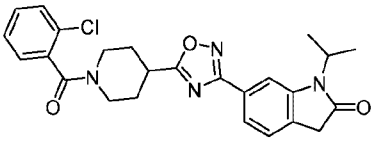
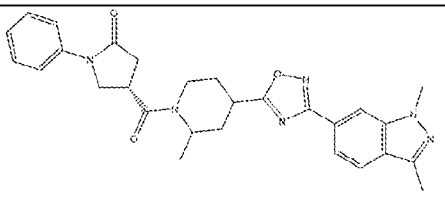
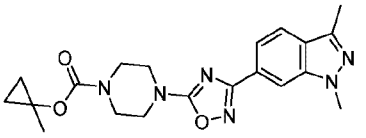
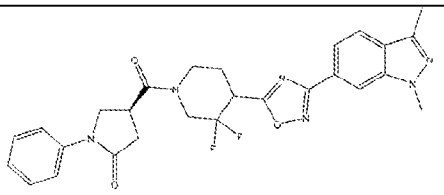
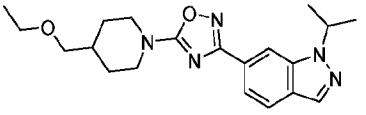
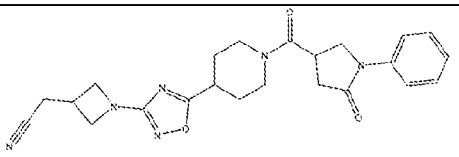
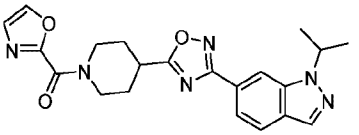
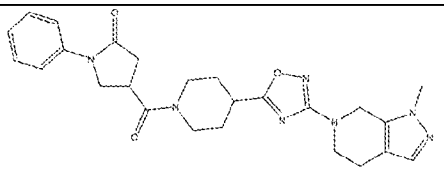
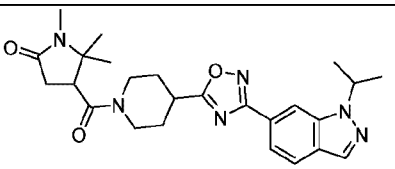
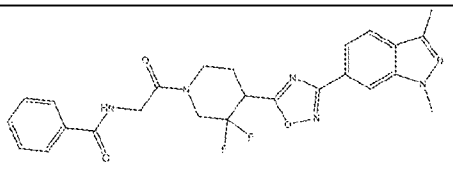
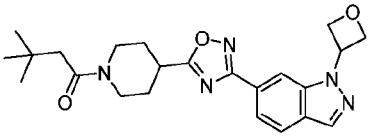
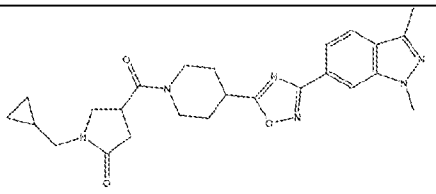
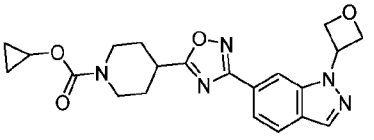
#	Structure	#	Structure
188		561	
189		562	
190		563	
191		564	
192		565	
193		566	
194		567	
195		568	
196		569	
197		570	

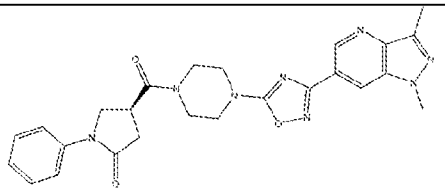
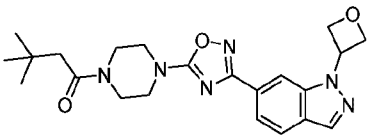
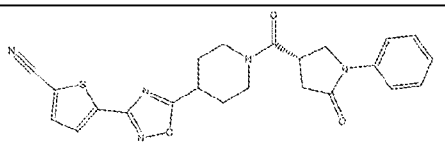
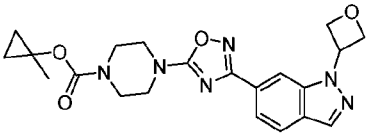
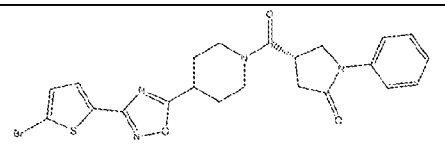
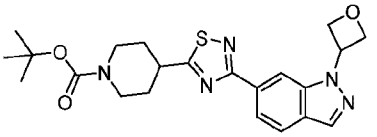
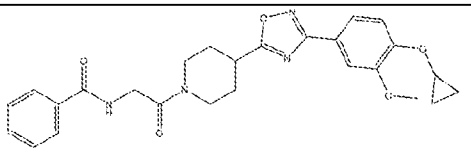
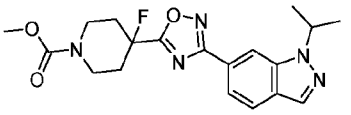
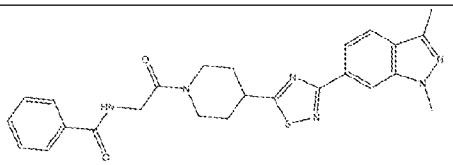
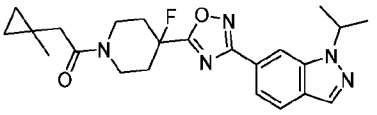
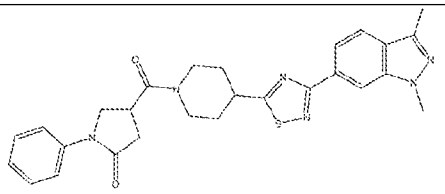
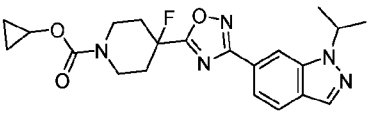
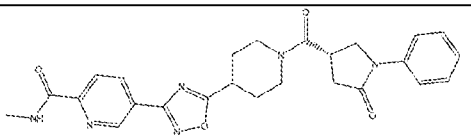
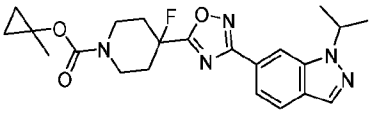
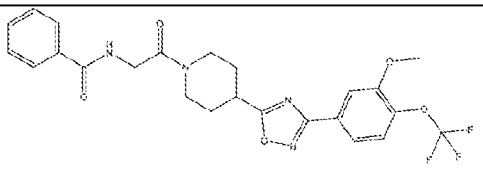
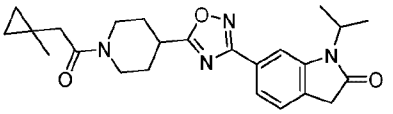
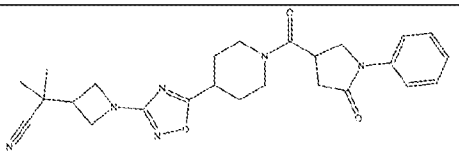
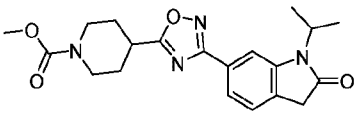
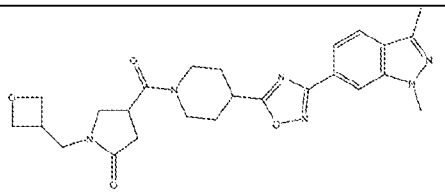
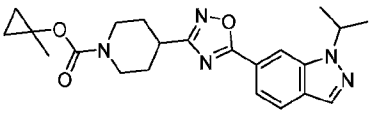
#	Structure	#	Structure
198		571	
199		572	
200		573	
201		574	
202		575	
203		576	
204		577	
205		578	
206		579	
207		580	

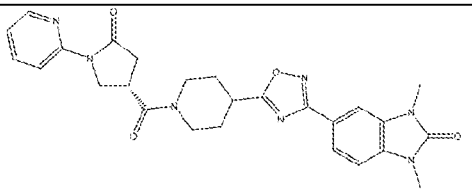
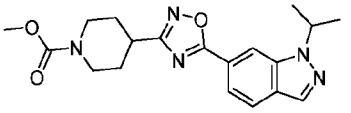
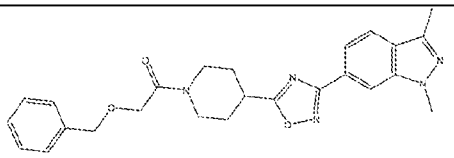
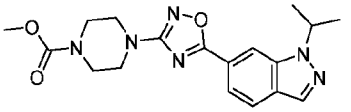
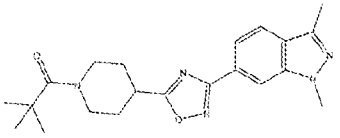
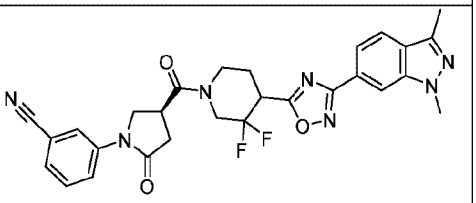
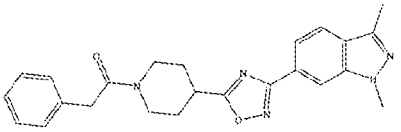
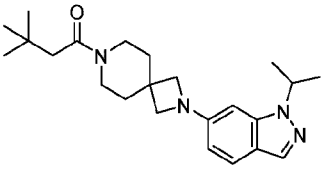
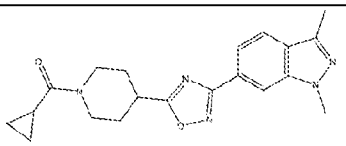
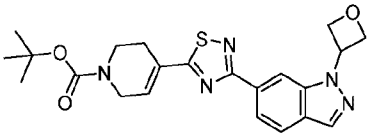
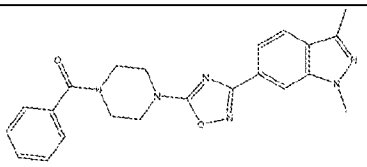
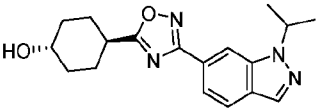
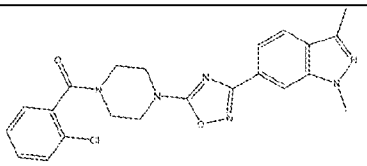
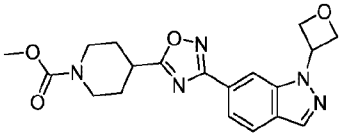
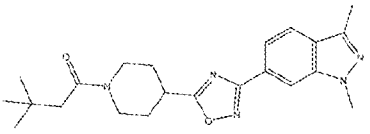
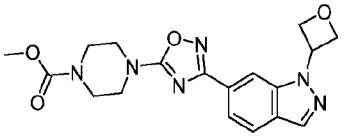
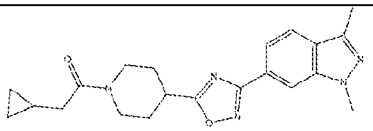
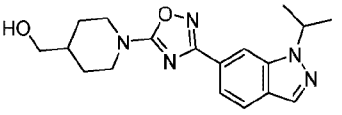
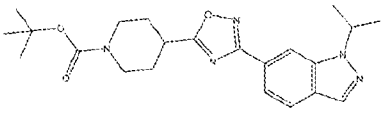
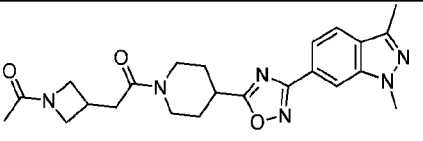
#	Structure	#	Structure
208		581	
209		582	
210		583	
211		584	
212		585	
213		586	
214		587	
215		588	
216		589	
217		590	

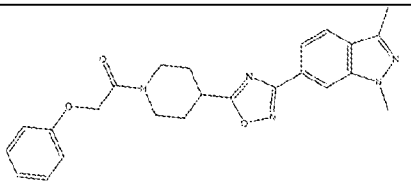
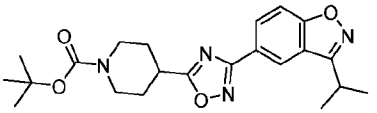
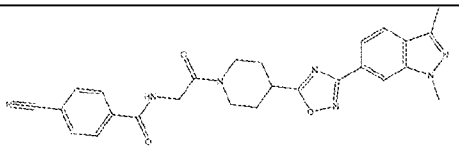
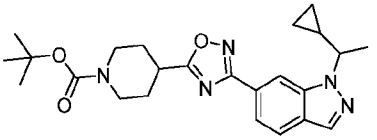
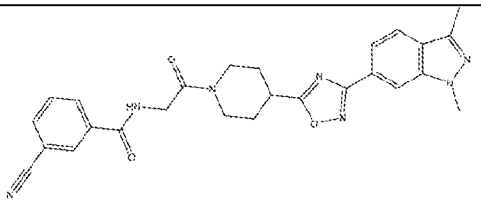
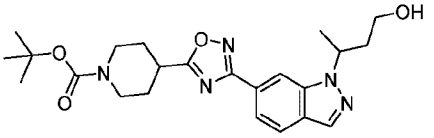
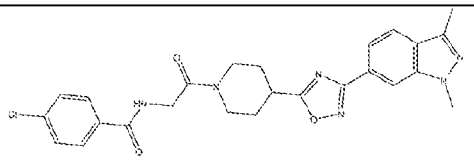
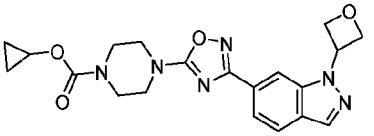
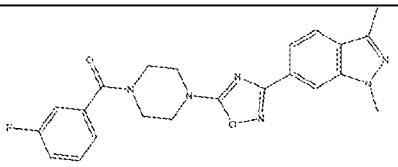
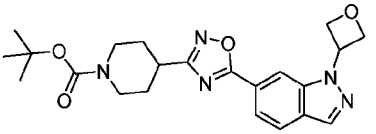
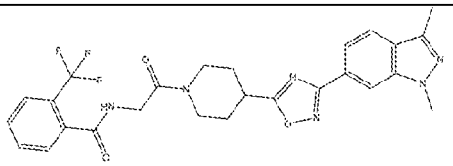
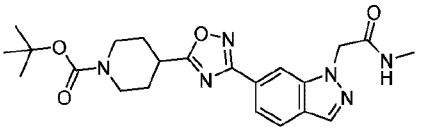
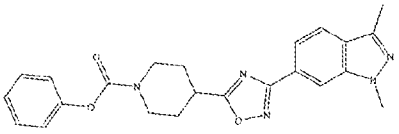
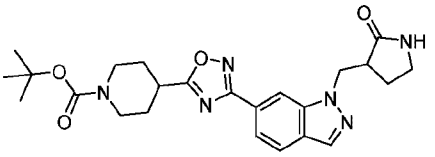
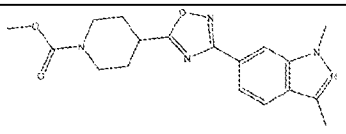
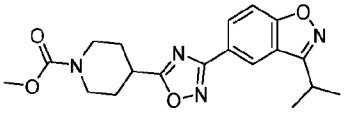
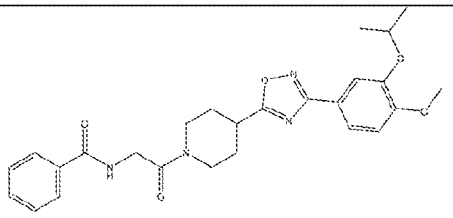
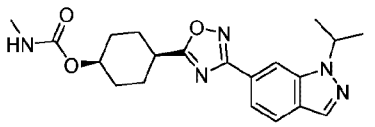
#	Structure	#	Structure
218		591	
219		592	
220		593	
221		594	
222		595	
223		596	
224		597	
225		598	
226		599	
227		600	

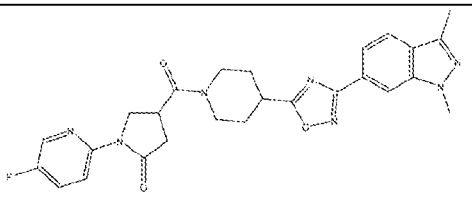
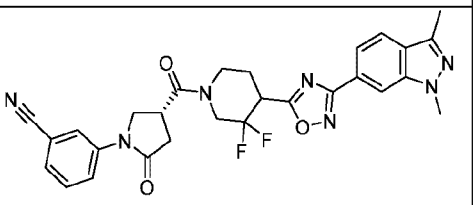
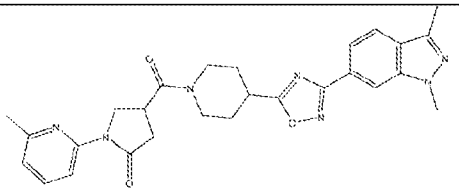
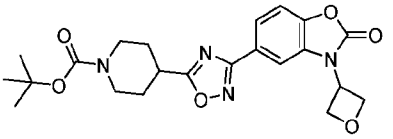
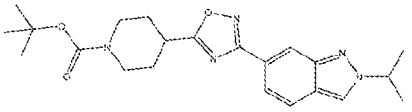
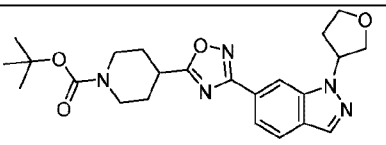
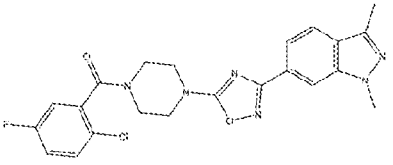
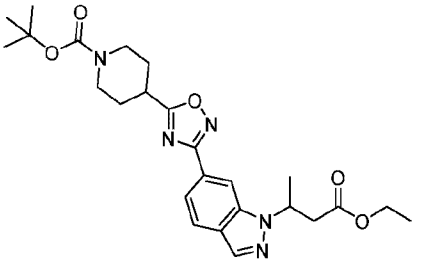
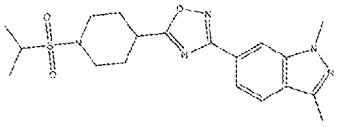
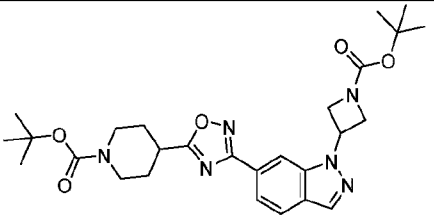
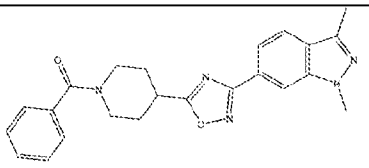
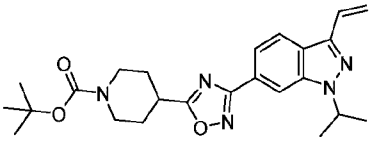
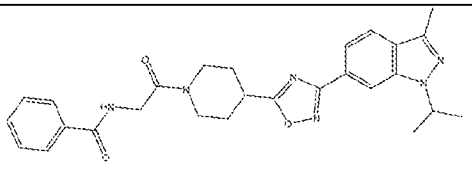
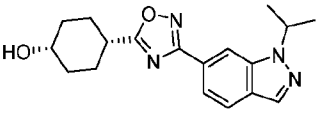
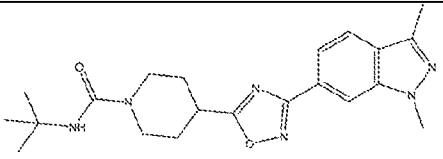
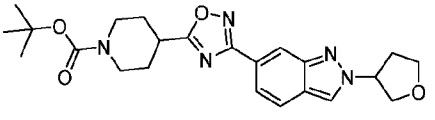
#	Structure	#	Structure
228		601	
229		602	
230		603	
231		604	
232		605	
233		606	
234		607	
235		608	
236		609	

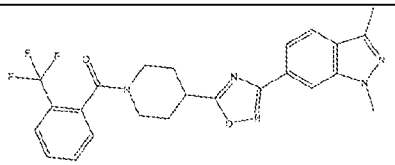
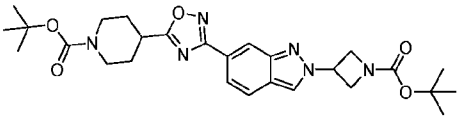
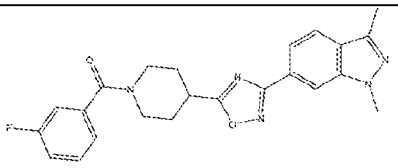
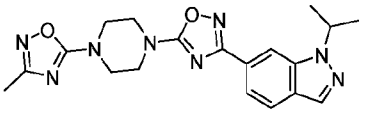
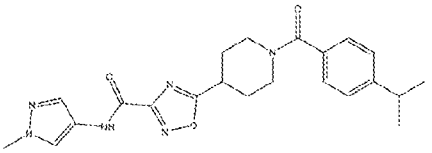
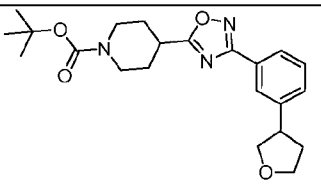
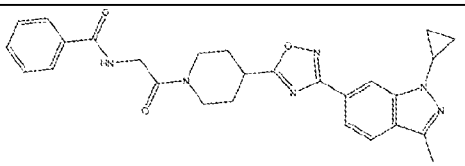
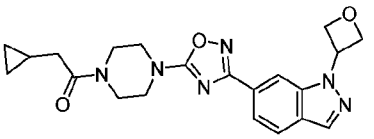
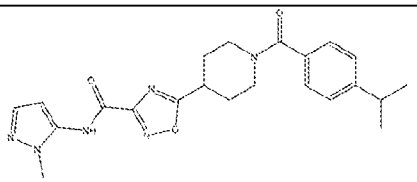
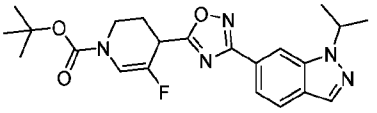
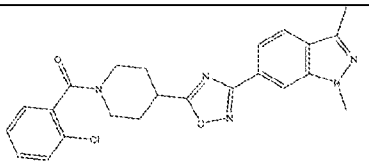
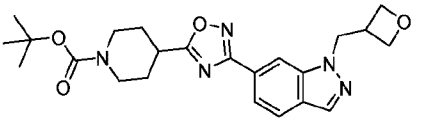
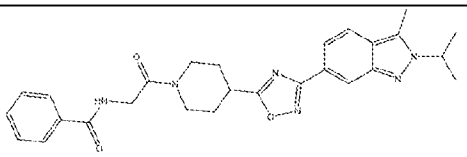
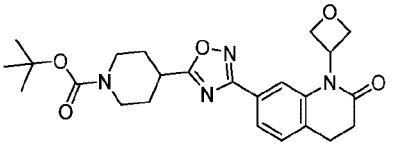
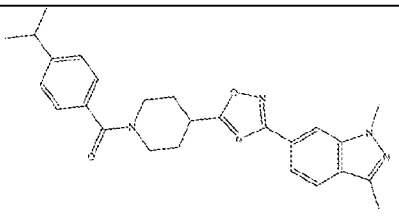
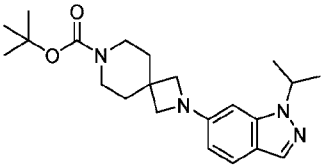
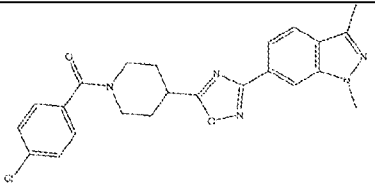
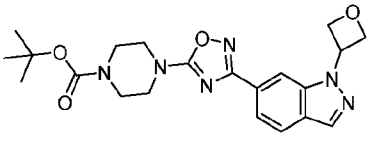
#	Structure	#	Structure
237		610	
238		611	
239		612	
240		613	
241		614	
242		615	
243		616	
244		617	
245		618	

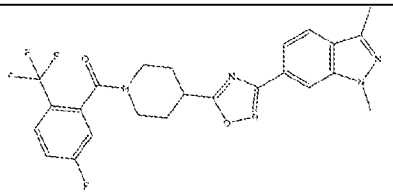
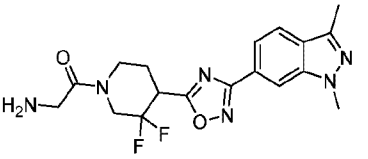
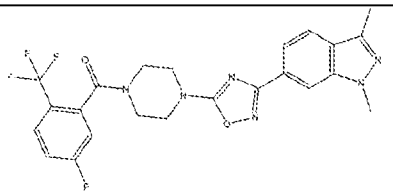
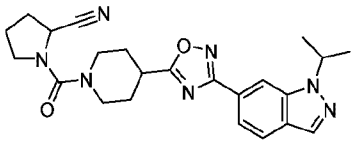
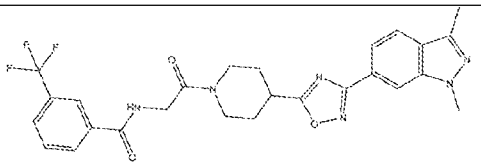
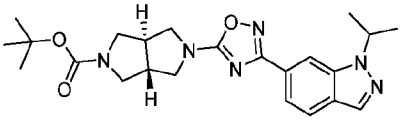
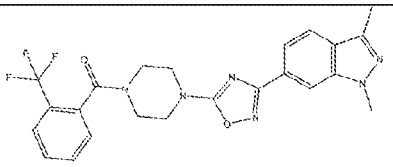
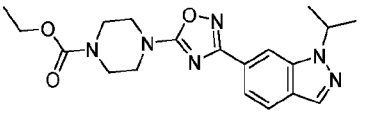
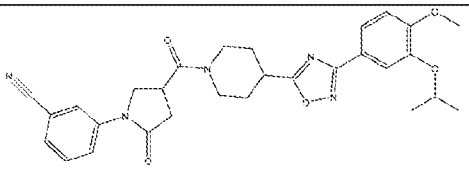
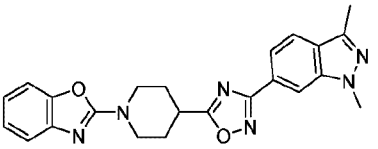
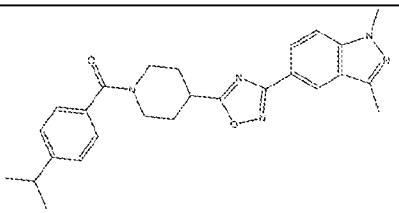
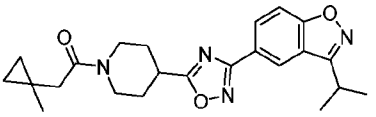
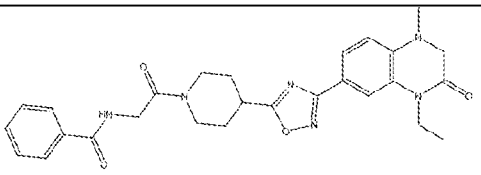
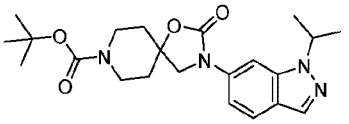
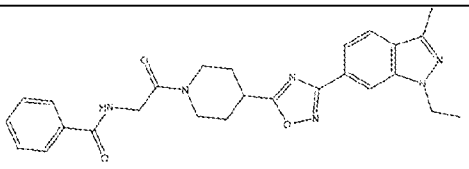
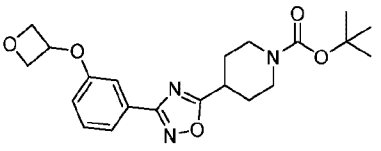
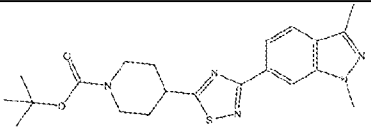
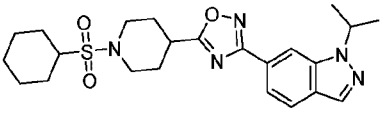
#	Structure	#	Structure
246		619	
247		620	
248		621	
249		622	
250		623	
251		624	
252		625	
253		626	
254		627	
255		628	

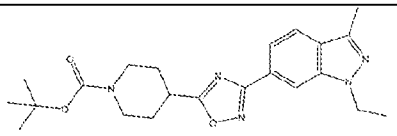
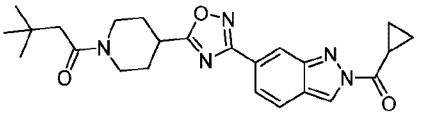
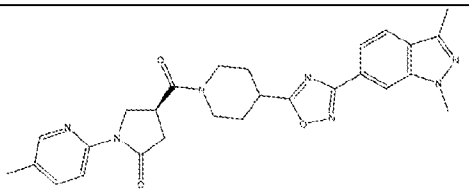
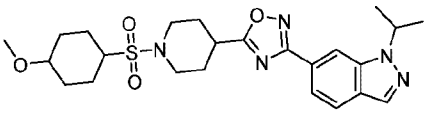
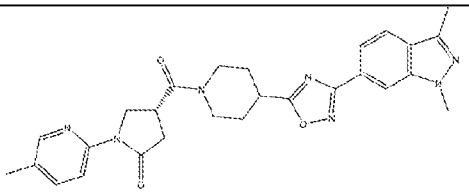
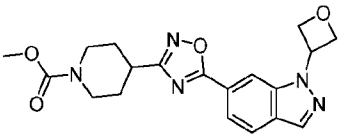
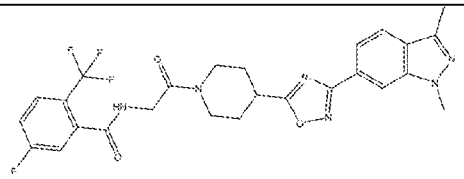
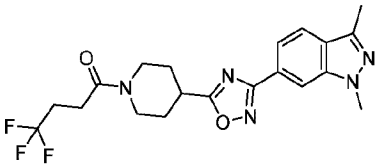
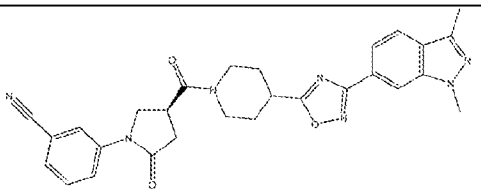
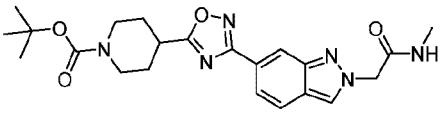
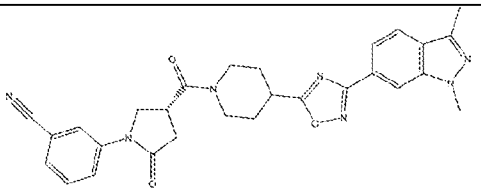
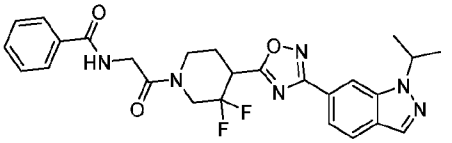
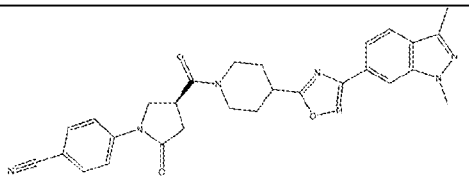
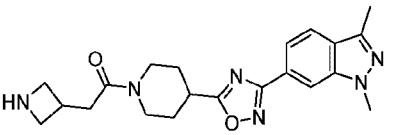
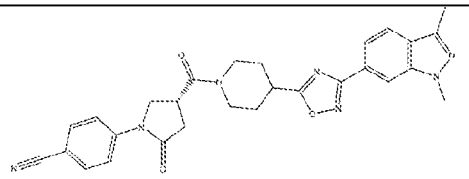
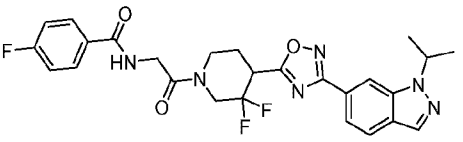
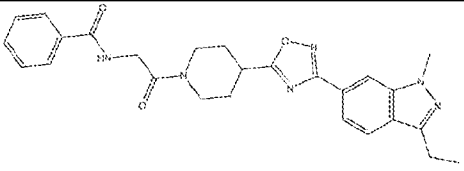
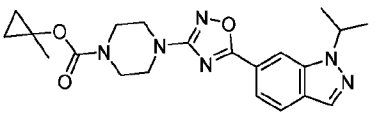
#	Structure	#	Structure
256		629	
257		630	
258		631	
259		632	
260		633	
261		634	
262		635	
263		636	
264		637	
265		638	

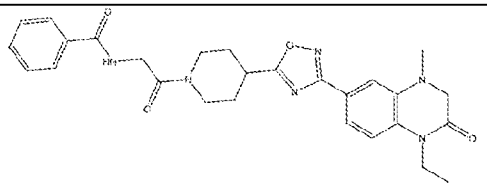
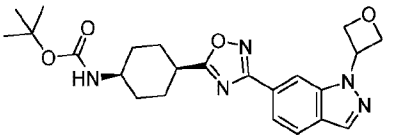
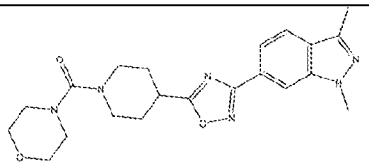
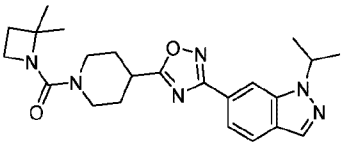
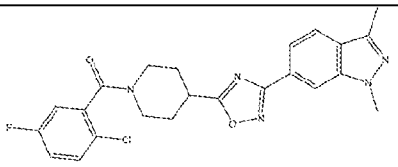
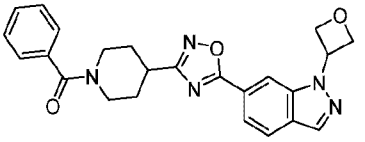
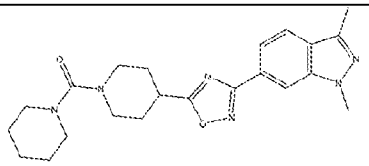
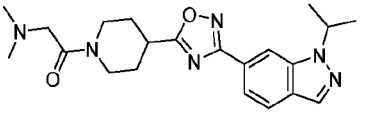
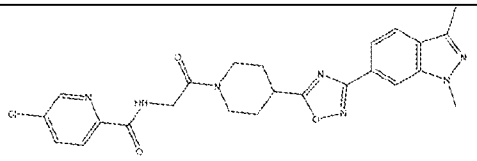
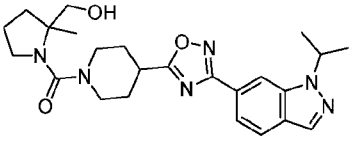
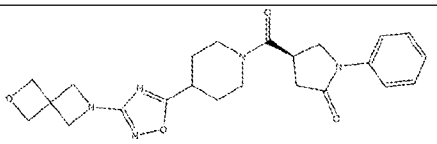
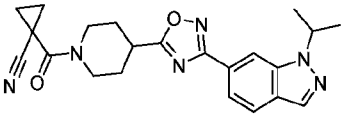
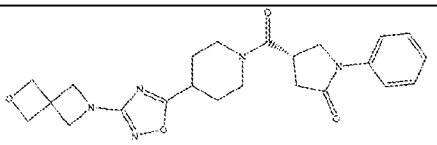
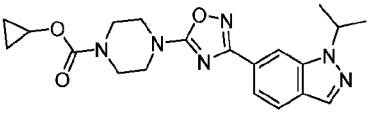
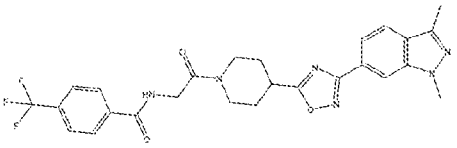
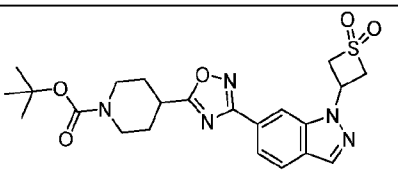
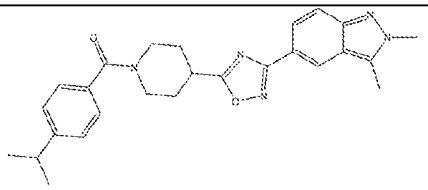
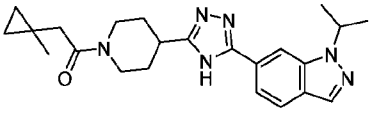
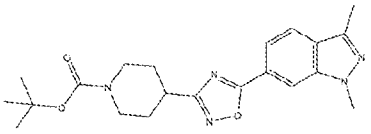
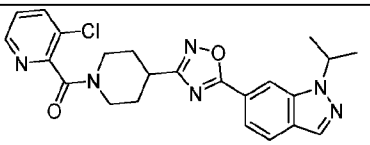
#	Structure	#	Structure
266		639	
267		640	
268		641	
269		642	
270		643	
271		644	
272		645	
273		646	
274		647	

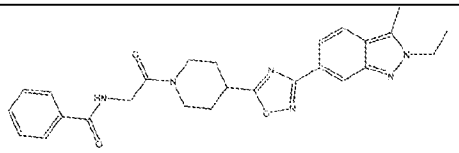
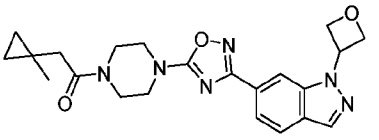
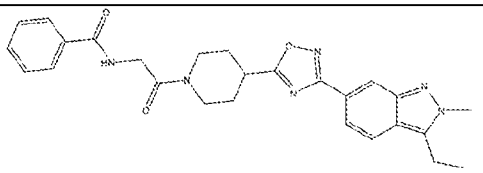
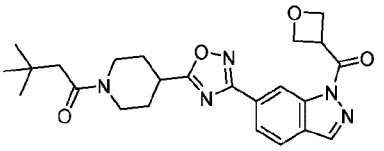
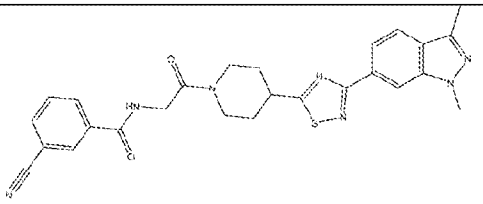
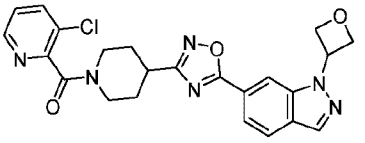
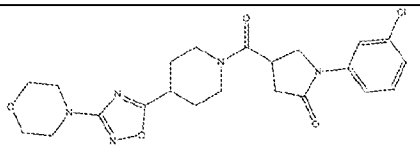
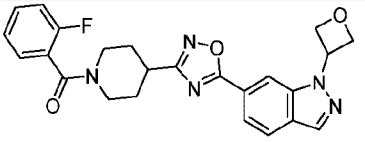
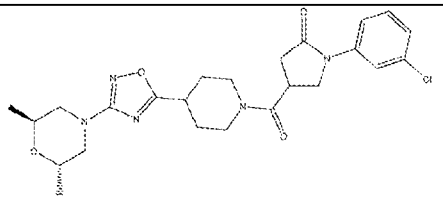
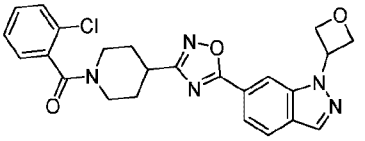
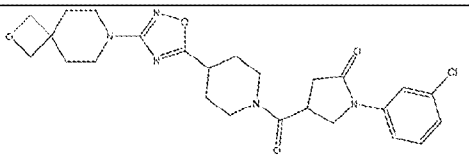
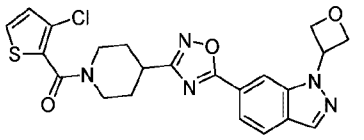
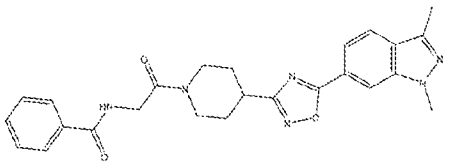
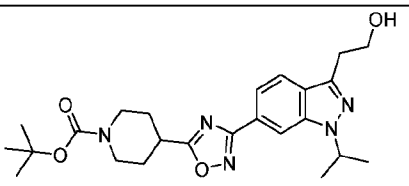
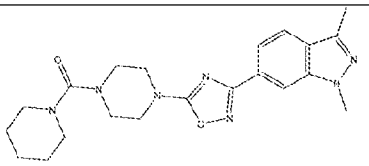
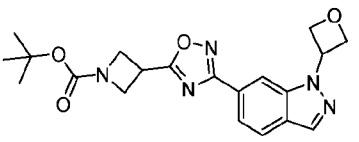
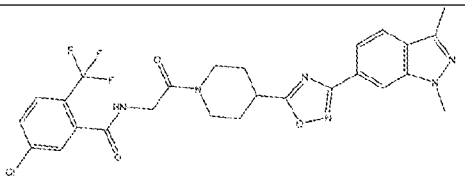
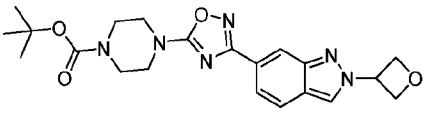
#	Structure	#	Structure
275		648	
276		649	
277		650	
278		651	
279		652	
280		653	
281		654	
282		655	

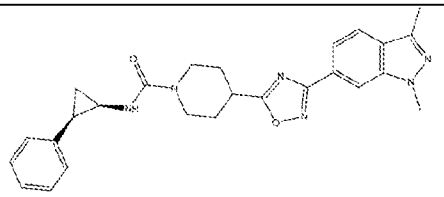
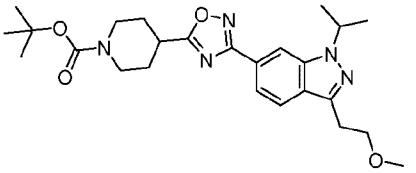
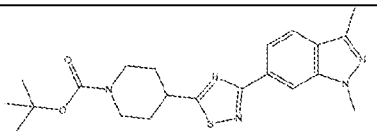
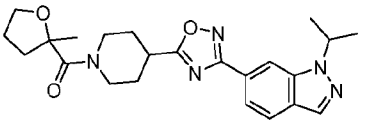
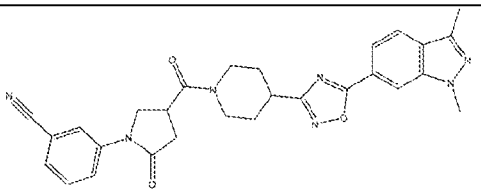
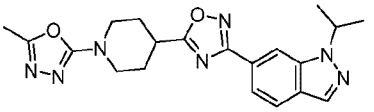
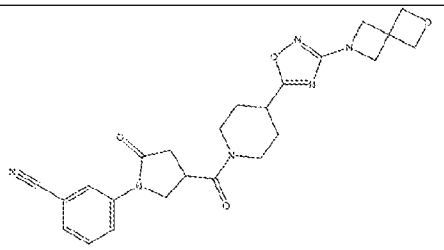
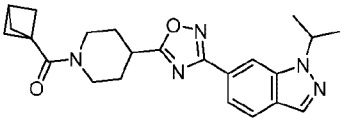
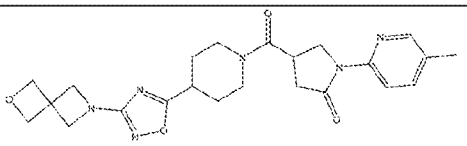
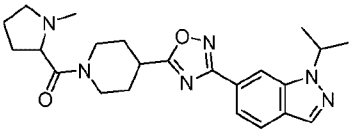
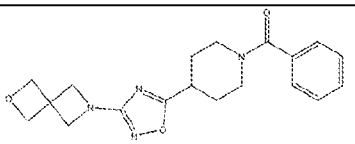
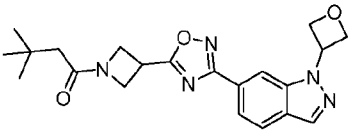
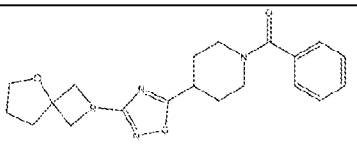
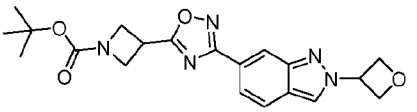
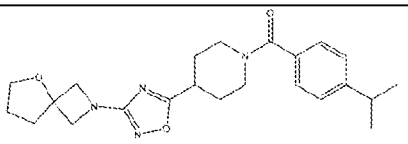
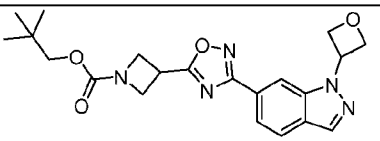
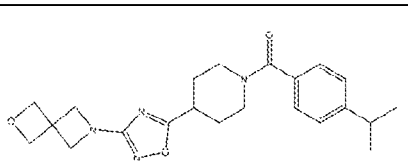
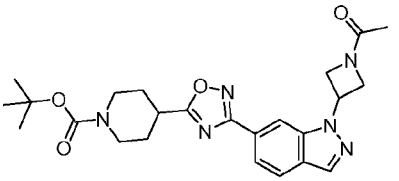
#	Structure	#	Structure
283		656	
284		657	
285		658	
286		659	
287		660	
288		661	
289		662	
290		663	
291		664	

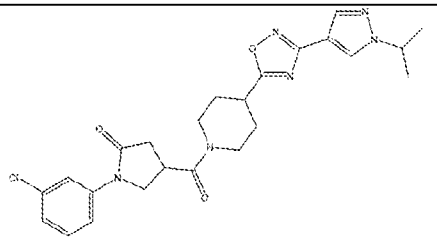
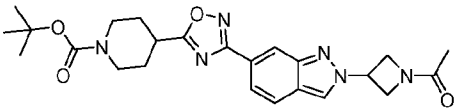
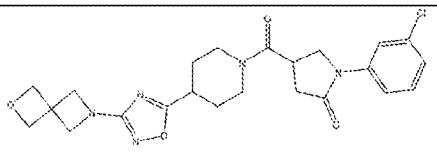
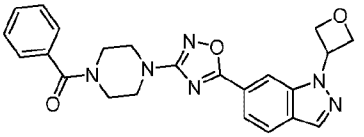
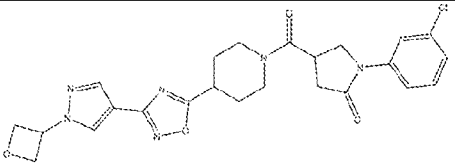
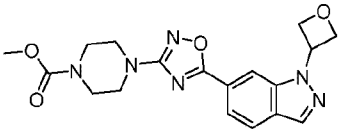
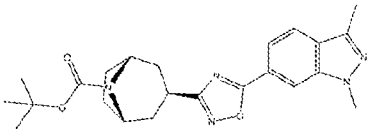
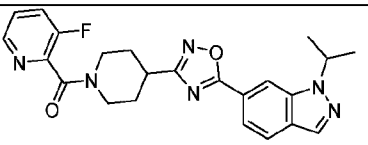
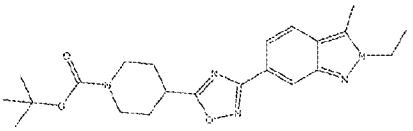
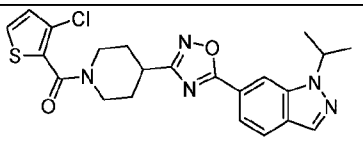
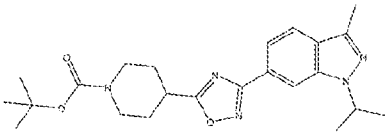
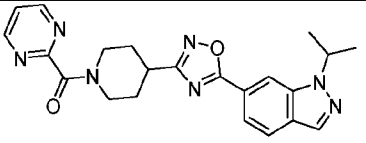
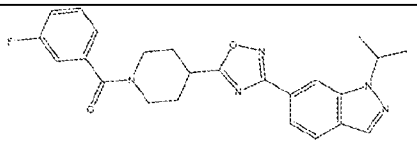
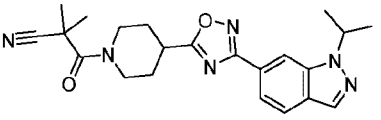
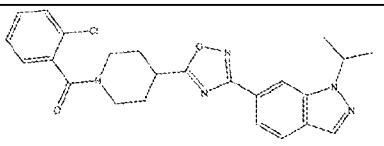
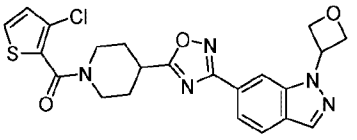
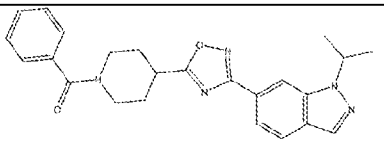
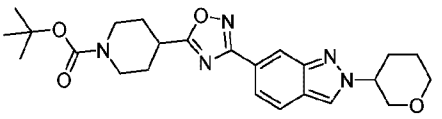
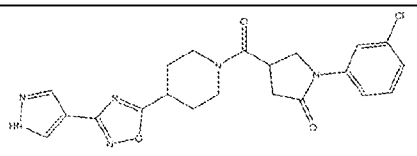
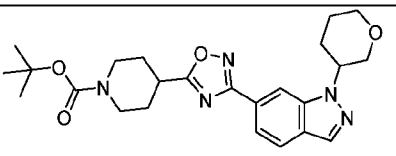
#	Structure	#	Structure
292		665	
293		666	
294		667	
295		668	
296		669	
297		670	
298		671	
299		672	
300		673	

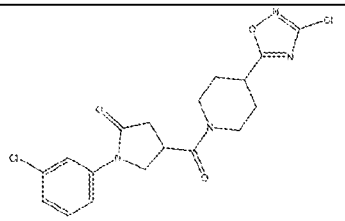
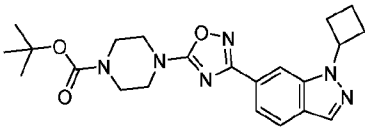
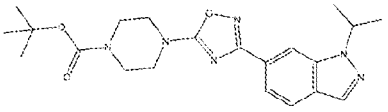
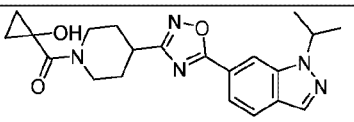
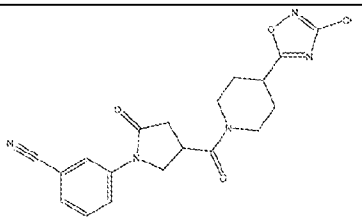
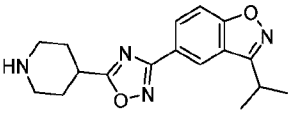
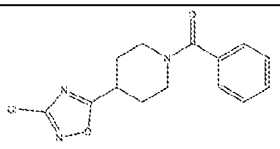
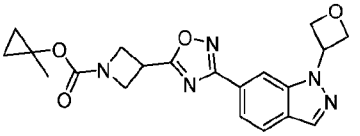
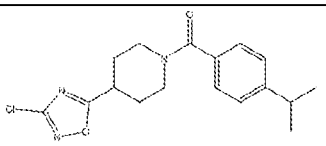
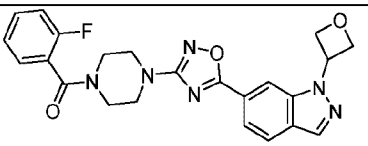
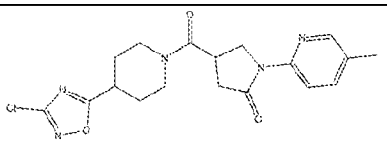
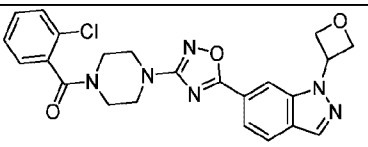
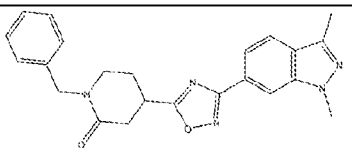
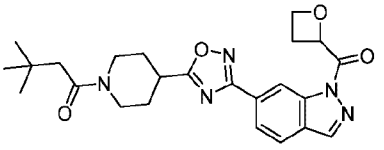
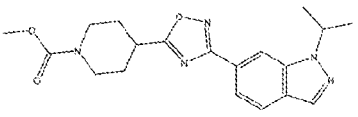
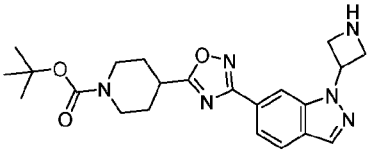
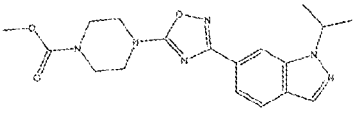
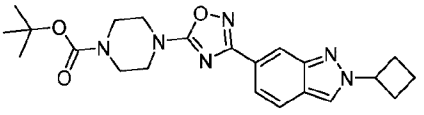
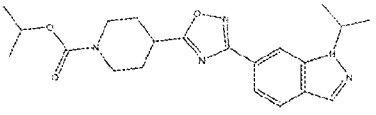
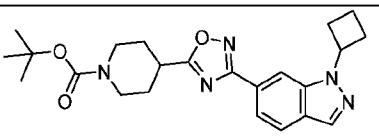
#	Structure	#	Structure
301		674	
302		675	
303		676	
304		677	
305		678	
306		679	
307		680	
308		681	
309		682	

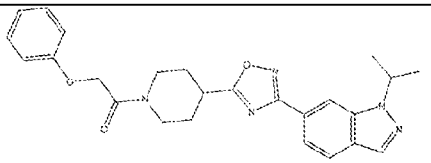
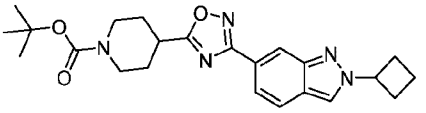
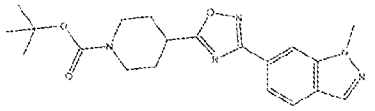
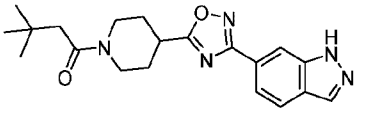
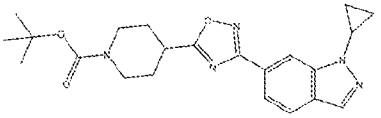
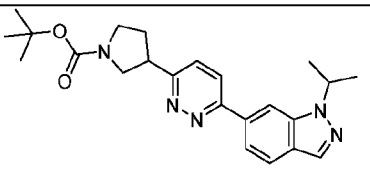
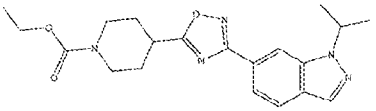
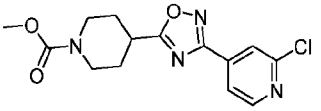
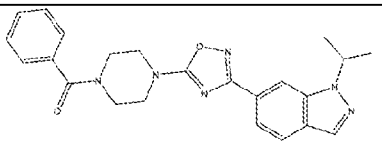
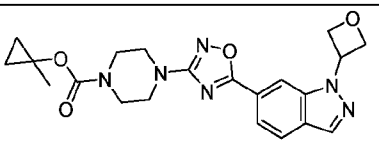
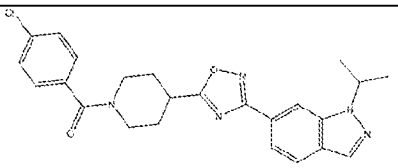
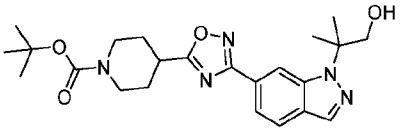
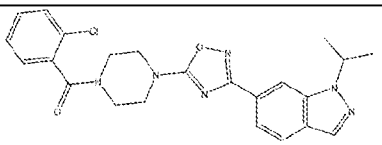
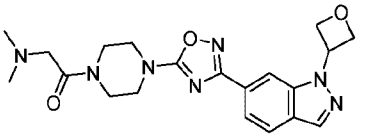
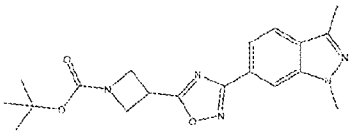
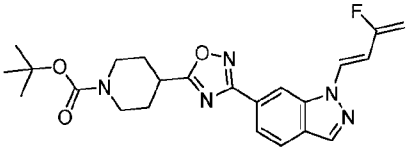
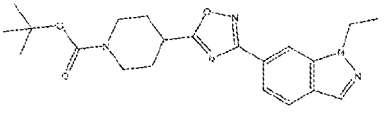
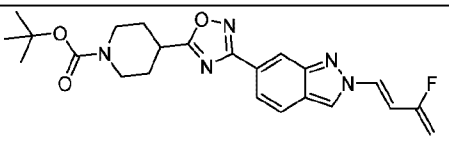
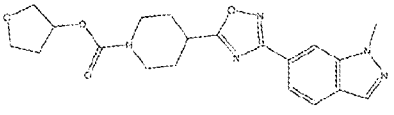
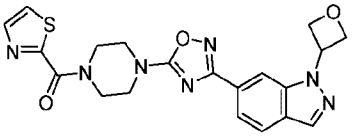
#	Structure	#	Structure
310		683	
311		684	
312		685	
313		686	
314		687	
315		688	
316		689	
317		690	
318		691	
319		692	

#	Structure	#	Structure
320		693	
321		694	
322		695	
323		696	
324		697	
325		698	
326		699	
327		700	
328		701	

#	Structure	#	Structure
329		702	
330		703	
331		704	
332		705	
333		706	
334		707	
335		708	
336		709	
337		710	

#	Structure	#	Structure
338		711	
339		712	
340		713	
341		714	
342		715	
343		716	
344		717	
345		718	
346		719	
347		720	

#	Structure	#	Structure
348		721	
349		722	
350		723	
351		724	
352		725	
353		726	
354		727	
355		728	
356		729	
357		730	

#	Structure	#	Structure
358		731	
359		732	
360		733	
361		734	
362		735	
363		736	
364		737	
365		738	
366		739	
367		740	

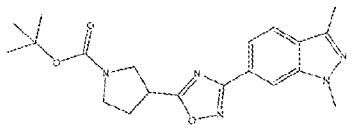
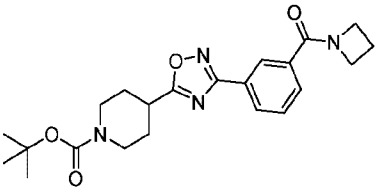
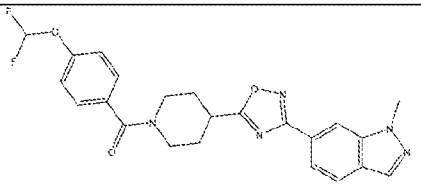
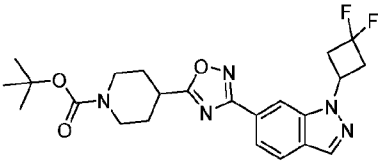
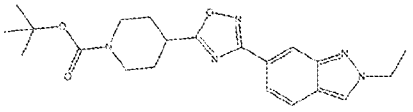
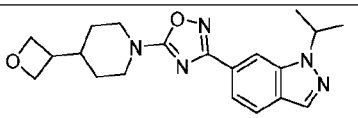
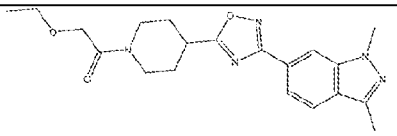
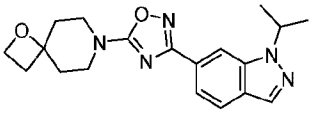
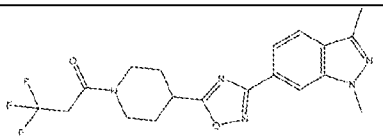
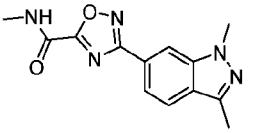
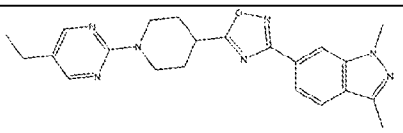
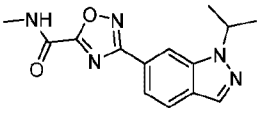
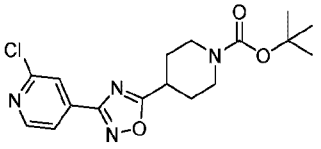
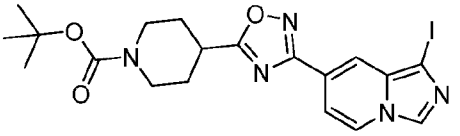
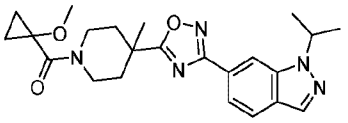
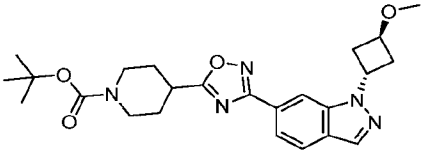
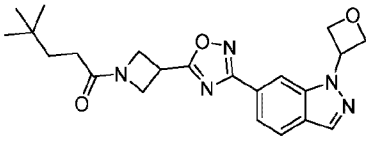
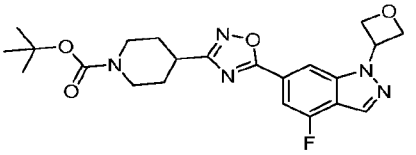
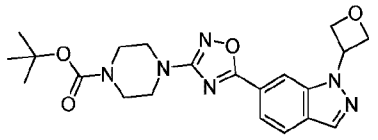
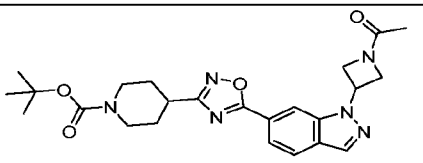
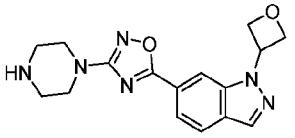
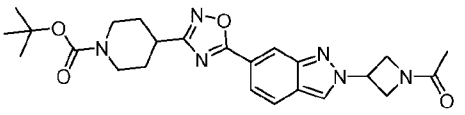
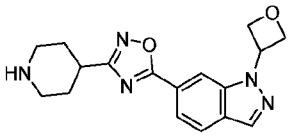
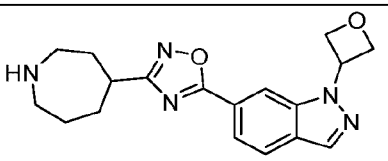
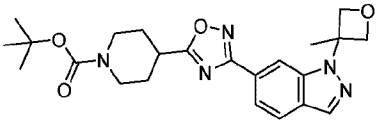
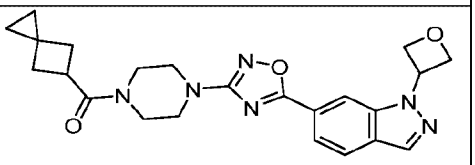
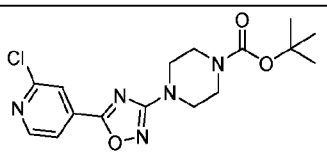
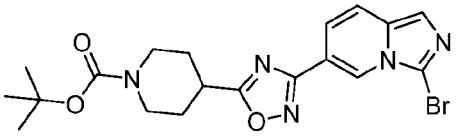
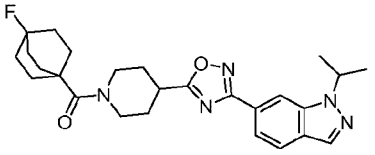
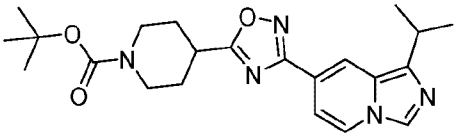
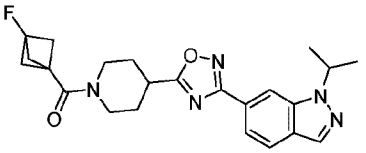
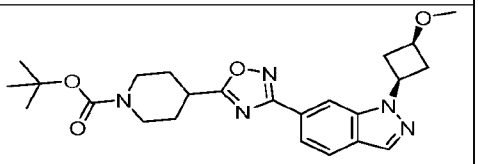
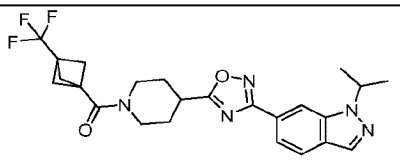
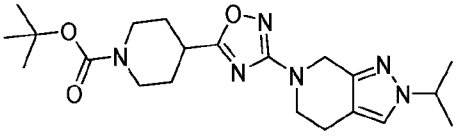
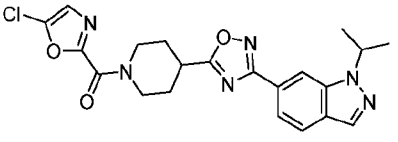
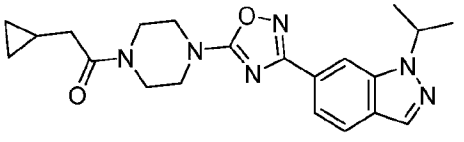
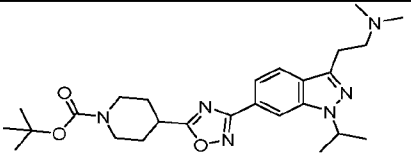
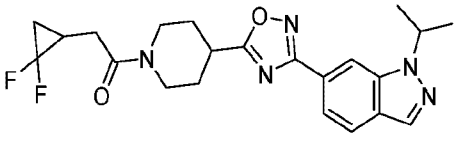
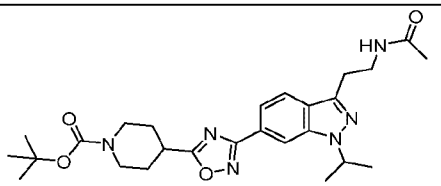
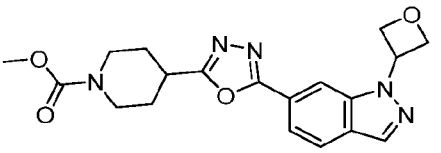
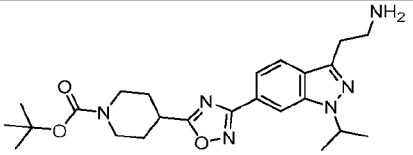
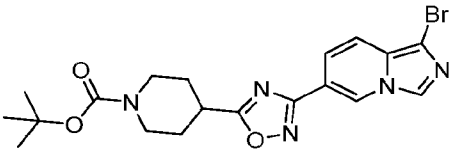
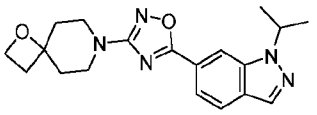
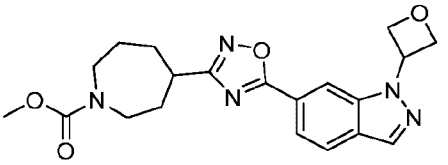
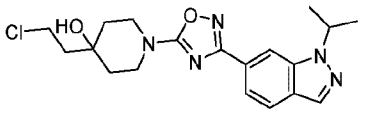
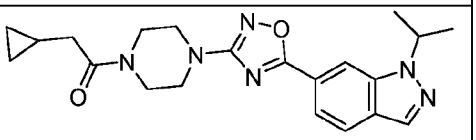
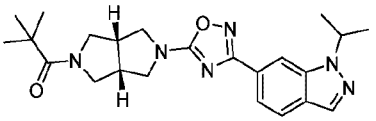
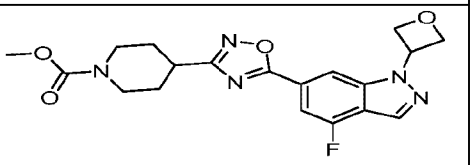
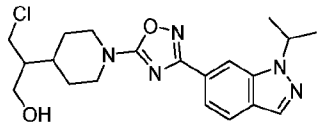
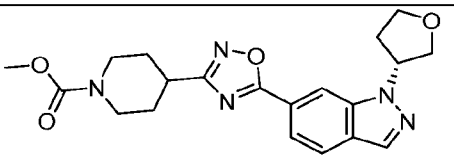
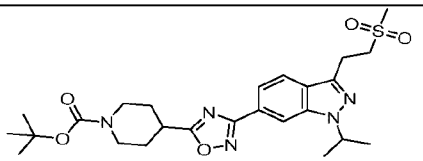
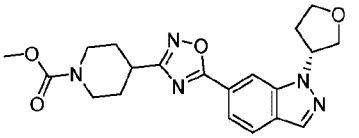
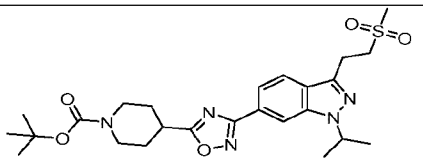
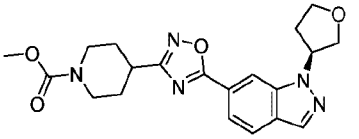
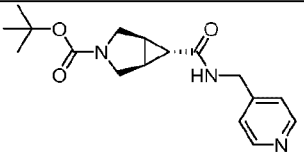
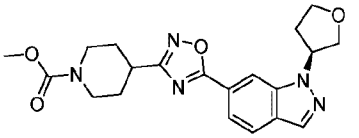
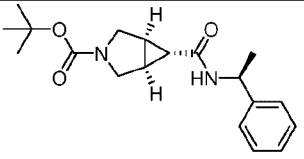
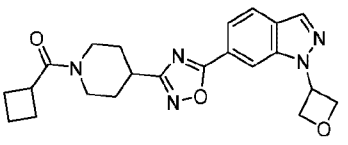
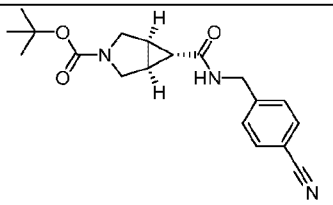
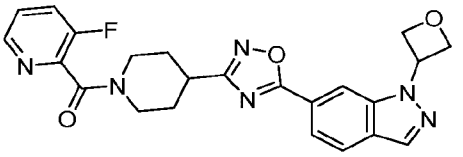
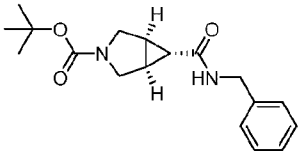
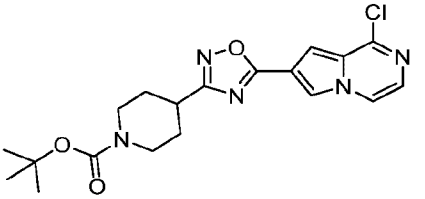
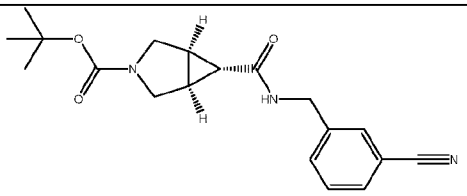
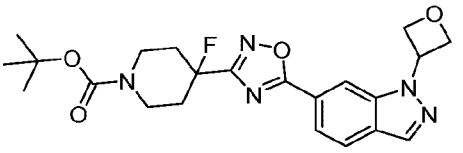
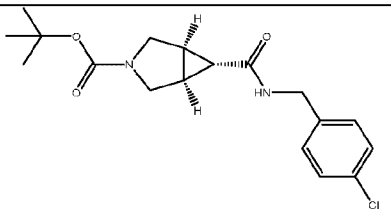
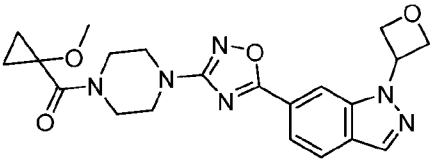
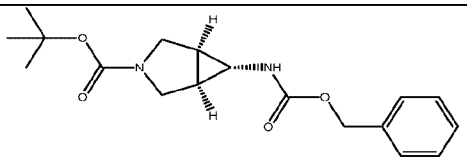
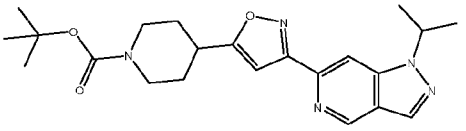
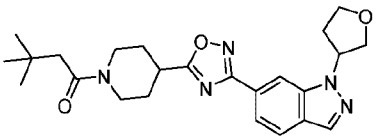
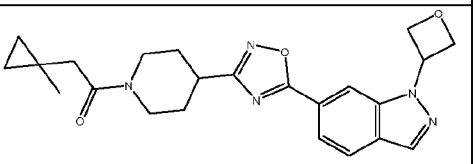
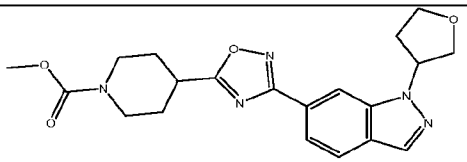
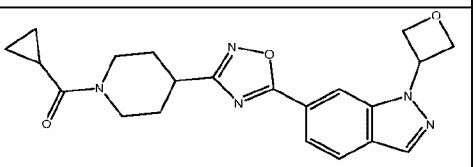
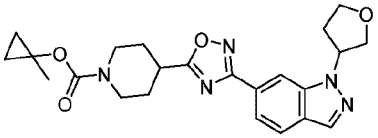
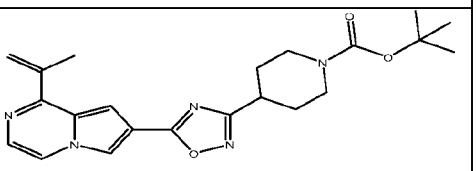
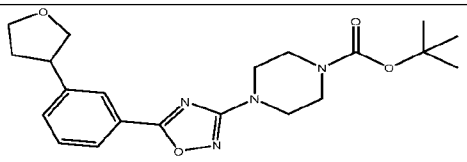
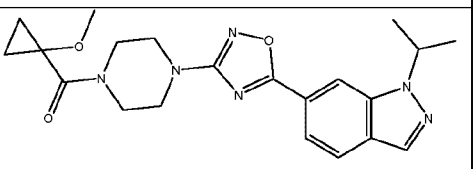
#	Structure	#	Structure
368		741	
369		742	
370		743	
371		744	
372		745	
373		746	

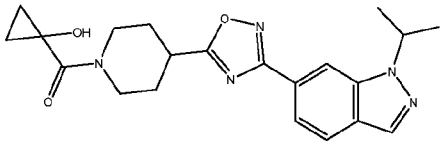
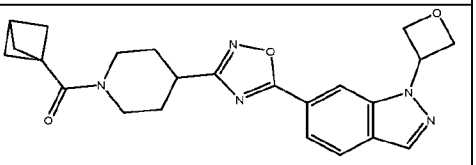
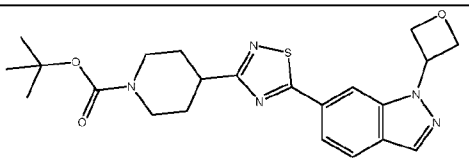
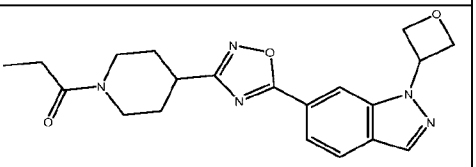
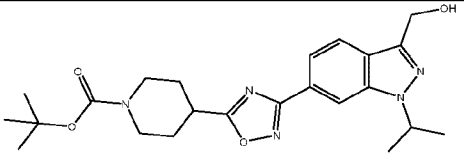
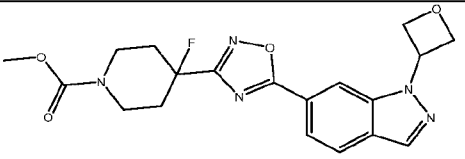
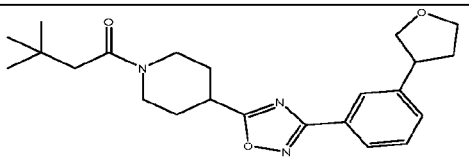
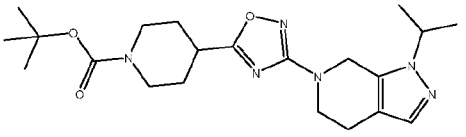
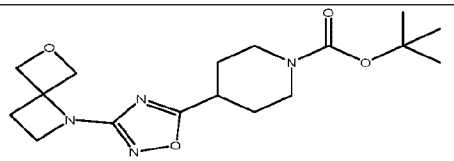
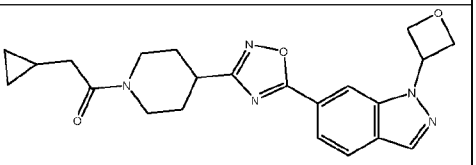
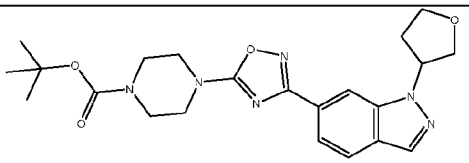
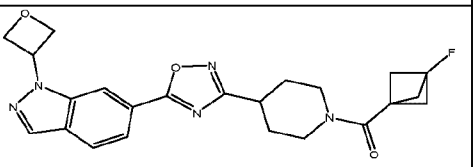
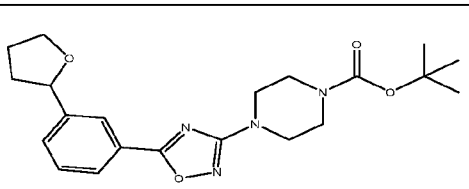
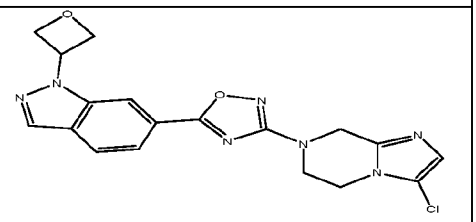
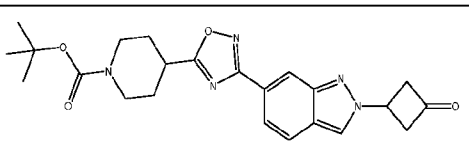
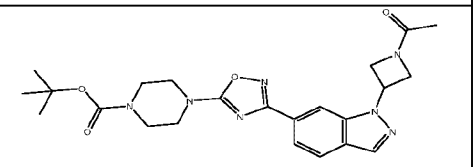
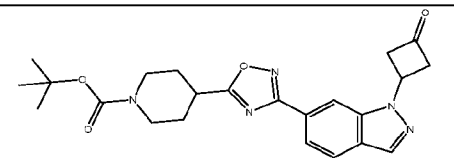
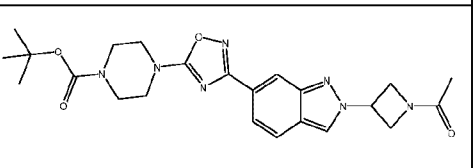
Table 2A. Compounds of the Invention

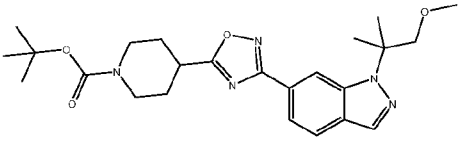
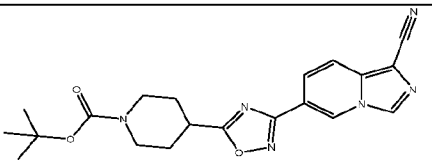
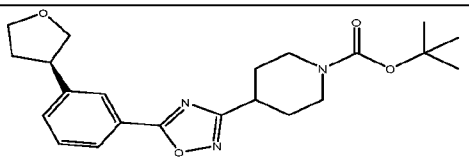
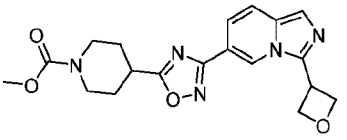
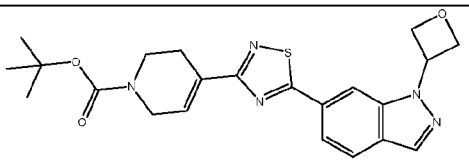
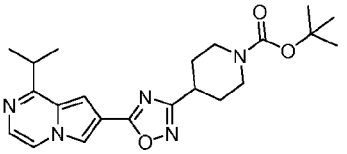
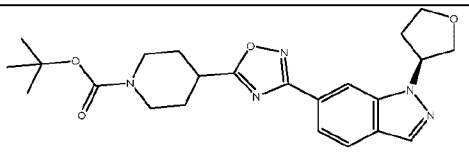
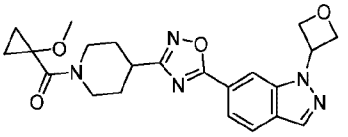
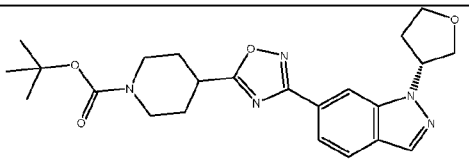
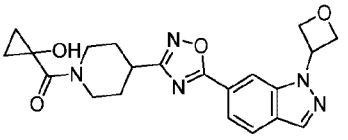
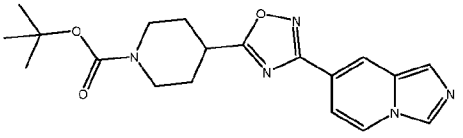
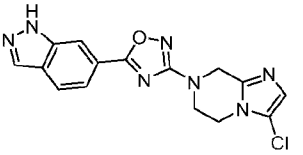
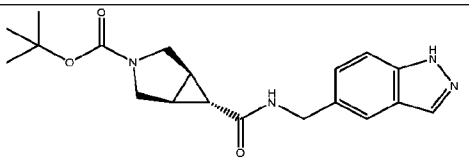
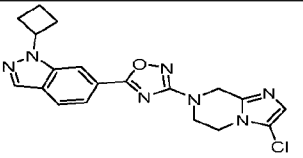
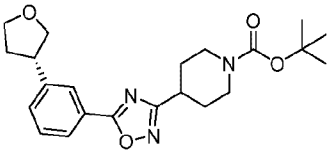
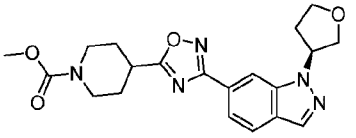
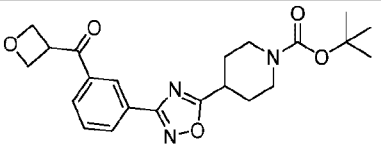
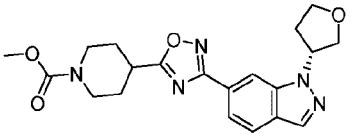
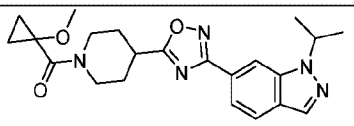
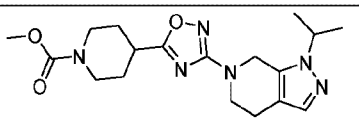
#	Structure	#	Structure
747		858	
748		859	
749		860	

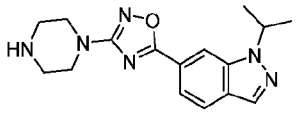
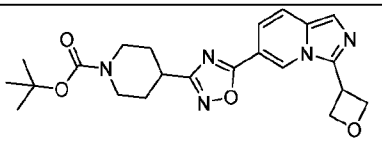
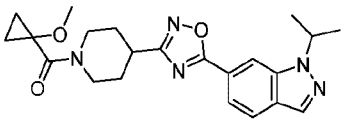
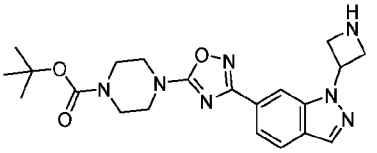
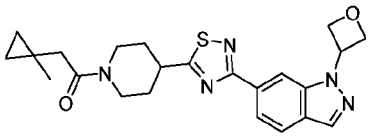
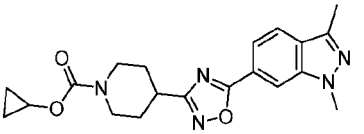
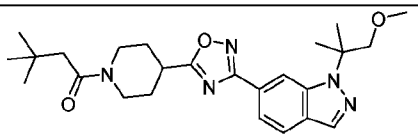
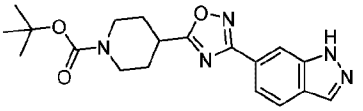
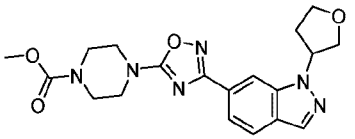
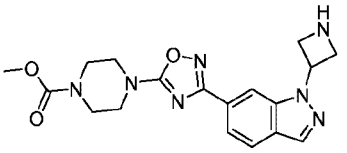
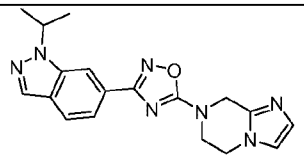
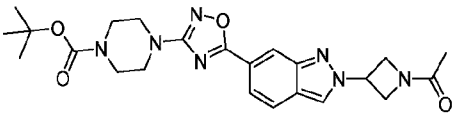
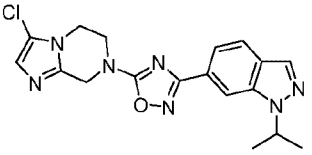
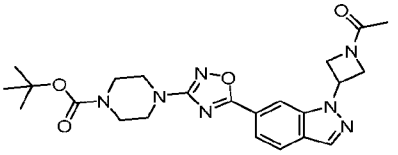
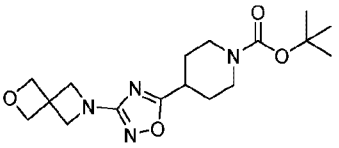
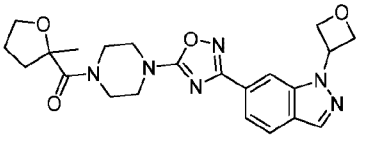
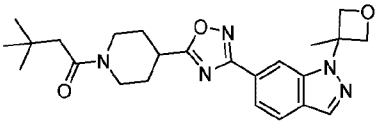
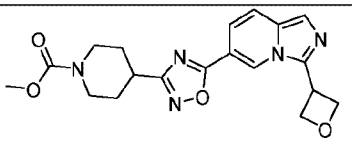
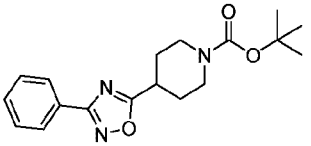
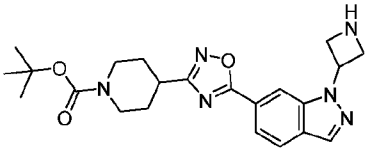
#	Structure	#	Structure
750		861	
751		862	
752		863	
753		864	
754		865	
755		866	
756		867	
757		868	
758		869	
759		870	

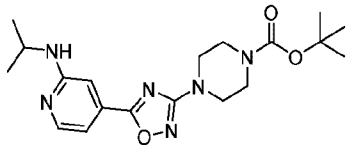
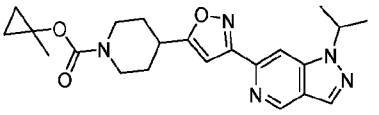
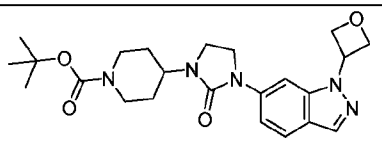
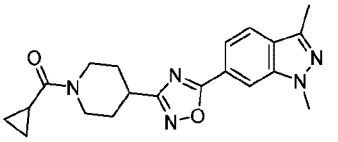
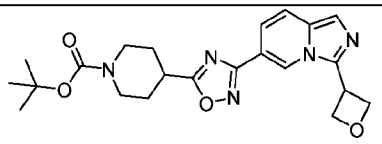
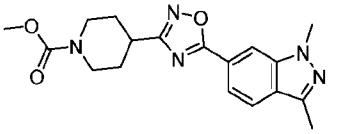
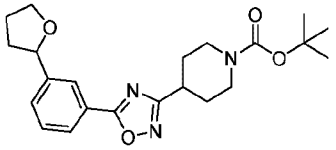
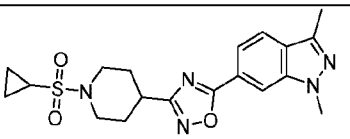
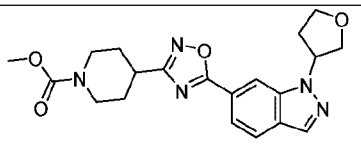
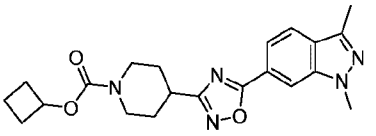
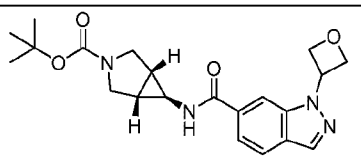
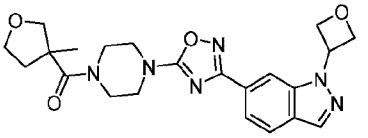
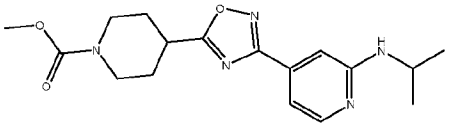
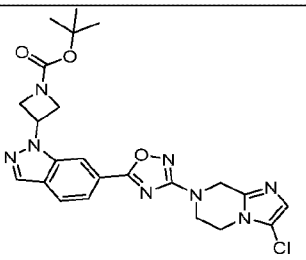
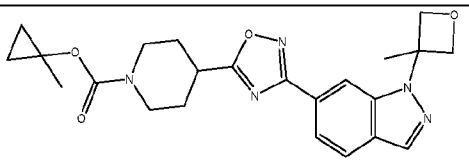
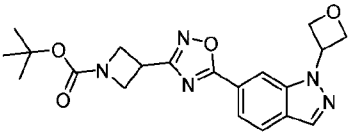
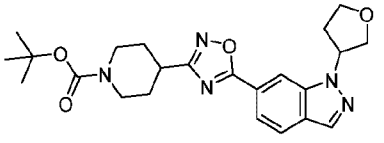
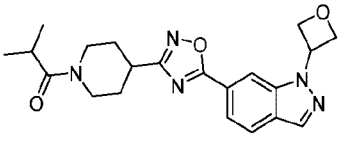
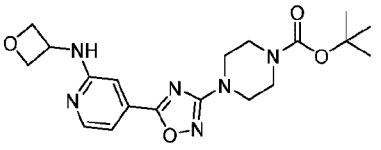
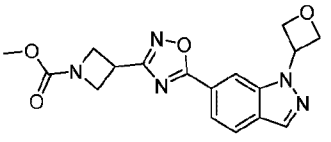
#	Structure	#	Structure
760		871	
761		872	
762		873	
763		874	
764		875	
765		876	
766		877	
767		878	
768		879	
769		880	

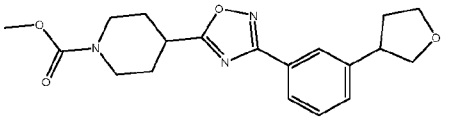
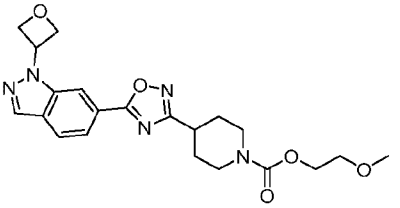
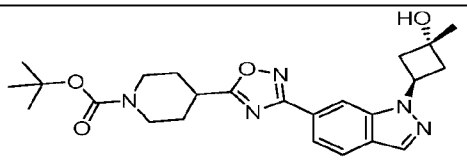
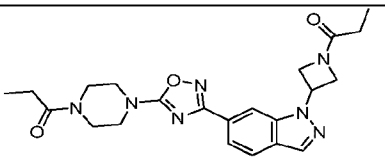
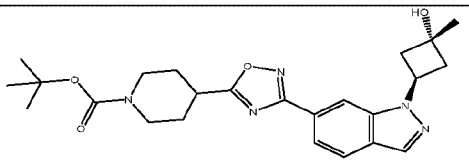
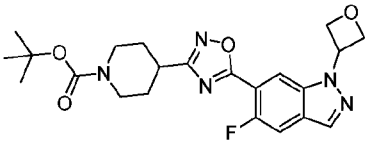
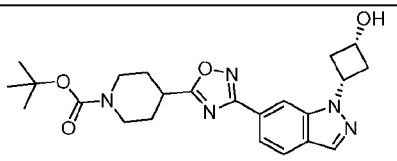
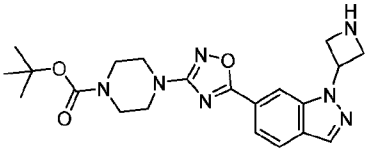
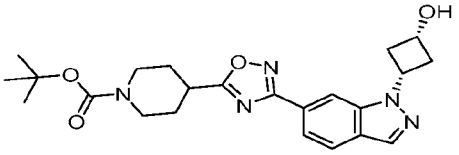
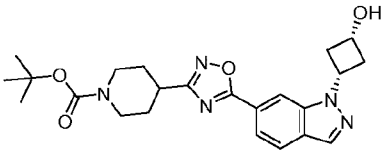
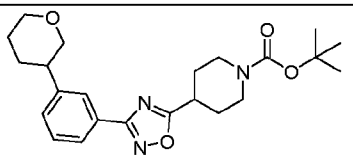
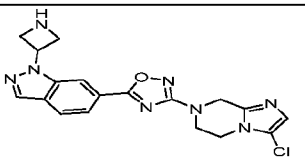
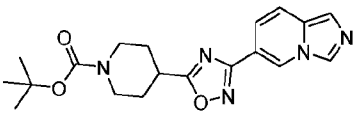
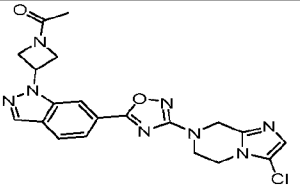
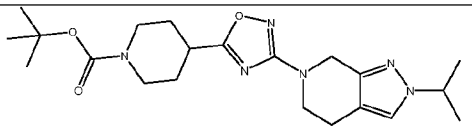
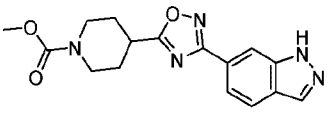
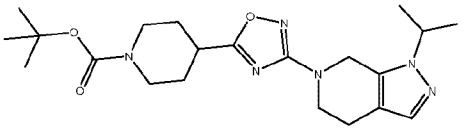
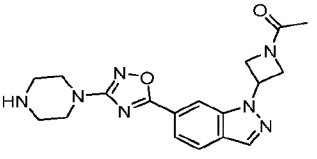
#	Structure	#	Structure
770		881	
771		882	
772		883	
773		884	
774		885	
775		886	
776		887	
777		888	
778		889	

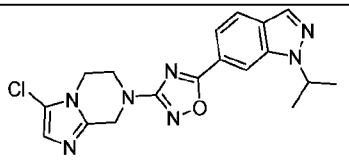
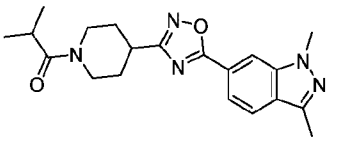
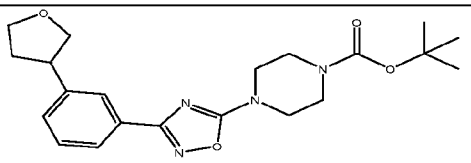
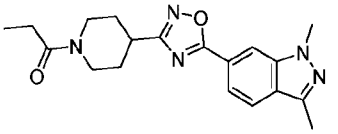
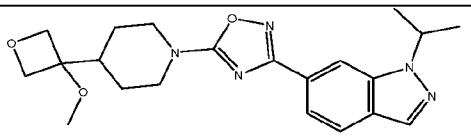
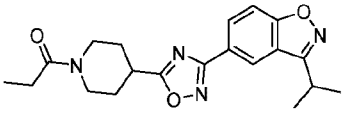
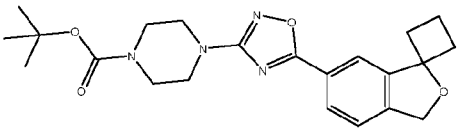
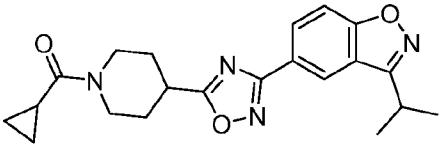
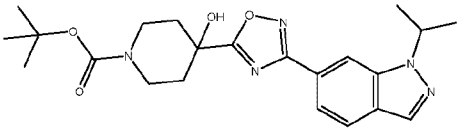
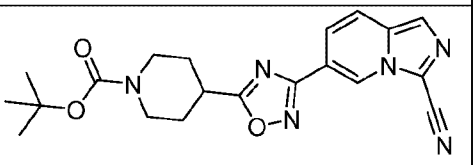
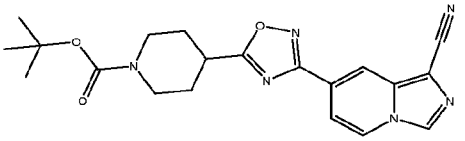
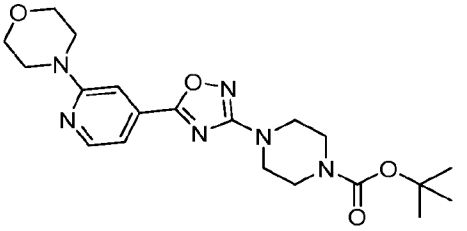
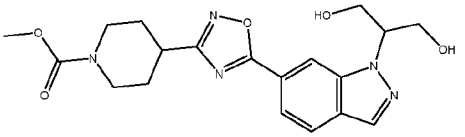
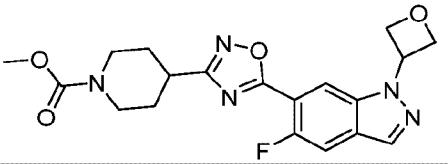
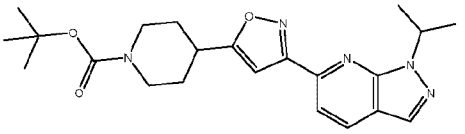
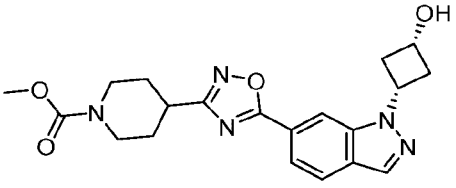
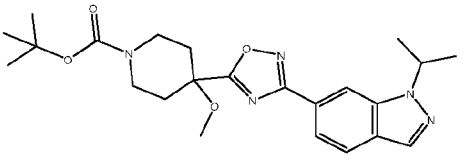
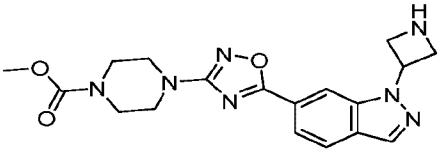
#	Structure	#	Structure
779		890	
780		891	
781		892	
782		893	
783		894	
784		895	
785		896	
786		897	
787		898	

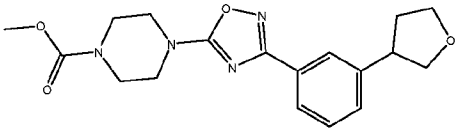
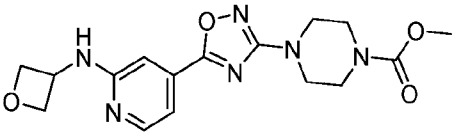
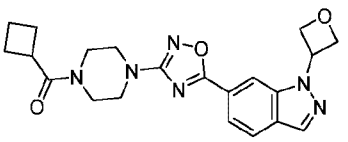
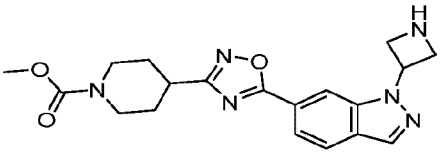
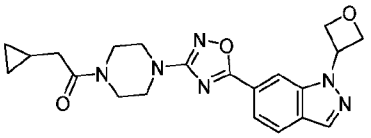
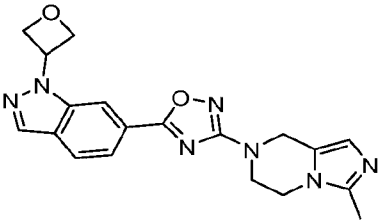
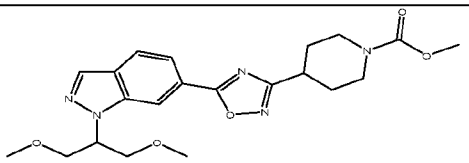
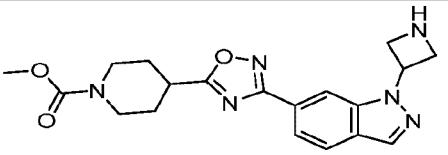
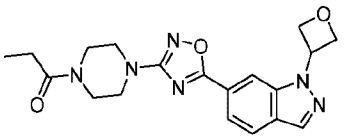
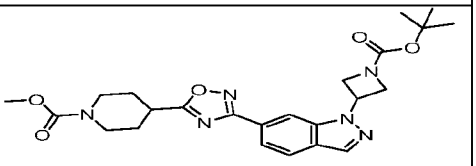
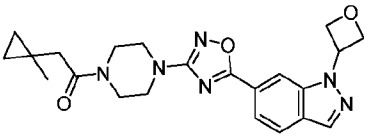
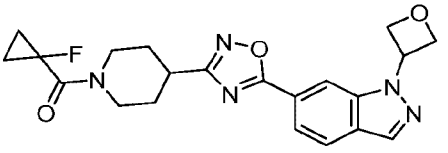
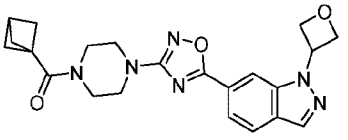
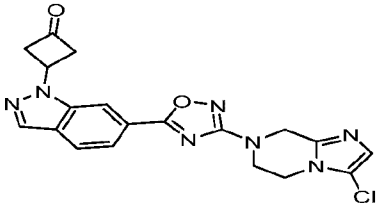
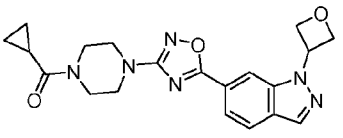
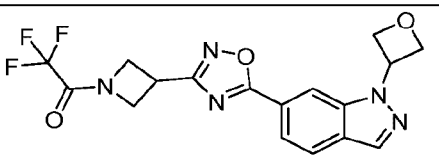
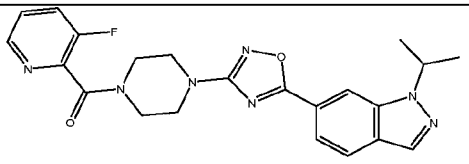
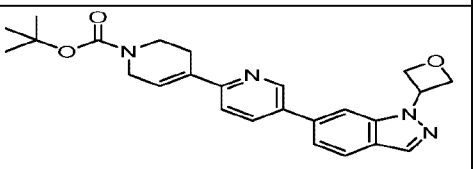
#	Structure	#	Structure
788		899	
789		900	
790		901	
791		902	
792		903	
793		904	
794		905	
795		906	
796		907	
797		908	

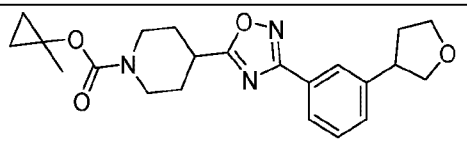
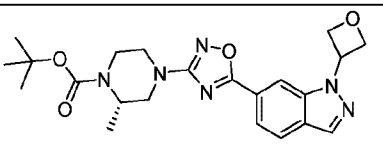
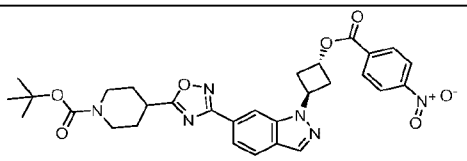
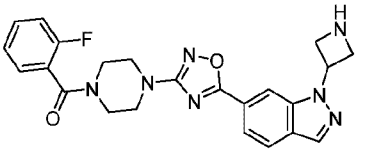
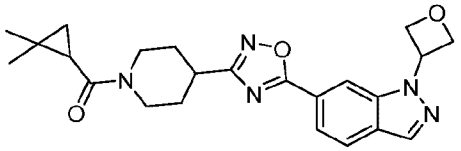
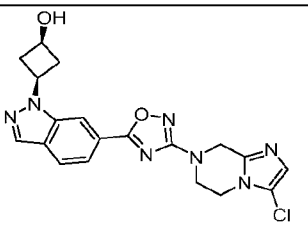
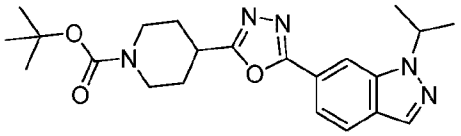
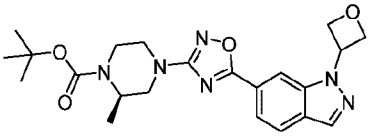
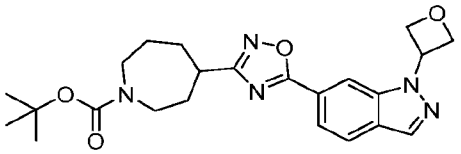
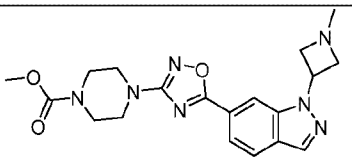
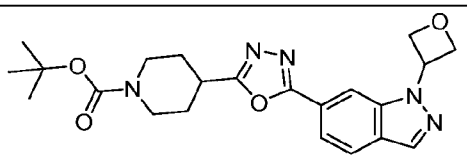
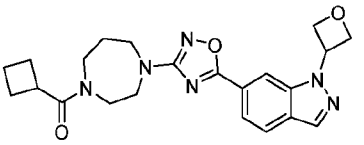
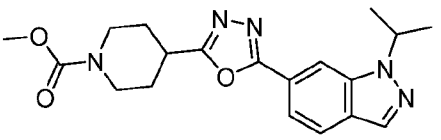
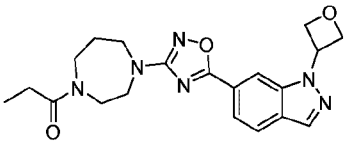
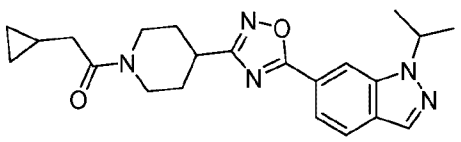
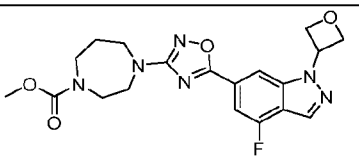
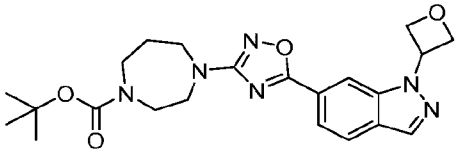
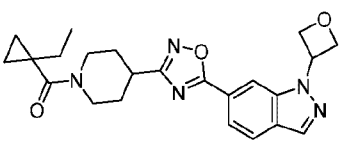
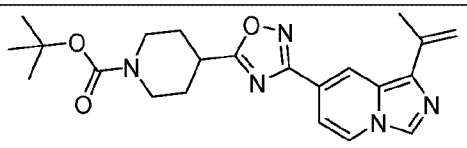
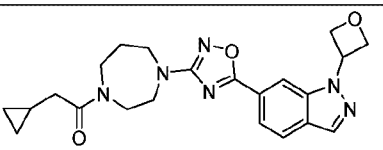
#	Structure	#	Structure
798		909	
799		910	
801		911	
802		912	
803		913	
804		914	
805		915	
806		916	
807		917	
808		918	

#	Structure	#	Structure
809		919	
810		920	
811		921	
812		922	
813		923	
814		924	
815		925	
816		926	
817		927	
818		928	

#	Structure	#	Structure
819		929	
820		930	
821		931	
822		932	
823		933	
824		934	
825		935	
826		936	
827		937	

#	Structure	#	Structure
828		938	
829		939	
830		940	
831		941	
832		942	
833		943	
834		944	
835		945	
836		946	

#	Structure	#	Structure
837		947	
838		948	
839		949	
840		950	
841		951	
842		952	
843		953	
844		954	
845		955	

#	Structure	#	Structure
846		956	
847		957	
848		958	
849		959	
850		960	
851		961	
852		962	
853		963	
854		964	
855		965	

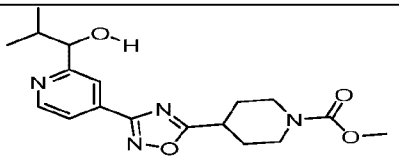
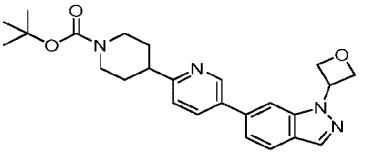
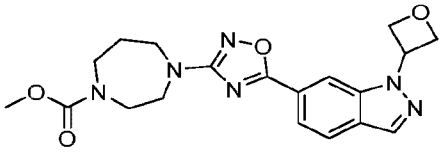
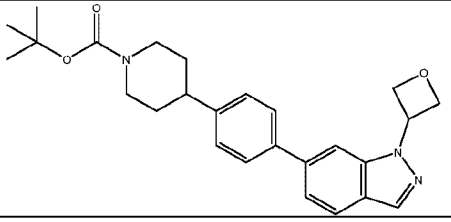
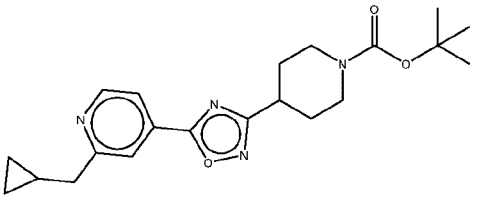
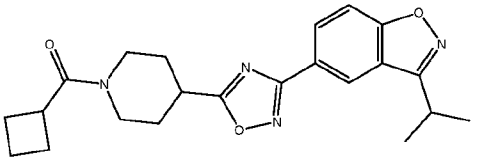
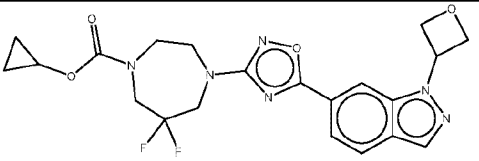
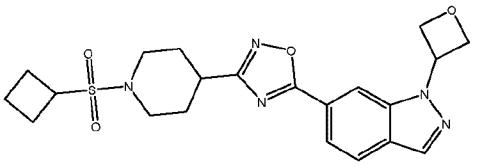
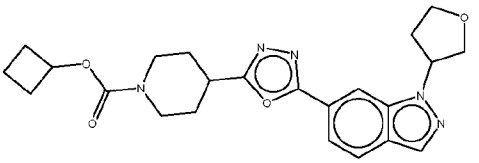
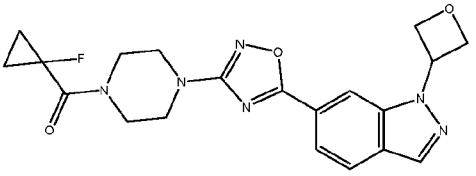
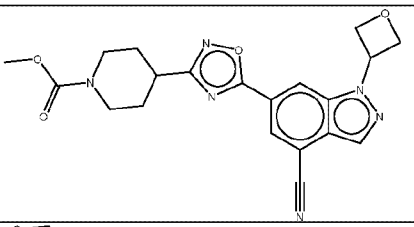
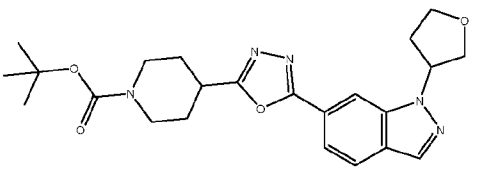
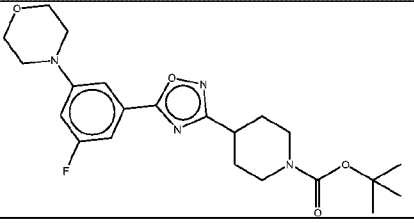
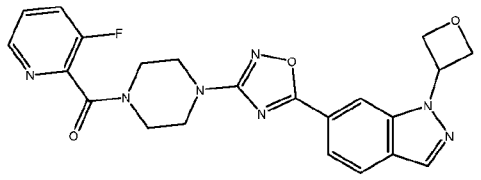
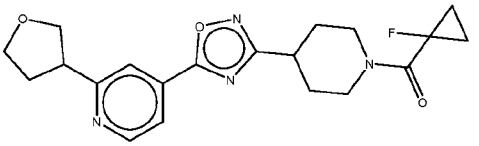
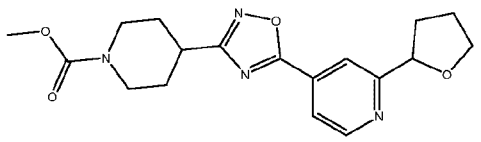
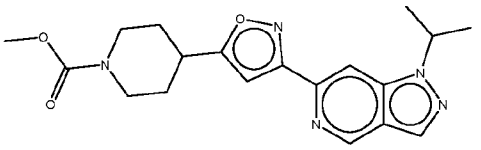
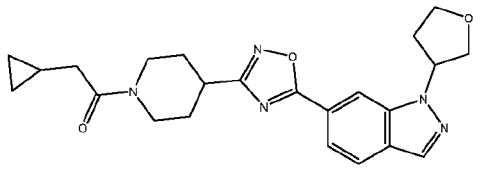
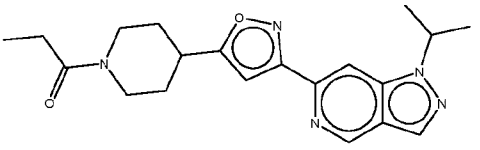
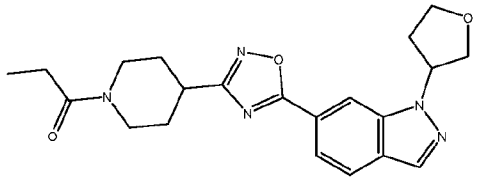
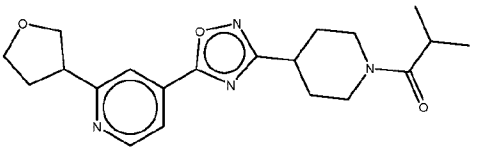
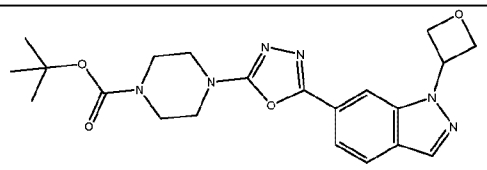
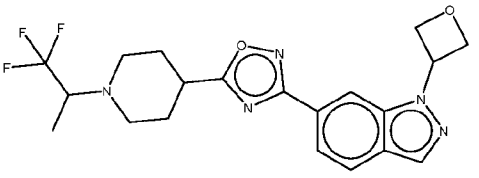
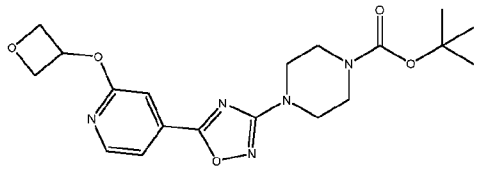
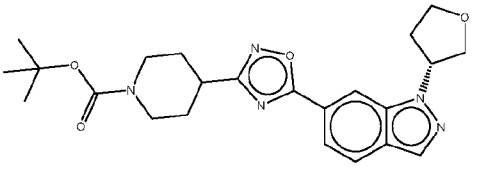
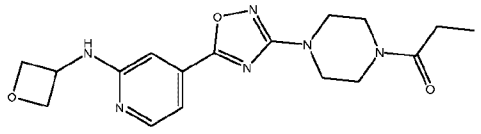
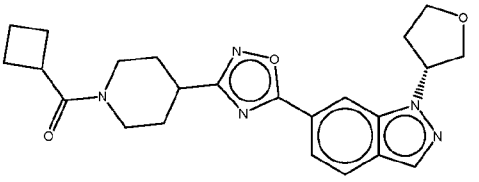
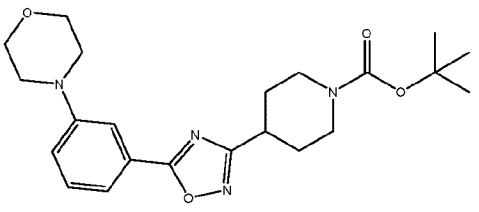
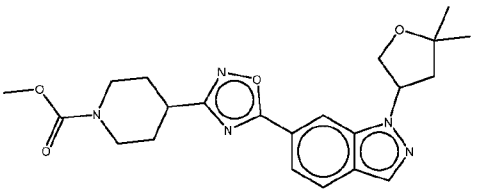
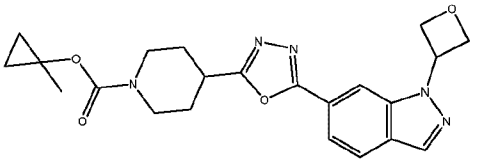
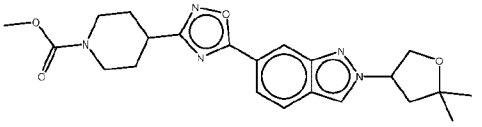
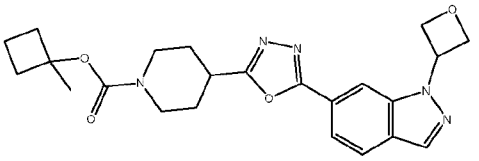
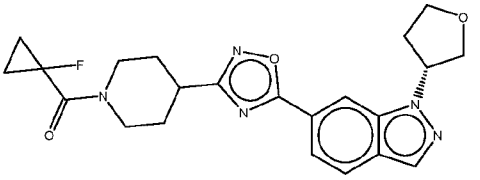
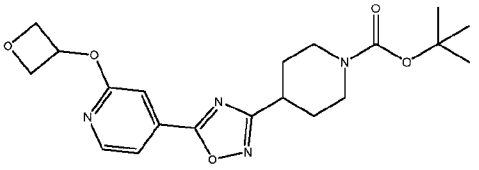
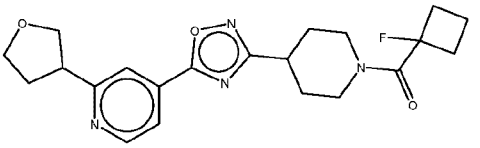
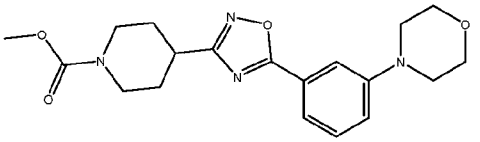
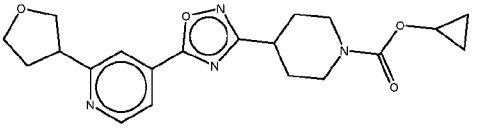
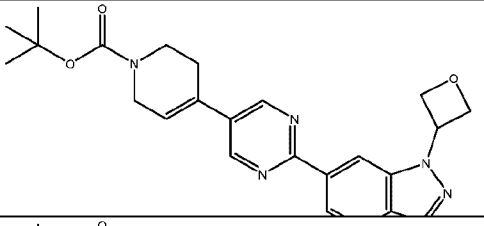
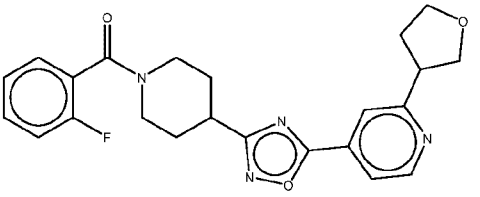
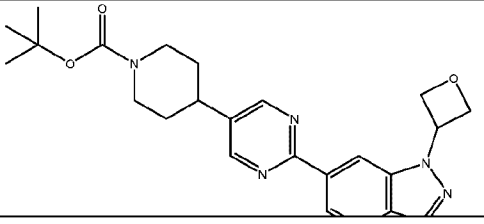
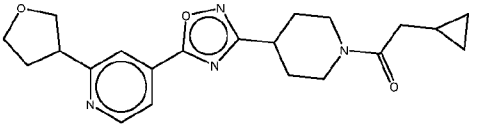
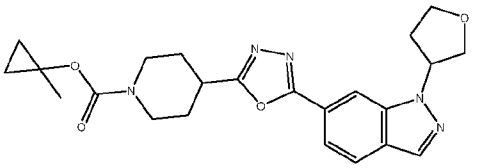
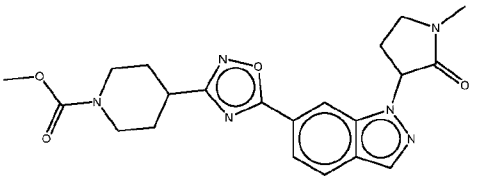
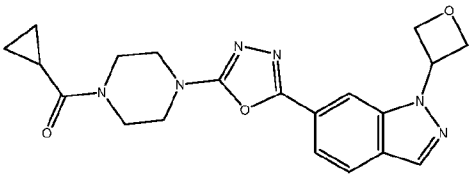
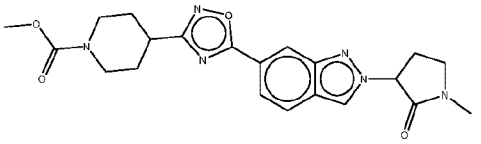
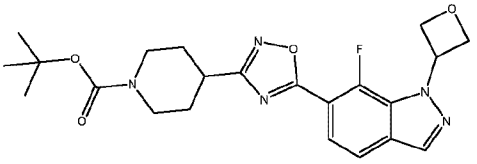
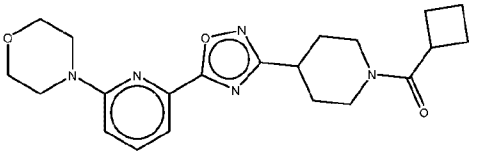
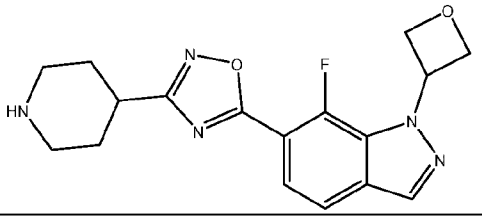
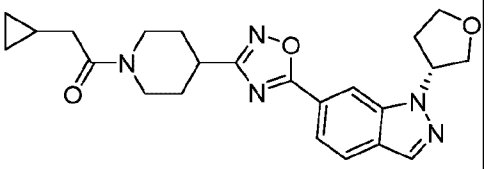
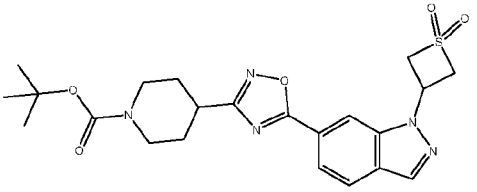
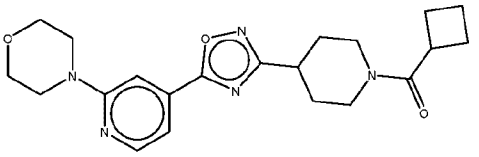
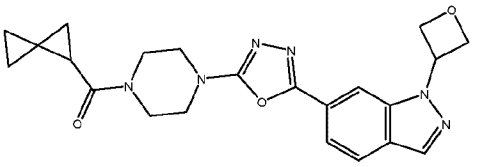
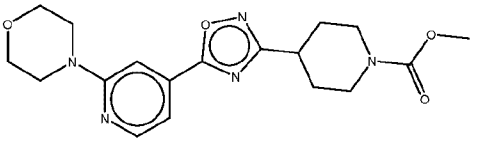
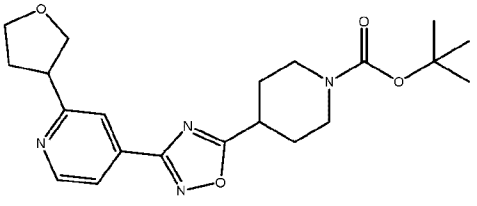
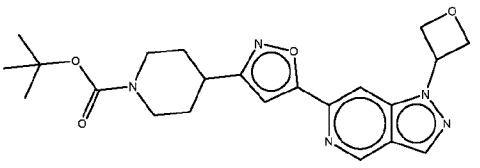
#	Structure	#	Structure
856		966	
857			

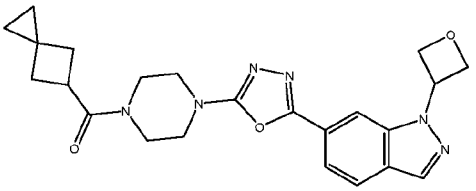
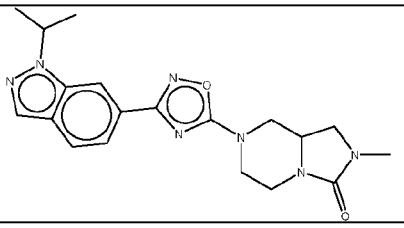
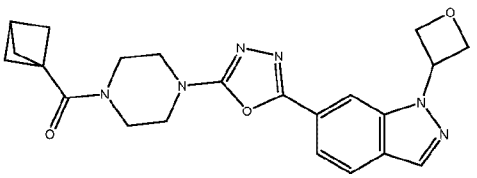
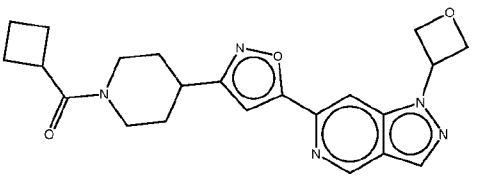
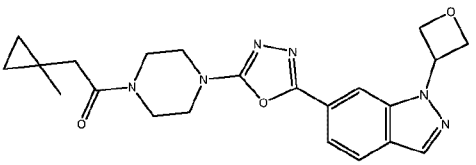
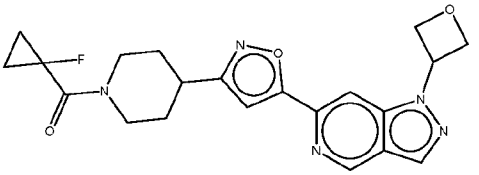
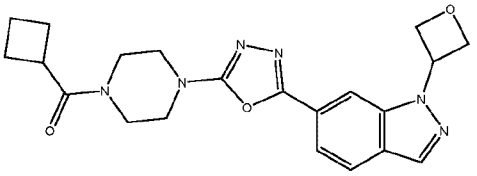
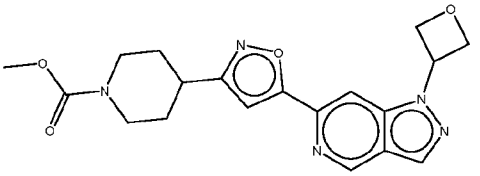
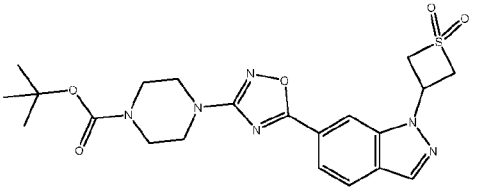
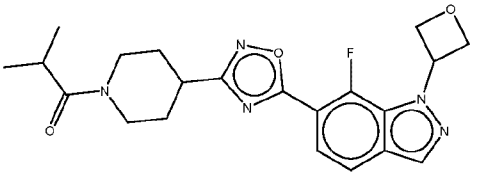
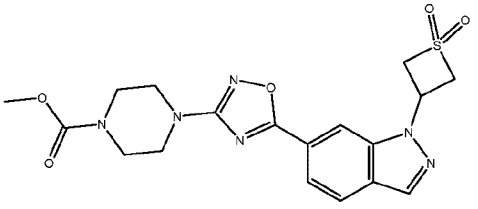
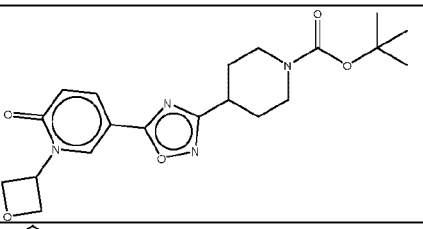
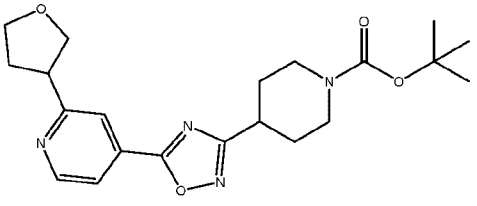
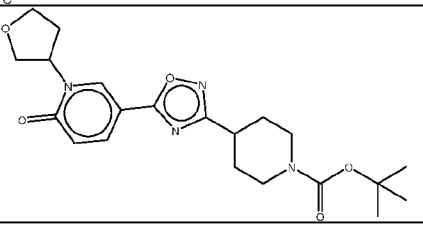
Table 2B. Compounds of the Invention

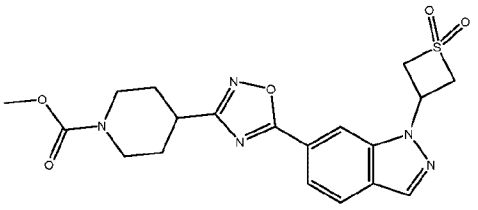
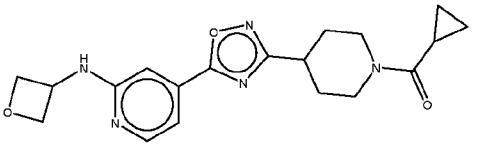
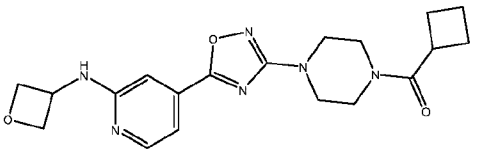
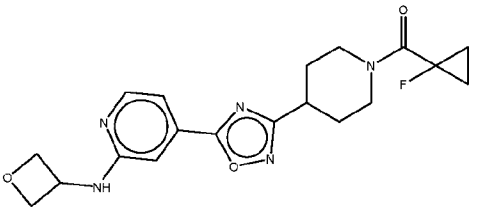
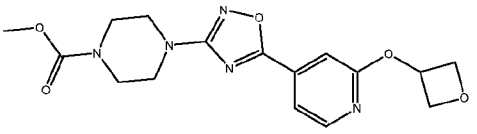
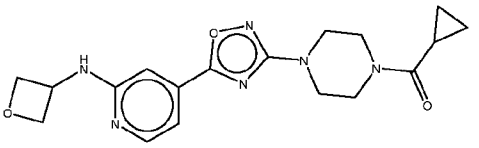
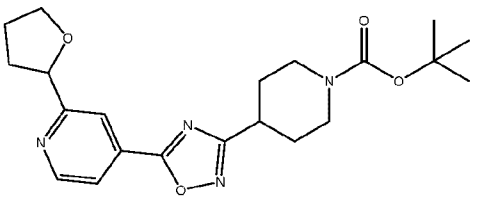
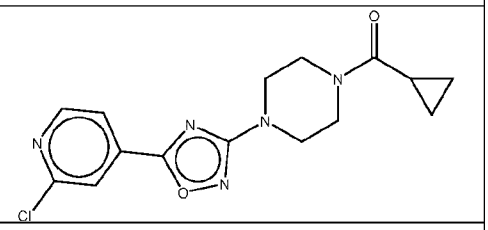
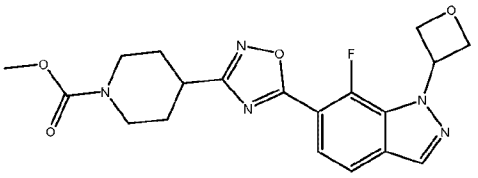
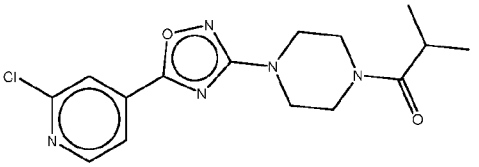
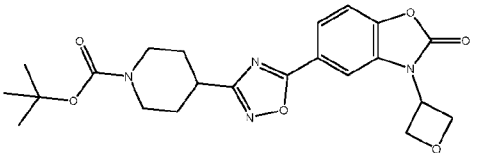
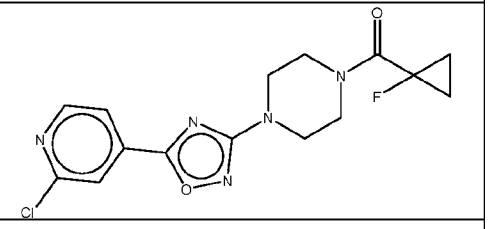
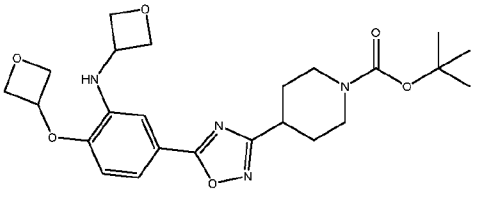
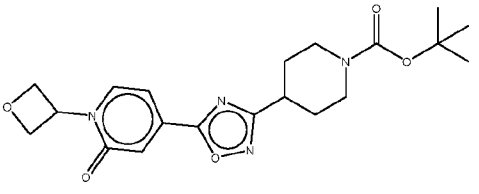
#	Structure	#	Structure
967		1082	
968		1083	
969		1084	
970		1085	
971		1086	

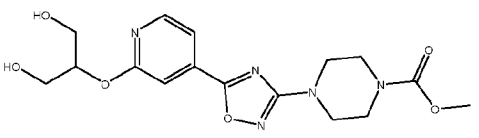
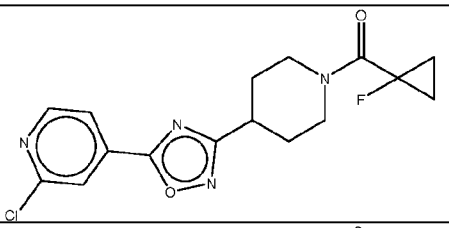
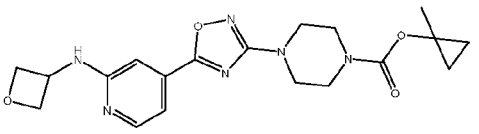
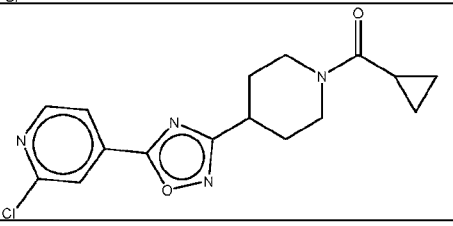
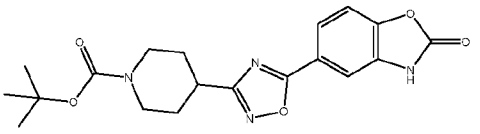
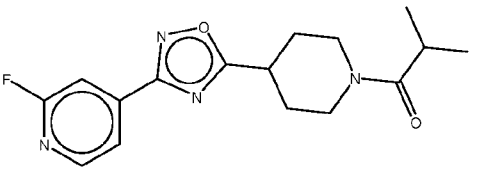
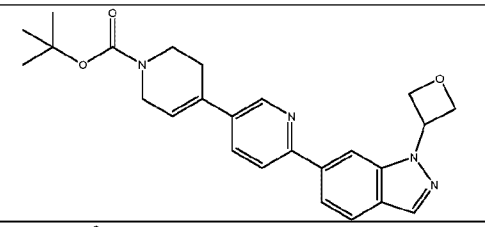
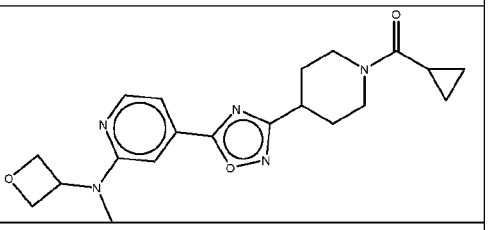
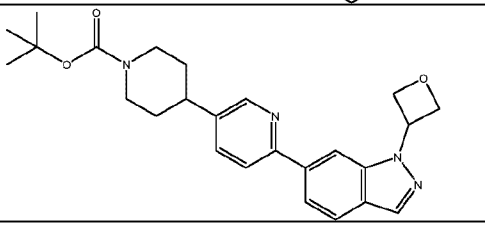
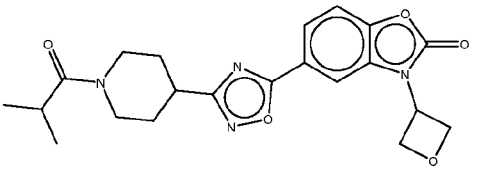
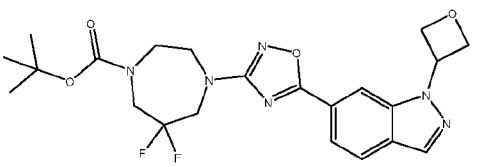
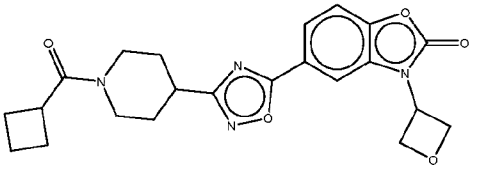
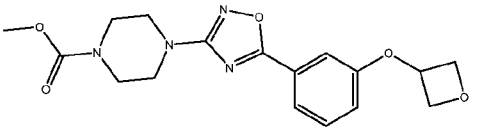
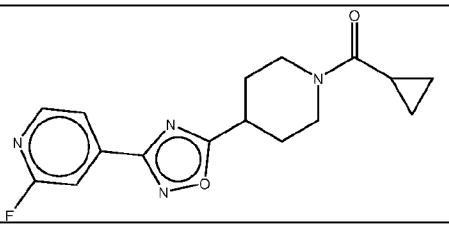
#	Structure	#	Structure
972		1087	
973		1088	
974		1089	
975		1090	
976		1091	
977		1092	
978		1093	

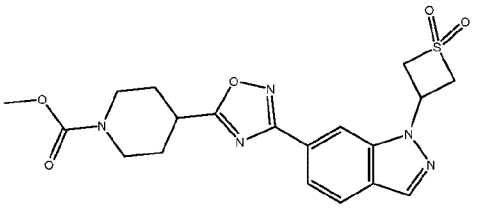
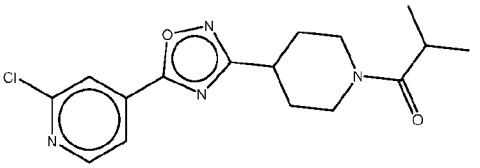
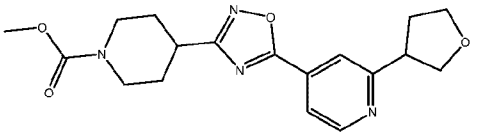
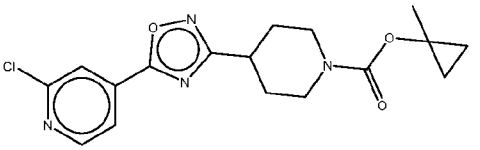
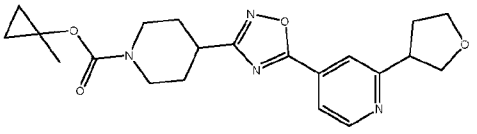
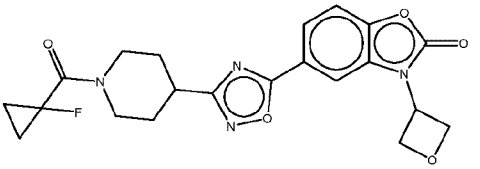
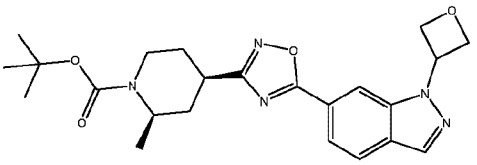
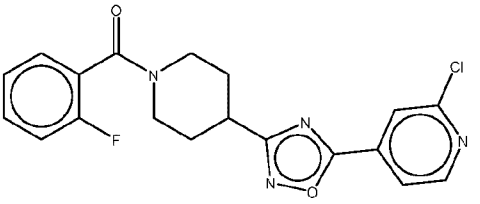
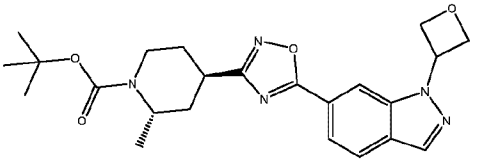
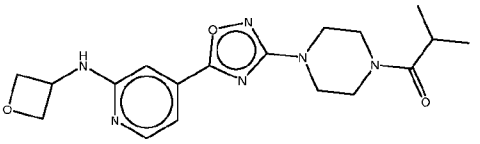
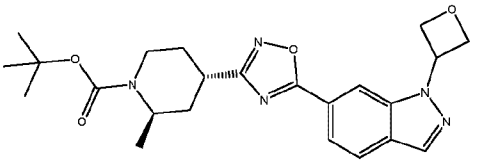
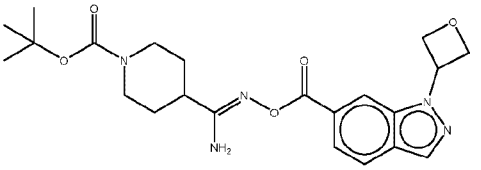
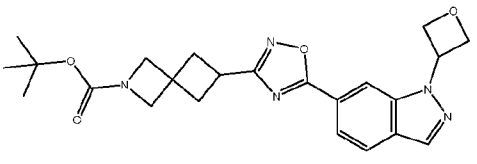
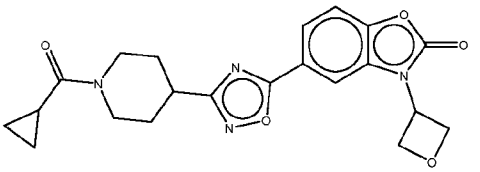
#	Structure	#	Structure
979		1094	
980		1095	
981		1096	
982		1097	
983		1098	
984		1099	
985		1100	

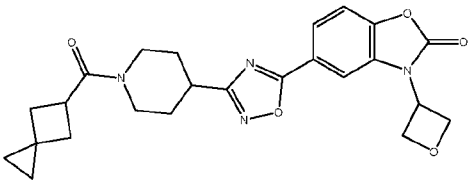
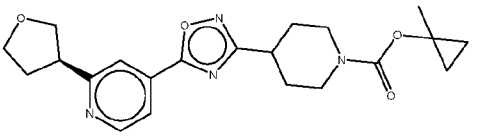
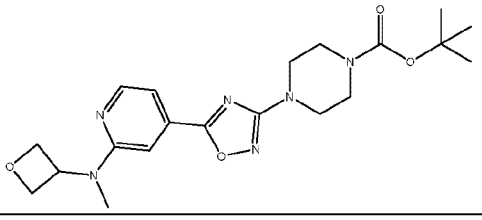
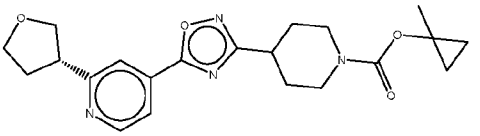
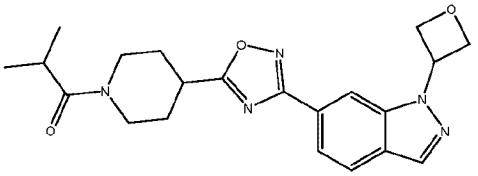
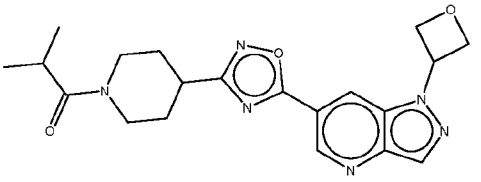
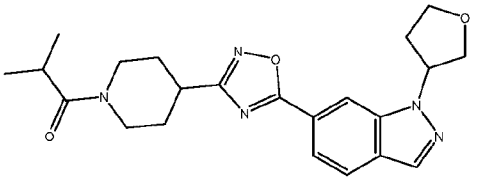
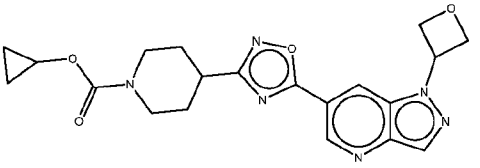
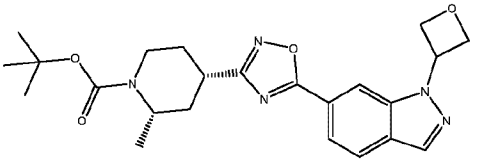
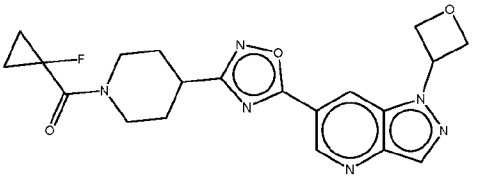
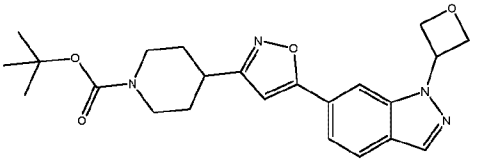
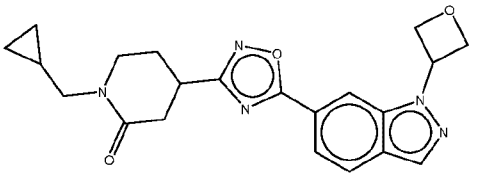
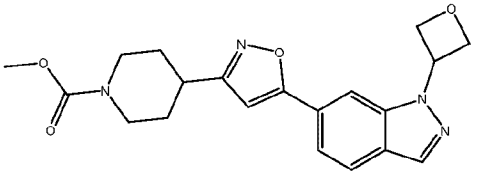
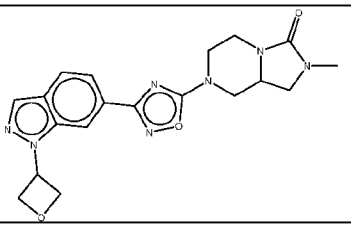
#	Structure	#	Structure
986		1101	
987		1102	
988		1103	
989		1104	
990		1105	
991		1106	
992		1107	

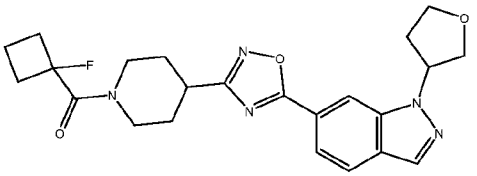
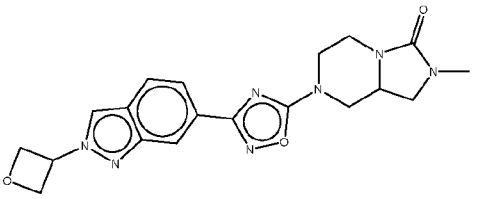
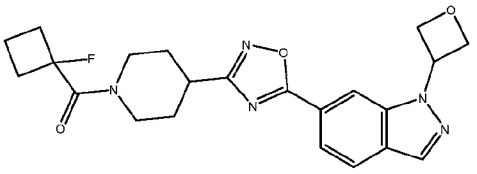
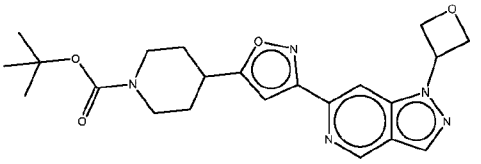
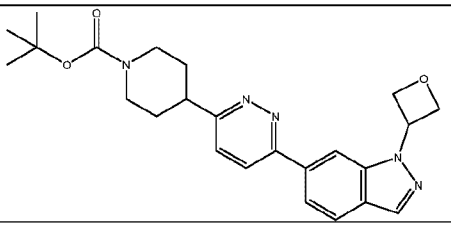
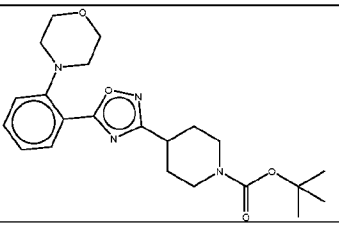
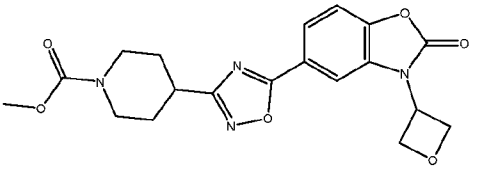
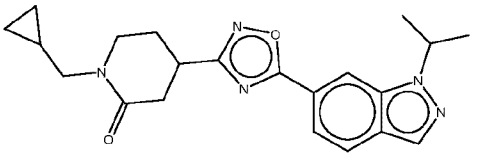
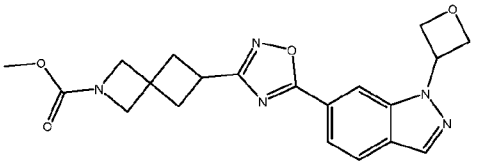
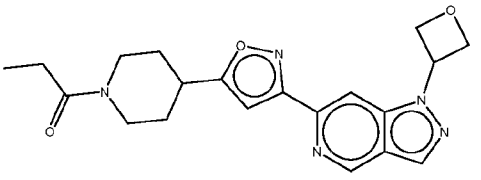
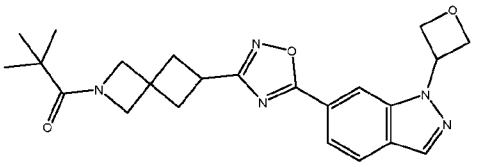
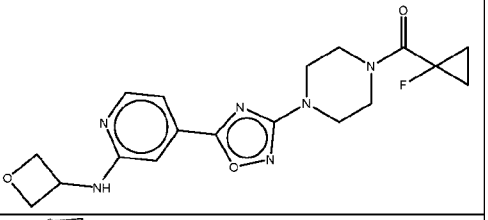
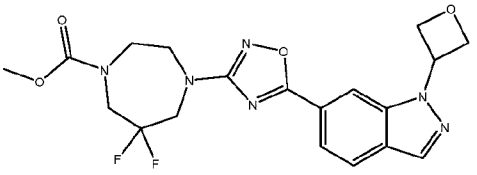
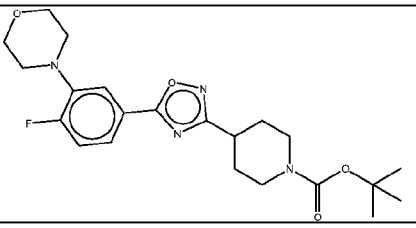
#	Structure	#	Structure
993		1108	
994		1109	
995		1110	
996		1111	
997		1112	
998		1113	
999		1114	

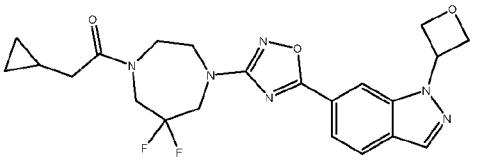
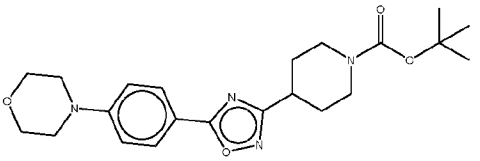
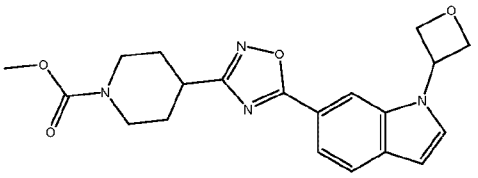
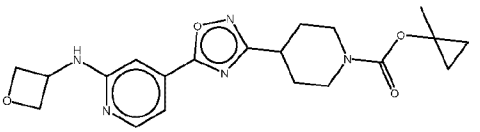
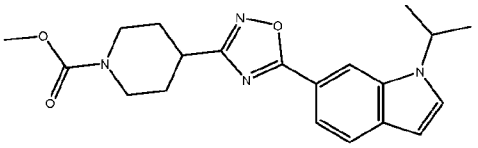
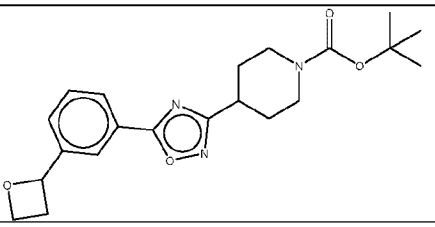
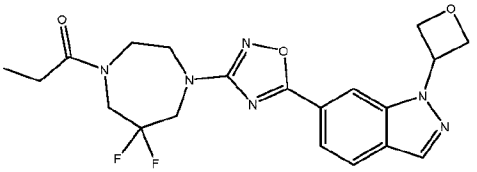
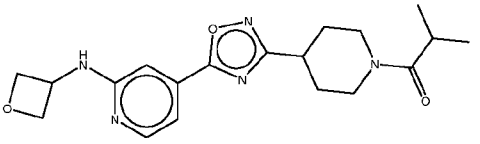
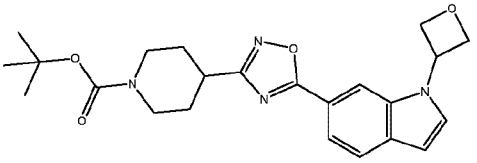
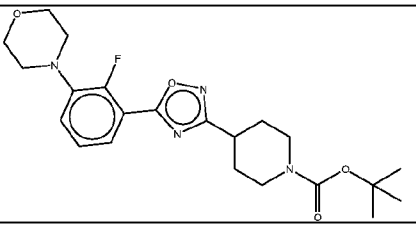
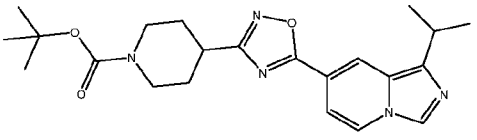
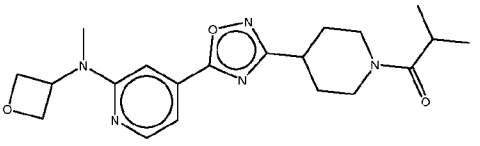
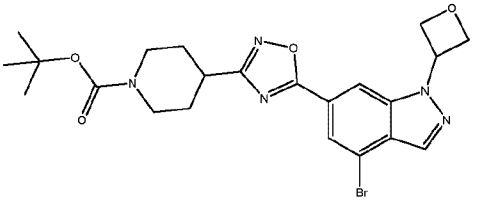
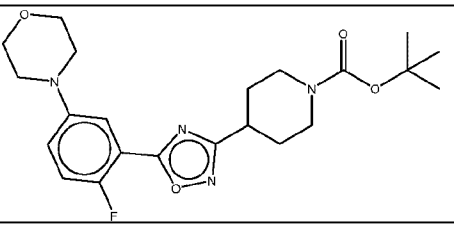
#	Structure	#	Structure
1000		1115	
1001		1116	
1002		1117	
1003		1118	
1004		1119	
1005		1120	
1006		1121	

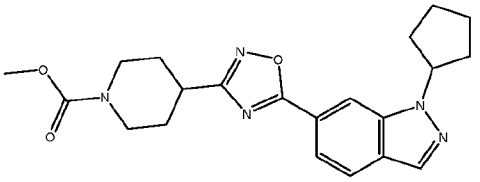
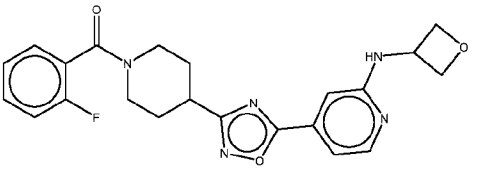
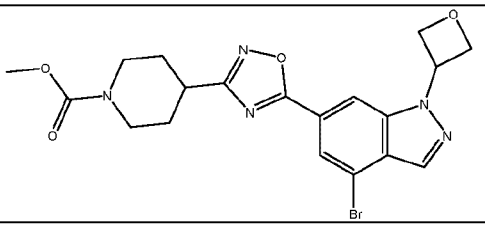
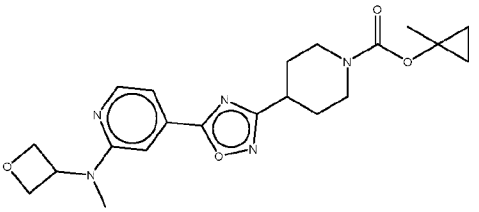
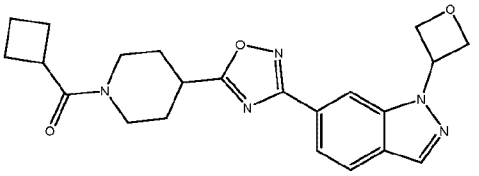
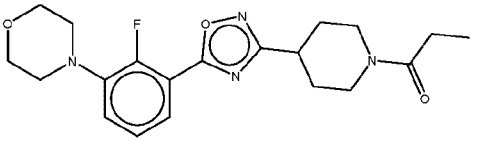
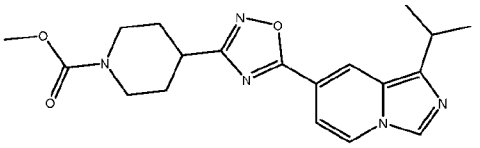
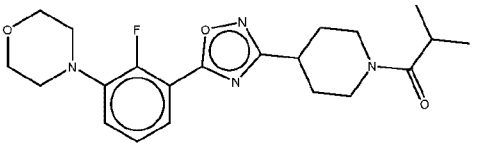
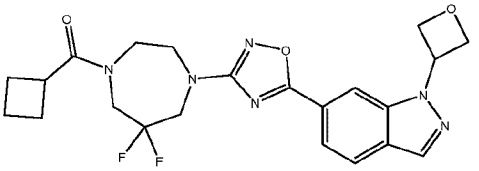
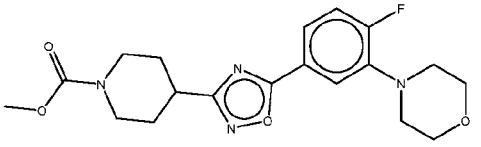
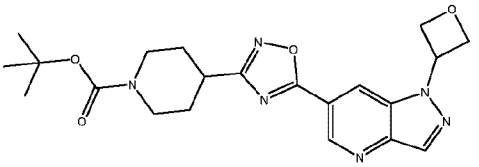
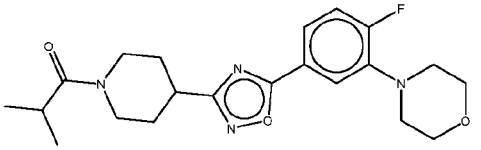
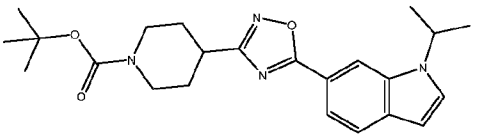
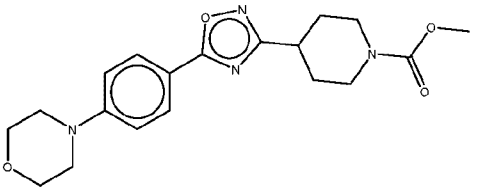
#	Structure	#	Structure
1007		1122	
1008		1123	
1009		1124	
1010		1125	
1011		1126	
1012		1127	
1013		1128	

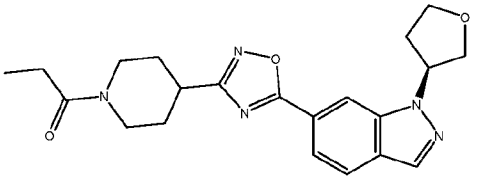
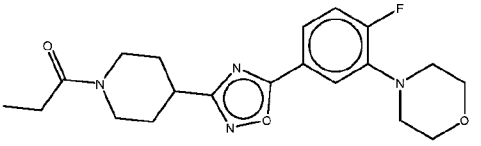
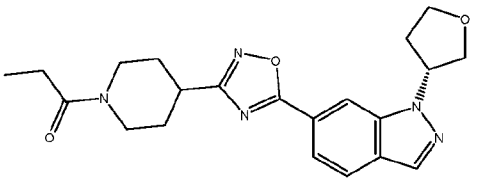
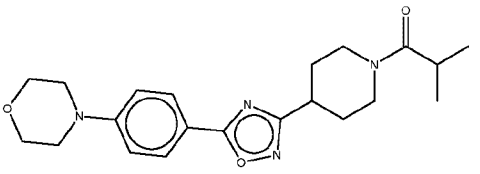
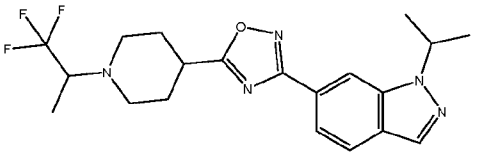
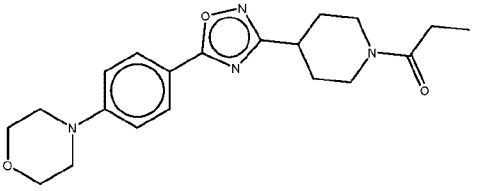
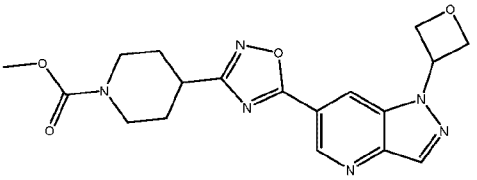
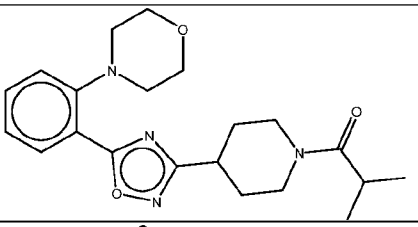
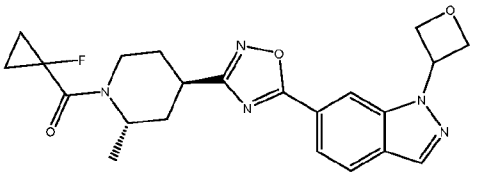
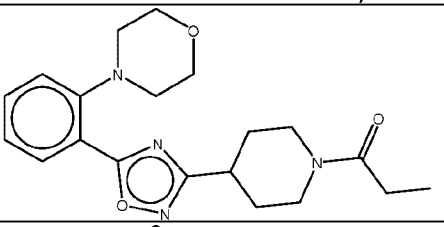
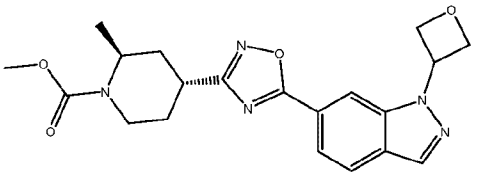
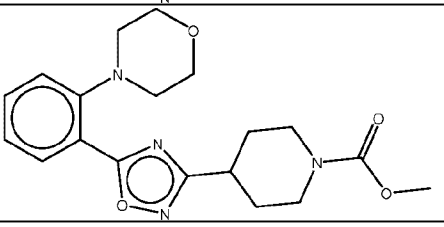
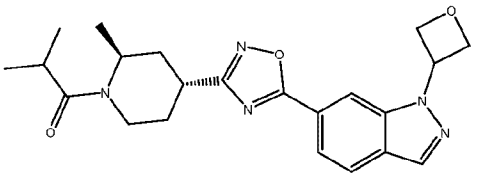
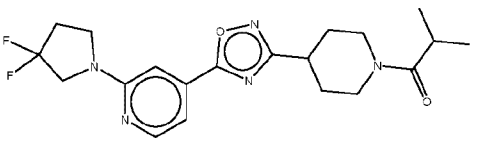
#	Structure	#	Structure
1014		1129	
1015		1130	
1016		1131	
1017		1132	
1018		1133	
1019		1134	
1020		1135	

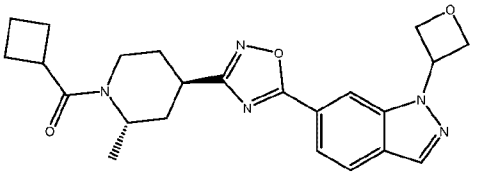
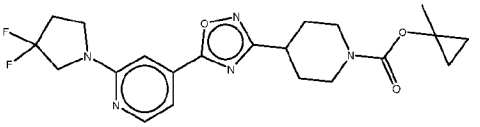
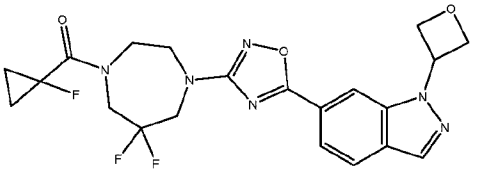
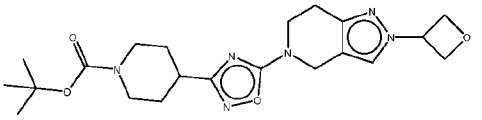
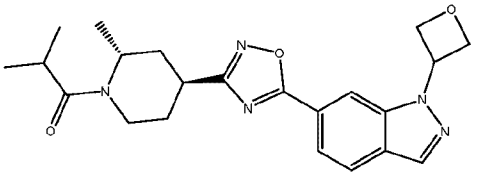
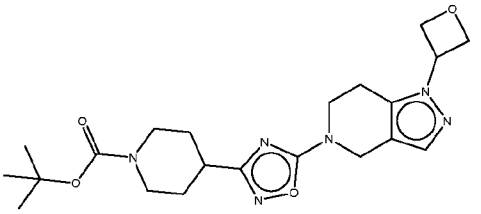
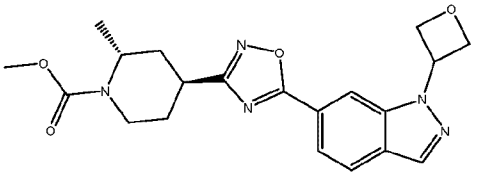
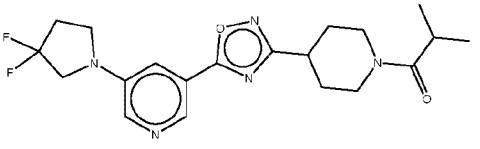
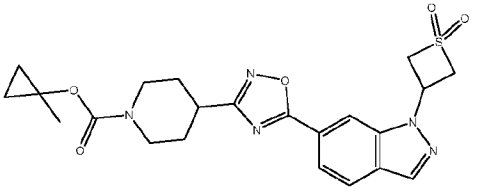
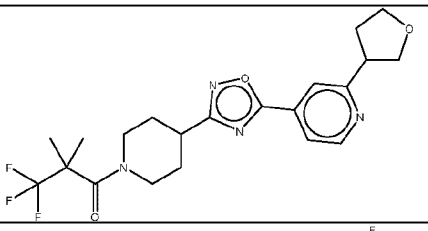
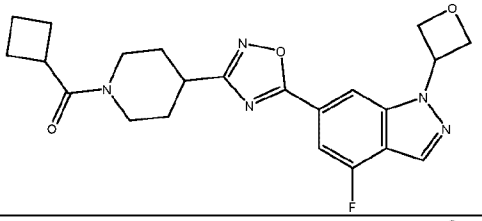
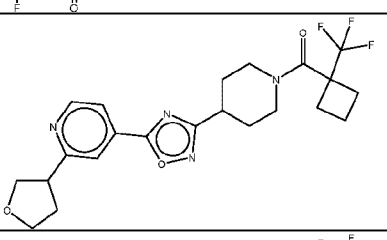
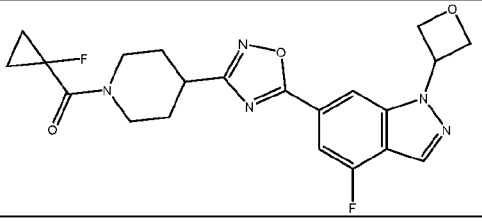
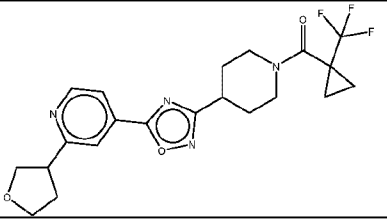
#	Structure	#	Structure
1021		1136	
1022		1137	
1023		1138	
1024		1139	
1025		1140	
1026		1141	
1027		1142	

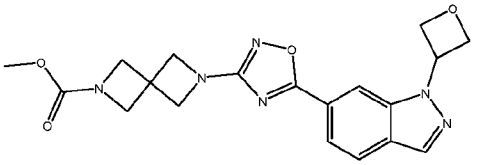
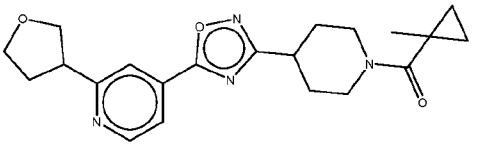
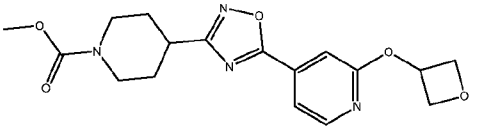
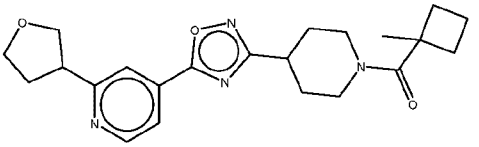
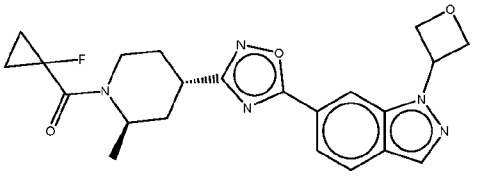
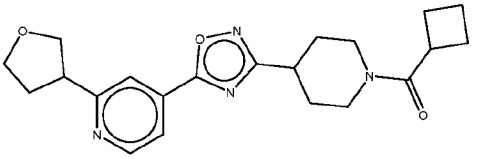
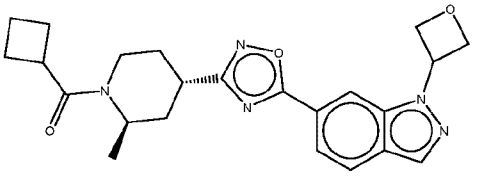
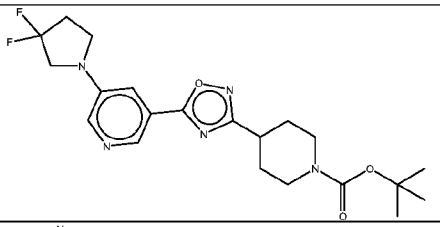
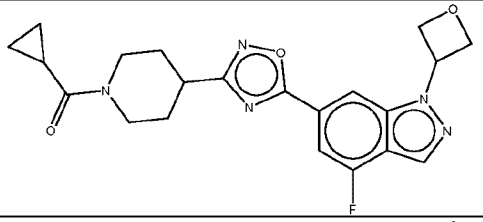
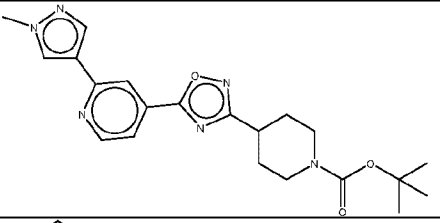
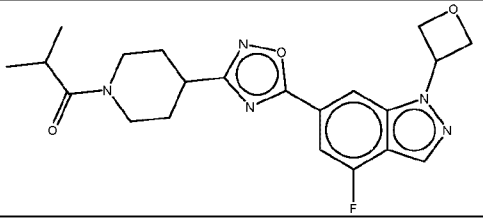
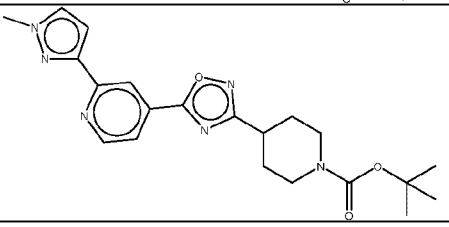
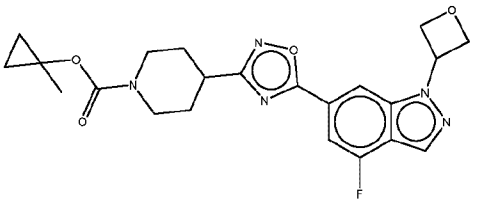
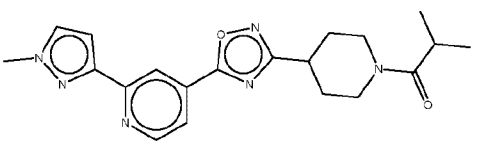
#	Structure	#	Structure
1028		1143	
1029		1144	
1030		1145	
1031		1146	
1032		1147	
1033		1148	
1034		1149	

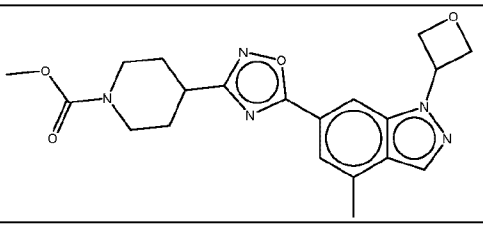
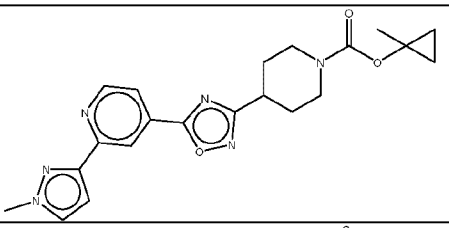
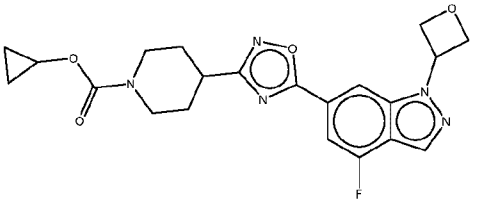
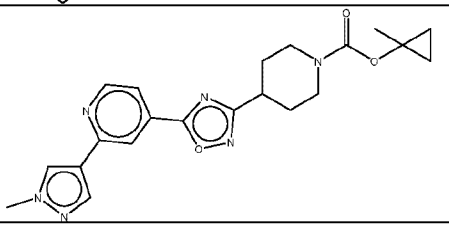
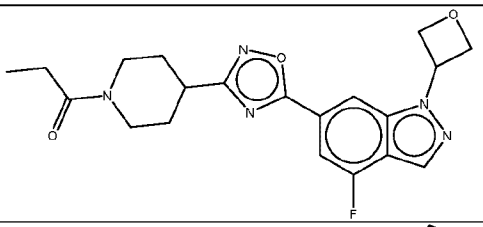
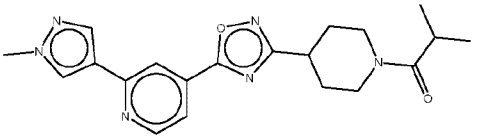
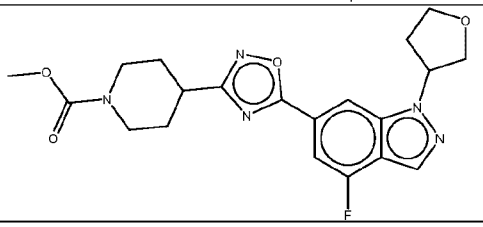
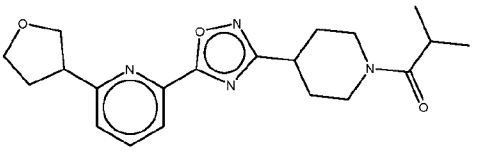
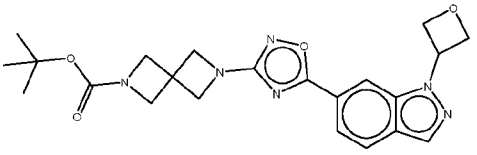
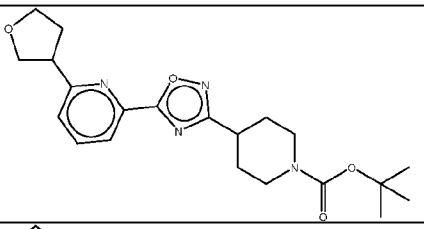
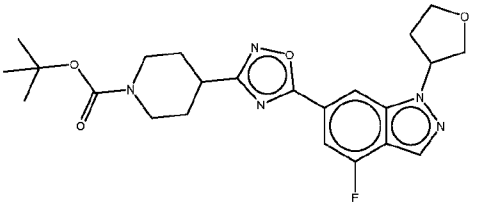
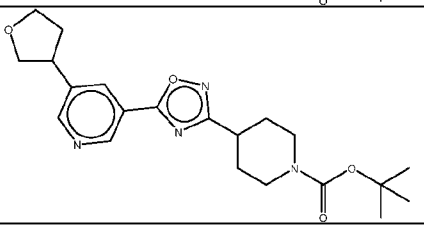
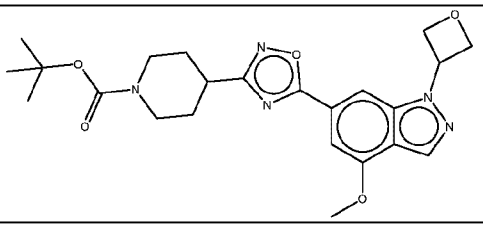
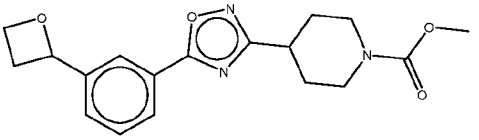
#	Structure	#	Structure
1035		1150	
1036		1151	
1037		1152	
1038		1153	
1039		1154	
1040		1155	
1041		1156	

#	Structure	#	Structure
1042		1157	
1043		1158	
1044		1159	
1045		1160	
1046		1161	
1047		1162	
1048		1163	

#	Structure	#	Structure
1049		1164	
1050		1165	
1051		1166	
1052		1167	
1053		1168	
1054		1169	
1055		1170	

#	Structure	#	Structure
1056		1171	
1057		1172	
1058		1173	
1059		1174	
1060		1175	
1061		1176	
1062		1177	

#	Structure	#	Structure
1063		1178	
1064		1179	
1065		1180	
1066		1181	
1067		1182	
1068		1183	
1069		1184	

#	Structure	#	Structure
1070		1185	
1071		1186	
1072		1187	
1073		1188	
1074		1189	
1075		1190	
1076		1191	

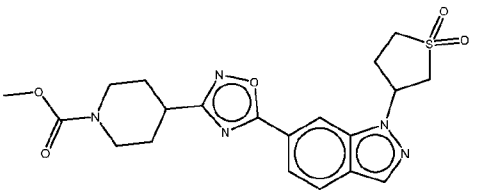
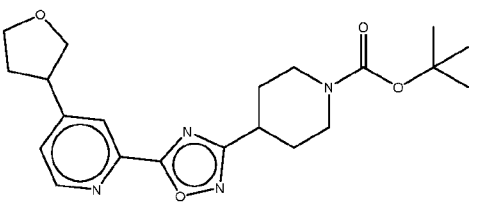
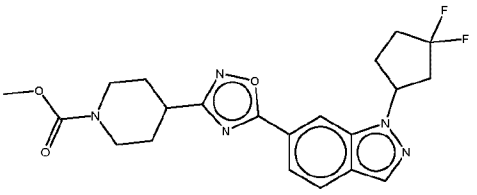
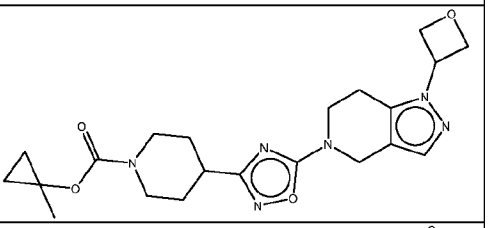
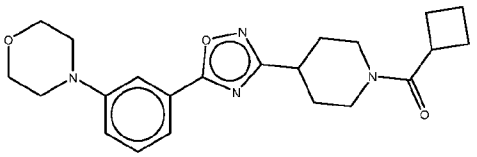
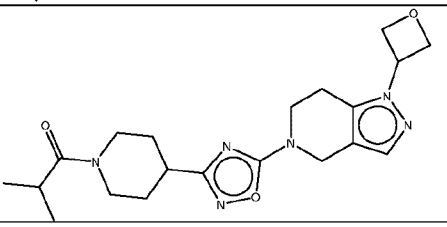
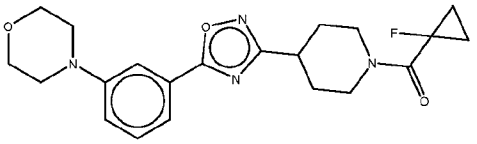
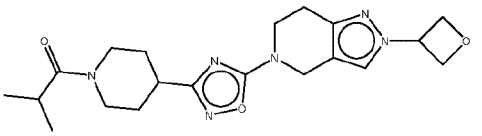
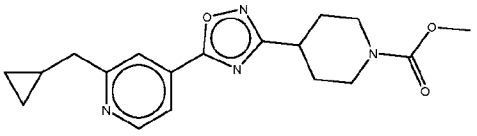
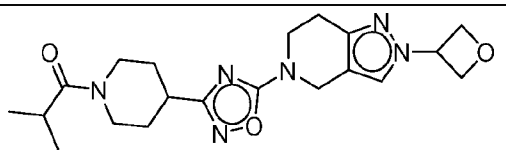
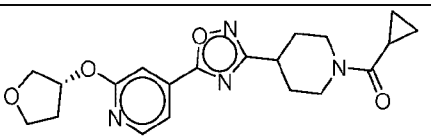
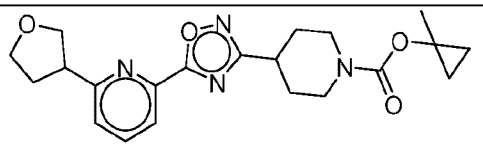
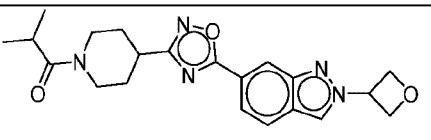
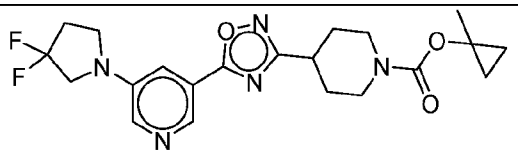
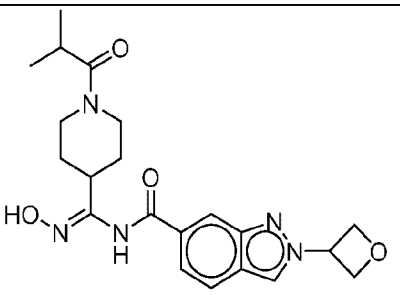
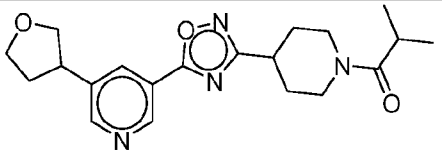
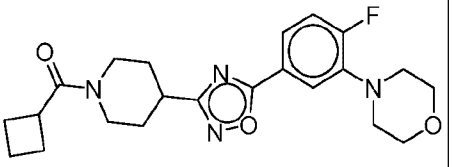
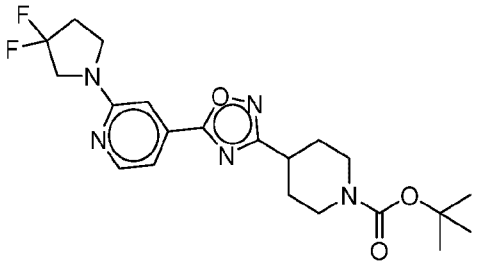
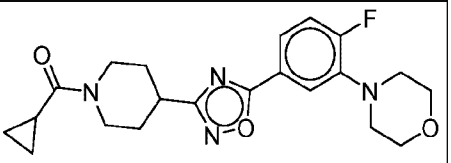
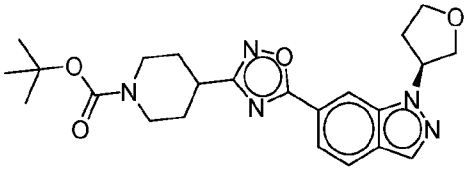
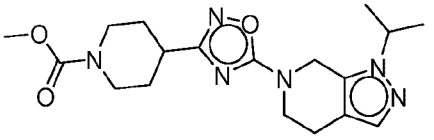
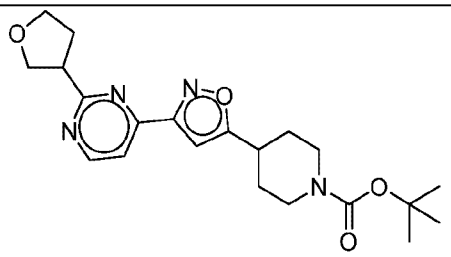
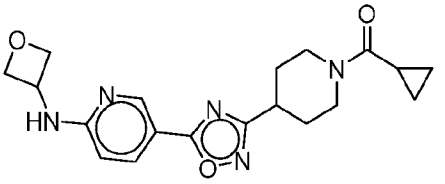
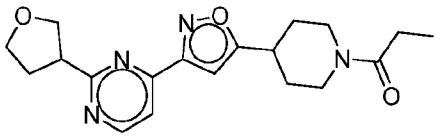
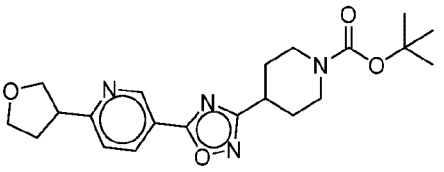
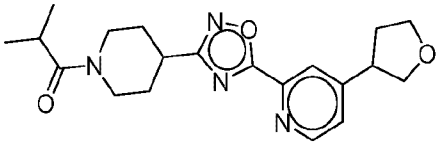
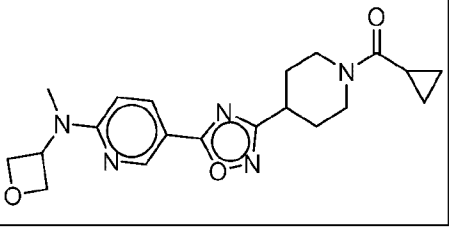
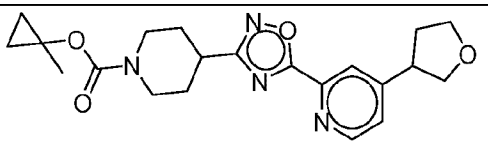
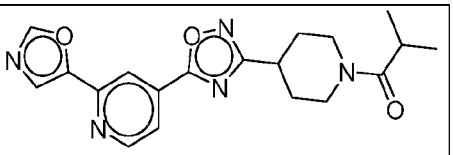
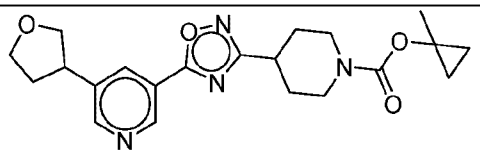
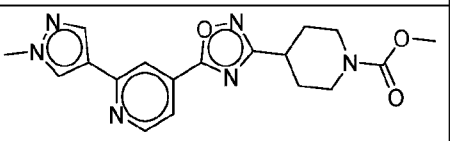
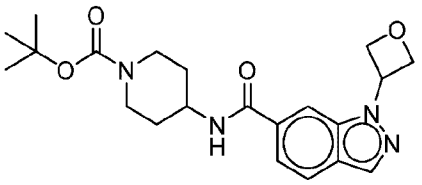
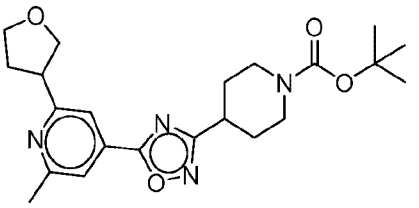
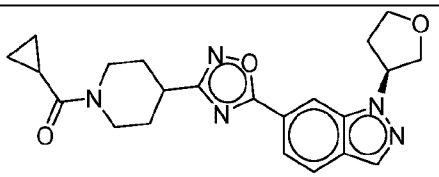
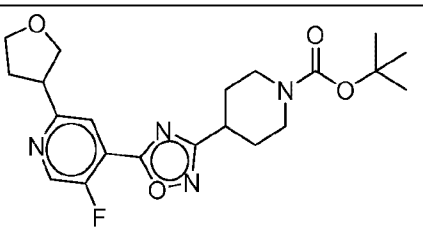
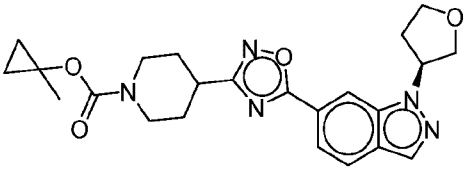
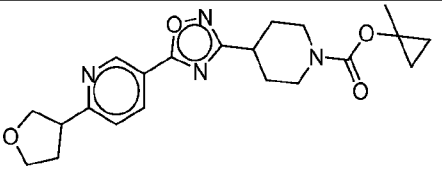
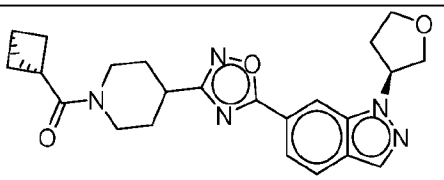
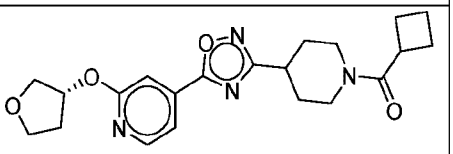
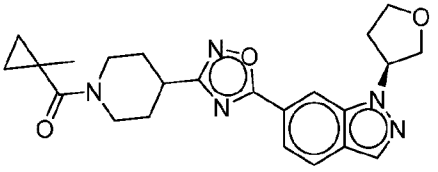
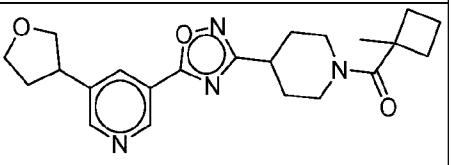
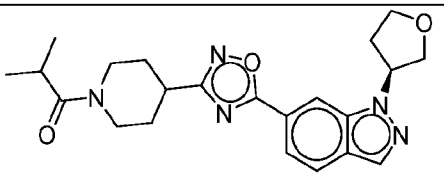
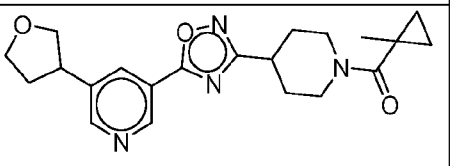
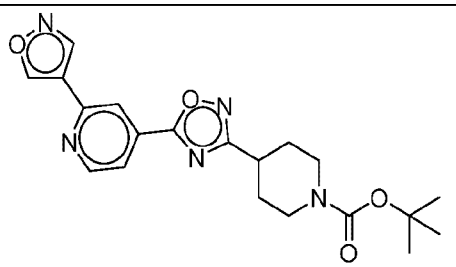
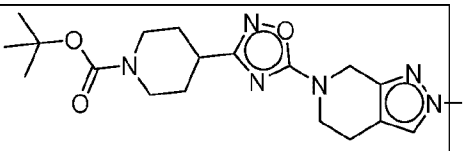
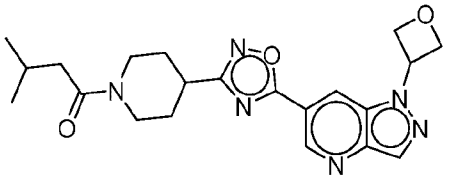
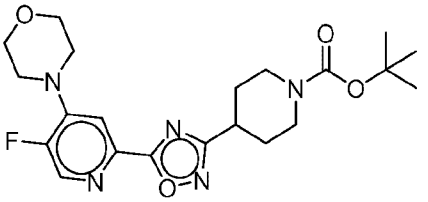
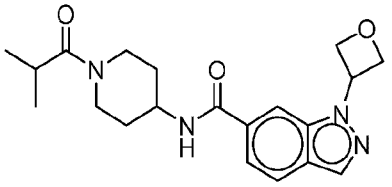
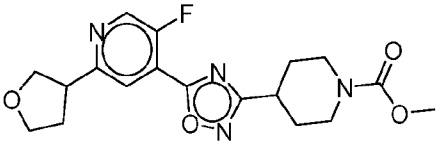
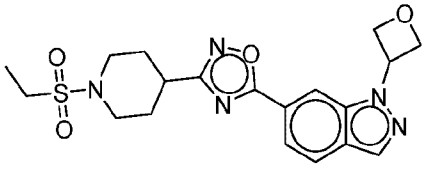
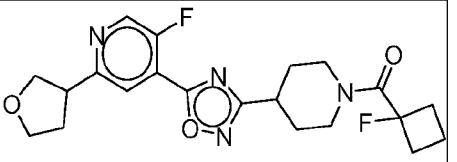
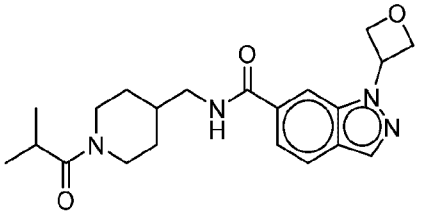
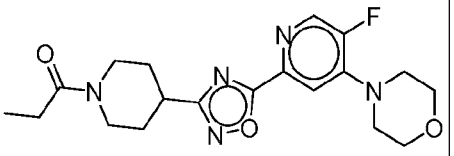
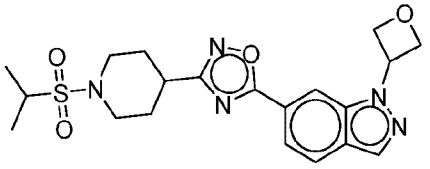
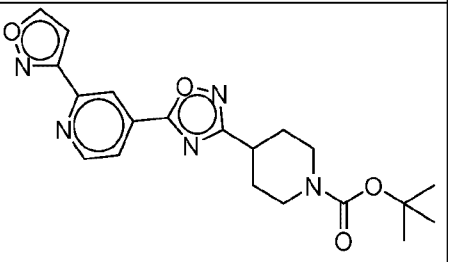
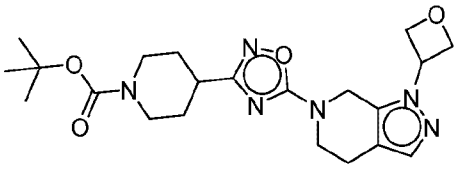
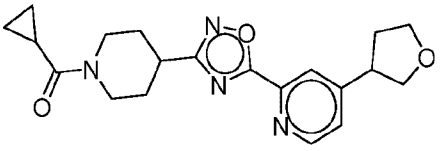
#	Structure	#	Structure
1077		1192	
1078		1193	
1079		1194	
1080		1195	
1081			

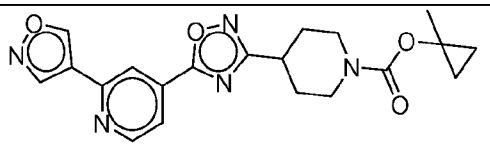
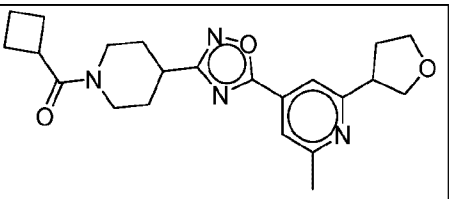
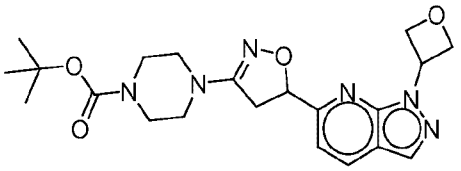
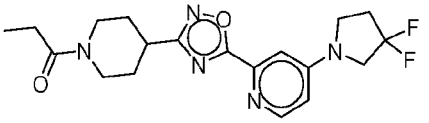
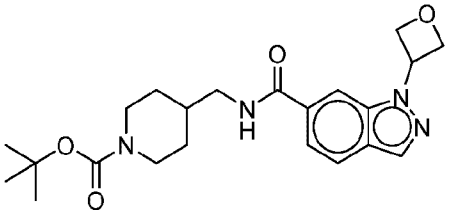
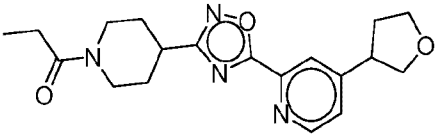
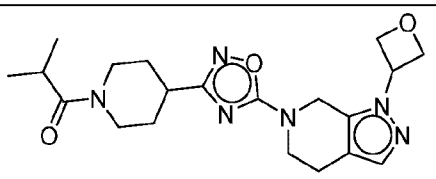
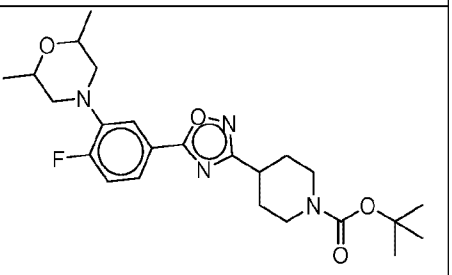
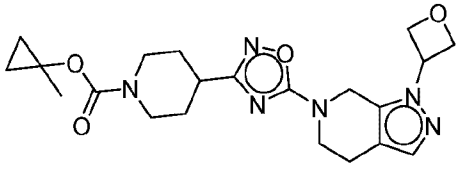
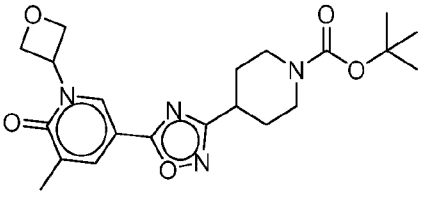
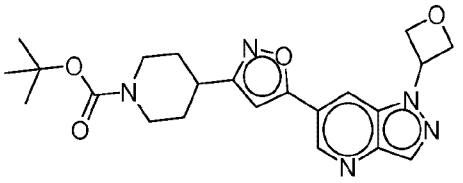
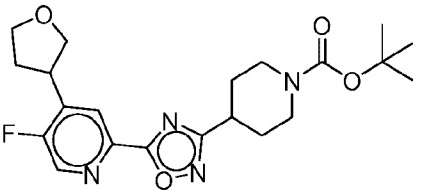
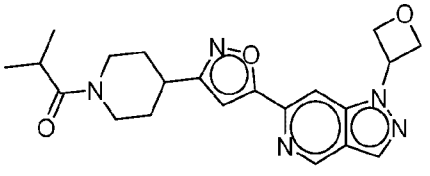
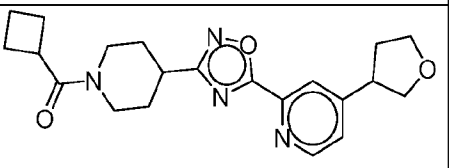
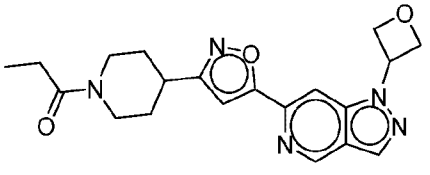
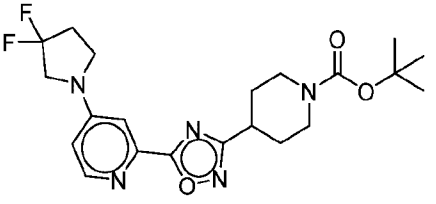
Table 2C. Compounds of the invention

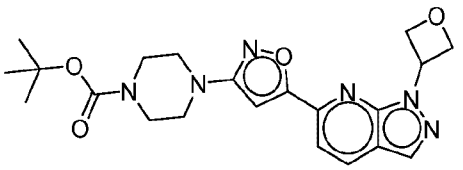
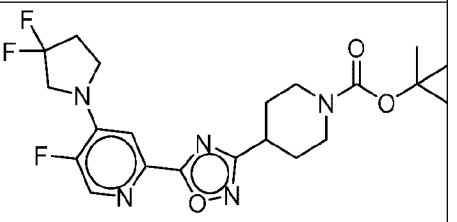
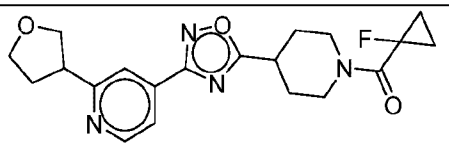
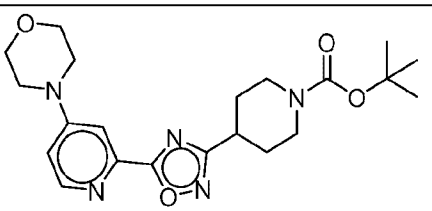
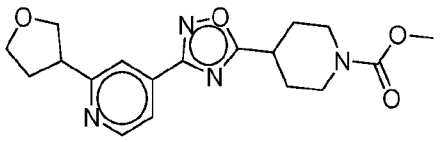
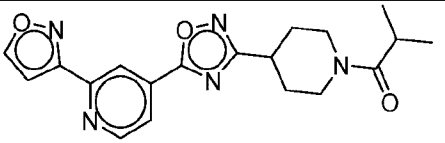
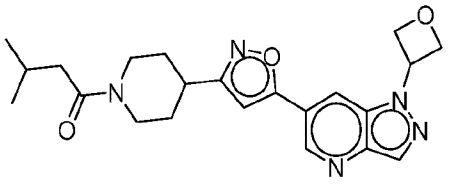
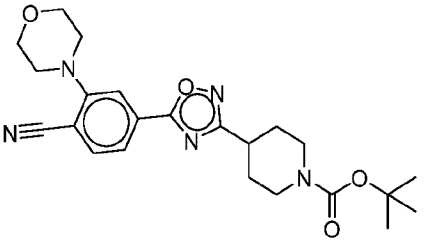
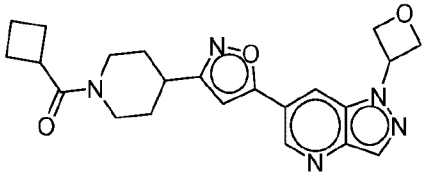
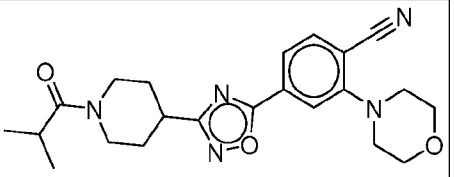
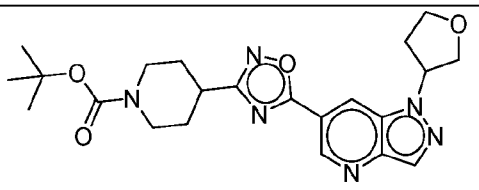
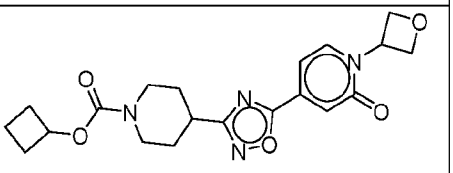
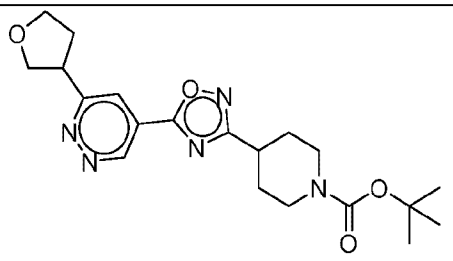
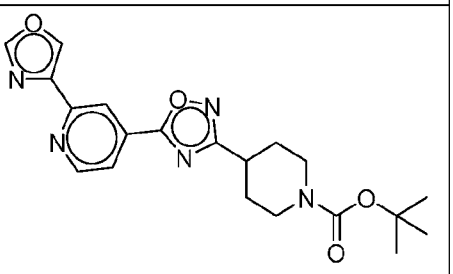
#	Structure	#	Structure
1196		1255	
1197		1256	

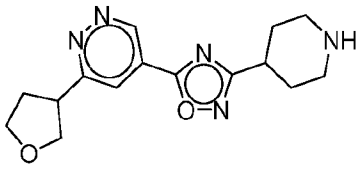
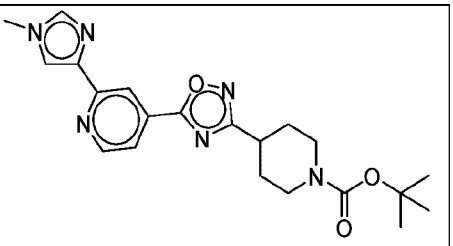
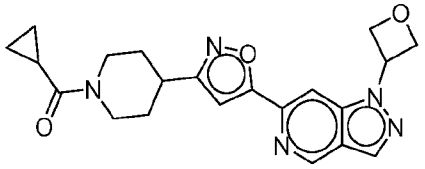
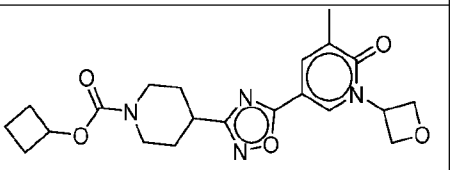
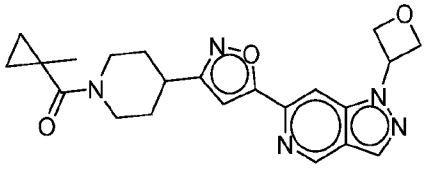
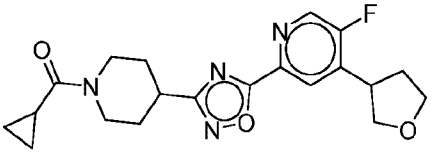
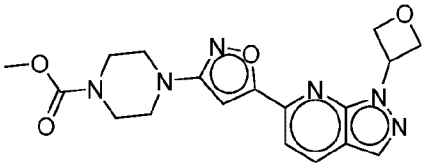
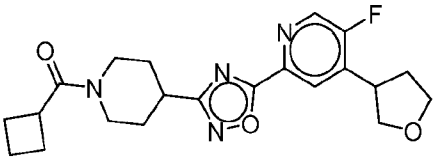
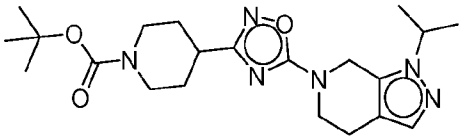
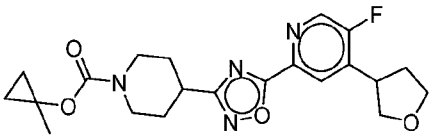
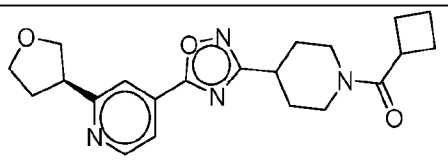
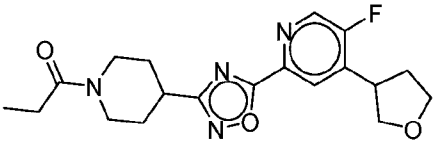
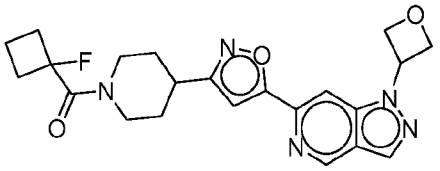
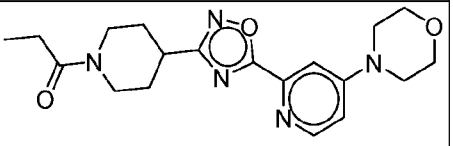
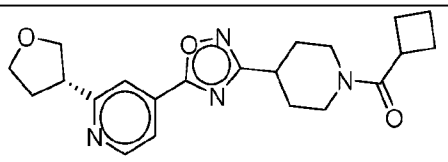
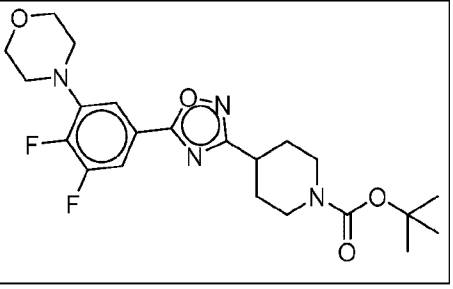
1198		1257	
1199		1258	
1200		1259	
1201		1260	
1202		1261	
1203		1262	
1204		1263	

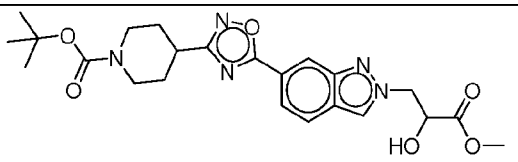
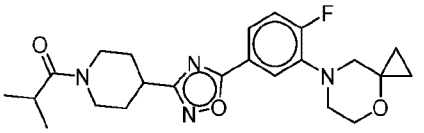
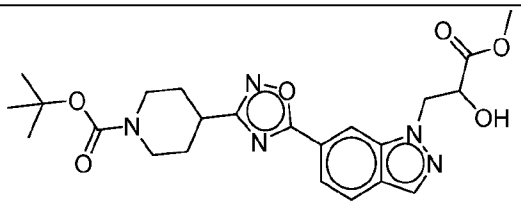
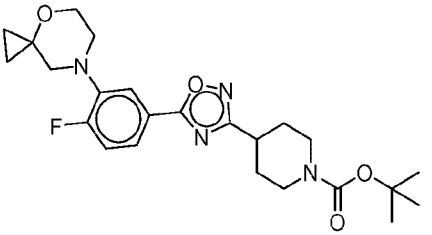
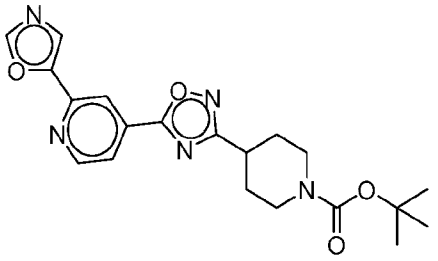
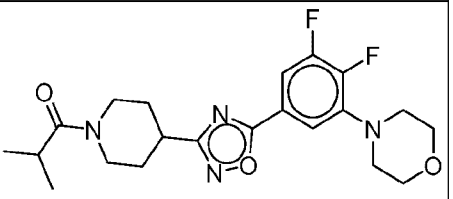
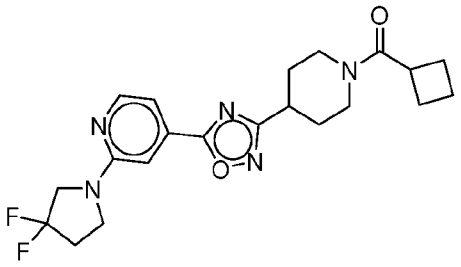
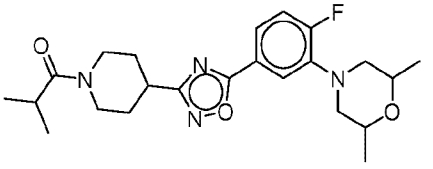
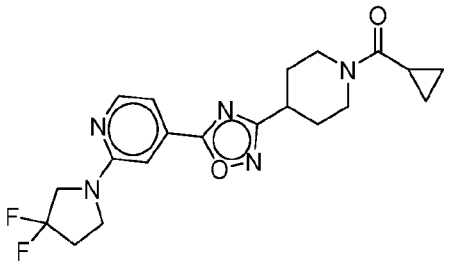
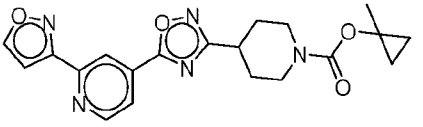
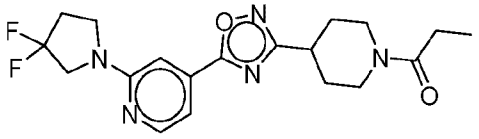
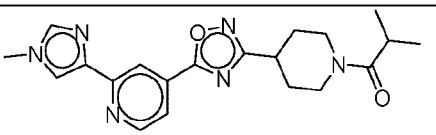
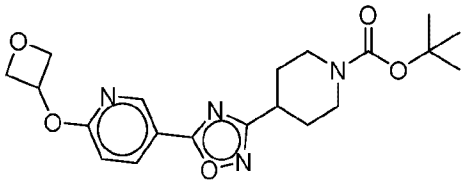
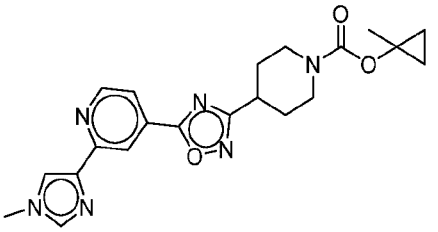
1205		1264	
1206		1265	
1207		1266	
1208		1267	
1209		1268	
1210		1269	
1211		1270	
1212		1271	

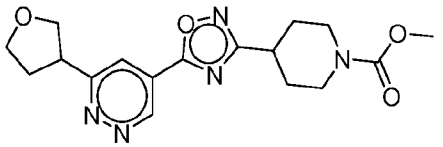
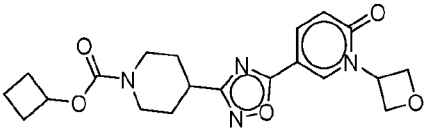
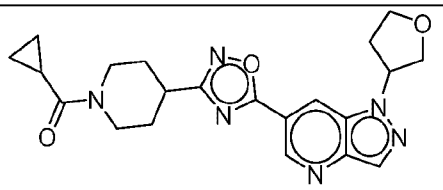
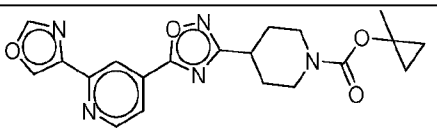
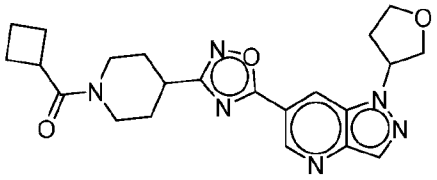
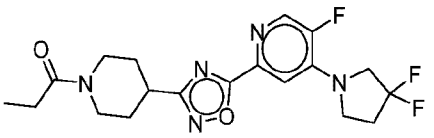
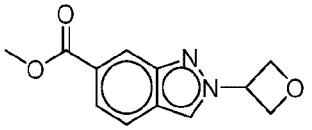
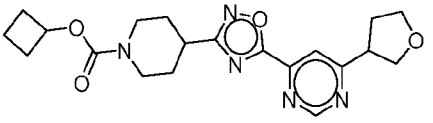
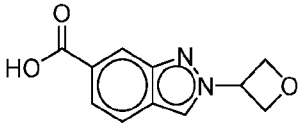
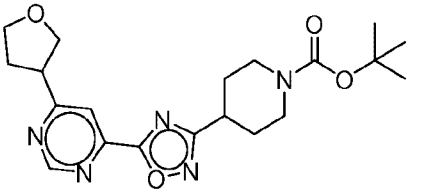
1213		1272	
1214		1273	
1215		1274	
1216		1275	
1217		1276	
1218		1277	
1219		1278	

1220		1279	
1221		1280	
1222		1281	
1223		1282	
1224		1283	
1225		1284	
1226		1285	
1227		1286	

1228		1287	
1229		1288	
1230		1289	
1231		1290	
1232		1291	
1233		1292	
1234		1293	

1235		1294	
1236		1295	
1237		1296	
1238		1297	
1239		1298	
1240		1299	
1241		1300	
1242		1301	

1243		1302	
1244		1303	
1245		1304	
1246		1305	
1247		1306	
1248		1307	
1249		1308	

1250		1309	
1251		1310	
1252		1311	
1253		1312	
1254		1313	

In another aspect, the disclosure provides pharmaceutical composition comprising any of the foregoing compounds, or pharmaceutically acceptable salts thereof and a pharmaceutically acceptable excipient.

In another aspect, the disclosure provides a method of treating a neurological disorder in a subject in need thereof, the method comprising administering an effective amount of any of the foregoing compounds, or pharmaceutically acceptable salts thereof, or any of the foregoing pharmaceutical compositions.

In another aspect, the disclosure provides a method of inhibiting toxicity in a cell (e.g., a mammalian neural cell) related to a protein (e.g., toxicity related to protein misfolding and/or aggregation such as protein aggregation related to misfolding of proteins such as α-synuclein or ApoE4), the method comprising administering, or contacting the cell with, an effective amount of any of the foregoing compounds, or pharmaceutically acceptable salts thereof. In some embodiments, the toxicity is α-synuclein-related toxicity. In some embodiments, the toxicity is ApoE4-related toxicity.

Non-limiting exemplary neurological disorders include, but are not limited to Alexander disease, Alper' s disease, AD, amyotrophic lateral sclerosis, ataxia telangiectasia, Canavan disease, Cockayne syndrome, corticobasal degeneration, Creutzfeldt-Jakob disease, Huntington disease, Kennedy's disease, Krabbe disease, Lewy body dementia, Machado-Joseph disease, multiple sclerosis, PD, Pelizaeus-Merzbacher disease, Pick's disease, primary lateral sclerosis, Ref sum's disease, Sandhoff

disease, Schilder' s disease, Steele-Richardson-Olszewski disease, tabes dorsalis, frontal temporal dementia, vascular dementia, Down's syndrome, and Guillain-Barre Syndrome.

In another aspect, the disclosure provides a method of treating a stearoyl-CoA desaturase (SCD)-associated disorder in a subject in need thereof, the method comprising administering, or contacting the cell with, an effective amount of any of the foregoing compounds, or pharmaceutically acceptable salts thereof.

Non-limiting exemplary SCD-associated disorders include, but are not limited to metabolic disorders (e.g., diabetes (e.g., Type I diabetes and Type II diabetes), hyperglycemia, metabolic syndrome, obesity, lipid disorders, fatty liver, nonalcoholic steatohepatitis (NASH), nonalcoholic fatty liver disease (NAFLD), and hypertension), cancer, cardiovascular diseases, cerebrovascular diseases, kidney diseases, liver diseases, skin disorders (e.g., acne (e.g., acne vulgaris)), central nervous system (CNS) disorders, dementia, multiple sclerosis, schizophrenia, mild cognitive impairment, Alzheimer's Disease, cerebral amyloid angiopathy, and dementia associated with Down Syndrome.

Chemical Terms

It is to be understood that the terminology employed herein is for the purpose of describing particular embodiments and is not intended to be limiting.

The term "acyl," as used herein, represents a hydrogen or an alkyl group, as defined herein, that is attached to a parent molecular group through a carbonyl group, as defined herein, and is exemplified by formyl (i.e., a carboxyaldehyde group), acetyl, trifluoroacetyl, propionyl, and butanoyl. Exemplary unsubstituted acyl groups include from 1 to 6, from 1 to 11, or from 1 to 21 carbons.

The term "alkyl," as used herein, refers to a branched or straight-chain monovalent saturated aliphatic hydrocarbon radical of 1 to 20 carbon atoms (e.g., 1 to 16 carbon atoms, 1 to 10 carbon atoms, or 1 to 6 carbon atoms). An alkylene is a divalent alkyl group.

The term "alkenyl," as used herein, alone or in combination with other groups, refers to a straight-chain or branched hydrocarbon residue having a carbon-carbon double bond and having 2 to 20 carbon atoms (e.g., 2 to 16 carbon atoms, 2 to 10 carbon atoms, 2 to 6, or 2 carbon atoms).

The term "alkynyl," as used herein, alone or in combination with other groups, refers to a straight-chain or branched hydrocarbon residue having a carbon-carbon triple bond and having 2 to 20 carbon atoms (e.g., 2 to 16 carbon atoms, 2 to 10 carbon atoms, 2 to 6, or 2 carbon atoms).

The term "amino," as used herein, represents $-N(R^{N1})_2$, wherein each R^{N1} is, independently, H, OH, NO_2, $N(R^{N2})_2$, SO_2OR^{N2}, SO_2R^{N2}, SOR^{N2}, an *N*-protecting group, alkyl, alkoxy, aryl, arylalkyl, cycloalkyl, acyl (e.g., acetyl, trifluoroacetyl, or others described herein), wherein each of these recited R^{N1} groups can be optionally substituted; or two R^{N1} combine to form an alkylene or heteroalkylene, and wherein each R^{N2} is, independently, H, alkyl, or aryl. The amino groups of the invention can be an unsubstituted amino (i.e., $-NH_2$) or a substituted amino (i.e., $-N(R^{N1})_2$).

The term "aryl," as used herein, refers to an aromatic mono- or polycarbocyclic radical of 6 to 12 carbon atoms having at least one aromatic ring. Examples of such groups include, but are not limited to, phenyl, naphthyl, 1,2,3,4-tetrahydronaphthyl, 1,2-dihydronaphthyl, indanyl, and 1H-indenyl.

The term "arylalkyl," as used herein, represents an alkyl group substituted with an aryl group. Exemplary unsubstituted arylalkyl groups are from 7 to 30 carbons (e.g., from 7 to 16 or from 7 to 20

carbons, such as C_{1-6} alkyl C_{6-10} aryl, C_{1-10} alkyl C_{6-10} aryl, or C_{1-20} alkyl C_{6-10} aryl), such as, benzyl and phenethyl. In some embodiments, the akyl and the aryl each can be further substituted with 1, 2, 3, or 4 substituent groups as defined herein for the respective groups.

The term "azido," as used herein, represents a $-N_3$ group.

The term "cyano," as used herein, represents a –CN group.

The terms "carbocyclyl," as used herein, refer to a non-aromatic C_{3-12} monocyclic, bicyclic, or tricyclic structure in which the rings are formed by carbon atoms. Carbocyclyl structures include cycloalkyl groups and unsaturated carbocyclyl radicals.

The term "cycloalkyl," as used herein, refers to a saturated, non-aromatic, monovalent mono- or polycarbocyclic radical of three to ten, preferably three to six carbon atoms. This term is further exemplified by radicals such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, norbornyl, and adamantyl.

The term "halogen," as used herein, means a fluorine (fluoro), chlorine (chloro), bromine (bromo), or iodine (iodo) radical.

The term "heteroalkyl," as used herein, refers to an alkyl group, as defined herein, in which one or more of the constituent carbon atoms have been replaced by nitrogen, oxygen, or sulfur. In some embodiments, the heteroalkyl group can be further substituted with 1, 2, 3, or 4 substituent groups as described herein for alkyl groups. Examples of heteroalkyl groups are an "alkoxy" which, as used herein, refers alkyl-O- (e.g., methoxy and ethoxy). A heteroalkylene is a divalent heteroalkyl group.

The term "heteroalkenyl," as used herein, refers to an alkenyl group, as defined herein, in which one or more of the constituent carbon atoms have been replaced by nitrogen, oxygen, or sulfur. In some embodiments, the heteroalkenyl group can be further substituted with 1, 2, 3, or 4 substituent groups as described herein for alkenyl groups. Examples of heteroalkenyl groups are an "alkenoxy" which, as used herein, refers alkenyl-O-. A heteroalkenylene is a divalent heteroalkenyl group.

The term "heteroalkynyl," as used herein, refers to an alkynyl group, as defined herein, in which one or more of the constituent carbon atoms have been replaced by nitrogen, oxygen, or sulfur. In some embodiments, the heteroalkynyl group can be further substituted with 1, 2, 3, or 4 substituent groups as described herein for alkynyl groups. Examples of heteroalkynyl groups are an "alkynoxy" which, as used herein, refers alkynyl-O-. A heteroalkynylene is a divalent heteroalkynyl group.

The term "heteroaryl," as used herein, refers to an aromatic mono- or polycyclic radical of 5 to 12 atoms having at least one aromatic ring containing one, two, or three ring heteroatoms selected from N, O, and S, with the remaining ring atoms being C. One or two ring carbon atoms of the heteroaryl group may be replaced with a carbonyl group. Examples of heteroaryl groups are pyridyl, pyrazoyl, benzooxazolyl, benzoimidazolyl, benzothiazolyl, imidazolyl, oxaxolyl, and thiazolyl.

The term "heteroarylalkyl," as used herein, represents an alkyl group substituted with a heteroaryl group. Exemplary unsubstituted heteroarylalkyl groups are from 7 to 30 carbons (e.g., from 7 to 16 or from 7 to 20 carbons, such as C_{1-6} alkyl C_{2-9} heteroaryl, C_{1-10} alkyl C_{2-9} heteroaryl, or C_{1-20} alkyl C_{2-9} heteroaryl). In some embodiments, the akyl and the heteroaryl each can be further substituted with 1, 2, 3, or 4 substituent groups as defined herein for the respective groups.

The term "heterocyclyl," as used herein, denotes a mono- or polycyclic radical having 3 to 12 atoms having at least one ring containing one, two, three, or four ring heteroatoms selected from N, O or

S, wherein no ring is aromatic. Examples of heterocyclyl groups include, but are not limited to, morpholinyl, thiomorpholinyl, furyl, piperazinyl, piperidinyl, pyranyl, pyrrolidinyl, tetrahydropyranyl, tetrahydrofuranyl, and 1,3-dioxanyl.

The term "heterocyclylalkyl," as used herein, represents an alkyl group substituted with a heterocyclyl group. Exemplary unsubstituted heterocyclylalkyl groups are from 7 to 30 carbons (e.g., from 7 to 16 or from 7 to 20 carbons, such as C_{1-6} alkyl C_{2-9} heterocyclyl, C_{1-10} alkyl C_{2-9} heterocyclyl, or C_{1-20} alkyl C_{2-9} heterocyclyl). In some embodiments, the akyl and the heterocyclyl each can be further substituted with 1, 2, 3, or 4 substituent groups as defined herein for the respective groups.

The term "hydroxyl," as used herein, represents an –OH group.

The term "*N*-protecting group," as used herein, represents those groups intended to protect an amino group against undesirable reactions during synthetic procedures. Commonly used *N*-protecting groups are disclosed in Greene, "Protective Groups in Organic Synthesis," 3rd Edition (John Wiley & Sons, New York, 1999). *N*-protecting groups include acyl, aryloyl, or carbamyl groups such as formyl, acetyl, propionyl, pivaloyl, t-butylacetyl, 2-chloroacetyl, 2-bromoacetyl, trifluoroacetyl, trichloroacetyl, phthalyl, o-nitrophenoxyacetyl, α-chlorobutyryl, benzoyl, 4-chlorobenzoyl, 4-bromobenzoyl, 4-nitrobenzoyl, and chiral auxiliaries such as protected or unprotected D, L or D, L-amino acids such as alanine, leucine, and phenylalanine; sulfonyl-containing groups such as benzenesulfonyl, and p-toluenesulfonyl; carbamate forming groups such as benzyloxycarbonyl, p-chlorobenzyloxycarbonyl, p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 3,5-dimethoxybenzyloxycarbonyl, 2,4-dimethoxybenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitro-4,5-dimethoxybenzyloxycarbonyl, 3,4,5-trimethoxybenzyloxycarbonyl, 1-(p-biphenylyl)-1-methylethoxycarbonyl, α,α-dimethyl-3,5-dimethoxybenzyloxycarbonyl, benzhydryloxy carbonyl, t-butyloxycarbonyl, diisopropylmethoxycarbonyl, isopropyloxycarbonyl, ethoxycarbonyl, methoxycarbonyl, allyloxycarbonyl, 2,2,2,-trichloroethoxycarbonyl, phenoxycarbonyl, 4-nitrophenoxy carbonyl, fluorenyl-9-methoxycarbonyl, cyclopentyloxycarbonyl, adamantyloxycarbonyl, cyclohexyloxycarbonyl, and phenylthiocarbonyl, arylalkyl groups such as benzyl, triphenylmethyl, and benzyloxymethyl, and silyl groups, such as trimethylsilyl. Preferred *N*-protecting groups are alloc, formyl, acetyl, benzoyl, pivaloyl, t-butylacetyl, alanyl, phenylsulfonyl, benzyl, t-butyloxycarbonyl (Boc), and benzyloxycarbonyl (Cbz).

The term "nitro," as used herein, represents an $–NO_2$ group.

The term "thiol," as used herein, represents an –SH group.

The alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl (e.g., cycloalkyl), aryl, heteroaryl, and heterocyclyl groups may be substituted or unsubstituted. When substituted, there will generally be 1 to 4 substituents present, unless otherwise specified. Substituents include, for example: aryl (e.g., substituted and unsubstituted phenyl), carbocyclyl (e.g., substituted and unsubstituted cycloalkyl), halogen (e.g., fluoro), hydroxyl, heteroalkyl (e.g., substituted and unsubstituted methoxy, ethoxy, or thioalkoxy), heteroaryl, heterocyclyl, amino (e.g., NH_2 or mono- or dialkyl amino), azido, cyano, nitro, or thiol. Aryl, carbocyclyl (e.g., cycloalkyl), heteroaryl, and heterocyclyl groups may also be substituted with alkyl (unsubstituted and substituted such as arylalkyl (e.g., substituted and unsubstituted benzyl)).

Compounds of the invention can have one or more asymmetric carbon atoms and can exist in the form of optically pure enantiomers, mixtures of enantiomers such as, for example, racemates, optically pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates or mixtures of diastereoisomeric racemates. The optically active forms can be obtained for example by resolution of the racemates, by asymmetric synthesis or asymmetric chromatography (chromatography with a chiral adsorbents or eluant). That is, certain of the disclosed compounds may exist in various stereoisomeric forms. Stereoisomers are compounds that differ only in their spatial arrangement. Enantiomers are pairs of stereoisomers whose mirror images are not superimposable, most commonly because they contain an asymmetrically substituted carbon atom that acts as a chiral center. "Enantiomer" means one of a pair of molecules that are mirror images of each other and are not superimposable. Diastereomers are stereoisomers that are not related as mirror images, most commonly because they contain two or more asymmetrically substituted carbon atoms and represent the configuration of substituents around one or more chiral carbon atoms. Enantiomers of a compound can be prepared, for example, by separating an enantiomer from a racemate using one or more well-known techniques and methods, such as, for example, chiral chromatography and separation methods based thereon. The appropriate technique and/or method for separating an enantiomer of a compound described herein from a racemic mixture can be readily determined by those of skill in the art. "Racemate" or "racemic mixture" means a compound containing two enantiomers, wherein such mixtures exhibit no optical activity; i.e., they do not rotate the plane of polarized light. “Geometric isomer" means isomers that differ in the orientation of substituent atoms in relationship to a carbon-carbon double bond, to a cycloalkyl ring, or to a bridged bicyclic system. Atoms (other than H) on each side of a carbon- carbon double bond may be in an E (substituents are on opposite sides of the carbon- carbon double bond) or Z (substituents are oriented on the same side) configuration. "R," "S," "S*," "R*," "E," "Z," "cis," and "trans," indicate configurations relative to the core molecule. Certain of the disclosed compounds may exist in atropisomeric forms. Atropisomers are stereoisomers resulting from hindered rotation about single bonds where the steric strain barrier to rotation is high enough to allow for the isolation of the conformers. The compounds of the invention may be prepared as individual isomers by either isomer-specific synthesis or resolved from an isomeric mixture. Conventional resolution techniques include forming the salt of a free base of each isomer of an isomeric pair using an optically active acid (followed by fractional crystallization and regeneration of the free base), forming the salt of the acid form of each isomer of an isomeric pair using an optically active amine (followed by fractional crystallization and regeneration of the free acid), forming an ester or amide of each of the isomers of an isomeric pair using an optically pure acid, amine or alcohol (followed by chromatographic separation and removal of the chiral auxiliary), or resolving an isomeric mixture of either a starting material or a final product using various well known chromatographic methods. When the stereochemistry of a disclosed compound is named or depicted by structure, the named or depicted stereoisomer is at least 60%, 70%, 80%, 90%, 99% or 99.9%) by weight relative to the other stereoisomers. When a single enantiomer is named or depicted by structure, the depicted or named enantiomer is at least 60%, 70%, 80%, 90%, 99% or 99.9% by weight optically pure. When a single diastereomer is named or depicted by structure, the depicted or named diastereomer is at least 60%, 70%, 80%, 90%, 99% or 99.9% by weight pure. Percent optical purity is the ratio of the weight of the enantiomer or over the weight of the enantiomer plus the weight of its optical isomer. Diastereomeric

purity by weight is the ratio of the weight of one diastereomer or over the weight of all the diastereomers. When the stereochemistry of a disclosed compound is named or depicted by structure, the named or depicted stereoisomer is at least 60%, 70%, 80%, 90%, 99% or 99.9% by mole fraction pure relative to the other stereoisomers. When a single enantiomer is named or depicted by structure, the depicted or named enantiomer is at least 60%, 70%, 80%, 90%, 99% or 99.9% by mole fraction pure. When a single diastereomer is named or depicted by structure, the depicted or named diastereomer is at least 60%, 70%, 80%, 90%, 99% or 99.9% by mole fraction pure. Percent purity by mole fraction is the ratio of the moles of the enantiomer or over the moles of the enantiomer plus the moles of its optical isomer. Similarly, percent purity by moles fraction is the ratio of the moles of the diastereomer or over the moles of the diastereomer plus the moles of its isomer. When a disclosed compound is named or depicted by structure without indicating the stereochemistry, and the compound has at least one chiral center, it is to be understood that the name or structure encompasses either enantiomer of the compound free from the corresponding optical isomer, a racemic mixture of the compound or mixtures enriched in one enantiomer relative to its corresponding optical isomer. When a disclosed compound is named or depicted by structure without indicating the stereochemistry and has two or more chiral centers, it is to be understood that the name or structure encompasses a diastereomer free of other diastereomers, a number of diastereomers free from other diastereomeric pairs, mixtures of diastereomers, mixtures of diastereomeric pairs, mixtures of diastereomers in which one diastereomer is enriched relative to the other diastereomer(s) or mixtures of diastereomers in which one or more diastereomer is enriched relative to the other diastereomers. The invention embraces all of these forms.

Definitions

In the practice of the methods of the present invention, an "effective amount" of any one of the compounds of the invention or a combination of any of the compounds of the invention or a pharmaceutically acceptable salt thereof, is administered via any of the usual and acceptable methods known in the art, either singly or in combination.

The term "pharmaceutical composition," as used herein, represents a composition containing a compound described herein formulated with a pharmaceutically acceptable excipient, and manufactured or sold with the approval of a governmental regulatory agency as part of a therapeutic regimen for the treatment of disease in a mammal. Pharmaceutical compositions can be formulated, for example, for oral administration in unit dosage form (e.g., a tablet, capsule, caplet, gelcap, or syrup); for topical administration (e.g., as a cream, gel, lotion, or ointment); for intravenous administration (e.g., as a sterile solution free of particulate emboli and in a solvent system suitable for intravenous use); or in any other pharmaceutically acceptable formulation.

A "pharmaceutically acceptable excipient," as used herein, refers any ingredient other than the compounds described herein (for example, a vehicle capable of suspending or dissolving the active compound) and having the properties of being substantially nontoxic and non-inflammatory in a patient. Excipients may include, for example: antiadherents, antioxidants, binders, coatings, compression aids, disintegrants, dyes (colors), emollients, emulsifiers, fillers (diluents), film formers or coatings, flavors, fragrances, glidants (flow enhancers), lubricants, preservatives, printing inks, sorbents, suspensing or dispersing agents, sweeteners, and waters of hydration. Exemplary excipients include, but are not limited

to: butylated hydroxytoluene (BHT), calcium carbonate, calcium phosphate (dibasic), calcium stearate, croscarmellose, crosslinked polyvinyl pyrrolidone, citric acid, crospovidone, cysteine, ethylcellulose, gelatin, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, magnesium stearate, maltitol, mannitol, methionine, methylcellulose, methyl paraben, microcrystalline cellulose, polyethylene glycol, polyvinyl pyrrolidone, povidone, pregelatinized starch, propyl paraben, retinyl palmitate, shellac, silicon dioxide, sodium carboxymethyl cellulose, sodium citrate, sodium starch glycolate, sorbitol, starch (corn), stearic acid, sucrose, talc, titanium dioxide, vitamin A, vitamin E, vitamin C, and xylitol.

As used herein, the term "pharmaceutically acceptable salt" means any pharmaceutically acceptable salt of the compound of formula (I). For example pharmaceutically acceptable salts of any of the compounds described herein include those that are within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and animals without undue toxicity, irritation, allergic response and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, pharmaceutically acceptable salts are described in: Berge et al., *J. Pharmaceutical Sciences* 66:1-19, 1977 and in *Pharmaceutical Salts: Properties, Selection, and Use*, (Eds. P.H. Stahl and C.G. Wermuth), Wiley-VCH, 2008. The salts can be prepared in situ during the final isolation and purification of the compounds described herein or separately by reacting a free base group with a suitable organic acid.

The compounds of the invention may have ionizable groups so as to be capable of preparation as pharmaceutically acceptable salts. These salts may be acid addition salts involving inorganic or organic acids or the salts may, in the case of acidic forms of the compounds of the invention be prepared from inorganic or organic bases. Frequently, the compounds are prepared or used as pharmaceutically acceptable salts prepared as addition products of pharmaceutically acceptable acids or bases. Suitable pharmaceutically acceptable acids and bases and methods for preparation of the appropriate salts are well-known in the art. Salts may be prepared from pharmaceutically acceptable non-toxic acids and bases including inorganic and organic acids and bases.

Representative acid addition salts include acetate, adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptonate, glycerophosphate, hemisulfate, heptonate, hexanoate, hydrobromide, hydrochloride, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, toluenesulfonate, undecanoate, and valerate salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, and magnesium, as well as nontoxic ammonium, quaternary ammonium, and amine cations, including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, and ethylamine.

As used herein, the term "stearoyl-CoA desaturase (SCD)-associated disorder" refers to an undesired physiological condition, disorder, or disease that is associated with and/or mediated at least in part by an SCD protein. In some instances, SCD-associated disorders are associated with excess SCD levels and/or activity. SCDs introduce a double bond in the C9-C10 position of saturated fatty acids such

as palmitoyl-CoA and stearoyl-CoA which are converted to palmitoleoyl-CoA and oleoyl-CoA, respectively. One SCD gene, SCD1, has been characterized in humans for which there are two isoforms, SCD1 and SCD5. An SCD-associated disorder may be associated with and/or mediated at least in part by SCD1 and/or SCD5. Exemplary SCD-associated disorders include SCD-associated disorders include, but are not limited to metabolic disorders (e.g., diabetes (e.g., Type I diabetes and Type II diabetes), hyperglycemia, metabolic syndrome, obesity, lipid disorders, fatty liver, nonalcoholic steatohepatitis (NASH), nonalcoholic fatty liver disease (NAFLD), and hypertension), cancer, cardiovascular diseases, cerebrovascular diseases, kidney diseases, liver diseases, skin disorders (e.g., acne (e.g., acne vulgaris)), central nervous system (CNS) disorders, dementia, multiple sclerosis, schizophrenia, mild cognitive impairment, Alzheimer's Disease, cerebral amyloid angiopathy, and dementia associated with Down Syndrome. Additional SCD-associated disorders are described herein or known in the art.

As used herein, the term "subject" refers to any organism to which a composition in accordance with the invention may be administered, e.g., for experimental, diagnostic, prophylactic, and/or therapeutic purposes. Typical subjects include any animal (e.g., mammals such as mice, rats, rabbits, non-human primates, and humans). A subject may seek or be in need of treatment, require treatment, be receiving treatment, be receiving treatment in the future, or be a human or animal who is under care by a trained professional for a particular disease or condition.

As used herein, the terms "treat," "treated," or "treating" mean both therapeutic treatment and prophylactic or preventative measures wherein the object is to prevent or slow down (lessen) an undesired physiological condition, disorder, or disease, or obtain beneficial or desired clinical results. Beneficial or desired clinical results include, but are not limited to, alleviation of symptoms; diminishment of the extent of a condition, disorder, or disease; stabilized (i.e., not worsening) state of condition, disorder, or disease; delay in onset or slowing of condition, disorder, or disease progression; amelioration of the condition, disorder, or disease state or remission (whether partial or total), whether detectable or undetectable; an amelioration of at least one measurable physical parameter, not necessarily discernible by the patient; or enhancement or improvement of condition, disorder, or disease. Treatment includes eliciting a clinically significant response without excessive levels of side effects. Treatment also includes prolonging survival as compared to expected survival if not receiving treatment.

Brief Description of the Drawings

FIGS. 1A and **1B** are graphs showing that growth inhibition by 1,2,4-oxadiazoles occurs through same mechanism as the rescue of toxicity in the apolipoprotein E4 (ApoE4) Alzheimer's disease yeast model. (**Fig. 1A**) Compound 7, a representative 1,2,4-oxadiazole, was profiled in ApoE4 (top) and control (bottom) non-inducing conditions at 12-point dose (x-axis). The Y-axis shows raw OD_{600}. Compound 7 exhibited a bell-shaped dose-response curve (DRC) in the ApoE4 model. Rescue decreased at concentrations just above the maximal efficacy (Emax). In the control condition (bottom panel), growth decreased at this same concentration. (**Fig. 1B**) The relationship between Emax (rescue in ApoE4) and growth inhibition (in control condition) correlated across 34 tested 1,2,4-oxadiazoles. The maximal rescue dose (EC100) is shown on the y-axis for ApoE4 and minimal inhibitory dose (IC100) in the control

condition is shown on the x-axis. This correlation indicates that growth inhibition is caused by the same on-target activity that rescues ApoE4 toxicity.

FIGS. 2A and **2B** are graphs showing that exogenous oleic acid reverses growth inhibition and model rescue by Ole1/SCD-targeting 1,2,4-oxadiazoles. Growth was measured by reading OD_{600} in a microplate reader and normalized to solvent control DMSO samples. (**Fig. 2A**) Growth inhibition (24 h) of strain GM *yap1 flr1* by Ole1/SCD-targeting 1,2,4-oxadiazoles is reversed by exogenous 0.5 mM oleic/palmitoleic acid, which did not affect growth inhibition by other compounds (black dots indicate other scaffolds tested). Maximal growth inhibition across a dose range from 33 nM to 33 µM is plotted. (**Fig. 2B**) Rescue (40 h) of the yeast alpha-synuclein ("aSyn") model by 1,2,4-oxadiazoles was reversed by exogenous 0.5 mM oleic/palmitoleic acid, which did not affect rescue by other scaffolds. Maximal model rescue across a dose range from 33 nM to 33 µM is plotted.

FIGS. 3A and **3B** are graphs showing that point mutations in yeast *OLE1* confer resistance to growth inhibition and alpha-synuclein model rescue by 1,2,4-oxadiazoles. Growth was measured by reading OD_{600} in a microplate reader. (**Fig. 3A**) Yeast cells deleted for the chromosomal copy of *OLE1* and expressing *OLE1* (wild-type), *ole1P123T*, or *ole1E188Q* mutants from a pRS316-based plasmid were grown in complete synthetic medium (CSM)-glucose media at the indicated doses of 1,2,4-oxadiazole Compound 95 for 24 h. Growth was normalized to samples treated with the solvent control dimethyl sulfoxide (DMSO), set as "1". (**Fig. 3B**) Yeast cells deleted for the chromosomal copy of *OLE1* and expressing *OLE1* (Wild-type), *ole1P123T*, or *ole1E188Q* mutants from a pRS316-based plasmid were grown in CSM-galactose media (inducing expression of alpha-Synuclein) at the indicated doses of the 1,2,4-oxadiazole Compound 95 for 40 h. Growth was normalized to samples treated with the solvent control DMSO, where rescue is set as "1".

FIG. 4 is a graph showing that a *ole1*Δ deletion mutant is resistant to the growth-inhibitory effects of 1,2,4-oxadiazoles, but not other compounds. Twenty-four hour growth (presented as raw OD_{600}) of the *ole1*Δ deletion strain in yeast extract-peptone-dextrose (YPD) media is shown, with drugs added at the indicated concentrations.

FIG. 5 is a graph showing that reducing *OLE1* expression by deleting *MGA2* rescues the growth of the ApoE4 yeast model. Yeast cells expressing ApoE4 were deleted for the *MGA2* gene and their growth was assessed over time (compared to their isogenic, MGA2 wild-type counterpart). Growth was assessed by OD_{600}. Where indicated, 0.08 or 0.32 mM of oleic and palmitoleic acids (each) as added to the growth media in 0.01% tween (final).

FIG. 6 is a series of graphs showing that commercial Scd inhibitors target human SCD1/SCD5 in yeast. Yeast surviving solely on yeast *OLE1*, or human SCD1 or SCD5, were treated with four commercial Scd inhibitors at indicated concentrations. Data are expressed as a percent of the DMSO-treated condition. All four compounds potently reduced growth of both SCD1-expressing yeast and SCD5-expressing yeast, but not the strain expressing Ole1. This growth inhibition was reversed by oleic/palmitoleic acid competition, similar to the results shown in Figs. 2A and 2B.

FIG. 7 is a series of graphs showing that 1,2,4-oxadiazoles target human SCD1 and SCD5. Three "SCD" strains expressing yeast *OLE1* or human SCD1 or SCD5 were treated with five representative 1,2,4-oxadiazoles and a cycloheximide toxicity control at concentrations indicated on the log_{10} x-axis. The y-axis indicates the percent of the DMSO-treated condition. All of the 1,2,4-oxadiazole

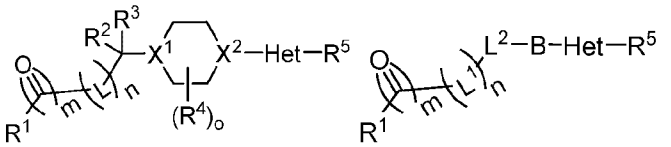
compounds potently inhibited Ole1-expressing yeast and showed variable growth inhibition of the SCD1 or SCD5 yeast strains. These data confirm that 1,2,4-oxadiazoles target the human protein and link Scd inhibition to rescue of neurodegenerative disease models. Approximately one half of all (250) 1,2,4-oxadiazoles tested inhibited SCD1 or SCD5 in a manner that was reversed by oleic/palmitoleic acid treatment. Cyclohexamide, a translation inhibitor (top left panel), inhibited growth of all three strains with the same potency, indicating differences in growth inhibition was due to targeting the human protein.

FIGS. 8A-8D are graphs showing that treatment of yeast cells with the 1,2,4-oxadiazole Compound 95 inhibits lipid desaturation. Exponentially-growing wild-type yeast cells were treated with the indicated doses of the 1,2,4-oxadiazole Compound 95 for the indicated times before cellular lysis, lipid extraction, and analysis by global LC-MS/MS profiling. The relative abundance (fraction of total cellular lipid signal) after 1.5 h and 8 h of the most abundant saturated lipid, phosphatidylcholine 26:0, is depicted in Figs. 8A and 8B, respectively. The relative abundance after 1.5 h and 8 h drug treatment of the most abundant lipid with 2 or more degrees of unsaturation, phosphatidylcholine 16:1; 18:1, is depicted in Figs. 8C and 8D, respectively. The data indicate a >300-fold increase in the abundance of the saturated lipid phosphatidylcholine 26:0 after 8 h treatment with Compound 95, and a >12-fold decrease in the abundance of the unsaturated lipid phosphatidylcholine 16:1, 18:1, indicating that Compound 95 blocks cellular fatty acid desaturase activity (Ole1 is the only fatty acid desaturase in yeast).

FIG. 9 shows *OLE1* mutations conferring resistance to growth inhibition to 1,2,4-oxadiazoles identified by genome sequencing of resistant mutants. Cells were plated on media containing 10 μM of the 1,2,4-oxadiazole Compound 155 and resistant colonies that emerged were isolated, and genomic DNA was prepared from mutants and the parental, drug-sensitive control strain. Genomic DNA sequence was aligned to the *Saccharomyces cerevisiae* reference and unique mutations in the 1,2,4-oxadiazole-resistant mutants were identified. The position of the mutations, the amino acid changes they encode, and the fold resistance (increase in minimal inhibitory concentration) of Compound 155 are shown.

Detailed Description of the Invention

The invention features compounds useful for the treatment of neurological disorders, e.g., by inhibiting α-synuclein toxicity in a cell such as a neural cell. Exemplary compounds described herein include compounds having a structure according to formula I or formula Ia:



Formula I **Formula Ia**

or pharmaceutically acceptable salts thereof.

In some embodiments, the compound has the structure of any one of compounds 1-746 in Table 1. In some embodiments, the compound has the structure of any one of compounds 747-966 in Table 2A. In some emobdiments, the compound has the structure of any one of compounds 967-1195 in Table 2B. In some emobdiments, the compound has the structure of any one of compounds 1196-1313 in Table 2C.

Other embodiments, as well as exemplary methods for the synthesis or production of these compounds, are described herein.

Pharmaceutical Uses

The compounds described herein are useful in the methods of the invention and, while not bound by theory, are believed to exert their desirable effects through their ability to inhibit toxicity caused by protein aggregation, e.g., α-synuclein aggregation, in a cell.

Another aspect of the present invention relates to methods of treating and/or preventing a neurological disorder such as neurodegenerative diseases in a subject in need thereof. The pathology of neurodegenerative disease, may be characterized by the presence of inclusion bodies in brain tissue of affected patients.

In certain embodiments, neurological disorders that may be treated and/or prevented by the inventive methods include, but are not limited to, Alexander disease, Alper' s disease, AD, amyotrophic lateral sclerosis, ataxia telangiectasia, Canavan disease, Cockayne syndrome, corticobasal degeneration, Creutzfeldt-Jakob disease, Huntington disease, Kennedy's disease, Krabbe disease, Lewy body dementia, Machado-Joseph disease, multiple sclerosis, PD, Pelizaeus-Merzbacher disease, Pick's disease, primary lateral sclerosis, Ref sum's disease, Sandhoff disease, Schilder' s disease, Steele-Richardson-Olszewski disease, tabes dorsalis, and Guillain-Barre Syndrome.

The compounds described herein are useful as inhibitors of stearoyl-CoA desaturase (SCD), including SCD1 and/or SCD5. SCD inhibitors are known in the art to be useful in methods of treating and/or preventing SCD-associated disorders. SCD-associated disorders are described, for example, in U.S. Patent No. 8,148,378, and in International Patent Application Publication Nos. WO 2011/047481, WO 2010/112520, WO 2010/045374, WO 2010/028761; WO 2009150196, and WO 2009/106991. Accordingly, another aspect of the present invention relates to methods of treating and/or preventing an SCD-associated disorder in a subject in need thereof.

SCD-associated disorders include metabolic disorders (e.g., insulin resistance, diabetes mellitus (e.g., Type I diabetes, Type II diabetes, non-insulin-dependent diabetes mellitus, gestational diabetes, and diabetic complications (e.g., diabetic peripheral neuropathy, diabetic nephropathy diseases, diabetic retinopathy, diabetic macroangiopathy, vascular complications of diabetes, and diabetic arteriosclerosis)), hyperglycemia, metabolic syndrome, hyperinsulinanemia, glucose intolerance, impaired glucose tolerance, body weight disorders (e.g., obesity (e.g., abdominal obesity), overweight, cachexia, body mass index, and anorexia), lipid disorders (e.g., abnormal lipid levels (e.g., elevated lipid levels, for example, in plasma), dyslipidemia (e.g., diabetic dyslipidemia), mixed dyslipidemia, hyperlipidemia, hypertriglyceridemia, hypoalphalipoproteinemia, hyperbetalipoproteinemia, atherosclerosis, hypercholesterolemia (e.g., familial hypercholesterolemia), low HDL, high LDL, diseases related to accumulation of lipids in liver, familial histiocytic reticulosis, lipoprotein lipase deficiency, polyunsaturated fatty acid (PUFA) disorder, fatty acid desaturation index (e.g. the ratio of 18:1/18:0 fatty acids, or other fatty acids), and abnormal lipid metabolism disorders), disorders of abnormal plasma lipoprotein, disorders of pancreatic beta cell regeneration, fatty liver, nonalcoholic steatohepatitis (NASH), nonalcoholic fatty liver disease (NAFLD), hypertension, and microalbuminemia, leptin related diseases,

hyperleptinaemia, appetite disorder, essential fatty acid deficiency, and adverse weight gain associated with a drug therapy).

Additional SCD-associated disorders include cancer, including solid tumors or hematological malignancies (e.g., esophageal cancer, pancreatic cancer, endometrial cancer, kidney cancer, hepatoma, thyroid cancer, gallbladder cancer, prostate cancer, leukemia (e.g., lymphomas and myelomas), ENT-related cancer, brain cancer, colon cancer, rectal cancer, colorectal cancer, ovarian cancer, uterine cancer, breast cancer, skin cancer, and prostate cancer), neoplasia, malignancy, metastases, tumors (benign or malignant), carcinogenesis, and hepatomas.

Further SCD-associated disorders include cardiovascular disease (e.g., heart disease, atherosclerosis, hypertension, lipidemia, dyslipidemia, elevated blood pressure, microalbuminemia, hyperuricaemia, hypercholesterolemia, hyperlipidemias, hypertriglyceridemias, arteriosclerosis, coronary artery disease, myocardial infarction, vascular complications of diabetes, and diabetic arteriosclerosis), inflammation, sinusitis, asthma, pancreatitis, osteoarthritis, rheumatoid arthritis, hepatitis (e.g., sexual hepatitis), meibomitis, cystic fibrosis, pre-menstrual syndrome, osteoporosis, thrombosis, cardiovascular risks, weight loss, angina, high blood pressure, ischemia, cardiac ischemia, reperfusion injury, angioplastic restenosis, infertility, liver disease (e.g., fatty liver, cirrhosis, nonalcoholic steatohepatitis, liver fibrosis, and hepatitis C related steatosis), kidney disease (e.g., tubulointerstitial fibrosis, kidney lipid accumulation, glomerular sclerosis, and proteinuria), osteoarthritis (e.g., osteoarthritis of the knee), gastro-esophageal disease, sleep apnea, secondary hyperparathyroidism of renal osteodystrophy, peripheral vascular disease, cerebrovascular disease (e.g., stroke, ischemic stroke and transient ischemic attack (TIA), and ischemic retinopathy), hyperandrogenism, malignant syndrome, extrapyramidal symptoms, hyperuricemia, hypercoagulability, syndrome X, cataract, polycystic ovary syndrome, breathing abnormalities, sleep-disordered breathing, low back pain, gout, gallstone disease, myopathies, lipid myopathies (e.g., carnitine palmitoyltransferase deficiency (CPT I or CPT II)), autoimmune diseases (e.g., lupus, host versus graft rejection, and rejection of organ transplants), asthma, inflammatory bowel diseases, nephropathy, retinopathy, erythrohepatic protoporphyria, iron overload disorders, and hereditary hemochromatosis.

Still further SCD-associated disorders include central nervous system (CNS) disorders, dementia, schizophrenia, mild cognitive impairment, Alzheimer's Disease, cerebral amyloid angiopathy, dementia associated with Down Syndrome, other neurodegenerative diseases, psychiatric disorders, eye diseases, immune disorders, multiple sclerosis, neuropathy, and depression.

Additional SCD-associated disorders include skin disorders (e.g., acne (e.g., acne vulgaris), psoriasis, hirsutism, rosacea, seborrheic skin, oily skin (syn seborrhea), seborrheic dermatitis, hyperseborrhea, eczema, keloid scar, skin ageing, diseases related to production or secretions from mucous membranes, wrinkles, lack of adequate skin firmness, lack of adequate dermal hydration, insufficient sebum secretion, oily hair, shiny skin, greasy-looking skin, greasy-looking hair, and other skin conditions caused by lipid imbalance).

An SCD-associated disorder can also include a disease or condition which is, or is related to, viral diseases or infections.

In some embodiments, the SCD-associated disorder is acne (e.g., acne vulgaris). In some embodiments, the SCD-associated disorder is diabetes (e.g., type II diabetes, including diabetes with

inadequate glycemic control). In some embodiments, the SCD-associated disorder is nonalcoholic fatty liver disease (NAFLD). In some embodiments, the SCD-associated disorder is nonalcoholic steatohepatitis (NASH). In some embodiments, the SCD- associated disorder is cancer. In some embodiments, the SCD- associated disorder is obesity. In some embodiments, the SCD-associated disorder is metabolic syndrome (e.g., dyslipidemia, obesity, insulin resistance, hypertension, microalbuminemia, hyperuricaemia, and hypercoagulability), syndrome X, diabetes, insulin resistance, decreased glucose tolerance, non-insulin-dependent diabetes mellitus, Type II diabetes, Type I diabetes, diabetic complications, body weight disorders (e.g., obesity, overweight, cachexia, and anorexia), weight loss, body mass index, leptin related diseases, or a skin disorder (e.g., eczema, acne, psoriasis, and keloid scar). In some embodiments, the SCD-associated disorder is diabetes, metabolic syndrome, insulin resistance, obesity, a cardiovascular disorder, a CNS disorder, schizophrenia, or Alzheimer's disease.

Combination Formulations and Uses Thereof

The compounds of the invention can be combined with one or more therapeutic agents. In particular, the therapeutic agent can be one that treats or prophylactically treats any neurological disorder described herein.

Combination Therapies

A compound of the invention can be used alone or in combination with other agents that treat neurological disorders or symptoms associated therewith, or in combination with other types of treatment to treat, prevent, and/or reduce the risk of any neurological disorders. In combination treatments, the dosages of one or more of the therapeutic compounds may be reduced from standard dosages when administered alone. For example, doses may be determined empirically from drug combinations and permutations or may be deduced by isobolographic analysis (e.g., Black et al., *Neurology* 65:S3-S6, 2005). In this case, dosages of the compounds when combined should provide a therapeutic effect.

Pharmaceutical Compositions

The compounds of the invention are preferably formulated into pharmaceutical compositions for administration to human subjects in a biologically compatible form suitable for administration *in vivo*. Accordingly, in another aspect, the present invention provides a pharmaceutical composition comprising a compound of the invention in admixture with a suitable diluent, carrier, or excipient.

The compounds of the invention may be used in the form of the free base, in the form of salts, solvates, and as prodrugs. All forms are within the scope of the invention. In accordance with the methods of the invention, the described compounds or salts, solvates, or prodrugs thereof may be administered to a patient in a variety of forms depending on the selected route of administration, as will be understood by those skilled in the art. The compounds of the invention may be administered, for example, by oral, parenteral, buccal, sublingual, nasal, rectal, patch, pump, or transdermal administration and the pharmaceutical compositions formulated accordingly. Parenteral administration includes intravenous, intraperitoneal, subcutaneous, intramuscular, transepithelial, nasal, intrapulmonary,

intrathecal, rectal, and topical modes of administration. Parenteral administration may be by continuous infusion over a selected period of time.

A compound of the invention may be orally administered, for example, with an inert diluent or with an assimilable edible carrier, or it may be enclosed in hard or soft shell gelatin capsules, or it may be compressed into tablets, or it may be incorporated directly with the food of the diet. For oral therapeutic administration, a compound of the invention may be incorporated with an excipient and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, and wafers.

A compound of the invention may also be administered parenterally. Solutions of a compound of the invention can be prepared in water suitably mixed with a surfactant, such as hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, DMSO and mixtures thereof with or without alcohol, and in oils. Under ordinary conditions of storage and use, these preparations may contain a preservative to prevent the growth of microorganisms. Conventional procedures and ingredients for the selection and preparation of suitable formulations are described, for example, in Remington's Pharmaceutical Sciences (2003, 20th ed.) and in The United States Pharmacopeia: The National Formulary (USP 24 NF19), published in 1999.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases the form must be sterile and must be fluid to the extent that may be easily administered via syringe.

Compositions for nasal administration may conveniently be formulated as aerosols, drops, gels, and powders. Aerosol formulations typically include a solution or fine suspension of the active substance in a physiologically acceptable aqueous or non-aqueous solvent and are usually presented in single or multidose quantities in sterile form in a sealed container, which can take the form of a cartridge or refill for use with an atomizing device. Alternatively, the sealed container may be a unitary dispensing device, such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve which is intended for disposal after use. Where the dosage form comprises an aerosol dispenser, it will contain a propellant, which can be a compressed gas, such as compressed air or an organic propellant, such as fluorochlorohydrocarbon. The aerosol dosage forms can also take the form of a pump-atomizer. Compositions suitable for buccal or sublingual administration include tablets, lozenges, and pastilles, where the active ingredient is formulated with a carrier, such as sugar, acacia, tragacanth, gelatin, and glycerine. Compositions for rectal administration are conveniently in the form of suppositories containing a conventional suppository base, such as cocoa butter.

The compounds of the invention may be administered to an animal, e.g., a human, alone or in combination with pharmaceutically acceptable carriers, as noted herein, the proportion of which is determined by the solubility and chemical nature of the compound, chosen route of administration, and standard pharmaceutical practice.

Dosages

The dosage of the compounds of the invention, and/or compositions comprising a compound of the invention, can vary depending on many factors, such as the pharmacodynamic properties of the compound; the mode of administration; the age, health, and weight of the recipient; the nature and extent

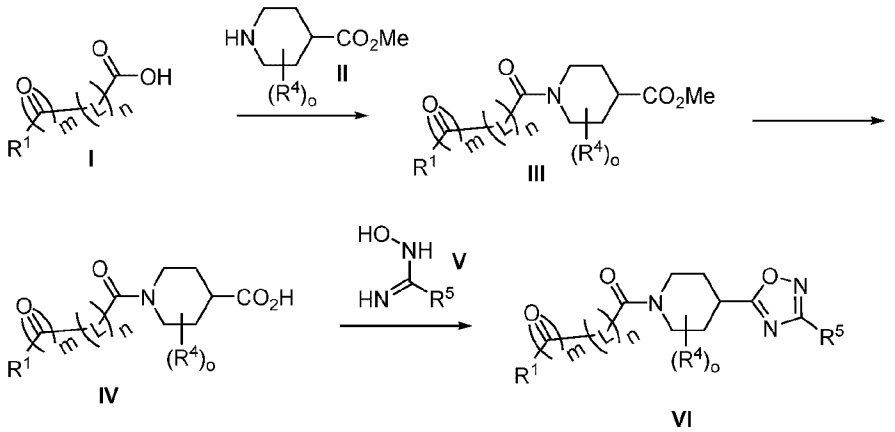
of the symptoms; the frequency of the treatment, and the type of concurrent treatment, if any; and the clearance rate of the compound in the animal to be treated. One of skill in the art can determine the appropriate dosage based on the above factors. The compounds of the invention may be administered initially in a suitable dosage that may be adjusted as required, depending on the clinical response. In general, satisfactory results may be obtained when the compounds of the invention are administered to a human at a daily dosage of, for example, between 0.05 mg and 3000 mg (measured as the solid form). Dose ranges include, for example, between 10-1000 mg (e.g., 50-800 mg). In some embodiments, 50, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, or 1000 mg of the compound is administered. Preferred dose ranges include, for example, between 0.05-15 mg/kg or between 0.5-15 mg/kg.

Alternatively, the dosage amount can be calculated using the body weight of the patient. For example, the dose of a compound, or pharmaceutical composition thereof, administered to a patient may range from 0.1-50 mg/kg (e.g., 0.25-25 mg/kg). In exemplary, non-limiting embodiments, the dose may range from 0.5-5.0 mg/kg (e.g., 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, or 5.0 mg/kg) or from 5.0-20 mg/kg (e.g., 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, 9.5, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 mg/kg).

EXAMPLES

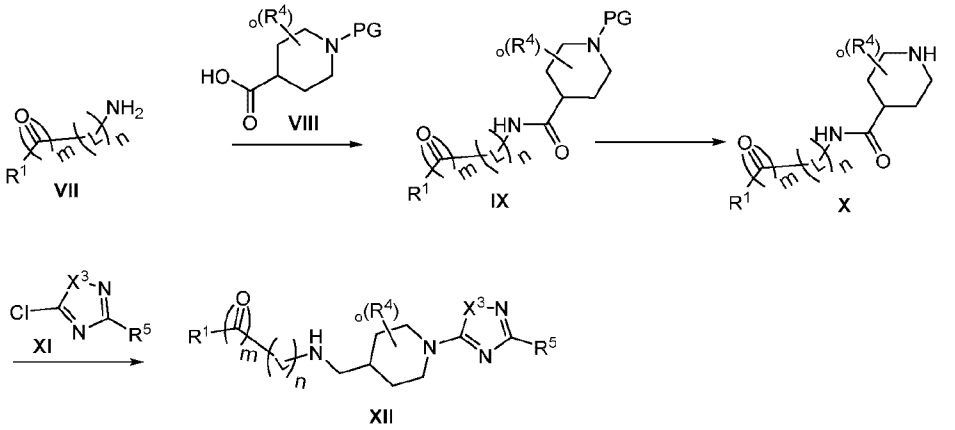
The synthesis of compounds of this invention can be synthesized according to one or more of the general schemes 1-10 shown below. The variables recited in the general schemes below are as defined for Formulae I, II, III, and IV.

General scheme 1



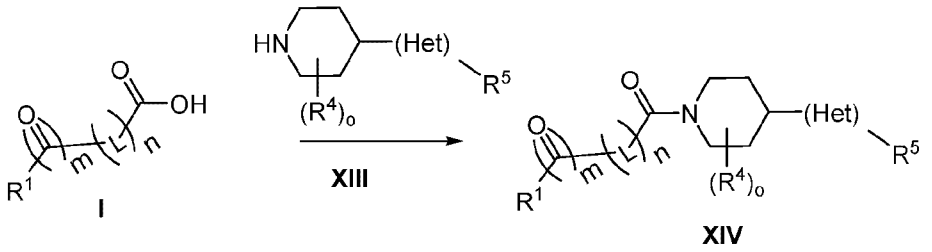
An appropriately substituted carboxylic acid **I** can be coupled with an appropriately substituted piperidine **II** to provide ester **III**. This can be hydrolysed under variety of conditions to provide carboxylic acid intermediate **IV**. This can be condensed with a substituted N-hydroxyimidamide **V** to give the desired 1,2,4-oxadiazole compound **VI**.

General Scheme 2



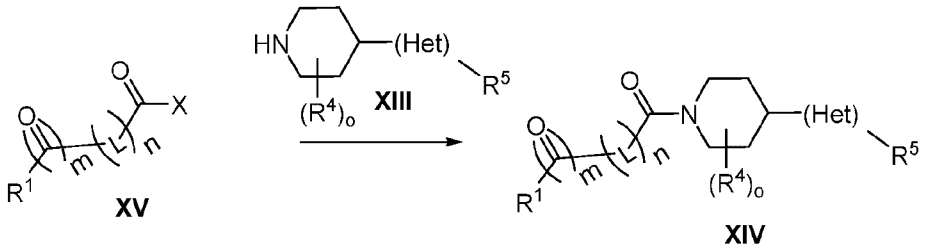
An appropriately substituted carboxylic acid **VII** can be coupled with an appropriately protected (where PG is an *N*-protecting group) and substituted piperidine carboxylic acid **VIII** to provide intermediate **IX**. This can be deprotected using a variety of conditions to provide free amine intermediate **X**. This compound can be coupled using metal catalysis or under thermal conditions with a halogenated heterocycle such as **XI** to give the desired 1,2,4-oxadiazole (X^3 = O) or 1,2,4-thiadiazole (X^3 = S) compound **XII**.

General scheme 3



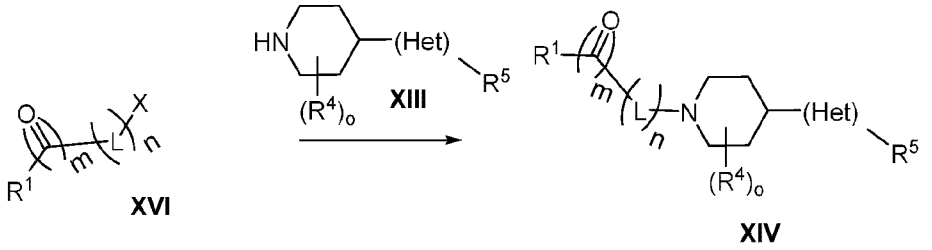
An appropriately substituted carboxylic acid **I** can be coupled with an appropriately substituted piperidine **XIII** to provide the desired heterocyclic compound **XIV**.

General scheme 4



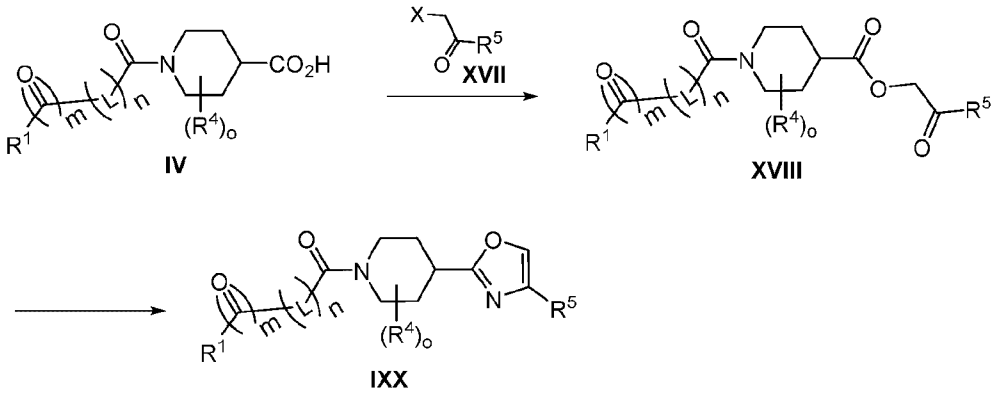
An appropriately substituted acyl halide **XV** (where X is a halogen atom, e.g., chlorine) can be coupled with an appropriately substituted piperidine **XIII** to provide the desired heterocyclic compound **XIV**.

General scheme 5



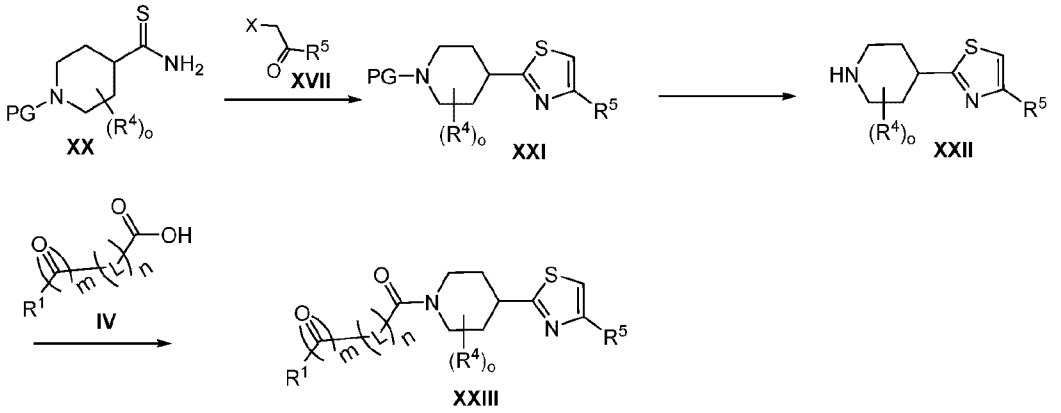
An appropriately substituted alkyl intermediate **XVI** (where X is a good leaving group, e.g., a halogen atom or triflate) can undergo nucleophilic displacement with an appropriately substituted piperidine **XIII** to provide the desired heterocyclic compound **XIV**.

General scheme 6



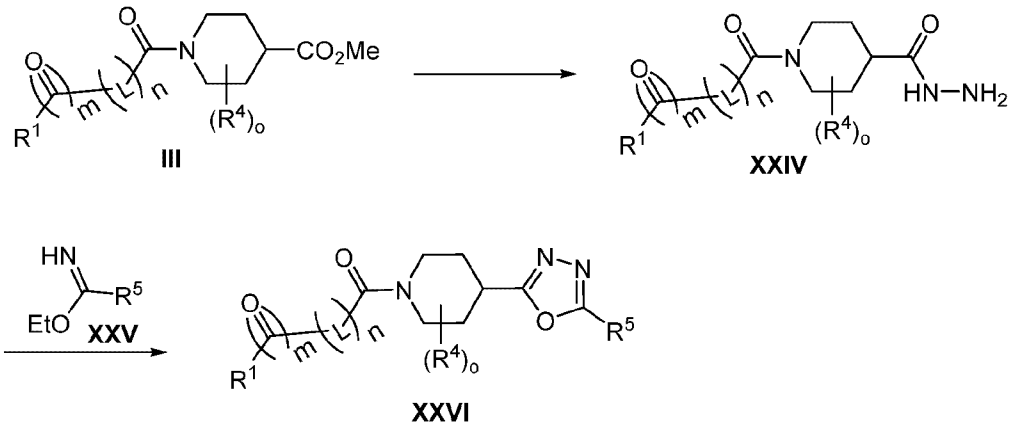
An appropriately substituted carboxylic acid **IV** can be coupled with an appropriately substituted ketone **XVII** (where X is a leaving group, e.g., bromine) to provide the intermediate compound **XVII**. This compound can be condensed with ammonium acetate to provide oxazole **IXX.**

General scheme 7



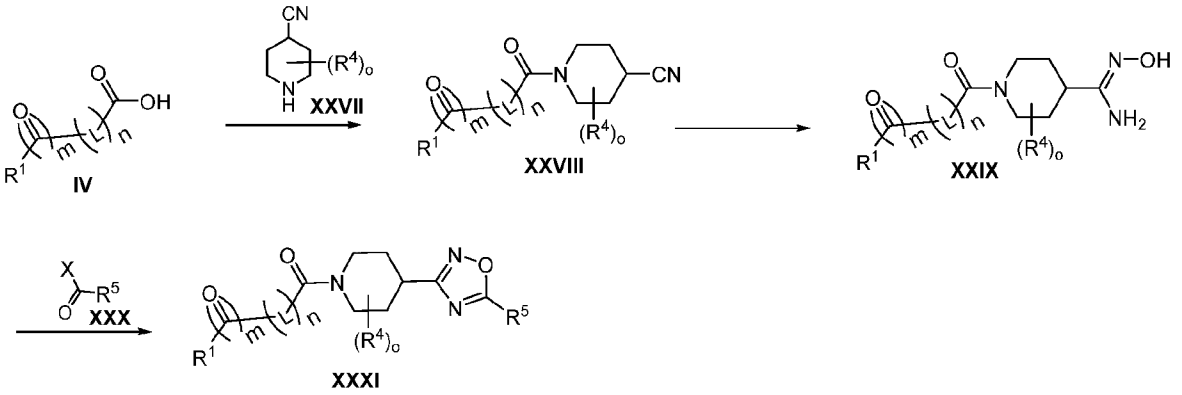
An appropriately protected and substituted thiomide **XX** can be coupled with an appropriately substituted ketone **XVII** (where X is a leaving group, most commonly bromine) to provide the protected (where PG is an amine protecting group, such as tert-butoxycarbonyl) thiazole compound **XXI**. This compound can be deprotected under appropriate conditions to give intermediate piperidine **XXII**. This can be coupled with and appropriately substituted carboxylic acid **IV** to provide thiazole **XXIII**.

General scheme 8



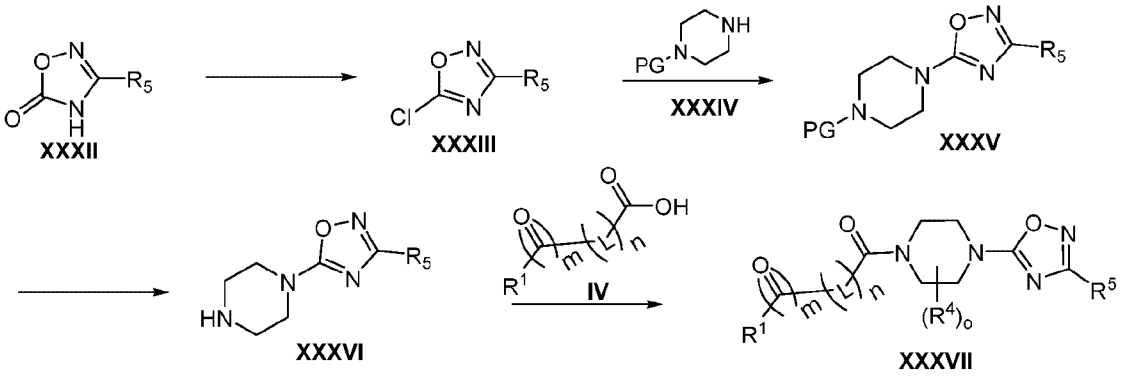
An appropriately protected and substituted ester **III** can be treated with hydrazine to provide the hydrazide compound **XXIV**. This compound can coupled with an appropriately substituted acetimidate **XXV** to provide 1,3,4-oxadiazole **XXVI.**

General scheme 9



An appropriately substituted carboxylic acid **IV** can be couple with and appropriately substituted piperidine compound **XXVII** to give a compound **XXVIII**. This compound can be converted to the corresponding hydroxyimidamide compound **XXIX**. This is can be treated with an appropriately substituted acid halide (most commonly an acid chloride, where X=Cl) **XXX** to provide 1,2,4-oxadiazole **XXXI.**

General scheme 10



An appropriately substituted oxadiazolone **XXXII** can be converted to the appropriately substituted compound **XXXIII**. This compound can be coupled with the appropriate protected piperazine compound **XXXIV** (where PG is an *N*-protecting group, for example, a tert-butyloxycarbonyl group) to give compound **XXXV**. This compound can be deprotected under the appropriate conditions to give piperazine compound **XXXVI**. This can be coupled with a carboxylic acid **IV** to provide 1,2,4-oxadiazole **XXXVII**.

Experimental procedures

The compounds of the invention can be synthesized according to the following procedures.

In the examples below, when purification by preparative HPLC was performed, a Gilson 281 semi-preparative HPLC system was used, using a variety of stationary and mobile phases which are described in the experimental section. For example, (column: Waters X bridge 150x2.5mm 5μm; mobile phase: [water (10 mM NH_4OAc)-acetonitrile]; B%: 36%-66%,12 min) indicates that the following purification conditions were used:

Mobile phase: A: 10mM NH_4OAc in H_2O; B: acetonitrile

Column: Waters Xbridge 150x2.5mm dimensions, 5 μm particle size

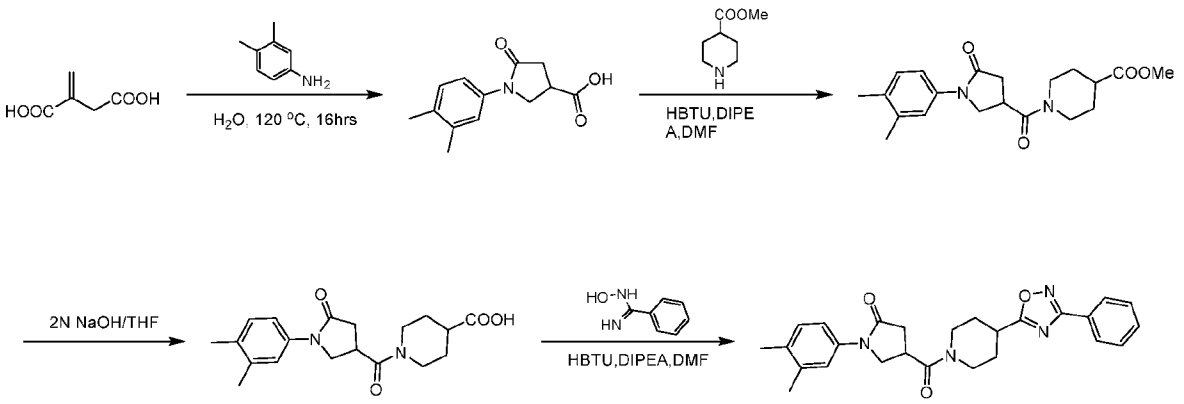
Flow rate: 25mL/min

Monitor wavelength: 220&254nm

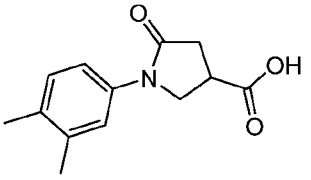
Gradient:

Time / minutes	B %
0.0	36
12.0	66
12.2	100
14.0	100
14.2	36
16.0	36

Example 1. Preparation of 1-(3,4-dimethylphenyl)-4-(4-(3-phenyl-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)pyrrolidin-2-one

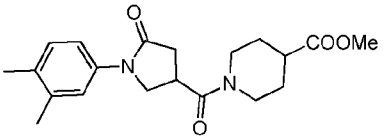


Step 1: Preparation of 1-(3,4-dimethylphenyl)-5-oxopyrrolidine-3-carboxylic acid



A mixture of 2-methylenesuccinic acid (2.0 g, 1.27 mL, 15.37 mmol) and 3,4-dimethylaniline (1.86 g, 15.37 mmol) in water (20 mL) was stirred at 120 °C (reflux) for 16 h. The mixture was cooled to 25 °C and filtered. The filter cake was washed with cold water (5 mL) to give 1-(3,4-dimethylphenyl)-5-oxopyrrolidine-3-carboxylic acid (3.0 g, 12.9 mmol, 84 %) as a yellow solid. This material was used directly in the next step without further purification. ^{1}H NMR (400MHz, DMSO-d6) δ 7.40-7.35 (m, 2H), 7.13-7.11 (d, 1H), 4.01-3.93 (m, 2H), 3.34-3.30 (m, 1H), 2.75-2.67 (m, 2H), 2.22 (s, 3H) 2.19 (s, 3H); LCMS (ESI) m/z: $[M-H]^-$ = 232.1.

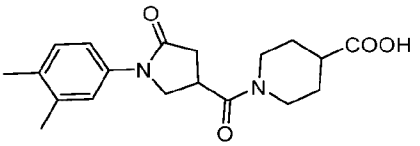
Step 2: Preparation of methyl 1-(1-(3,4-dimethylphenyl)-5-oxopyrrolidine-3-carbonyl)piperidine-4-carboxylate



To a stirred solution of 1-(3,4-dimethylphenyl)-5-oxopyrrolidine-3-carboxylic acid (1.0 g, 4.29 mmol) and methyl piperidine-4-carboxylate (737 mg, 5.15 mmol) in N,N-dimethylformamide (10 mL) was added (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (1.63 g, 4.29 mmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (1.11 g, 8.58 mmol, 1.50 mL). After stirring at 15 °C for 16 h, to the mixture was added water (20 mL) and the mixture extracted with ethyl acetate (20 mL x 4). The organic layer was washed with water (10 mL), saturated aqueous sodium chloride solution (10 mL), then dried over anhydrous sodium sulfate, filtered and concentrated to give crude product that was purified by chromatography on silica gel eluted with Petroleum ether/ethyl acetate from 1/1 to 0/1 to give methyl 1-(1-

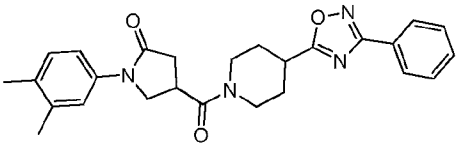
(3,4-dimethylphenyl)-5-oxopyrrolidine-3-carbonyl)piperidine-4-carboxylate (1.90 g, 5.30 mmol, quantitative) as a red oil. LCMS (ESI) m/z: [M+H]+ = 359.3.

Step 3: Preparation of 1-(1-(3,4-dimethylphenyl)-5-oxopyrrolidine-3-carbonyl)piperidine-4-carboxylic acid



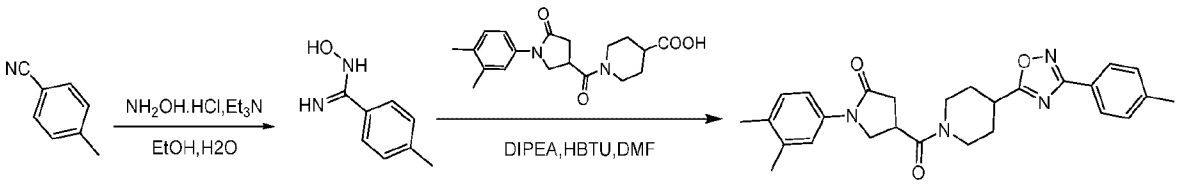
To a stirred solution of methyl 1-(1-(3,4-dimethylphenyl)-5-oxopyrrolidine-3-carbonyl)piperidine-4-carboxylate (400 mg, 1.12 mmol) in tetrahydrofuran (4 mL) was added aqueous sodium hydroxide (2 M, 1.68 mL). The mixture was stirred at 40 °C for 2 h, then the mixture was acidified with concentrated hydrochloric acid until pH 1. The mixture was extracted with dichloromethane (20 mL x 3), then the organic layer was washed with saturated aqueous sodium chloride solution (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give 1-(1-(3,4-dimethylphenyl)-5-oxopyrrolidine-3-carbonyl)piperidine-4-carboxylic acid (300 mg, 871 µmol, 78 %) as a white solid that was used directly without further purification.

Step 4: Preparation of 1-(3,4-dimethylphenyl)-4-(4-(3-phenyl-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)pyrrolidin-2-one

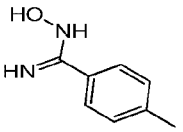


To a stirred solution of 1-(1-(3,4-dimethylphenyl)-5-oxopyrrolidine-3-carbonyl)piperidine-4-carboxylic acid (253 mg, 734 µmol) in N,N-dimethylformamide (1 mL) was added (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (279 mg, 734 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (285 mg, 2.20 mmol, 384 µL). The mixture was stirred at 25 °C for 5 min, then N-hydroxybenzimidamide (100 mg, 734 µmol) was added. The mixture was warmed to 25 °C, stirred for 16 h, then the mixture was diluted with water (5 mL) and extracted with ethyl acetate (20 mL x 3). The organic layers were combined and washed with water (5 mL x 2) and saturated aqueous sodium chloride solution (5 mL), then dried over anhydrous sodium sulfate, filtered and concentrated to give a crude product which was dissolved in N,N-dimethylformamide (2 mL) and then heated at 120 °C for 3 h. Without any additional work-up, the mixture was purified by prep-HPLC (Waters X bridge 150x25 5 µm column; 36-66 % acetonitrile in a 10 mM ammonium acetate solution in water, 12 min gradient) to give 1-(3,4-dimethylphenyl)-4-(4-(3-phenyl-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)pyrrolidin-2-one (73 mg, 164 µmol, 22 %) as a white solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 8.10-8.09 (m, 2H), 7.55-7.49 (m, 3H), 7.39 (s, 1H), 7.30 (s, 1H), 7.15-7.13 (d, 1H), 4.54-4.53 (m, 1H), 4.31-4.27 (m, 1H), 3.98-3.90 (m., 2H), 3.60-3.56 (m, 1H), 3.42-3.36 (m, 2H).3.15-2.95 (m, 2H), 2.86-2.79 (m, 1 H), 2.29-2.26(m, 8H), 2.03-1.97 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 445.3.

Example 2: Preparation of 1-(3,4-dimethylphenyl)-4-(4-(3-(p-tolyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)pyrrolidin-2-one

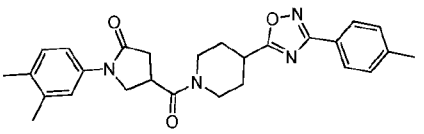


Step 1: Preparation of N-hydroxy-4-methylbenzimidamide



To a stirred solution of 4-methylbenzonitrile (1.0 g, 8.54 mmol, 1.02 mL) in ethanol (10 mL) and water (1 mL) was added hydroxylamine hydrochloride (1.19 g, 17.1 mmol) and triethylamine (1.73 g, 17.1 mmol, 2.37 mL). The mixture was heated at 75 °C for 16 h, then the reaction mixture was concentrated under reduced pressure to give a residue that was diluted with water (5 mL), and then extracted with dichloromethane (8 mL x 10). The combined organic layers were washed with saturated aqueous sodium chloride solution (8 mL x 5), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a N-hydroxy-4-methylbenzimidamide (900 mg, 5.99 mmol, 70 %) as a light green solid. ^{1}H NMR (400MHz, METHANOL-d4) d = 7.49 (d, J=8.2 Hz, 2H), 7.18 (d, J=7.9 Hz, 2H), 2.33 (s, 3H).

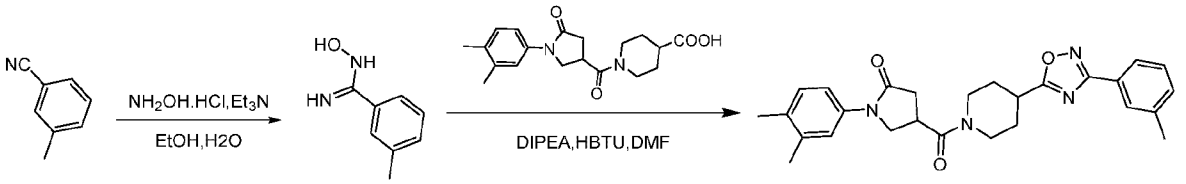
Step 2: Preparation of methyl 1-(3,4-dimethylphenyl)-4-(4-(3-(p-tolyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)pyrrolidin-2-one



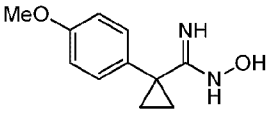
To a stirred solution of methyl 1-(1-(3,4-dimethylphenyl)-5-oxopyrrolidine-3-carbonyl)piperidine-4-carboxylate (229 mg, 666 µmol) in N,N-dimethylformamide (1 mL) was added (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (253 mg, 666 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (258 mg, 2.00 mmol, 349 µL). The mixture was stirred at 25 °C for 5 mins, then N-hydroxy-4-methylbenzimidamide (100 mg, 666 µmol) was added. After 16 h, the reaction mixture was extracted with ethyl acetate (5 mL x 3). The organic layers were combined, washed with saturated aqueous sodium chloride solution (5 mL x 2), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a residue that was purified by prep-HPLC (column: Waters Xbridge 150x25 5µm; mobile phase: [water(10mM NH_4HCO_3)-acetonitrile]; B%: 40%-70%,12min) to give 1-(3,4-dimethylphenyl)-4-(4-(3-(p-tolyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)pyrrolidin-2-one (38 mg, 81 µmol, 12%, 98.4% purity) as a white solid. ^{1}H NMR (400MHz, CHLOROFORM-d) d = 7.89 (d, J=7.1 Hz, 2H), 7.29 (s, 1H), 7.22 (t, J=7.9 Hz, 3H), 7.05 (d, J=8.2 Hz, 1H), 4.50 - 4.38 (m, 1H), 4.20 (t, J=8.4 Hz,

1H), 3.95 - 3.79 (m, 2H), 3.49 (td, J=8.5, 16.9 Hz, 1H), 3.36 - 3.20 (m, 2H), 3.12 - 2.97 (m, 1H), 2.89 (td, J=8.7, 17.1 Hz, 1H), 2.79 - 2.69 (m, 1H), 2.35 (s, 3H), 2.18 (d, J=13.0 Hz, 7H), 2.00 - 1.82 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 459.3.

Example 3: Preparation of 1-(3,4-dimethylphenyl)-4-[4-[3-(m-tolyl)-1,2,4-oxadiazol-5-yl]piperidine-1-carbonyl]pyrrolidin-2-one

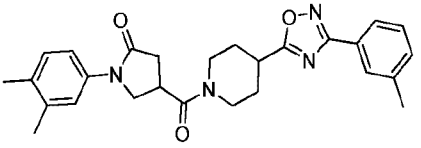


Step 1: Preparation of N-hydroxy-3-methylbenzimidamide.



To a stirred solution of 3-methylbenzonitrile (1.0 g, 8.54 mmol, 1.02 mL) in ethanol (10 mL) and water (1 mL) was added hydroxylamine hydrochloride (1.19 g, 17.1 mmol) and triethylamine (1.73 g, 17.1 mmol, 2.37 mL). The mixture was heated at 75 °C for 16 h and then concentrated under reduced pressure to give a residue that was then diluted with dichloromethane. The organic phase was washed with saturated aqueous sodium chloride solution (5mL x 2), dried over anhydrous sodium sulfate, filtered and concentrated to give N-hydroxy-3-methyl-benzamidine (1.05 g, solid) as a crude solid that was used directly in the next step without further purification. ^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.42 - 7.31 (m, 2H), 7.24 - 7.12 (m, 2H), 4.93 - 4.71 (s, 1H), 3.67 - 3.58 (m, 1H), 2.97 (q, J=7.3 Hz, 1H), 2.30 (s, 3H), 1.32 - 1.23 (m, 1H), 1.18 - 1.11 (m, 1H).

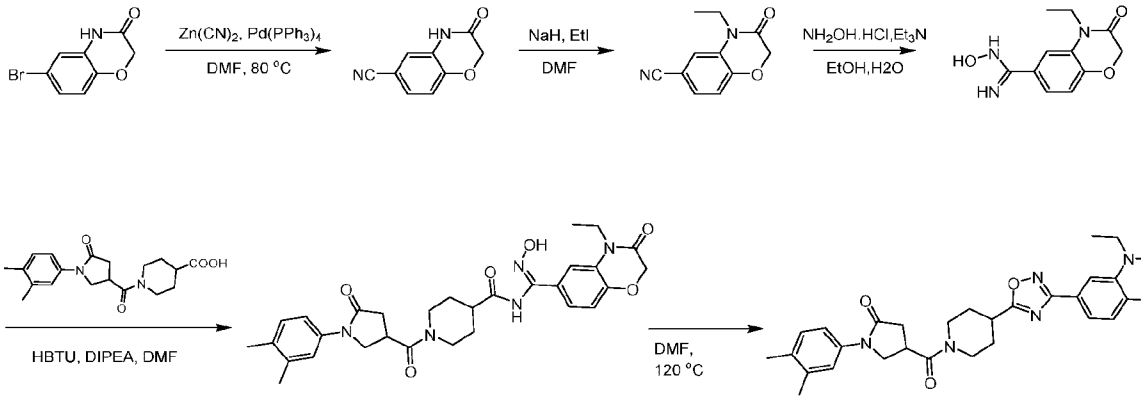
Step 2: Preparation of 1-(3,4-dimethylphenyl)-4-(4-(3-(m-tolyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)pyrrolidin-2-one



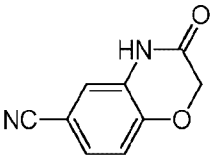
To a stirred solution of 1-[1-(3,4-dimethylphenyl)-5-oxo-pyrrolidine-3-carbonyl]piperidine-4-carboxylic acid (229 mg, 666 µmol) in N,N-dimethylformamide (1 mL) was added (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (253 mg, 666 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (258 mg, 2.00 mmol, 349 µL). The mixture was stirred at 25 °C for 5 mins then N-hydroxy-3-methyl-benzamidine (100 mg, 666 µmol) was added. After 16 h, the reaction mixture was diluted with water (1 mL) extracted with ethyl acetate (5 mL x 3). The organic layers were combined, washed with saturated aqueous sodium chloride solution (5 mL x 2), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a crude residue that was purified by prep-HPLC (Waters X bridge 150x25 5µm column, 41%-71% acetonitrile in an a 10 mM ammonium acetate solution in water, 12 min gradient) to give 1-(3,4-dimethylphenyl)-4-[4-[3-(m-tolyl)-1,2,4-oxadiazol-

5-yl]piperidine-1-carbonyl]pyrrolidin-2-one (118 mg, 266 µmol, 38 %) as a yellow solid. ^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.93 - 7.83 (m, 1H), 7.40 – 7.30 (m, 3H), 7.16 - 7.07 (m, 1H), 4.58 - 4.45 (m, 1H), 4.29 – 4.25 (m 1H), 4.00 -3.90 (m, 2H), 3.59 – 3.55 (m, 1H), 3.43 - 3.24 (m, 2H), 3.19 - 3.01 (m, 1H), 3.01 - 2.89 (m, 1H), 2.87 - 2.74 (m, 1H), 2.43 (s, 3H), 2.27 – 2.22 (m, 8H), 2.07 - 1.90 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 459.3.

Example 4. 6-(5-(1-(1-(3,4-Dimethylphenyl)-5-oxopyrrolidine-3-carbonyl)piperidin-4-yl)-1,2,4-oxadiazol-3-yl)-4-ethyl-2H-benzo[b][1,4]oxazin-3(4H)-one

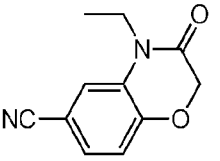


Step 1: Preparation of 3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-6-carbonitrile



To a stirred solution of 6-bromo-2H-benzo[b][1,4]oxazin-3(4H)-one (3.0g, 13.2 mmol) in N,N-dimethylformamide (35 mL) was added zinc cyanide (1.24 g, 10.5 mmol, 668 µL) and tetrakis(triphenylphosphine)palladium(0) (760 mg, 658 µmol) under nitrogen. The mixture was then stirred at 80 °C for 16 h, cooled to room temperature, and extracted with ethyl acetate (60 mL x 4). The combined organic layers were washed with saturated aqueous sodium chloride solution (15 mL) and dried over anhydrous sodium sulfate. The combined organic layers were concentrated to dryness to give the crude product. The crude product was further purified by trituration in ethyl acetate and used in the next step without further purification. 3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-6-carbonitrile (3.40 g) was obtained as a white solid. LCMS (ESI) m/z: $[M+H]^+$ = 175.0.

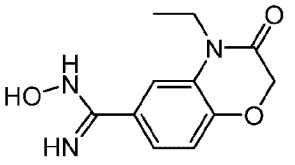
Step 2: Preparation of 4-ethyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-6-carbonitrile



To a stirred solution of 3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-6-carbonitrile (3.30 g, 19.0 mmol) in N,N-dimethylformamide (35 mL) was added sodium hydride (758 mg, 19 mmol, 60% dispersion

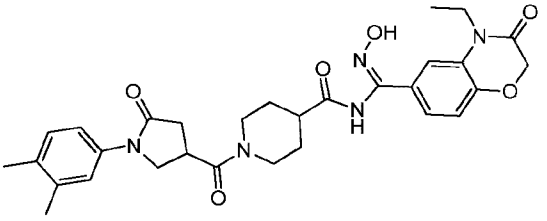
in mineral oil) and iodoethane (3.84 g, 25 mmol, 1.97 mL) at 0 °C. The mixture was warmed to 20 °C. After 3 h, the mixture was cooled to 0 °C, quenched by addition of water (50 mL), and extracted with ethyl acetate (60 mL x 4). The combined organic phases were washed with saturated aqueous sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to give crude product that was purified by chromatography (silica, petroleum ether : ethyl acetate = 50:1 to 5:1) to give 4-ethyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-6-carbonitrile (1.30 g, 6.43 mmol, 34 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (dd, *J* = 1.8, 8.3 Hz, 1H), 7.17 (d, *J* = 1.8 Hz, 1H), 6.98 (d, *J* = 8.3 Hz, 1H), 4.62 (s, 2H), 3.93 (q, *J* = 7.2 Hz, 2H), 1.23 (t, *J* = 7.2 Hz, 3H); LCMS (ESI) m/z = 203.1 $[M+H]^+$.

Step 3: Preparation of 4-ethyl-N-hydroxy-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-6-carboximidamide



To a stirred solution of 4-ethyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-6-carbonitrile (1.20 g, 5.93 mmol) in ethanol (20 mL) was added hydroxylamine hydrochloride (825 mg, 11.9 mmol), triethylamine (1.20 g, 11.9 mmol, 1.64 mL) and water (2 mL), then the mixture was heated at 75 °C. After 5 h, the mixture was cooled to 20 °C and water (20 mL) added. The mixture was extracted with ethyl acetate (30 mL x 3), then the combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to give 4-ethyl-N-hydroxy-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-6-carboximidamide (1.20 g, 5.10 mmol, 86 %) as a white solid that was used directly without further purification. ^{1}H NMR (400 MHz, DMSO-d6) δ 9.61 (s, 1H), 7.44 (d, *J* = 1.6 Hz, 1H), 7.35 (dd, *J* = 1.8, 8.4 Hz, 1H), 7.00 (d, *J* = 8.4 Hz, 1H), 5.87 (s, 2H), 4.66 (s, 2H), 3.96 (q, *J* = 7.0 Hz, 2H), 1.18 (t, *J* = 7.0 Hz, 3H).

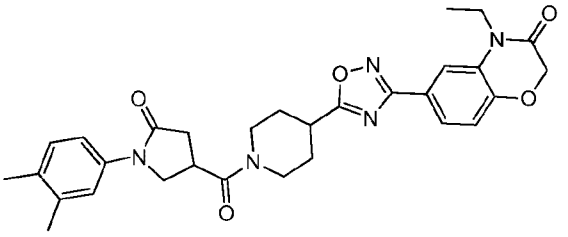
Step 4: Preparation of (E)-1-(1-(3,4-dimethylphenyl)-5-oxopyrrolidine-3-carbonyl)-N-((4-ethyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)(hydroxyimino)methyl)piperidine-4-carboxamide



To a stirred solution of 4-ethyl-N-hydroxy-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-6-carboximidamide (150 mg, 638 µmol) in N,N-dimethylformamide (5 mL) was added 1-(1-(3,4-dimethylphenyl)-5-oxopyrrolidine-3-carbonyl)piperidine-4-carboxylic acid (220 mg, 638 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (242 mg, 638 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (247 mg, 1.91 mmol, 334 µL). After 16 h at 20 °C, the reaction mixture was quenched with water (10 mL). The mixture was extracted with ethyl acetate (20 mL x 4), then the combined organic phases were washed with saturated aqueous sodium chloride solution (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to give (E)-1-(1-(3,4-dimethylphenyl)-5-

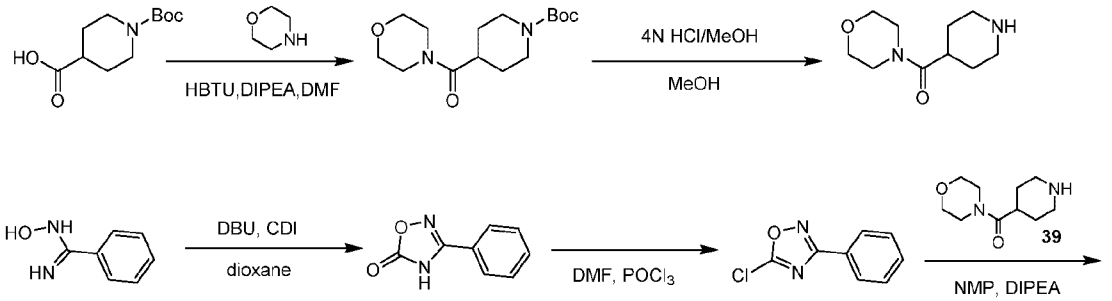
oxopyrrolidine-3-carbonyl)-N-((4-ethyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)(hydroxyimino)methyl)piperidine-4-carboxamide (450 mg) as a yellow oil. This material was used directly without further purification. LCMS (ESI) m/z = 562.3 $[M+H]^+$.

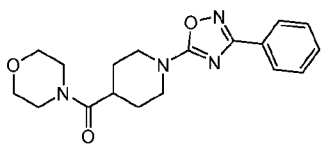
Step 5: Preparation of 6-(5-(1-(1-(3,4-dimethylphenyl)-5-oxopyrrolidine-3-carbonyl)piperidin-4-yl)-1,2,4-oxadiazol-3-yl)-4-ethyl-2H-benzo[b][1,4]oxazin-3(4H)-one



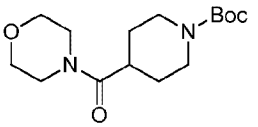
(E)-1-(1-(3,4-dimethylphenyl)-5-oxopyrrolidine-3-carbonyl)-N-((4-ethyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)(hydroxyimino)methyl)piperidine-4-carboxamide (450 mg, 801 µmol) was heated in N,N-dimethylformamide (3 mL) at 120 °C for 3 h. The mixture was cooled and purified directly by prep-HPLC (column: Luna C8 100x30 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 40%-65%,12 min) to give 6-(5-(1-(1-(3,4-dimethylphenyl)-5-oxopyrrolidine-3-carbonyl)piperidin-4-yl)-1,2,4-oxadiazol-3-yl)-4-ethyl-2H-benzo[b][1,4]oxazin-3(4H)-one (142 mg, 255 µmol, 32 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70-7.60 (m, 2H), 7.29 (s, 1H), 7.22-7.19 (m, 1H), 7.03 (dd, *J* = 8.3, 16.9 Hz, 2H), 4.60 (s, 2H), 4.56-4.40 (m, 1H), 4.21 (d, *J* = 7.3 Hz, 1H), 4.00 (d, *J* = 6.5 Hz, 2H), 3.96-3.78 (m, 2H), 3.49 (quin, *J* = 8.3 Hz, 1H), 3.37-3.19 (m, 2H), 3.09-2.82 (m, 2H), 2.81-2.69 (m, 1H), 2.18 (d, *J* = 12.8 Hz, 8H), 1.98-1.82 (m, 2H), 1.26 (t, *J* = 6.8 Hz, 3H); LCMS (ESI) $[M+H]^+$ = 544.2.

Example 5: Morpholino(1-(3-phenyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)methanone.



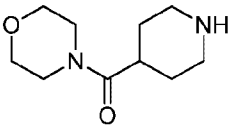


Step 1: Preparation of tert-butyl 4-(morpholine-4-carbonyl)piperidine-1-carboxylate



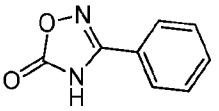
To a stirred solution of 1-(tert-butoxycarbonyl)piperidine-4-carboxylic acid (300 mg, 1.31 mmol) in N,N-dimethylformamide (10 mL) was added morpholine (136 mg, 1.57 mmol, 138 µL), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (496 mg, 1.31 mmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (338 mg, 2.62 mmol, 457 µL). The mixture was stirred at 20 °C for 16 h, then quenched with water (10 mL) and extracted with ethyl acetate (20 mL x 4). The combined organic phases were washed with saturated aqueous sodium chloride solution (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give tert-butyl 4-(morpholine-4-carbonyl)piperidine-1-carboxylate (700 mg) as a yellow oil. This material was used directly without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72-3.51 (m, 5H), 3.45 (br. s., 1H), 3.18-3.05 (m, 1H), 2.93-2.86 (m, 3H), 2.81 (s, 3H), 2.75-2.71 (m, 2H), 2.59-2.48 (m, 1H), 1.39 (s, 9H).

Step 2: Preparation of morpholino(piperidin-4-yl)methanone



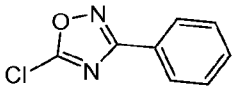
To a stirred solution of tert-butyl 4-(morpholine-4-carbonyl)piperidine-1-carboxylate (700 mg, 2.35 mmol) in methanol (5 mL) was added 4N hydrochloric acid in methanol (15 mL). The mixture was stirred at 20 °C for 16 h then concentrated under reduced pressure to give morpholino(4-piperidyl)methanone (300 mg) as a colorless oil that was used directly without further purification. LCMS (ESI) $[M+H]^+$ = 199.1.

Step 3: Preparation of 3-phenyl-1,2,4-oxadiazol-5(4H)-one



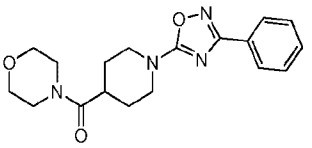
To a stirred solution of N-hydroxybenzamidine (2.0 g, 14.69 mmol) in dioxane (10 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (2.46 g, 16 mmol, 2.44 mL) and 1,1'-carbonyldiimidazole (3.57 g, 22 mmol). The mixture was stirred at 110 °C for 16 h, then cooled and quenched with water (10 mL). The mixture was extracted with dichloromethane (50 mL x 4), then the combined organic phases were washed with saturated aqueous sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to give crude product that was purified by chromatography (silica, petroleum ether : ethyl acetate = 1:1) to give 3-phenyl-1,2,4-oxadiazol-5(4H)-one (1.30 g, 8.02 mmol, 55 %) as a yellow solid. ^{1}H NMR (400 MHz, Methanol-d4) δ 7.83-7.75 (m, 2H), 7.66-7.52 (m, 3H); LCMS (ESI) m/z = 163.2 $[M+H]^+$.

Step 4: Preparation of 5-chloro-3-phenyl-1,2,4-oxadiazole



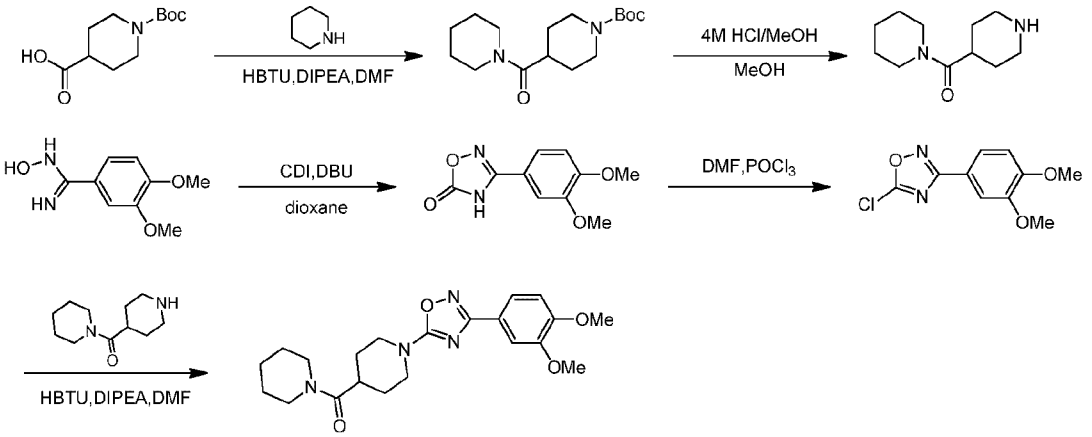
To a stirred solution of 3-phenyl-1,2,4-oxadiazol-5(4H)-one (500 mg, 3.08 mmol) equipped with calcium chloride tube was added N,N-dimethylformamide (1 mL). Phosphoryl chloride (10 mL) was added dropwise, and the resulting mixture was heated at 110 ℃ for 16 h. The reaction mixture was cooled to 20 ℃ and poured onto ice water (100 mL), and the resulting mixture was stirred for 30 min. The mixture was extracted with dichloromethane (20 mL x 5), then the combined organic phases were washed with saturated aqueous sodium chloride solution (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to give crude product that was purified by chromatography (silica, petroleum ether : ethyl acetate = 50:1) to give 5-chloro-3-phenyl-1,2,4-oxadiazole (180 mg, 997 µmol, 32 %) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10-7.98 (m, 2H), 7.57-7.46 (m, 3H).

Step 5: Preparation of morpholino(1-(3-phenyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)methanone

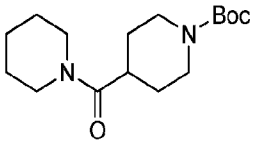


To a stirred solution of morpholino(piperidin-4-yl)methanone (180 mg, 908 µmol) in N-methyl-2-pyrrolidone (5 mL) was added 5-chloro-3-phenyl-1,2,4-oxadiazole (163 mg, 908 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (234 mg, 1.82 mmol, 317 µL). The mixture was stirred at 120 ℃ for 16 h then cooled and purified directly by prep-HPLC (column: Waters Xbridge 150x25 5µm; mobile phase: [water (10 mM ammonium carbonate)-acetonitrile]; B%: 20%-50%,12 min) to give morpholino(1-(3-phenyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)methanone (130 mg, 380 µmol, 42 %) as a yellow solid. ^{1}H NMR (400 MHz, Methanol-d4) δ 8.00-7.94 (m, 2H), 7.55-7.45 (m, 3H), 4.26 (d, J = 13.3 Hz, 2H), 3.74-3.59 (m, 8H), 3.32-3.26 (m, 2H), 3.08-2.98 (m, 1H), 1.92-1.75 ppm (m, 4H); LCMS (ESI) $[M+H]^+$ = 343.2.

Example 6: (1-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-4-yl)(piperidin-1-yl)methanone

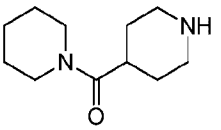


Step 1: Preparation of tert-butyl 4-(piperidine-1-carbonyl)piperidine-1-carboxylate.



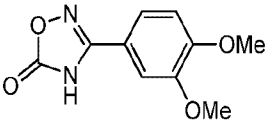
To a mixture of 1-(tert-butoxycarbonyl)piperidine-4-carboxylic acid (300 mg, 1.31 mmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (496 mg, 1.31 mmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (338 mg, 2.62 mmol, 457 µL) in N,N-dimethylformamide (1 mL) was added piperidine (133 mg, 1.57 mmol, 155 µL) at 0 °C. The mixture was stirred at 25 °C for 2 h. The residue was poured into water (5 mL). The aqueous phase was extracted with ethyl acetate (10 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to give tert-butyl 4-(piperidine-1-carbonyl)piperidine-1-carboxylate (600 mg) as a yellow oil. This material was used directly without further purification. ^{1}H NMR (400MHz, $CDCl_3$) δ 3.73 (dd, *J* = 6.4, 9.9 Hz, 1H), 3.55 (br. s., 2H), 3.44 (br. s., 2H), 3.29-3.15 (m, 2H), 2.68-2.57 (m, 1H), 1.96-1.83 (m, 1H), 1.77-1.62 (m, 8H), 1.56 (br. s., 4H), 1.46 (s, 9H); LCMS (ESI) m/z = 297.3 $[M+H]^+$.

Step 2: Preparation of piperidin-1-yl(piperidin-4-yl)methanone.



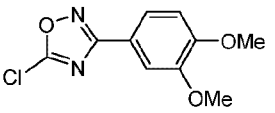
To a mixture of tert-butyl 4-(piperidine-1-carbonyl)piperidine-1-carboxylate (500 mg, 1.69 mmol) in methanol (5 mL) was added 4M methanolic hydrochloric acid (10 mL) at 0 °C. The mixture was stirred at 25 °C for 2 h. The mixture was concentrated in vacuo to give piperidin-1-yl(piperidin-4-yl)methanone (300 mg) as a yellow oil which was used in the next step directly without further purification. LCMS (ESI) $[M+H]^+$ = 197.3.

Step 3: Preparation of 3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5(4H)-one.



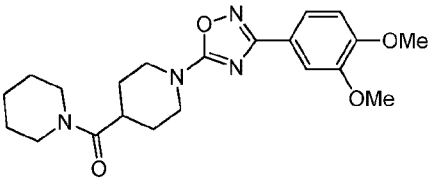
A mixture of N-hydroxy-3,4-dimethoxybenzimidamide (1.0 g, 5.10 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (853 mg, 5.61 mmol, 845 µL) and 1,1'-carbonyldiimidazole (1.24 g, 7.65 mmol) in dioxane (10 mL) was prepared at 15 °C. The mixture was warmed to 110 °C for 12 h. The mixture was cooled to 15 °C and then poured into water (5 mL). The aqueous phase was extracted with dichloromethane (10 mL x 5), then the combined organic phases were washed with saturated aqueous sodium chloride solution (5 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to afford 3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5(4H)-one (800 mg) as a yellow solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.60-7.52 (m, 2H), 6.88 (d, *J* = 8.8 Hz, 1H), 3.91 (d, *J* = 6.1 Hz, 6H); LCMS (ESI) m/z = 223.2 $[M+H]^+$.

Step 4: Preparation of 5-chloro-3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazole.



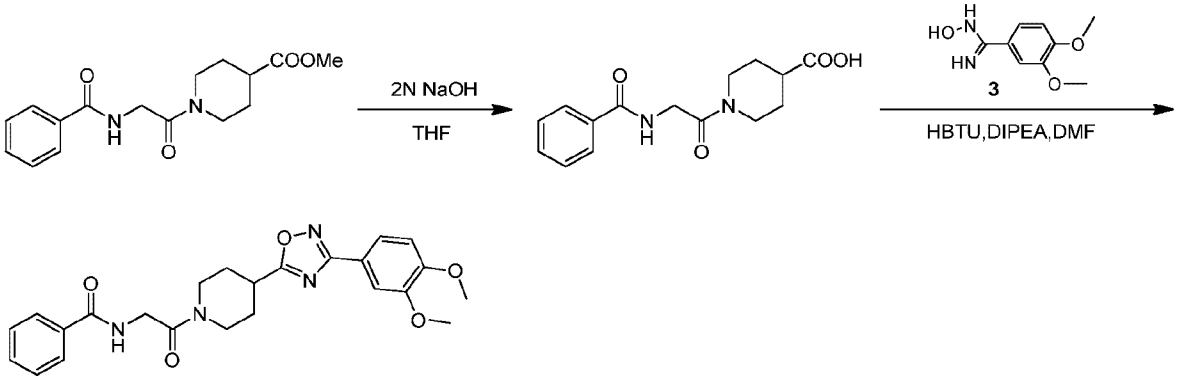
3-(3,4-Dimethoxyphenyl)-1,2,4-oxadiazol-5(4H)-one (500 mg, 2.25 mmol) was added to a mixture of phosphoryl chloride (13.2 g, 86.1 mmol, 8 mL) and N,N-dimethylformamide (1 mL). The mixture was equipped with a calcium chloride tube and heated at 100 °C for 16 h, at which time the mixture was cooled and concentrated in vacuo at 45°C. The residue was poured into ice-water (w/w = 10/1) (11mL) and stirred for 10 min. The mixture was extracted with dichloromethane (10 mL x 5), then the combined organic phases were washed with saturated aqueous sodium chloride solution (2 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by chromatography (silica, petroleum ether: ethyl acetate = 5:1 to 1:1 gradient) to afford 5-chloro-3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazole (200 mg, 0.83 mmol, 37 %) as a yellow solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.67 (dd, *J* = 2.0, 8.4 Hz, 1H), 7.53 (d, *J* = 2.0 Hz, 1H), 6.97 (d, *J* = 8.4 Hz, 1H), 3.96 (d, *J* = 2.4 Hz, 6H); LCMS (ESI) m/z =241.1 $[M+H]^+$.

Step 5: Preparation of (1-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-4-yl)(piperidin-1-yl)methanone.

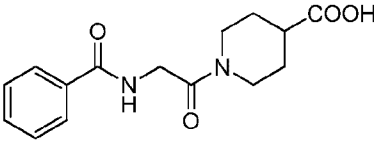


To a stirred solution of 5-chloro-3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazole (200 mg, 831 µmol) and triethylamine (252 mg, 2.49 mmol, 345 µL) in dichloromethane (2 mL) was added piperidin-1-yl(piperidin-4-yl)methanone (163 mg, 831 µmol) at 0 °C. The mixture was warmed to 15 °C and stirred for 2h, then concentrated in vacuo to afford crude product. The residue was purified by prep-HPLC (column: Luna C8 100x30 5µm; mobile phase: [water (10 mM ammonium carbonate)-acetonitrile]; B%: 20%-55%,12 min) to give (1-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-4-yl)(piperidin-1-yl)methanone (36 mg, 89.7 µmol, 11 %) as a yellow solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.4 Hz, 1H), 7.51 (s, 1H), 6.92 (d, *J* = 8.4 Hz, 1H), 4.28 (d, *J* = 13.2 Hz, 2H), 3.95 (d, *J* = 8.8 Hz, 6H), 3.65-3.41 (m, 4H), 3.30-3.15 (m, 2H), 2.85-2.69 (m, 1H), 2.01-1.89 (m, 2H), 1.88-1.79 (m, 2H), 1.68 (d, *J* = 4.9 Hz, 2H), 1.61 (br. s., 1H); LCMS (ESI) m/z = $[M+H]^+$: 401.2.

Example 7: N-(2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.

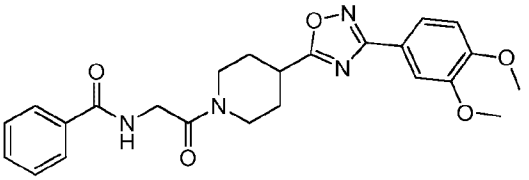


Step 1: Preparation of 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid.



To a stirred solution of methyl 1-(2-benzamidoacetyl)piperidine-4-carboxylate (5.0 g, 16.4 mmol) in tetrahydrofuran (50 mL) was added aqueous sodium hydroxide (2 M, 16.4 mL). The mixture was stirred at 20 °C for 2 h and then acidified by the addition of concentrated hydrochloric acid until pH 1. The mixture was extracted with dichloromethane (80 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to give crude product 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid (3.25 g, 11.2 mmol, 68 %) as a yellow solid. ^{1}H NMR (400 MHz, Methanol-d4) δ 7.87 (d, *J*=7.5 Hz, 2H), 7.59 - 7.42 (m, 3H), 4.39 - 4.20 (m, 3H), 3.92 (d, *J*=14.1 Hz, 1H), 3.24 (t, *J*=11.5 Hz, 1H), 2.98 - 2.88 (m, 1H), 2.62 (s, 1H), 2.08 - 1.89 (m, 2H), 1.81 - 1.53 (m, 2H).

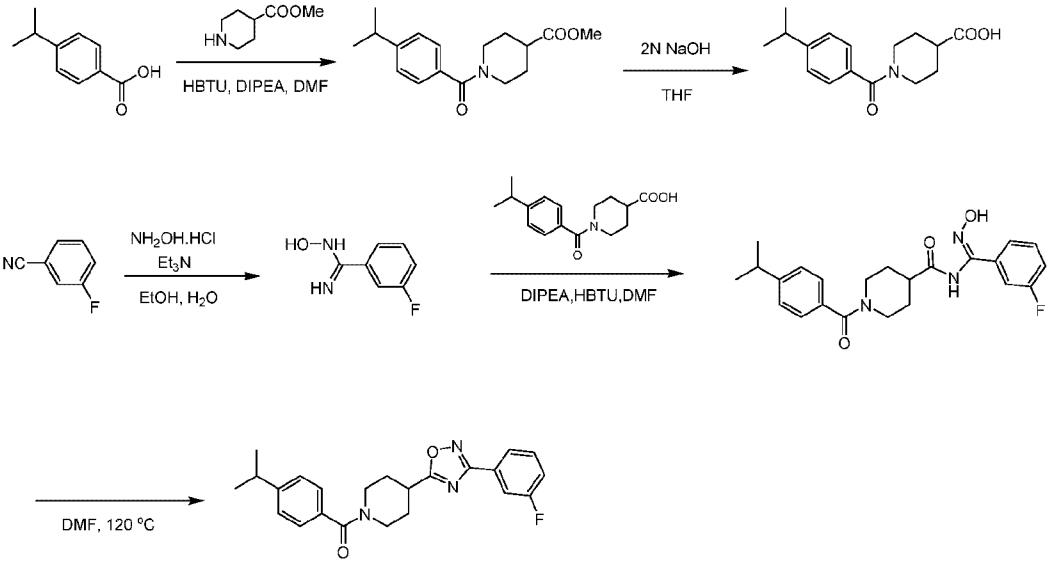
Step 2: Preparation of N-(2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.



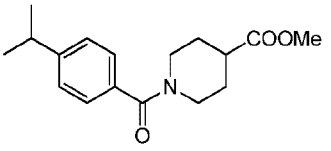
To a stirred solution of 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid (2.0 g, 6.89 mmol) in N,N-dimethylformamide (30 mL) was added N-hydroxy-3,4-dimethoxybenzimidamide (1.62 g, 8.27 mmol), N-ethyl-N-(propan-2-yl)propan-2-amine (2.67 g, 20.67 mmol, 3.61 mL) and 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (2.62 g, 6.89 mmol). The mixture was stirred at 20 °C for 2 h and then warmed at 120 °C for 2 h. The reaction mixture was quenched by addition of water (40 mL), then the mixture was extracted with ethyl acetate (80 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to give crude product that was purified by chromatography (silica, petroleum ether : ethyl acetate = 20 : 1 to 1 : 2) to give a yellow solid.

The yellow solid was washed with ethyl acetate (30 mL), then the mixture was filtered, and the filter cake was dried in vacuo to give N-(2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide (1.29 g, 2.86 mmol, 42 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 - 7.84 (m, 2H), 7.80 (s, 1H), 7.58 - 7.44 (m, 3H), 7.41 - 7.35 (m, 1H), 7.28 - 7.26 (m, 2H), 6.92 (d, *J*=8.9 Hz, 1H), 4.58 - 4.47 (m, 1H), 4.32 (d, *J*=3.9 Hz, 2H), 3.99 - 3.88 (m, 7H), 3.37 - 3.06 (m, 3H), 2.28 - 2.13 (m, 2H), 2.07 - 1.89 (m, 2H); LCMS (ESI) $[M+H]^+$ = 451.3.

Example 8: (4-(3-(3-fluorophenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)(4-isopropylphenyl)methanone.

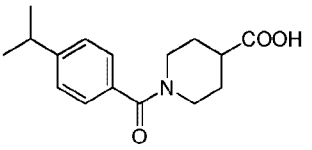


Step 1: Preparation of methyl 1-(4-isopropylbenzoyl)piperidine-4-carboxylate.



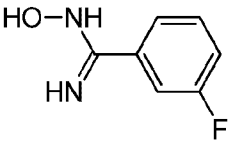
To a stirred solution of 4-isopropylbenzoic acid (250 mg, 1.52 mmol) in N,N-dimethylformamide (10 mL) was added methyl piperidine-4-carboxylate (261 mg, 1.82 mmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (576 mg, 1.52 mmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (392 mg, 3.04 mmol, 530 µL). The mixture was stirred at 20 °C for 16 h. The reaction mixture was quenched with water (10 mL), then the mixture was extracted with ethyl acetate (20 mL x 4). The combined organic phases were washed with saturated aqueous sodium chloride solution (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to give crude product methyl 1-(4-isopropylbenzoyl)piperidine-4-carboxylate (900 mg) as a yellow oil. LCMS (ESI) m/z: 290.3 $[M+H]^+$.

Step 2: Preparation of 1-(4-isopropylbenzoyl)piperidine-4-carboxylic acid.



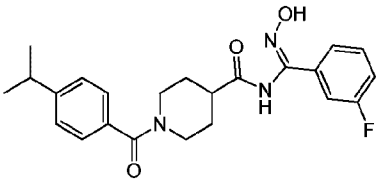
To a stirred solution of methyl 1-(4-isopropylbenzoyl)piperidine-4-carboxylate (900 mg, 3.11 mmol) in tetrahydrofuran (10 mL) was added aqueous sodium hydroxide (2 M, 3.11 mL). The mixture was stirred at 20 °C for 16 h. The mixture was acidified to pH 1 by dropwise addition of concentrated hydrochloric acid. The mixture was extracted with dichloromethane (20 mL x 4). The combined organic phases were washed with saturated aqueous sodium chloride solution (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to give crude product 1-(4-isopropylbenzoyl)piperidine-4-carboxylic acid (400 mg) as a yellow solid. LCMS (ESI) $[M+H]^+$ = 276.2.

Step 3: Preparation of 3-fluoro-N-hydroxybenzimidamide.



To a stirred solution of 3-fluorobenzonitrile (1.0 g, 8.26 mmol, 884 µL) in ethanol (10 mL) were added hydroxylamine hydrochloride (1.15 g, 16.5 mmol), triethylamine (2.09 g, 20.7 mmol, 2.86 mL), and water (1 mL). Then the mixture was heated at 75 °C for 16 h. After cooling to 20 °C, water (10 mL) was added to the solution. The mixture was extracted with ethyl acetate (20 mL x 5). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to give 3-fluoro-N-hydroxybenzimidamide (2.0 g) as a green solid that was used directly in the next step without further purification. LCMS (ESI) m/z: 155.1 $[M+H]^+$.

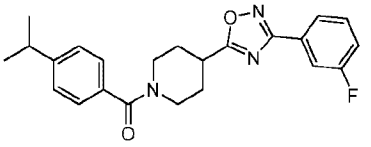
Step 4: Preparation of (E)-N-((3-fluorophenyl)(hydroxyimino)methyl)-1-(4-isopropylbenzoyl)piperidine-4-carboxamide.



To a stirred solution of 1-(4-isopropylbenzoyl)piperidine-4-carboxylic acid (400 mg, 1.45 mmol) in N,N-dimethylformamide (10 mL) were added 3-fluoro-N-hydroxybenzimidamide (223 mg, 1.45 mmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (550 mg, 1.45 mmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (563 mg, 4.36 mmol, 761 µL). The mixture was stirred at 20 °C for 16 h. The reaction mixture was quenched with water (10 mL) and then extracted with ethyl acetate (20 mL x 4). The combined organic phases were washed with saturated aqueous sodium chloride solution (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to give (E)-N-((3-

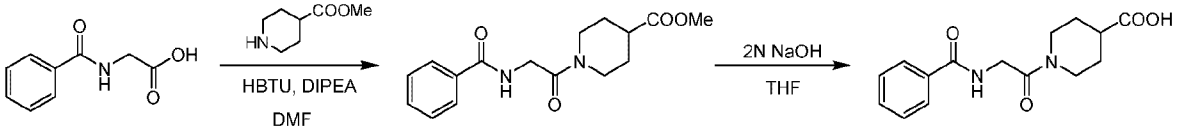
fluorophenyl)(hydroxyimino)methyl)-1-(4-isopropylbenzoyl)piperidine-4-carboxamide (350 mg) as a yellow oil. LCMS (ESI) m/z: 412.3 $[M+H]^+$.

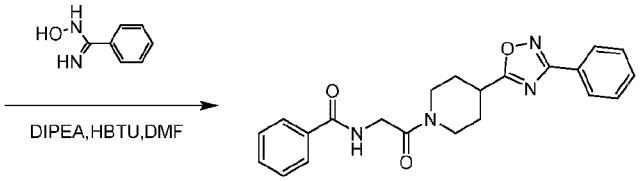
Step 5: Preparation of (4-(3-(3-fluorophenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)(4-isopropylphenyl)methanone.



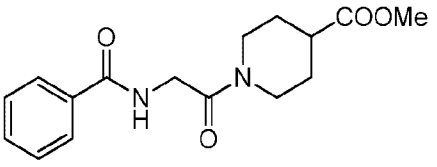
(E)-N-((3-Fluorophenyl)(hydroxyimino)methyl)-1-(4-isopropylbenzoyl)piperidine-4-carboxamide (350 mg, 851 µmol) was added to N,N-dimethylformamide (3 mL), and the mixture was stirred at 120 °C for 16 h. The reaction mixture was cooled and purified by direct injection and prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 50%-80%,12 min) to give (4-(3-(3-fluorophenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)(4-isopropylphenyl)methanone (82 mg, 210 µmol, 25 %) as a yellow oil. ^{1}H NMR (400 MHz, Methanol-d4) δ 7.92 (d, *J* = 7.8 Hz, 1H), 7.79 (d, *J* = 9.7 Hz, 1H), 7.57 (d, *J* = 5.6 Hz, 1H), 7.42-7.28 (m, 5H), 4.69-4.50 (m, 1H), 3.89 (br. s., 1H), 3.53-3.42 (m, 1H), 3.39-3.34 (m, 1H), 3.32-3.28 (m, 1H), 2.99 (td, *J* = 6.9, 13.8 Hz, 1H), 2.43-2.09 (m, 2H), 2.07-1.83 (m, 2H), 1.30 (s, 3H), 1.29 (s, 3H); LCMS (ESI) m/z $[M+H]^+$ = 394.2.

Example 9: N-(2-oxo-2-(4-(3-phenyl-1,2,4-oxadiazol-5-yl)piperidin-1-yl)ethyl)benzamide.





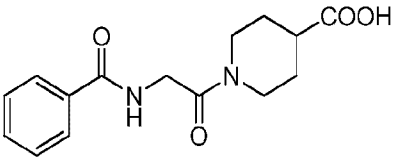
Step 1: Preparation of methyl 1-(2-benzamidoacetyl)piperidine-4-carboxylate.



To a stirred solution of 2-benzamidoacetic acid (3.0 g, 16.7 mmol) in N,N-dimethylformamide (30 mL) were added methyl piperidine-4-carboxylate (2.88 g, 20.09 mmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (6.35 g, 16.7 mmol), and N-ethyl-N-(propan-2-yl)propan-2-amine (6.49 g, 50.2 mmol, 8.77 mL). The mixture was stirred at 20 °C for 3 h and then quenched by addition of water (40 mL). The mixture was extracted with ethyl acetate (80 mL x 4). The combined organic phases were washed with saturated aqueous sodium chloride solution (30 mL), dried over

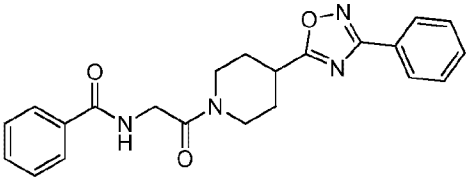
anhydrous sodium sulfate, filtered, and concentrated to give crude product that was purified by chromatography (silica, petroleum ether : ethyl acetate = 5:1 to 1:1) to give methyl 1-(2-benzamidoacetyl)piperidine-4-carboxylate (7.0 g, 23.0 mmol, quantitative), as a yellow oil. LCMS (ESI) m/z = 305.1 $[M+H]^+$.

Step 2: Preparation of 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid.



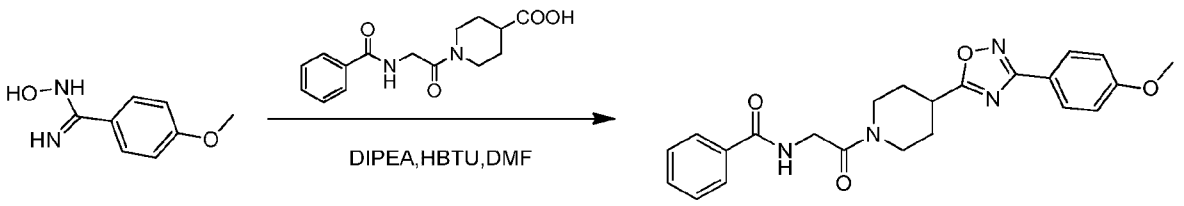
To a stirred solution of methyl 1-(2-benzamidoacetyl)piperidine-4-carboxylate (7.0 g, 23.0 mmol) in tetrahydrofuran (50 mL) was added aqueous sodium hydroxide (2 M, 23 mL). The mixture was then stirred at 20 °C for 16 h. The mixture was then acidified to pH 1 using concentrated hydrochloric acid and then extracted with dichloromethane (80 mL x 4). The organic phases were combined, washed with saturated aqueous sodium chloride solution (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to give 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid (4.20 g, 14.47 mmol, 63 %) as a yellow solid. This was used directly in the next step without further purification. ^{1}H NMR (400 MHz, Methanol-d4) δ 7.93-7.85 (m, 2H), 7.59-7.54 (m, 1H), 7.52-7.46 (m, 2H), 4.42-4.33 (m, 1H), 4.29 (s, 2H), 4.01-3.87 (m, 1H), 3.30-3.20 (m, 1H), 2.97-2.88 (m, 1H), 2.63-2.52 (m, 1H), 2.06-1.92 (m, 2H), 1.80-1.55 (m, 2H).

Step 3: Preparation of N-(2-oxo-2-(4-(3-phenyl-1,2,4-oxadiazol-5-yl)piperidin-1-yl)ethyl)benzamide.



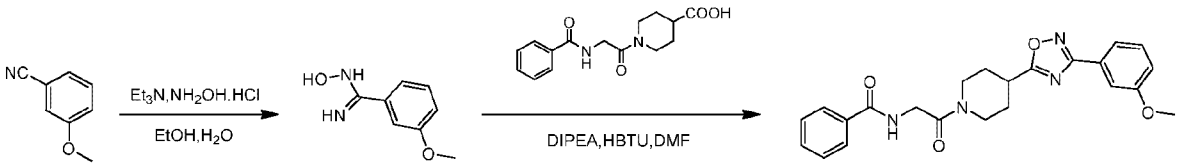
To a stirred solution of 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid (200 mg, 689 µmol) in N,N-dimethylformamide (4 mL) were added *N*-hydroxybenzamidine (112 mg, 826 µmol), N,N,N′,N′-tetramethyl-O-(1H-benzotriazol-1-yl)uronium hexafluorophosphate (261 mg, 689 µmol), and N,N-diisopropylethylamine (267 mg, 2.07 mmol, 360.96 µL). The reaction mixture was then stirred at 20 °C for 2 h, quenched by addition of water (5 mL), and extracted with ethyl acetate (20 mL x4). The organic extracts were combined, washed with saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and concentrated in vacuo to provide a crude residue. To the residue was added N,N-dimethylformamide (4 mL), and the resulting mixture was stirred at 120 °C for 2 h, concentrated under vacuum, and purified by prep-HPLC (column: Luna C8 100x30 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 30%-60%,12 min) to give N-(2-oxo-2-(4-(3-phenyl-1,2,4-oxadiazol-5-yl)piperidin-1-yl)ethyl)benzamide (74 mg, 189 µmol, 27 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13-8.08 (m, 2H), 7.88 (d, *J* = 7.2 Hz, 2H), 7.55-7.46 (m, 6H), 7.36 (br. s., 1H), 4.51 (d, *J* = 13.7 Hz, 1H), 4.33 (d, *J* = 3.8 Hz, 2H), 3.94 (d, *J* = 13.3 Hz, 1H), 3.42-3.32 (m, 2H), 3.20 (t, *J* = 10.5 Hz, 1H), 2.28 (br. s., 2H), 2.11-1.96 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 391.1.

Example 10: N-(2-(4-(3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.

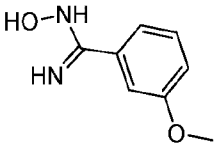


To a stirred solution of 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid (120 mg, 413 µmol) and N-hydroxy-4-methoxybenzimidamide (82 mg, 496 µmol) in N,N-dimethylformamide (2 mL) were added N,N-diisopropylamine (106 mg, 827 µmol, 144 µL) and (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (156 mg, 413 µmol) at 15 °C, then the mixture was stirred for 15h. The mixture was heated to 110 °C and stirred for 5h. After cooling, the mixture was purified directly by prep-HPLC (column: Luna C8 100x30 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 30%-65%,12 min) to give N-(2-(4-(3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide (87 mg, 205 µmol, 50 %) as a yellow solid. ^{1}H NMR (400 MHz, Methanol-d4) δ 7.98 (d, J=8.8 Hz, 2H), 7.88 (d, J=7.5 Hz, 2H), 7.60 - 7.51 (m, 1H), 7.51 - 7.38 (m, 2H), 7.04 (d, J=8.4 Hz, 2H), 4.46 (d, J=13.2 Hz, 1H), 4.38 - 4.21 (m, 2H), 4.04 (d, J=13.7 Hz, 1H), 3.86 (s, 3H), 3.47 - 3.34 (m, 2H), 3.07 (t, J=11.9 Hz, 1H), 2.31 - 2.15 (m, 2H), 2.05 - 1.80 (m, 2H); LCMS (ESI) m/z $[M+H]^+$ = 421.1.

Example 11

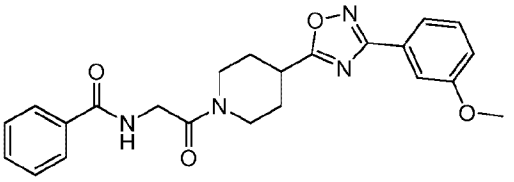


Step 1: Preparation of N-hydroxy-3-methoxybenzimidamide.



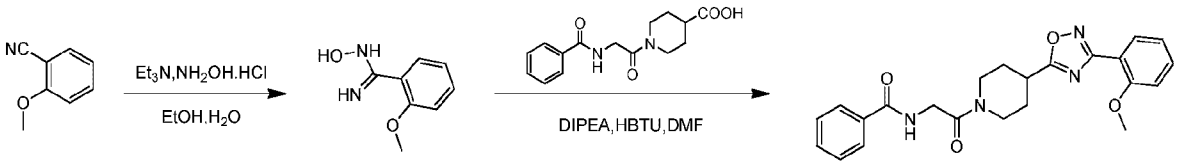
To a stirred solution of 3-methoxybenzonitrile (2.0 g, 15.0 mmol, 1.83 mL) in ethanol (20 mL) was added hydroxylamine hydrochloride (2.09 g, 30.0 mmol), triethylamine (3.04 g, 30.0 mmol, 4.16 mL) and water (2 mL). Then the mixture was heated at 75 °C for 5 h. After cooling to 20 °C, water (20 mL) was added to the solution. The mixture was extracted with dichloromethane (40 mL x 4). The combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL) and dried over anhydrous sodium sulfate. The combined organic phases were concentrated in vacuo to give N-hydroxy-3-methoxybenzimidamide (2.60 g) as a white solid. This was used directly without further purification. ^{1}H NMR (400 MHz, DMSO-d6) δ 9.67 (s, 1H), 7.37-7.24 (m, 3H), 7.10-6.88 (m, 1H), 5.84 (br. s., 2H), 3.82 (s, 3H).

Step 2: Preparation of N-(2-(4-(3-(3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.

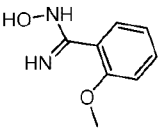


To a stirred solution of 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid (120 mg, 413 μmol) in N,N-dimethylformamide (3 mL) were added N-hydroxy-3-methoxybenzimidamide (82 mg, 496 μmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (156 mg, 413 μmol), and N-ethyl-N-(propan-2-yl)propan-2-amine (160 mg, 1.24 mmol, 216 μL). The mixture was stirred at 20 °C for 2 h, then heated at 120 °C for 2 h. The reaction mixture was cooled and purified directly by prep-HPLC (column: Luna C8 100x30 5μm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 35%-60%,12 min) to give N-(2-(4-(3-(3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide (83 mg, 198 μmol, 48 %) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91-7.85 (m, 2H), 7.72-7.68 (m, 1H), 7.62 (dd, *J* = 1.5, 2.5 Hz, 1H), 7.57-7.52 (m, 1H), 7.51-7.45 (m, 2H), 7.42 (t, *J* = 8.0 Hz, 1H), 7.38-7.32 (m, 1H), 7.08 (ddd, *J* = 0.9, 2.6, 8.3 Hz, 1H), 4.52 (d, *J* = 13.6 Hz, 1H), 4.33 (d, *J* = 4.0 Hz, 2H), 3.95 (br. s., 1H), 3.91 (s, 3H), 3.42-3.32 (m, 2H), 3.25-3.13 (m, 1H), 2.33-2.22 (m, 2H), 2.11-1.94 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 421.2.

Example 12: N-(2-(4-(3-(2-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide

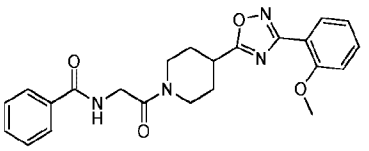


Step 1: Preparation of N-hydroxy-2-methoxybenzimidamide.



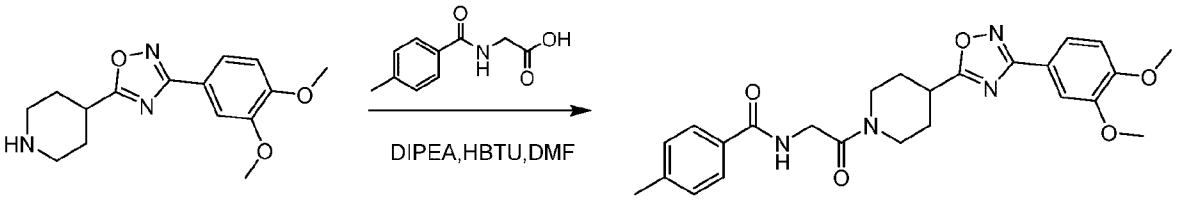
To a stirred solution of 2-methoxybenzonitrile (2.0 g, 15.0 mmol, 1.83 mL) in ethanol (20 mL) were added hydroxylamine hydrochloride (2.09 g, 30.0 mmol), triethylamine (3.04 g, 30.0 mmol, 4.16 mL), and water (2 mL), then the mixture was heated to 70 °C for 15h. The mixture was cooled and quenched with water (20 mL), extracted with dichloromethane (30 mL x 3), and the combined organic phases were washed with water (20 mL), saturated aqueous sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to give N-hydroxy-2-methoxybenzimidamide (2.80 g) as a light green solid, which was used in next step directly. ^{1}H NMR (400 MHz, Methanol-d4) δ 7.47 - 7.30 (m, 2H), 7.06 (d, J=8.4 Hz, 1H), 6.95 (t, J=7.5 Hz, 1H), 3.86 (s, 3H).

Step 2: Preparation of N-(2-(4-(3-(2-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.

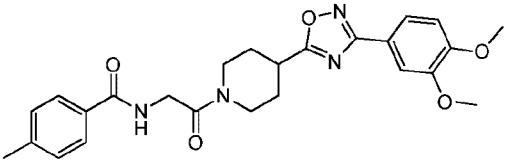


To a stirred solution of 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid (120 mg, 413 µmol) and N-hydroxy-2-methoxybenzimidamide (68 mg, 413 µmol) in N,N-dimethylformamide (2 mL) were added N-ethyl-N-(propan-2-yl)propan-2-amine (106 mg, 826 µmol, 144 µL) and (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (156 mg, 413 µmol), and the mixture was stirred for 15 h at 15 °C. The mixture was then heated to 110 °C and stirred for 5h. After cooling, the mixture was purified directly by prep-HPLC (column: Luna C8 100x30 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 25%-60%,12 min) to give N-(2-(4-(3-(2-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide (90 mg, 212 µmol, 51 %) as a yellow solid. ^{1}H NMR (400 MHz, Methanol-d4) δ 7.96 (d, J=7.5 Hz, 1H), 7.88 (d, J=7.9 Hz, 2H), 7.61 - 7.41 (m, 4H), 7.18 (d, J=8.8 Hz, 1H), 7.09 (t, J=7.5 Hz, 1H), 4.47 (d, J=13.2 Hz, 1H), 4.37 - 4.23 (m, 2H), 4.12 - 4.00 (m, 1H), 3.93 (s, 3H), 3.50 - 3.35 (m, 2H), 3.08 (t, J=11.5 Hz, 1H), 2.33 - 2.15 (m, 2H), 2.12 - 1.79 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 421.1.

Example 13: N-[2-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-2-oxo-ethyl]-4-methyl-benzamide.



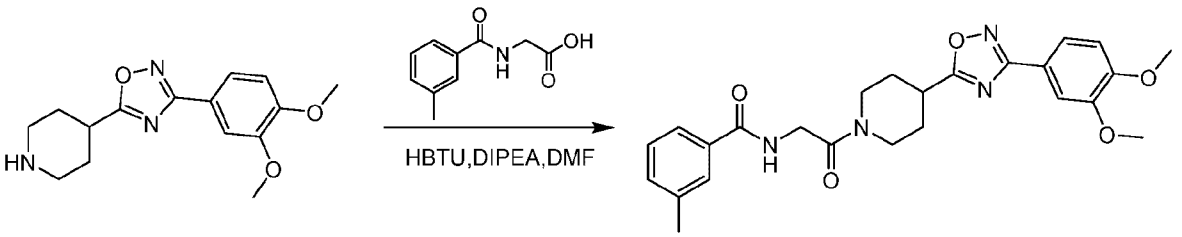
Step 1: Preparation of N-(2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)-4-methylbenzamide.



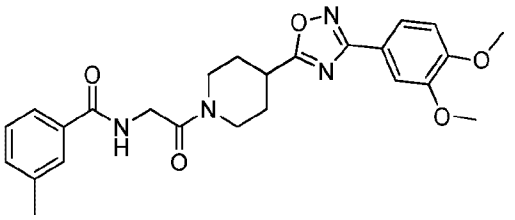
To a stirred solution of 3-(3,4-dimethoxyphenyl)-5-(4-piperidyl)-1,2,4-oxadiazole (150 mg, 518 µmol) in N,N-dimethylformamide (2 mL) were added (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (196 mg, 518 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (201 mg, 1.56 mmol, 271 µL) and 2-[(4-methylbenzoyl)amino]acetic acid (105 mg, 544 µmol). The mixture was stirred at 20 °C for 5 h. The crude product was purified by prep-HPLC (column: Luna C8 100x30mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%:30%-60%,12 min) to give N-(2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)-4-methylbenzamide.

^{1}H NMR (400MHz, METHANOL-d4) δ = 7.77 (d, J=7.5 Hz, 2H), 7.66 (d, J=8.2 Hz, 1H), 7.59 (s, 1H), 7.29 (d, J=7.7 Hz, 2H), 7.08 (d, J=8.4 Hz, 1H), 4.47 (d, J=12.8 Hz, 1H), 4.29 (m, J=6.0 Hz, 2H), 4.05 (d, J=14.1 Hz, 1H), 3.89 (s, 6H), 3.50 - 3.34 (m, 3H), 3.06 (t, J=12.0 Hz, 1H), 2.40 (s, 3H), 2.32 - 2.13 (t, 2H), 2.07 - 1.79 (m, 3H); LCMS (ESI) m/z: $[M+H]^+$ = 465.3.

Example 14: N-(2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)-3-methylbenzamide.

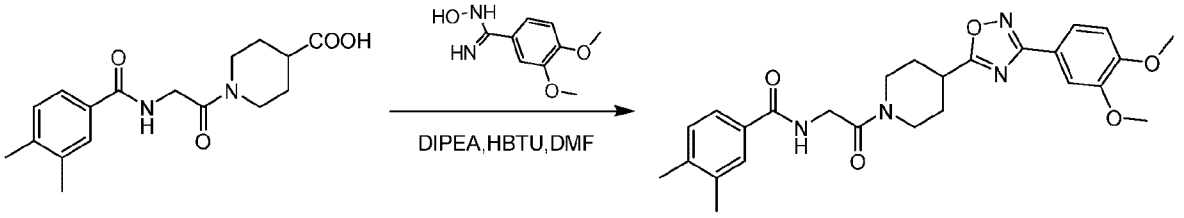


Preparation of N-(2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)-3-methylbenzamide

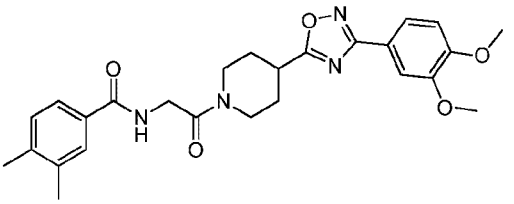


To a stirred solution of 3-(3,4-dimethoxyphenyl)-5-(4-piperidyl)-1,2,4-oxadiazole (200 mg, 691 µmol) in N,N-dimethylformamide (2 mL) was added N-ethyl-N-(propan-2-yl)propan-2-amine (268 mg, 2.07 mmol, 362 µL), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (262 mg, 691 µmol) and 2-[(3-methylbenzoyl)amino]acetic acid (133 mg, 691 µmol). The mixture was stirred at 20 °C for 16 h. The crude product was purified by prep-HPLC (column: Luna C8 100x30 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 30%-60%,12 min) to give N-[2-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-2-oxo-ethyl]-3-methyl-benzamide (157 mg, 338 µmol, 49 %) as a white solid. ^{1}H NMR (400MHz, DMSO-d6) δ = 8.48 (t, J=5.5 Hz, 1H), 7.72 - 7.63 (m, 2H), 7.58 (dd, J=2.0, 8.4 Hz, 1H), 7.46 (d, J=1.8 Hz, 1H), 7.34 (d, J=4.9 Hz, 2H), 7.11 (d, J=8.4 Hz, 1H), 4.32 (br d, J=13.0 Hz, 1H), 4.15 (dd, J=2.3, 5.4 Hz, 2H), 3.96 (d, J=13.7 Hz, 1H), 3.87 - 3.77 (m, 6H), 3.51 - 3.39 (m, 1H), 3.24 (s, 1H), 2.90 (t, J=11.6 Hz, 1H), 2.35 (s, 3H), 2.20 - 2.04 (m, 2H), 1.89 - 1.75 (m, 1H), 1.72 - 1.54 (m, 1H); LCMS (ESI) m/z: $[M+H]^+$ = 465.3.

Example 15: N-(2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)-3,4-dimethylbenzamide

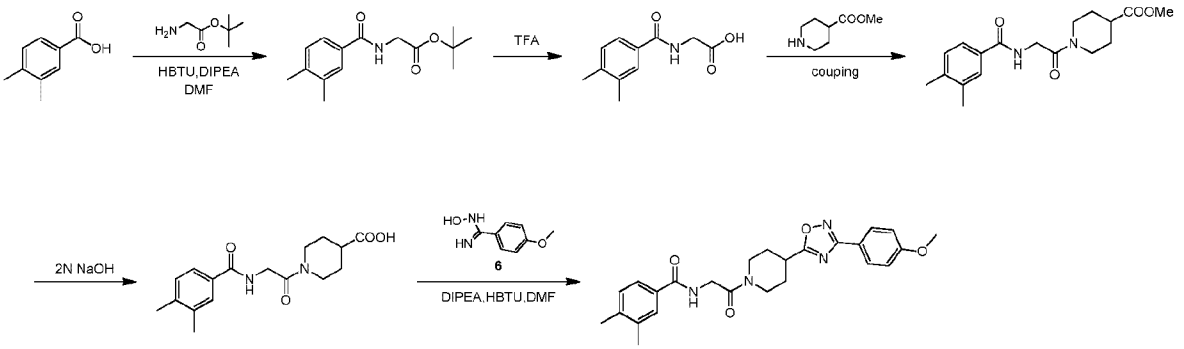


Preparation of N-(2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)-3,4-dimethylbenzamide

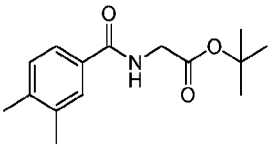


To a stirred solution of 1-[2-[(3,4-dimethylbenzoyl)amino]acetyl]piperidine-4-carboxylic acid (200 mg, 628 µmol) and N-hydroxy-3,4-dimethoxy-benzamidine (184 mg, 942 µmol) in N,N-dimethylformamide (1.50 mL) were added (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (238 mg, 628 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (243 mg, 1.88 mmol, 329 µL). The mixture was stirred at 20 ℃ for 16 h. The reaction mixture was diluted with water (5 mL) and extracted with ethyl acetate (10 mL x 3). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL x 2), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. N,N-Dimethylformamide (2 mL) was added, then the mixture was heated to 120 ℃ and stirred for a further 4 h. The mixture was cooled to 25 ℃, then water (5mL) was added, and the mixture extracted with ethyl acetate (10 mL x 3). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL x 2), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. This residue was purified by prep-HPLC (column: Luna C8 100x30 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 30%-65%,12 min) to give N-[2-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-2-oxo-ethyl]-3,4-dimethyl-benzamide (209 mg, 436 µmol, 69 %) as a yellow solid. ^{1}H NMR (400MHz, DMSO-d6) δ = 8.40 (s, 1H), 7.66 (s, 1H), 7.59 (br d, J=7.9 Hz, 2H), 7.46 (s, 1H), 7.21 (br d, J=7.7 Hz, 1H), 7.11 (br d, J=8.4 Hz, 1H), 4.32 (br d, J=12.6 Hz, 1H), 4.14 (br s, 2H), 3.96 (br d, J=13.5 Hz, 1H), 3.89 - 3.72 (m, 6H), 3.43 (br t, J=10.8 Hz, 1H), 3.28 - 3.17 (m, 1H), 2.90 (br t, J=11.5 Hz, 1H), 2.26 (s, 6H), 2.20-2.10 (m, 2H), 1.80 (br d, J=10.4 Hz, 1H), 1.64 (br d, J=10.1 Hz, 1H). (ESI) m/z: $[M+H]^+$ = 479.3.

Example 16: N-(2-(4-(3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)-3,4-dimethylbenzamide

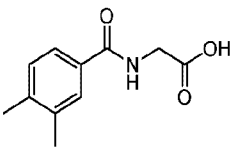


Step 1: Preparation of tert-butyl 2-(3,4-dimethylbenzamido)acetate.



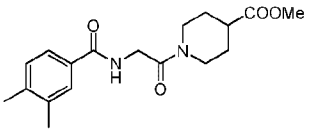
To a stirred solution of 3,4-dimethylbenzoic acid (2.0 g, 13.3 mmol) and tert-butyl 2-aminoacetate (1.92 g, 14.7 mmol) in N,N-dimethylformamide (20 mL) were added N-ethyl-N-(propan-2-yl)propan-2-amine (3.44 g, 26.6 mmol, 4.65 mL) and 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (5.06 g, 13.3 mmol). After stirring at 15 °C for 3h, the mixture was treated with water (30 mL), extracted with ethyl acetate (30 mL x 3), and the combined organic phases were washed with water (20 mL), 1N hydrochloric acid (30 mL), saturated aqueous sodium hydrogen carbonate (30 mL), saturated aqueous sodium chloride solution (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to give tert-butyl 2-(3,4-dimethylbenzamido)acetate (4.0 g) as light brown oil, which was used in the next step directly without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, J=1.6 Hz, 1H), 7.46 (dd, J=1.9, 7.9 Hz, 1H), 7.11 (d, J=7.8 Hz, 1H), 4.08 - 4.04 (m, 2H), 2.23 (s, 6H), 1.44 (s, 9H).

Step 2: Preparation of 2-(3,4-dimethylbenzamido)acetic acid



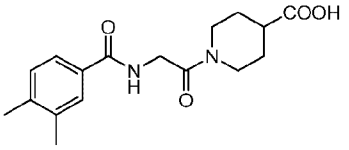
A solution of tert-butyl 2-(3,4-dimethylbenzamido)acetate (4.0 g, 15.2 mmol) in TFA (20 mL) and dichloromethane (20 mL) was stirred for 20 h at 15 °C. The mixture was concentrated, and the residue was treated with water (10 mL) and extracted with dichloromethane/methanol (20/1, 20 mL x 3). The combined organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated to give 2-(3,4-dimethylbenzamido)acetic acid (3.20 g) as a yellow oil, which was used in next step directly without further purification.

Step 3: Preparation of methyl 1-(2-(3,4-dimethylbenzamido)acetyl)piperidine-4-carboxylate.



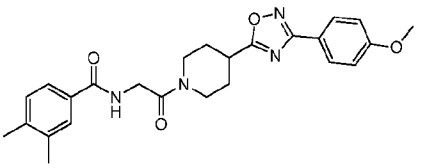
To a stirred solution of 2-(3,4-dimethylbenzamido)acetic acid (3.20 g, 15.4 mmol) and methyl piperidine-4-carboxylate (2.65 g, 18.5 mmol) in N,N-dimethylformamide (20 mL) were added N-ethyl-N-(propan-2-yl)propan-2-amine (3.99 g, 30.9 mmol, 5.39 mL) and (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (5.86 g, 15.4 mmol) at 0 ℃, then the mixture was warmed slowly to 15 ℃ and stirred for 15h. The mixture was treated with water (30 mL) at 0 ℃, extracted with ethyl acetate (50 mL x 3). The combined organic phase was washed with water (20 mL), 1N hydrochloric acid (30 mL), saturated aqueous sodium hydrogen carbonate solution (30 mL), saturated aqueous sodium chloride solution (30 mL), and dried over anhydrous sodium sulfate, filtered, and concentrated to give a crude product. Purification by chromatography (silica, petroleum ether/ethyl acetate from 10:1 to 1:2) gave methyl 1-(2-(3,4-dimethylbenzamido)acetyl)piperidine-4-carboxylate (3.50 g, 10.5 mmol, 68 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.57 (d, *J*=7.9 Hz, 1H), 7.28 (m, 1H), 7.19 (d, *J*=7.5 Hz, 1H), 4.39 (d, *J*=13.2 Hz, 1H), 4.24 (d, *J*=3.5 Hz, 2H), 3.78 (d, *J*=13.7 Hz, 1H), 3.71 (s, 3H), 3.17 (t, *J*=11.0 Hz, 1H), 3.02 - 2.91 (m, 1H), 2.67 - 2.54 (m, 1H), 2.30 (s, 6H), 1.98 (m, 2H), 1.80 - 1.64 (m, 2H).

Step 4: Preparation of 1-(2-(3,4-dimethylbenzamido)acetyl)piperidine-4-carboxylic acid.



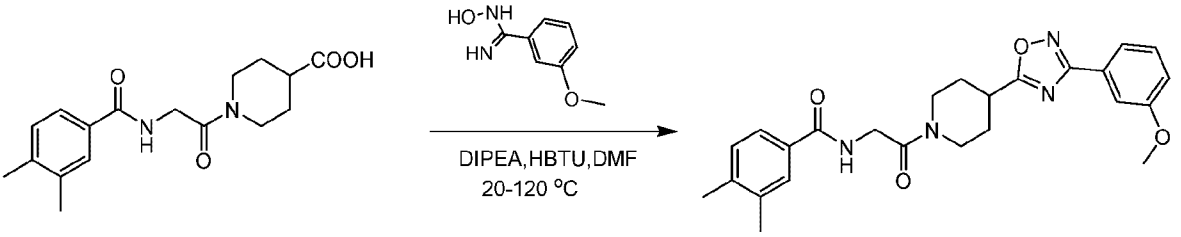
To a stirred solution of methyl 1-(2-(3,4-dimethylbenzamido)acetyl)piperidine-4-carboxylate (3.50 g, 10.5 mmol) in tetrahydrofuran (20 mL) and methanol (20 mL) was added aqueous sodium hydroxide (2 M, 7.90 mL), and the mixture was stirred at 15 ℃ for 5h. The mixture was concentrated to remove tetrahydrofuran and methanol, then then residue was acidified by 1N hydrochloric acid to pH = 2-3 at 0 ℃. The mixture was then extracted with dichloromethane (20 mL x 3), dried over anhydrous sodium sulfate, filtered, concentrated, and purified by prep-HPLC (column: Phenomenex luna C18 250x50mm 10 μm;mobile phase: [water (0.1%TFA)-acetonitrile]; B%: 10%-40%, 20min) to give 1-(2-(3,4-dimethylbenzamido)acetyl)piperidine-4-carboxylic acid (1.80 g, 5.65 mmol, 54 %) as a white solid. ^{1}H NMR (400 MHz, DMSO-d6) δ8.39 (s, 1H), 7.67 (s, 1H), 7.61 (d, *J*=7.7 Hz, 1H), 7.24 (d, *J*=7.7 Hz, 1H), 4.21 (d, *J*=12.7 Hz, 1H), 4.12 (d, *J*=4.9 Hz, 2H), 3.85 (d, *J*=13.8 Hz, 1H), 3.14 (t, *J*=11.7 Hz, 1H), 2.79 (t, *J*=11.5 Hz, 1H), 2.28 (s, 6H), 1.86 (m, 2H), 1.63 - 1.32 (m, 2H).

Step 5: Preparation of N-(2-(4-(3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)-3,4-dimethylbenzamide.



To a stirred solution of 1-(2-(3,4-dimethylbenzamido)acetyl)piperidine-4-carboxylic acid (150 mg, 471 µmol) and N-hydroxy-4-methoxybenzimidamide (93 mg, 565 µmol) in N,N-dimethylformamide (2 mL) was added N-ethyl-N-(propan-2-yl)propan-2-amine (121 mg, 942 µmol, 164 µL) and (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (178 mg, 471 µmol) at 15 °C. After 15 h, the mixture was heated to 110 °C and stirred for 5 h. The mixture was cooled and directly purified by prep-HPLC (column: Waters Xbridge 150x25 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 40%-70%,12 min) to give N-(2-(4-(3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)-3,4-dimethylbenzamide (110 mg, 244 µmol, 52 %) as a light yellow solid. ^{1}H NMR (400 MHz, Methanol-d4) δ7.98 (d, J=9.3 Hz, 2H), 7.66 (s, 1H), 7.60 (d, J=7.5 Hz, 1H), 7.23 (d, J=7.9 Hz, 1H), 7.05 (d, J=9.3 Hz, 2H), 4.46 (d, J=13.2 Hz, 1H), 4.34 - 4.23 (m, 2H), 4.04 (d, J=13.7 Hz, 1H), 3.86 (s, 3H), 3.47 - 3.36 (m, 2H), 3.07 (t, J=11.0 Hz, 1H), 2.42 - 2.26 (s, 6H), 2.21 (d, J=17.6 Hz, 2H), 2.04 - 1.82 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 449.2.

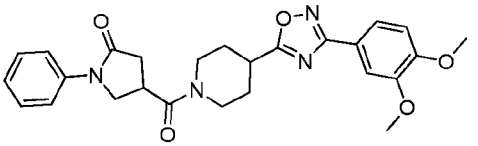
Example 17: N-(2-(4-(3-(3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)-3,4-dimethylbenzamide.



To a stirred solution of 1-(2-(3,4-dimethylbenzamido)acetyl)piperidine-4-carboxylic acid (150 mg, 471 µmol) in N,N-dimethylformamide (3 mL) were added N-hydroxy-3-methoxybenzimidamide (93 mg, 565 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (178 mg, 471 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (182 mg, 1.41 mmol, 246 µL). The mixture was stirred at 20 °C for 2 h and then heated at 120 °C for 2 h. The reaction mixture was cooled and then purified directly by prep-HPLC (column: Luna C8 100x30 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 40%-70%,12 min) to give N-(2-(4-(3-(3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)-3,4-dimethylbenzamide (119 mg, 263 µmol, 56 %) as a white solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.63-7.47 (m, 4H), 7.32 (t, *J* = 7.9 Hz, 1H), 7.23-7.20 (m, 1H), 7.15-7.10 (m, 1H), 6.98 (dd, *J* = 1.8, 8.3 Hz, 1H), 4.48-4.37 (m, 1H), 4.22 (d, *J* = 3.9 Hz, 2H), 3.88-3.82 (m, 1H), 3.81 (s, 3H), 3.31-3.22 (m, 2H), 3.13-3.04 (m, 1H), 2.24 (s, 6H), 2.22-2.12 (m, 2H), 2.00-1.87 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 449.3.

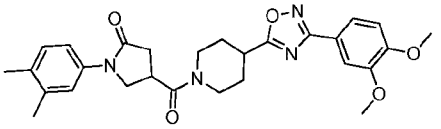
***Example 18**: 4-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)-1-phenylpyrrolidin-2-one*

Step 1: Preparation of 4-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)-1-phenylpyrrolidin-2-one.



To a stirred solution of 3-(3,4-dimethoxyphenyl)-5-(4-piperidyl)-1,2,4-oxadiazole (150 mg, 518 µmol) in N,N-dimethylformamide (1.5 mL) were added (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (196 mg, 518 µmol), N-ethyl-N-(propan-2-yl)propan-2-amine (201 mg, 1.56 mmol, 271 µL) and 5-oxo-1-phenyl-pyrrolidine-3-carboxylic acid (111 mg, 544 µmol). The mixture was stirred at 20 °C for 16 h. The mixture was filtered, and the filtrate was purified directly by prep-HPLC (column: Luna C8 100x30 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 30%-60%,12 min) to give 4-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]piperidine-1-carbonyl]-1-phenyl-pyrrolidin-2-one (86 mg, 181 µmol, 35 %) as a white solid. ^{1}H NMR (400MHz, METHANOL-d4) δ = 7.69 - 7.56 (m, 4H), 7.38 (br t, J=7.2 Hz, 2H), 7.22 - 7.16 (m, 1H), 7.08 (br d, J=8.4 Hz, 1H), 4.56 - 4.42 (m, 1H), 4.19 - 4.04 (m, 3H), 3.89 (s, 6H), 3.86 - 3.81 (m, 1H), 3.50 - 3.37 (m, 2H), 3.14 - 3.00 (m, 1H), 2.94 - 2.78 (m, 2H), 2.31 - 2.16 (m, 2H), 2.01 - 1.81 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 477.3.

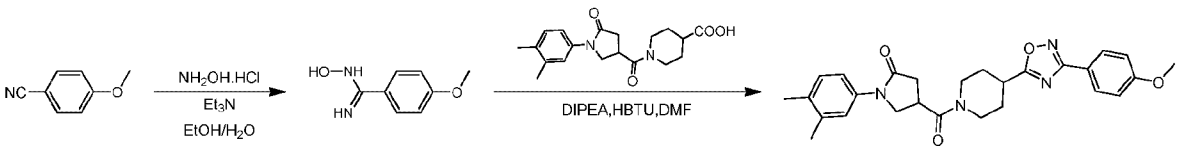
Example 19: 4-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)-1-(3,4-dimethylphenyl)pyrrolidin-2-one.



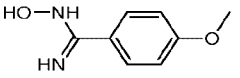
To a stirred solution of 1-[1-(3,4-dimethylphenyl)-5-oxo-pyrrolidine-3-carbonyl]piperidine-4-carboxylic acid (200 mg, 581 µmol) in N,N-dimethylformamide (1.5 mL) were added (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (220 mg, 581 µmol), N-ethyl-N-(propan-2-yl)propan-2-amine (225 mg, 1.74 mmol, 304 µL), and N-hydroxy-3,4-dimethoxy-benzamidine (125 mg, 639 µmol). The mixture was stirred at 20 °C for 12 h. The reaction mixture was diluted with water (5mL) and extracted with ethyl acetate (10 mL x 3). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL x 2), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The residue was dissolved in N,N-dimethylformamide (2 mL) then heated at 120 °C for 5 h. The mixture was cooled to 25 °C then diluted with water (5mL) and extracted with ethyl acetate (10 mL x 3). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL x 2), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a residue that was purified by prep-

HPLC (column: Waters Xbridge 150x25 5μm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 35%-65%,12 min), to give 4-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]piperidine-1-carbonyl]-1-(3,4-dimethylphenyl)pyrrolidin-2-one (7 mg, 15 μmol, 3 %) as a pink solid. ^{1}H NMR (400MHz, METHANOL-d4) δ = 7.66 (br d, J=8.2 Hz, 1H), 7.58 (s, 1H), 7.36 (s, 1H), 7.27 (br d, J=8.2 Hz, 1H), 7.16 - 7.04 (m, 2H), 4.49 (br d, J=8.4 Hz, 1H), 4.18 - 3.98 (m, 3H), 3.93 - 3.77 (m, 7H), 3.48 - 3.36 (m, 2H), 3.12 - 2.97 (m, 1H), 2.92 - 2.78 (m, 2H), 2.32 - 2.14 (m, 8H), 2.01 - 1.79 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 505.4.

Example 20: 1-(3,4-dimethylphenyl)-4-(4-(3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)pyrrolidin-2-one.

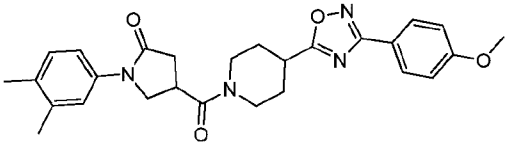


Step 1: Preparation of N-hydroxy-4-methoxybenzimidamide.



To a stirred solution of 4-methoxybenzonitrile (2.0 g, 15.02 mmol) in ethanol (20 mL) was added hydroxylamine hydrochloride (2.09 g, 30.0mmol) and triethylamine (3.04 g, 30.0mmol, 4.16 mL) and water (2 mL), then the mixture was heated to 70 ℃ for 15h. The mixture was treated with water (20 mL) and extracted with dichloromethane (30 mL x 3). The combined organic phases were washed with water (20 mL), saturated aqueous sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to give crude N-hydroxy-4-methoxybenzimidamide (2.50 g) as a white solid, which was used in the next step directly. ^{1}H NMR (400 MHz, Methanol-d4) δ 7.61 - 7.48 (m, 2H), 6.98 - 6.85 (m, 2H), 3.81 (s, 3H).

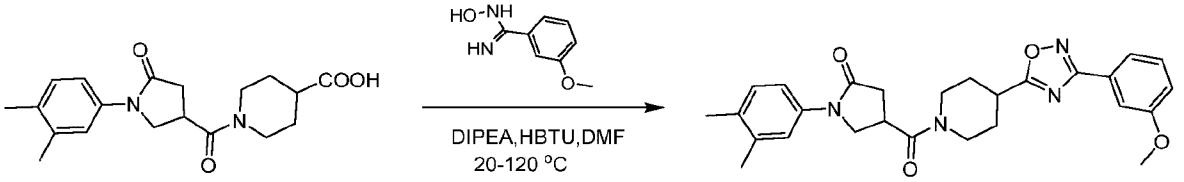
Step 2: Preparation of 1-(3,4-dimethylphenyl)-4-(4-(3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)pyrrolidin-2-one.



To a stirred solution of 1-(1-(3,4-dimethylphenyl)-5-oxopyrrolidine-3-carbonyl)piperidine-4-carboxylic acid (250 mg, 726 μmol) and N-hydroxy-4-methoxybenzimidamide (120 mg, 726 μmol) in N,N-dimethylformamide (3 mL) was added N-ethyl-N-(propan-2-yl)propan-2-amine (187 mg, 1.45 mmol, 253 μL) and (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (275 mg, 726 μmol), After 15h at 15 ℃, the mixture was heated to 110 ℃ and stirred for 5 h. The reaction mixture was cooled and purified directly by prep-HPLC (column: Waters Xbridge 150x25 5μm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 36%-66%,12 min) to give 1-(3,4-dimethylphenyl)-4-(4-(3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)pyrrolidin-2-one (101 mg, 213 μmol, 29 %) as a light yellow solid. ^{1}H NMR (400 MHz, Methanol-d4) δ 7.98 (d, J=7.5 Hz, 2H), 7.36 (s, 1H), 7.27 (d, J=7.9

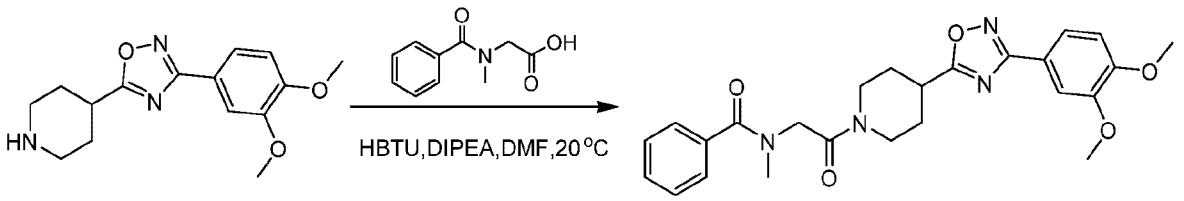
Hz, 1H), 7.13 (d, J=8.4 Hz, 1H), 7.04 (d, J=8.4 Hz, 2H), 4.47 (m., 1H), 4.19 - 3.96 (m, 3H), 3.86 (s, 3H), 3.84 - 3.78 (m, 1H), 3.42 (m, 2H), 3.16 - 2.98 (m, 1H), 2.93 - 2.74 (m, 2H), 2.37 - 2.10 (m, 8H), 2.02 - 1.78 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 475.3.

Example 21: 1-(3,4-dimethylphenyl)-4-(4-(3-(3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)pyrrolidin-2-one.



To a stirred solution of 1-(1-(3,4-dimethylphenyl)-5-oxopyrrolidine-3-carbonyl)piperidine-4-carboxylic acid (200 mg, 581 µmol) in N,N-dimethylformamide (3 mL) was added N-hydroxy-3-methoxybenzimidamide (96 mg, 581 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (220 mg, 581 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (225 mg, 1.74 mmol, 304 µL). The mixture was stirred at 20 °C for 2 h, then heated at 120 °C for 2 h. The reaction mixture was purified directly by prep-HPLC (column: Luna C8 100x30 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 40%-60%,12 min) to give 1-(3,4-dimethylphenyl)-4-(4-(3-(3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)pyrrolidin-2-one (80 mg, 168 µmol, 29 %) as a yellow solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.72-7.67 (m, 1H), 7.62 (s, 1H), 7.45-7.37 (m, 2H), 7.30 (d, *J* = 2.3 Hz, 1H), 7.15 (d, *J* = 8.3 Hz, 1H), 7.11-7.06 (m, 1H), 4.61-4.47 (m, 1H), 4.30 (dd, *J* = 7.3, 9.5 Hz, 1H), 3.91 (s, 5H), 3.64-3.54 (m, 1H), 3.46-3.30 (m, 2H), 3.21-3.05 (m, 1H), 3.03-2.92 (m, 1H), 2.89-2.79 (m, 1H), 2.28 (d, *J* = 13.1 Hz, 8H), 2.10-1.90 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 475.3.

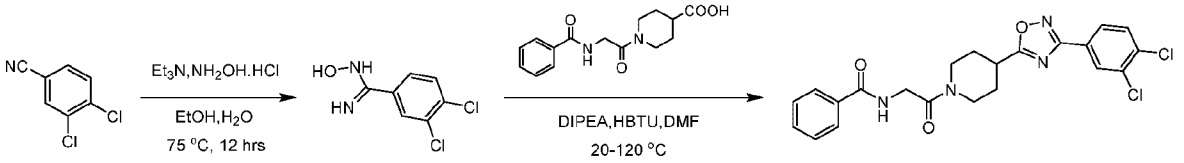
Example 22: N-(2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)-N-methylbenzamide.



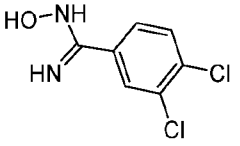
To a stirred solution of 3-(3,4-dimethoxyphenyl)-5-(4-piperidyl)-1,2,4-oxadiazole (150 mg, 518 µmol) in N,N-dimethylformamide (2 mL) was added (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (196 mg, 518 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (201 mg, 1.56 mmol, 271 µL) and 2-[benzoyl(methyl)amino]acetic acid (105 mg, 544 µmol). The mixture was stirred at 20 °C for 5 h, then cooled and purified directly by prep-HPLC (column: Luna C8 100x30 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 30%-60%,12 min) to give N-[2-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-2-oxo-ethyl]-N-methyl-benzamide (133 mg, 282 µmol, 54 %) as a white solid. ^{1}H NMR (400MHz, DMSO-d_6) δ = 7.59 (dd, *J*=1.8, 8.4 Hz, 1H), 7.49 - 7.32 (m,

5H), 7.27 (br d, *J*=6.8 Hz, 1H), 7.16 - 7.08 (m, 1H), 4.44 - 4.24 (m, 2H), 4.21 - 4.03 (m, 1H), 4.02 - 3.88 (m, 1H), 3.88 - 3.74 (m, 6H), 3.56 (br d, *J*=13.7 Hz, 1H), 3.48 - 3.33 (m, 1H), 3.11 - 2.77 (m, 5H), 2.20 - 1.99 (m, 2H), 1.86 (br t, *J*=12.6 Hz, 1H), 1.74 - 1.48 (m, 2H), 1.43 - 1.26 (m, 1H); LCMS (ESI) m/z: $[M+H]^+$ = 465.3.

Example 23: N-(2-(4-(3-(3,4-dichlorophenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.

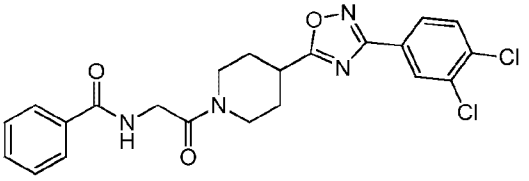


Step 1: Preparation of 3,4-dichloro-N-hydroxybenzimidamide.



To a stirred solution of 3,4-dichlorobenzonitrile (1.0 g, 5.81 mmol) in ethanol (20 mL) was added hydroxylamine hydrochloride (807 mg, 11.6 mmol), triethylamine (1.18 g, 11.6 mmol, 1.61 mL) and water (2 mL). The mixture was heated at 75 °C for 5 h, then cooled to 20 °C. Water (20 mL) was added to the solution. The mixture was extracted with dichloromethane (40 mL x 4). The combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL) and dried over anhydrous sodium sulfate, then filtered and concentrated in vacuo to give 3,4-dichloro-N-hydroxybenzimidamide (1.20 g) as a white solid. This was used directly without further purification. ^{1}H NMR (400 MHz, DMSO-d6) δ 9.86 (s, 1H), 7.87 (d, *J* = 1.8 Hz, 1H), 7.69-7.58 (m, 2H), 5.95 (s, 2H).

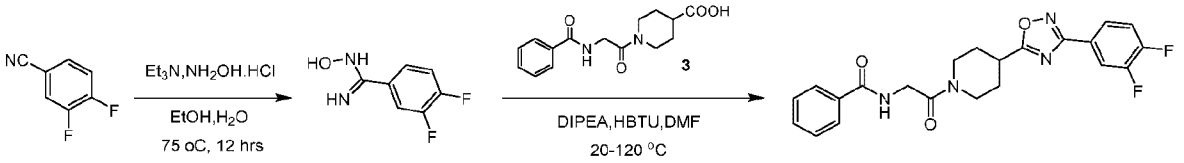
Step 2: Preparation of N-(2-(4-(3-(3,4-dichlorophenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.



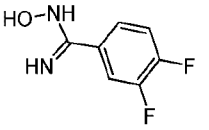
To a stirred solution of 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid (200 mg, 688.92 µmol) in N,N-dimethylformamide (4 mL) was added 3,4-dichloro-N-hydroxybenzimidamide (169 mg, 826 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (261 mg, 688.92 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (267 mg, 2.07 mmol, 360 µL). The mixture was stirred at 20 °C for 2 h, then heated at 120 °C for 2 h. The reaction mixture cooled then purified directly by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 40%-70%,12 min) to give N-(2-(4-(3-(3,4-dichlorophenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide (92 mg, 201 µmol, 29 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14-8.09 (m, 1H), 7.85 (dd, *J* = 2.0, 8.2 Hz, 1H), 7.78 (d, *J* = 7.1 Hz, 2H), 7.39 (s, 4H), 7.25 (br. s., 1H), 4.43

(d, J = 13.7 Hz, 1H), 4.24 (d, J = 3.5 Hz, 2H), 3.84 (d, J = 14.1 Hz, 1H), 3.33-3.22 (m, 2H), 3.14-3.03 (m, 1H), 2.23-2.13 (m, 2H), 1.99-1.86 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 459.1.

Example 24: N-(2-(4-(3-(3,4-difluorophenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.

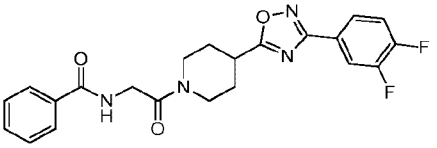


Step 1: Preparation of 3,4-difluoro-N-hydroxybenzimidamide.



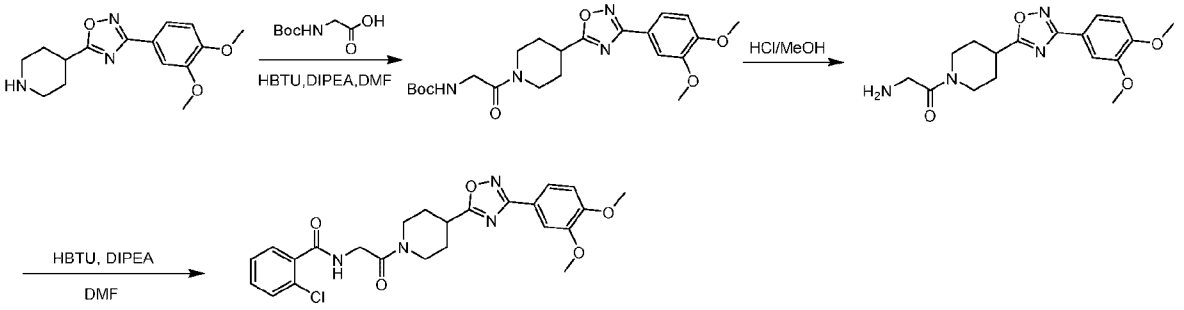
To a stirred solution of 3,4-difluorobenzonitrile (1.0 g, 7.19 mmol) in ethanol (20 mL) were added hydroxylamine hydrochloride (999 mg, 14.4 mmol), triethylamine (1.46 g, 14.4 mmol, 1.99 mL), and water (2 mL). The mixture was heated at 75 °C for 2 h. After cooling to 20 °C, water (20 mL) was added to the solution. The mixture was extracted with dichloromethane (30 mL x 4). The combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, then filtered, and concentrated in vacuo to give 3,4-difluoro-N-hydroxybenzimidamide (1.24 g) as a white solid. This was used directly without further purification. ^{1}H NMR (400 MHz, DMSO-d6) δ 9.79 (s, 1H), 7.68 (ddd, J = 2.0, 8.0, 12.2 Hz, 1H), 7.55 (br. s., 1H), 7.50-7.39 (m, 1H), 5.92 (br. s., 2H).

Step 2: Preparation of N-(2-(4-(3-(3,4-difluorophenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.

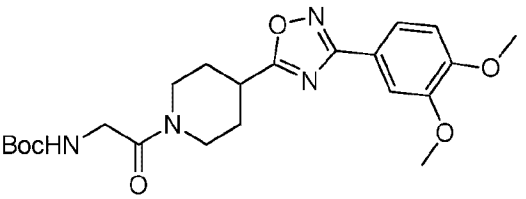


To a stirred solution of 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid (120 mg, 413 µmol) in N,N-dimethylformamide (4 mL) were added 3,4-difluoro-N-hydroxybenzimidamide (85 mg, 496 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (156 mg, 413 µmol), and N-ethyl-N-(propan-2-yl)propan-2-amine (160 mg, 1.24 mmol, 216 µL). The mixture was stirred at 20 °C for 2 h, then heated at 120 °C for 2 h. The reaction mixture was cooled then purified directly by prep-HPLC (column: Luna C8 100x30 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 35%-60%,12 min) to give N-(2-(4-(3-(3,4-difluorophenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide (50 mg, 118 µmol, 28 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 7.1 Hz, 4H), 7.44 (d, J = 7.1 Hz, 1H), 7.42-7.35 (m, 2H), 7.23 (d, J = 8.4 Hz, 2H), 4.43 (d, J = 13.7 Hz, 1H), 4.23 (d, J = 4.0 Hz, 2H), 3.84 (d, J = 13.7 Hz, 1H), 3.32-3.21 (m, 2H), 3.13-3.03 (m, 1H), 2.23-2.12 (m, 2H), 1.99-1.84 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 427.2.

Example 25: 2-chloro-N-(2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.

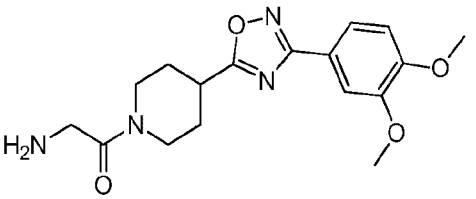


Step 1: Preparation of tert-butyl (2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)carbamate.



To a stirred solution of 3-(3,4-dimethoxyphenyl)-5-(piperidin-4-yl)-1,2,4-oxadiazole (2.0 g, 6.91 mmol) in N,N-dimethylformamide (20 mL) was added 2-(tert-butoxycarbonylamino)acetic acid (1.21 g, 6.91 mmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (2.62 g, 6.91 mmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (2.68 g, 20.7 mmol, 3.62 mL). The mixture was stirred at 15 ℃ for 2 h. The reaction mixture was quenched by addition of water (20 mL), then the mixture was extracted with ethyl acetate (60 mL x 4). The combined organic phases were washed with saturated aqueous sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to give a crude residue. Purification by chromatography (silica, petroleum ether : ethyl acetate = 5:1 to 1:1) gave tert-butyl (2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)carbamate (2.60 g, 5.82 mmol, 84 %) as a brown solid that was used directly without further purification. LCMS (ESI) m/z: $[M+H]^+$ = 447.2.

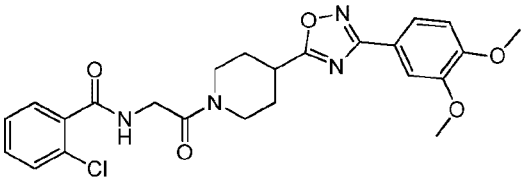
Step 2: Preparation of 2-amino-1-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)ethanone.



To a stirred solution of tert-butyl (2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)carbamate (2.50 g, 5.60 mmol) in methanol (10 mL) was added methanolic hydrogen chloride solution (4M, 30 mL). The mixture was stirred at 20 ℃ for 1 h. The reaction mixture was concentrated to give crude product. A part of crude product (0.1 g) was purified by prep-HPLC (column: Waters Xbridge 150x2.5mm 5μm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%:

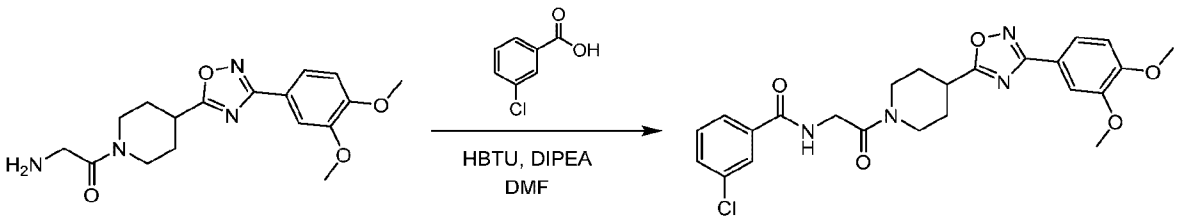
20%-50%,12 min) to give 2-amino-1-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)ethanone (32 mg) for analysis. The remaining crude 2-amino-1-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)ethanone (1.90 g, 5.49 mmol, 98 %), obtained as a brown solid, was used directly. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73-7.67 (m, 1H), 7.58 (d, J = 1.5 Hz, 1H), 6.98 (d, J = 8.4 Hz, 1H), 4.54 (d, J = 12.2 Hz, 1H), 3.98 (d, J = 7.2 Hz, 6H), 3.84 (d, J = 12.0 Hz, 1H), 3.54 (s, 2H), 3.34-3.21 (m, 2H), 3.08 (d, J = 12.3 Hz, 1H), 2.21 (d, J = 13.1 Hz, 2H), 1.98 (d, J = 9.4 Hz, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 347.1.

Step 3: Preparation of 2-chloro-N-(2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.



To a stirred solution of 2-amino-1-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)ethanone (185 mg, 537 µmol) in N,N-dimethylformamide (3 mL) was added 2-chlorobenzoic acid (70 mg, 447 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (169 mg, 447 µmol), and N-ethyl-N-(propan-2-yl)propan-2-amine (231 mg, 1.79 mmol, 312 µL). The mixture was stirred at 20 ℃ for 2 h, then purified directly by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 26%-56%,12 min) to give 2-chloro-N-(2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide (124 mg, 256 µmol, 57 %) as a pink solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (ddd, *J* = 1.9, 6.3, 7.9 Hz, 2H), 7.59 (d, *J* = 1.9 Hz, 1H), 7.49-7.33 (m, 4H), 6.98 (d, *J* = 8.4 Hz, 1H), 4.52 (d, *J* = 13.6 Hz, 1H), 4.36 (d, *J* = 4.0 Hz, 2H), 3.99 (d, *J* = 7.8 Hz, 6H), 3.92 (d, *J* = 13.8 Hz, 1H), 3.41-3.30 (m, 2H), 3.16 (t, *J* = 10.9 Hz, 1H), 2.33-2.21 (m, 2H), 2.11-1.94 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 485.2.

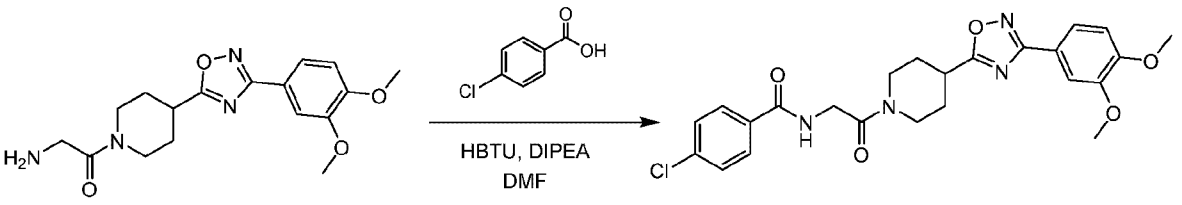
Example 26: 3-chloro-N-(2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.



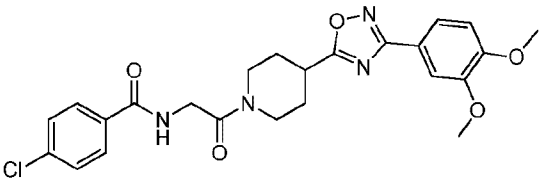
To a stirred solution of 2-amino-1-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)ethanone (185 mg, 537 µmol) in N,N-dimethylformamide (3 mL) were added 3-chlorobenzoic acid (70 mg, 447 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (169 mg, 447 µmol), and N-ethyl-N-(propan-2-yl)propan-2-amine (231 mg, 1.79 mmol, 312 µL). The mixture was stirred at 20 ℃ for 2 h. The reaction mixture was purified directly by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 26%-56%,12

min) to give 3-chloro-N-(2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide (126 mg, 261 µmol, 58 %) as a white solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.89-7.86 (m, 1H), 7.72 (d, *J* = 2.0 Hz, 2H), 7.59 (d, *J* = 1.9 Hz, 1H), 7.54-7.50 (m, 1H), 7.45-7.39 (m, 1H), 7.34 (br. s., 1H), 6.98 (d, *J* = 8.5 Hz, 1H), 4.53 (d, *J* = 14.3 Hz, 1H), 4.31 (d, *J* = 3.9 Hz, 2H), 3.98 (d, *J* = 7.4 Hz, 6H), 3.96-3.87 (m, 1H), 3.41-3.30 (m, 2H), 3.18 (t, *J* = 10.9 Hz, 1H), 2.33-2.22 (m, 2H), 2.10-1.94 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 485.3.

Example 27: 4-chloro-N-(2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.

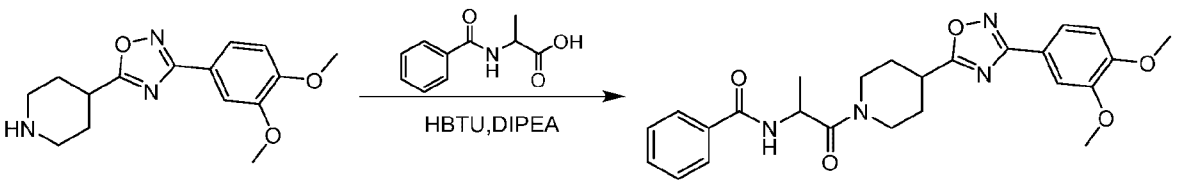


Step 1: Preparation of 4-chloro-N-(2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.



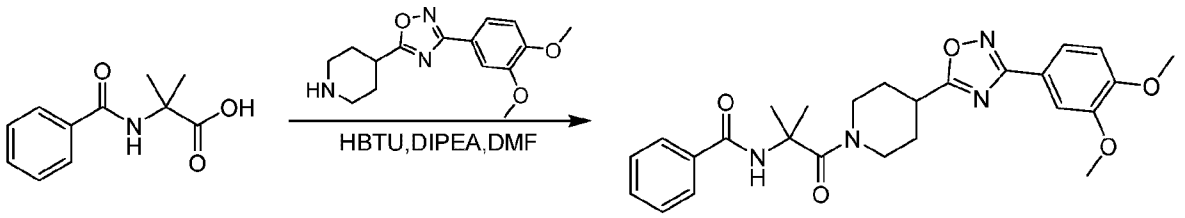
To a stirred solution of 2-amino-1-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)ethanone (185 mg, 536.5 µmol) in N,N-dimethylformamide (3 mL) were added 4-chlorobenzoic acid (70 mg, 447 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (169 mg, 447 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (231 mg, 1.79 mmol, 312 µL). The mixture was stirred at 20 ℃ for 2 h. The reaction mixture was purified directly by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 30%-60%,12 min) to give 4-chloro-N-(2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide (144 mg, 294 µmol, 66 %) as a white solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.5 Hz, 2H), 7.71 (dd, *J* = 1.9, 8.3 Hz, 1H), 7.59 (d, *J* = 1.8 Hz, 1H), 7.45 (d, *J* = 8.5 Hz, 2H), 7.33 (br. s., 1H), 6.98 (d, *J* = 8.4 Hz, 1H), 4.52 (d, *J* = 14.2 Hz, 1H), 4.31 (d, *J* = 3.9 Hz, 2H), 3.98 (d, *J* = 7.3 Hz, 6H), 3.92 (d, *J* = 13.7 Hz, 1H), 3.41-3.30 (m, 2H), 3.17 (t, *J* = 10.7 Hz, 1H), 2.34-2.21 (m, 2H), 2.10-1.94 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 485.2.

Example 28: N-(1-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-1-oxopropan-2-yl)benzamide.



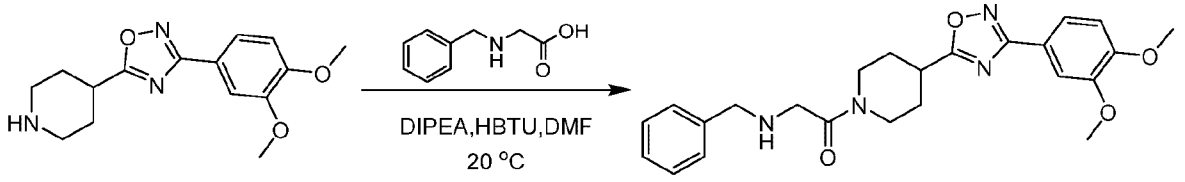
To a stirred solution of 3-(3,4-dimethoxyphenyl)-5-(4-piperidyl)-1,2,4-oxadiazole (150 mg, 518 µmol) in N,N-dimethylformamide (2 mL) were added (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (196 mg, 518 µmol), N-ethyl-N-(propan-2-yl)propan-2-amine (201 mg, 1.56 mmol, 271 µL), and 2-benzamidopropanoic acid (105 mg, 544 µmol). The mixture was stirred at 20 °C for 7 h, then the crude product was purified directly by prep-HPLC (column: Luna C8 100x30 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile; B%: 35%-60%,12 min] to give N-[2-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-1-methyl-2-oxo-ethyl]benzamide (52 mg, 112 µmol, 22 %) as a white solid. ^{1}H NMR (400MHz, DMSO-d6) δ = 8.63 (br dd, J=7.3, 16.1 Hz, 1H), 7.88 (br d, J=7.3 Hz, 2H), 7.66 - 7.34 (m, 5H), 7.11 (br d, J=7.9 Hz, 1H), 4.97 (br d, J=6.0 Hz, 1H), 4.45 - 4.22 (m, 1H), 4.08 - 3.94 (m, 1H), 3.82 (s, 6H), 3.42 (br t, J=10.7 Hz, 1H), 3.29 - 3.21 (m, 1H), 3.00 - 2.80 (m, 1H), 2.09 (br d, J=11.9 Hz, 2H), 1.87 - 1.56 (m, 1H), 1.29 (s, 3H); LCMS (ESI) m/z: $[M+H]^+$ = 465.3.

Example 29: N-(1-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-methyl-1-oxopropan-2-yl)benzamide.



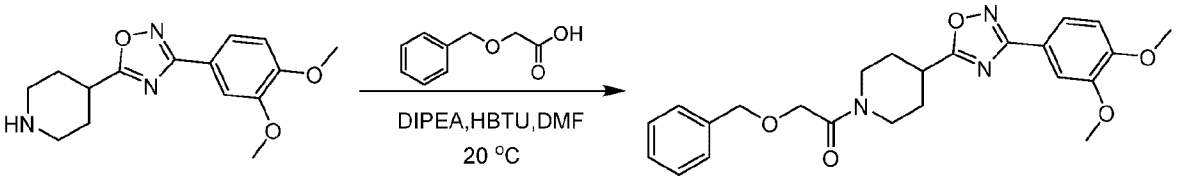
To a stirred solution of 3-(3,4-dimethoxyphenyl)-5-(4-piperidyl)-1,2,4-oxadiazole (150 mg, 518 µmol) in N,N-dimethylformamide (2 mL) was added (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (196 mg, 518 µmol), N-ethyl-N-(propan-2-yl)propan-2-amine (201 mg, 1.56 mmol, 271 µL) and 2-benzamido-2-methyl-propanoic acid (112 mg, 544 µmol). The mixture was stirred at 20 °C for 5 h. The crude product was purified directly by prep-HPLC (column: Waters Xbridge 150x25 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 27%-57%,12 min) to give N-[2-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-1,1-dimethyl-2-oxo-ethyl]benzamide (47 mg, 99 µmol, 19 %) as a pale yellow solid. ^{1}H NMR (400MHz, METHANOL-d4) δ = 7.88 - 7.81 (m, 2H), 7.62 (dd, J=2.0, 8.4 Hz, 1H), 7.57 - 7.51 (m, 2H), 7.49 - 7.42 (m, 2H), 7.06 (d, J=8.4 Hz, 1H), 4.61 - 4.45 (m, 2H), 3.88 (d, J=5.1 Hz, 6H), 3.13 (s, 3H), 2.08 (br s, 2H), 1.90 - 1.74 (m, 2H), 1.60 (s, 6H); LCMS (ESI) m/z: $[M+H]^+$ = 477.1.

Example 30: 2-(benzylamino)-1-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)ethanone.



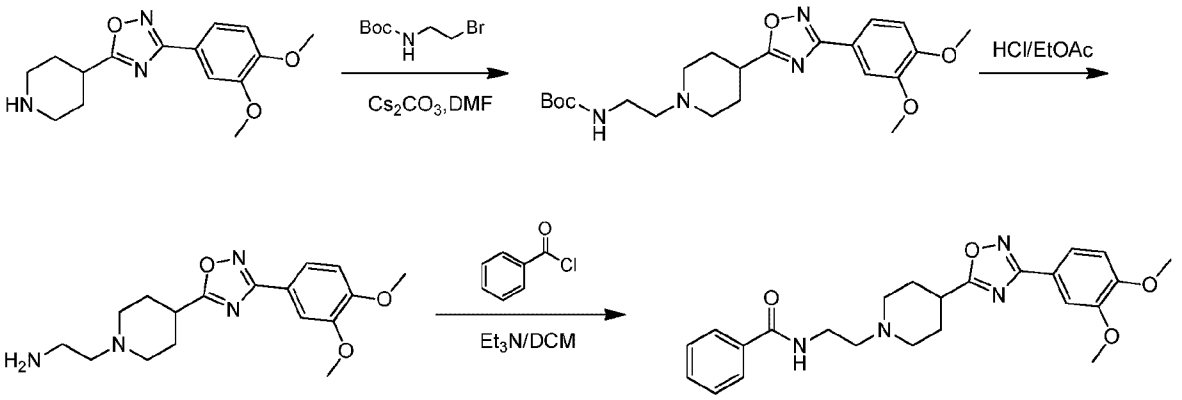
To a stirred solution of 3-(3,4-dimethoxyphenyl)-5-(4-piperidyl)-1,2,4-oxadiazole (150 mg, 518 µmol) in N,N-dimethylformamide (1.50 mL) were added (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (196 mg, 518 µmol), N-ethyl-N-(propan-2-yl)propan-2-amine (201 mg, 1.56 mmol, 271 µL), and 2-(benzylamino)acetic acid (89 mg, 544 µmol). The mixture was stirred at 20 °C for 16 h and filtered, and the crude filtrate was purified directly by prep-HPLC (column: Luna C8 100x30 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 30%-60%,12 min) to give 2-(benzylamino)-1-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]ethanone (48 mg, 110 µmol, 21 %) as a yellow solid. ^{1}H NMR (400MHz, METHANOL-d4) δ = 7.65 (dd, J=1.8, 8.2 Hz, 1H), 7.57 (d, J=1.8 Hz, 1H), 7.40 - 7.30 (m, 4H), 7.28 - 7.22 (m, 1H), 7.06 (d, J=8.4 Hz, 1H), 4.45 (br d, J=13.7 Hz, 1H), 3.94 - 3.83 (m, 7H), 3.78 (s, 2H), 3.57 - 3.44 (m, 2H), 3.40 - 3.33 (m, 1H), 3.27 - 3.20 (m, 1H), 3.01 (t, J=11.2 Hz, 1H), 2.17 (dd, J=2.8, 13.3 Hz, 2H), 1.93 - 1.73 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 437.3.

Example 31: 2-(benzyloxy)-1-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)ethanone.

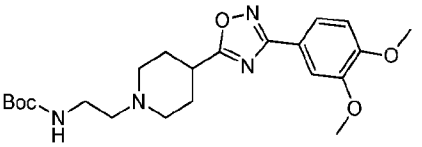


To a stirred solution of 3-(3,4-dimethoxyphenyl)-5-(4-piperidyl)-1,2,4-oxadiazole (150 mg, 518 µmol) in N,N-dimethylformamide (2 mL) were added (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (196 mg, 518 µmol), N-ethyl-N-(propan-2-yl)propan-2-amine (201 mg, 1.56 mmol, 271 µL), and 2-benzyloxyacetic acid (90 mg, 544 µmol, 77 µL). The mixture was stirred at 20 °C for 5 h. The crude product was purified directly by prep-HPLC (column: Waters Xbridge 150x25 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 32%-62%,12 min) to give 2-benzyloxy-1-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]ethanone (68 mg, 157 µmol, 30 %) as a white solid. ^{1}H NMR (400MHz, DMSO-d6) δ = 7.60 (dd, J=1.9, 8.3 Hz, 1H), 7.48 (d, J=1.9 Hz, 1H), 7.40 - 7.35 (m, 4H), 7.34 - 7.26 (m, 1H), 7.14 (d, J=8.4 Hz, 1H), 4.54 (s, 2H), 4.33 (br d, J=13.2 Hz, 1H), 4.25 (br d, J=7.8 Hz, 2H), 3.93 - 3.78 (m, 7H), 3.43 (tt, J=3.9, 11.0 Hz, 1H), 3.22 (br t, J=11.7 Hz, 1H), 2.90 (br t, J=11.7 Hz, 1H), 2.17 - 2.04 (m, 2H), 1.88 - 1.59 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 438.3.

Example 32: N-[2-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]ethyl]benzamide

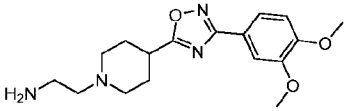


Step 1: Preparation of tert-butyl (2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)ethyl)carbamate



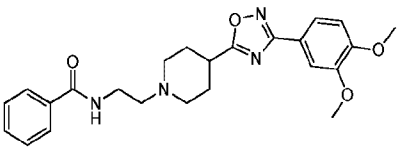
To a stirred solution of 3-(3,4-dimethoxyphenyl)-5-(4-piperidyl)-1,2,4-oxadiazole (750 mg, 2.59 mmol) in N,N-dimethylformamide (1 mL) were added cesium carbonate (844 mg, 2.59 mmol) and tert-butyl N-(2-bromoethyl)carbamate (871 mg, 3.89 mmol). The mixture was stirred at 50 °C for 16 h. The reaction mixture was cooled then extracted with ethyl acetate (5 mL x 2). The combined organic extracts were washed with saturated aqueous sodium chloride solution (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give tert-butyl N-[2-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]ethyl]carbamate (1.30 g) which was used directly without further purification. LCMS (ESI) m/z = 433.3 $[M+H]^+$.

Step 2: Preparation of 2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)ethanamine



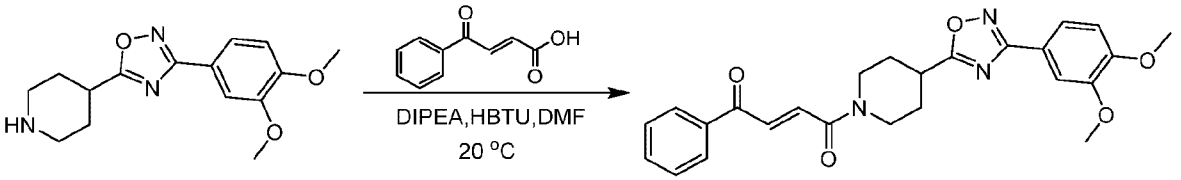
A solution of tert-butyl N-[2-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]ethyl]carbamate (1.0 g, 2.31 mmol) in hydrochloric acid/ethyl acetate (4M, 25 mL) was stirred at 25 °C for 30 mins. The reaction mixture was concentrated under reduced pressure to give 2-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]ethanamine (750 mg) which was used directly without further purification. LCMS (ESI) m/z = 333.1 $[M+H]^+$.

Step 3: Preparation of N-(2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)ethyl)benzamide



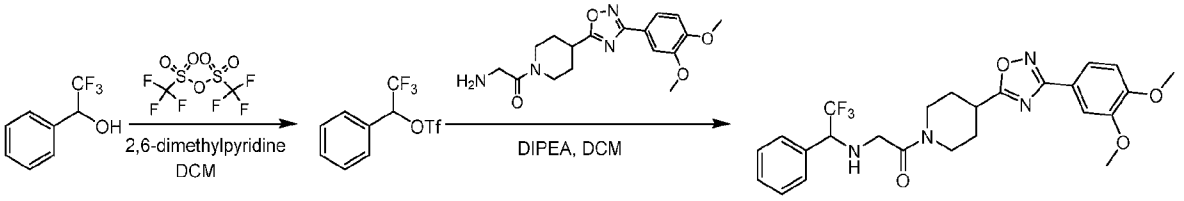
To a mixture of 2-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]ethanamine (200 mg, 602 µmol) and benzoyl chloride (109 mg, 782 µmol, 90 µL) in dichloromethane (1 mL) was added triethylamine (182 mg, 1.81 mmol, 250 µL) at 0 °C. The mixture was stirred at 20 °C for 5 h, then purified directly by prep-HPLC (column: Luna C8 100x30 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 35%-50%,12 min) to give N-[2-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]ethyl]benzamide (25 mg, 56 µmol, 9 %) as a white solid. ^{1}H NMR (400MHz, METHANOL-d4) δ = 7.86 - 7.79 (m, 2H), 7.66 (dd, J=1.8, 8.4 Hz, 1H), 7.58 (d, J=1.8 Hz, 1H), 7.55 - 7.43 (m, 3H), 7.07 (d, J=8.6 Hz, 1H), 3.89 (s, 6H), 3.58 (t, J=6.8 Hz, 2H), 3.16 - 3.09 (m, 2H), 2.67 (t, J=6.8 Hz, 2H), 2.37 - 2.29 (m, 2H), 2.18 (br d, J=11.2 Hz, 2H), 2.07 - 1.91 (m, 3H); LCMS (ESI) m/z: $[M+H]^+$ = 437.3.

Example 33: (E)-1-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-4-phenylbut-2-ene-1,4-dione

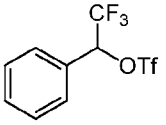


To a stirred solution of 3-(3,4-dimethoxyphenyl)-5-(4-piperidyl)-1,2,4-oxadiazole (250 mg, 864 µmol) in N,N-dimethylformamide (4 mL) were added (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (327 mg, 864 µmol), N-ethyl-N-(propan-2-yl)propan-2-amine (335 mg, 2.59 mmol, 452 µL) and (E)-4-oxo-4-phenyl-but-2-enoic acid (152 mg, 864 µmol). The mixture was stirred at 20 °C for 5 h, then the crude mixture was purified directly by prep-HPLC (column: Luna C8 100x30 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 40%-70%,12 min) to give (E)-1-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-4-phenyl-but-2-ene-1,4-dione (118 mg, 251 µmol, 29 %) as a yellow solid. ^{1}H NMR (400MHz, DMSO-d6) δ = 8.03 (br d, J=7.3 Hz, 2H), 7.75 (d, J=15.4 Hz, 1H), 7.71 - 7.65 (m, 1H), 7.61 - 7.53 (m, 3H), 7.51 - 7.43 (m, 2H), 7.11 (d, J=8.4 Hz, 1H), 4.41 (br d, J=13.2 Hz, 1H), 4.11 - 3.99 (m, 1H), 3.88 - 3.77 (m, 6H), 3.54 - 3.34 (m, 2H), 3.02 (br t, J=11.2 Hz, 1H), 2.15 (br d, J=13.0 Hz, 2H), 1.88 - 1.67 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 448.2.

Example 34: 1-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-((2,2,2-trifluoro-1-phenylethyl)amino)ethanone.

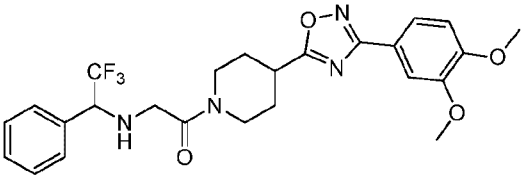


Step 1: Preparation of 2,2,2-trifluoro-1-phenylethyl trifluoromethanesulfonate.



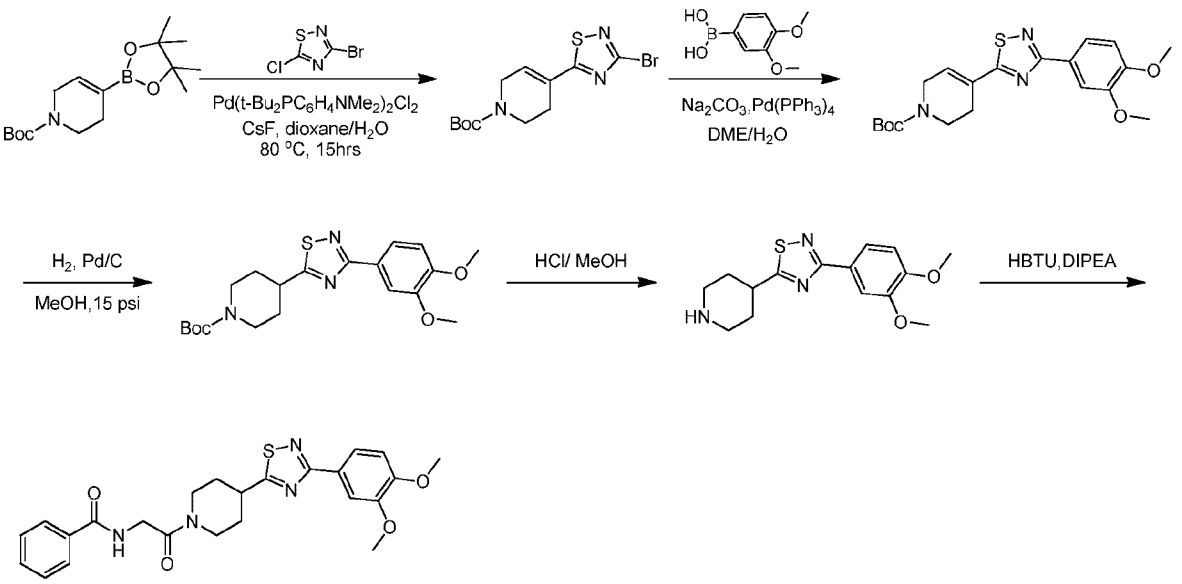
To a stirred solution of 2,2,2-trifluoro-1-phenylethanol (100 mg, 568 µmol, 76 µL) in dichloromethane (2 mL) were added 2,6-dimethylpyridine (121 mg, 1.14 mmol, 132 µL) and trifluoromethanesulfonic anhydride (288 mg, 1.02 mmol, 168 µL) at 0 °C. The mixture was stirred at 0 °C for 0.5 h and then diluted with dichloromethane (5 mL) and water (5 mL), and the phases separated. The aqueous phase was extracted with dichloromethane (15 mL x 2), then the combined organic phases were dried over anhydrous sodium sulfate, filtered, and concentrated to give 2,2,2-trifluoro-1-phenylethyl trifluoromethanesulfonate (380 mg) as a brown oil. This material was used directly without further purification.

Step 2: Preparation of 1-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-((2,2,2-trifluoro-1-phenylethyl)amino)ethanone

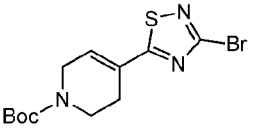


To a stirred solution of 2-amino-1-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)ethanone (120 mg, 346 µmol) in dichloromethane (2.5 mL) was added 2,2,2-trifluoro-1-phenylethyl trifluoromethanesulfonate (213 mg, 692.88 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (179 mg, 1.39 mmol, 242 µL). The mixture was stirred at 40 °C for 16 h. The reaction mixture was concentrated in vacuo to give a crude product that was purified by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 40%-70%,12 min) to give 1-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-((2,2,2-trifluoro-1-phenylethyl)amino)ethanone (52 mg, 101 µmol, 29 %) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 7.63-7.56 (m, 1H), 7.51-7.37 (m, 6H), 7.14 (d, J = 8.4 Hz, 1H), 4.53-4.43 (m, 1H), 4.30 (br. s., 1H), 3.84 (s, 6H), 3.71 (d, J = 10.2 Hz, 1H), 3.44-3.36 (m, 2H), 3.18-3.07 (m, 1H), 2.99 (d, J = 5.5 Hz, 1H), 2.87 (br. s., 1H), 2.08 (d, J = 12.5 Hz, 2H), 1.75-1.56 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 505.3.

Example 35: N-(2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-thiadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide

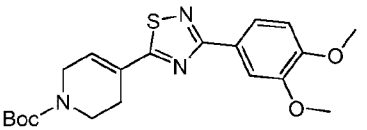


Step 1: Preparation of tert-butyl 4-(3-bromo-1,2,4-thiadiazol-5-yl)-5,6-dihydropyridine-1(2H)-carboxylate



A mixture of 3-bromo-5-chloro-1,2,4-thiadiazole (500 mg, 2.51 mmol), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylate (931 mg, 3.01 mmol), cesium fluoride (762 mg, 5.02 mmol, 185 µL) in dioxane (3.5 mL) was degassed and purged with nitrogen 3 times, then 4-ditert-butylphosphanyl-N,N-dimethyl-aniline;dichloropalladium (88 mg, 125.50 µmol, 88 µL, 0.05 eq) was added. The mixture was stirred at 80 °C for 2 h under an atmosphere of nitrogen. The mixture was cooled to 25 °C and concentrated in vacuo at 40 °C. The residue was poured into water (15 mL), the aqueous phase was extracted with dichloromethane (20 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to afford crude product. The crude product was purified by chromatography (silica, petroleum ether/ ethyl acetate (from 20/1 to 2/1) to give tert-butyl 4-(3-bromo-1,2,4-thiadiazol-5-yl)-3,6-dihydro-2H-pyridine-1-carboxylate (260 mg, 750.92 µmol, 30 %) as a yellow oil. LCMS (ESI) m/z: 368.3 $[M+Na]^+$.

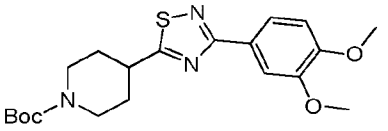
Step 2: Preparation of tert-butyl 4-(3-(3,4-dimethoxyphenyl)-1,2,4-thiadiazol-5-yl)-5,6-dihydropyridine-1(2H)-carboxylate



A mixture of tert-butyl 4-(3-bromo-1,2,4-thiadiazol-5-yl)-3,6-dihydro-2H-pyridine-1-carboxylate (260 mg, 751 µmol), (3,4-dimethoxyphenyl)boronic acid (163 mg, 901 µmol), and sodium carbonate (103 mg, 976 µmol) in water (400 µL) and dimethoxyethane(1.2 mL) was degassed and purged with nitrogen 3

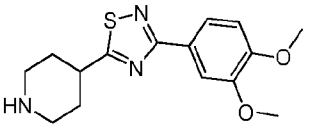
times, and then tetrakis(triphenylphosphine)palladium(0) (17 mg, 15 µmol) was added. The mixture was stirred at 100 °C for 6 h under a nitrogen atmosphere. The mixture was cooled to 25 °C and concentrated in vacuo at 40 °C. The residue was poured into water (5 mL), and the aqueous phase was extracted with dichloromethane (10 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to afford crude product. The crude residue was purified by prep-TLC (silica, petroleum ether/ ethyl acetate=3:1) to give tert-butyl 4-[3-(3,4-dimethoxyphenyl)-1,2,4-thiadiazol-5-yl]-3,6-dihydro-2H-pyridine-1-carboxylate (122 mg, 303 µmol, 40 %) as a yellow oil. LCMS (ESI) m/z: 404.1 $[M+H]^+$.

Step 3: Preparation of tert-butyl 4-(3-(3,4-dimethoxyphenyl)-1,2,4-thiadiazol-5-yl)piperidine-1-carboxylate



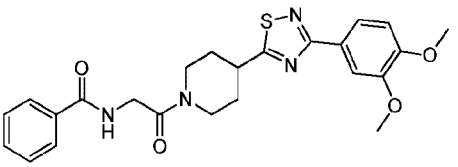
To a stirred solution of tert-butyl 4-[3-(3,4-dimethoxyphenyl)-1,2,4-thiadiazol-5-yl]-3,6-dihydro-2H-pyridine-1-carboxylate (100 mg, 248 µmol) in methanol (10 mL) was added palladium(0) on carbon (10%, 150 mg) under nitrogen. The suspension was degassed under vacuum and purged with hydrogen three times. The mixture was stirred under hydrogen (15 psi) at 20 °C for 48 h. The reaction mixture was filtered and concentrated under reduced pressure to give tert-butyl 4-[3-(3,4-dimethoxyphenyl)-1,2,4-thiadiazol-5-yl]piperidine-1-carboxylate (79 mg) that was used into the next step without further purification. LCMS (ESI) m/z: 406.2 $[M+H]^+$.

Step 4: Preparation of 3-(3,4-dimethoxyphenyl)-5-(piperidin-4-yl)-1,2,4-thiadiazole



A solution of tert-butyl 4-[3-(3,4-dimethoxyphenyl)-1,2,4-thiadiazol-5-yl]piperidine-1-carboxylate (79 mg, 195 µmol) in hydrochloric acid/ethyl acetate (4M, 15 mL) was stirred at 20 °C for 3 h. The reaction mixture was concentrated in vacuo to give 3-(3,4-dimethoxyphenyl)-5-(4-piperidyl)-1,2,4-thiadiazole (65 mg) that was used into the next step without further purification.

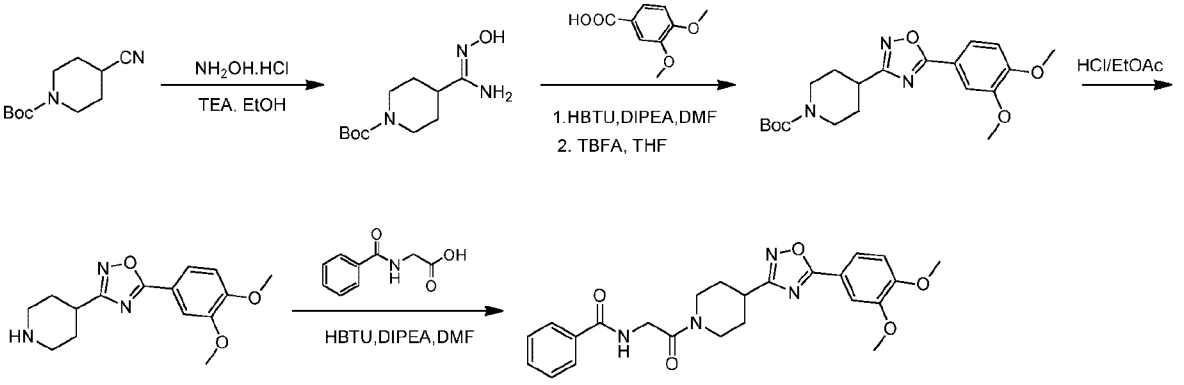
Step 5: Preparation of N-(2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-thiadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide



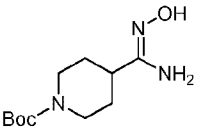
To a stirred solution of 3-(3,4-dimethoxyphenyl)-5-(4-piperidyl)-1,2,4-thiadiazole (65 mg, 214 µmol) and 2-benzamidoacetic acid (46 mg, 257 µmol) in N,N-dimethylformamide (1 mL) were added (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (81 mg, 214 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (69 mg, 536 µmol, 93 µL). After 2 h, the reaction mixture purified directly by prep-HPLC (column: Waters Xbridge 150x25 5µm; mobile phase: [water (10mM ammonium

carbonate)-acetonitrile]; B%: 26%-56%,12 min) to give N-[2-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-thiadiazol-5-yl]-1-piperidyl]-2-oxo-ethyl]benzamide (10 mg, 22 µmol, 10 %) as a yellow solid. ^{1}H NMR (400MHz, METHANOL-d4) δ = 7.92 - 7.82 (m, 4H), 7.59 - 7.52 (m, 1H), 7.51 - 7.44 (m, 2H), 7.06 (d, J=8.4 Hz, 1H), 4.61 (d, J=12.9 Hz, 1H), 4.41 - 4.24 (m, 2H), 4.11 (br d, J=14.9 Hz, 1H), 3.98 - 3.84 (m, 6H), 3.63 - 3.52 (m, 1H), 3.39 (br t, J=11.7 Hz, 1H), 2.99 (br t, J=11.6 Hz, 1H), 2.35 - 2.20 (m, 2H), 2.03 - 1.74 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 467.2.

Example 36: N-(2-(4-(5-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-3-yl)piperidin-1-yl)-2-oxoethyl)benzamide

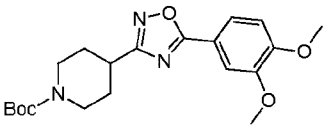


Step 1: Preparation of (Z)-tert-butyl 4-(N'-hydroxycarbamimidoyl)piperidine-1-carboxylate



A mixture of tert-butyl 4-cyanopiperidine-1-carboxylate (2.0 g, 9.51 mmol), hydroxylamine hydrochloride (1.32 g, 19.0 mmol), and triethylamine (1.92 g, 19.0 mmol, 2.64 mL) in ethanol (20 mL) and water (2 mL) was heated at 75 °C for 16 h. The reaction mixture was cooled, diluted with water (10 mL), and extracted with ethyl acetate (15 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (10 mL x 2), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give tert-butyl 4-[(Z)-N'-hydroxycarbamimidoyl]piperidine-1-carboxylate (1.90 g) which was used directly without further purification. ^{1}H NMR (400MHz, METHANOL-d4) δ = 4.15 (br d, J=13.3 Hz, 2H), 2.78 (br s, 2H), 2.27 (tt, J=3.6, 12.1 Hz, 1H), 1.84 - 1.70 (m, 2H), 1.62 (dq, J=4.3, 12.6 Hz, 2H), 1.53 - 1.39 (m, 9H).

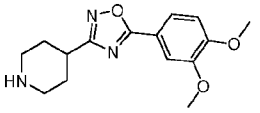
Step 2: Preparation of tert-butyl 4-(5-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-3-yl)piperidine-1-carboxylate



To a stirred solution of tert-butyl 4-[(Z)-N'-hydroxycarbamimidoyl]piperidine-1-carboxylate (750 mg, 3.08 mmol) in N,N-dimethylformamide (5 mL) was added (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (1.17 g, 3.08 mmol), N-ethyl-N-(propan-2-yl)propan-2-amine (1.19 g, 9.24 mmol, 1.61 mL) and 3,4-dimethoxybenzoic acid (561 mg, 3.08 mmol). The mixture was stirred at 20 °C for 16 h. The reaction mixture was diluted with water (10 mL) and extracted with ethyl

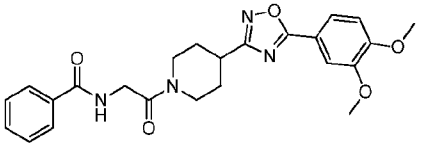
acetate (15 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (10 mL x 2), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. Tetrahydrofuran (500 µL) and tetrabutylammonium fluoride / tetrahydrofuran (1 M, 4.62 mL) were added to the residue, and the resulting mixture was heated at 50 °C for 16 h. The residue was purified by chromatography (silica, petroleum ether / ethyl acetate=5:1) to give tert-butyl 4-[5-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-3-yl]piperidine-1-carboxylate (970 mg, 2.49 mmol, 81 %) as a white solid. LCMS (ESI) m/z: 412.3 $[M+Na]^+$ = 334.2.

Step 3: Preparation of 5-(3,4-dimethoxyphenyl)-3-(piperidin-4-yl)-1,2,4-oxadiazole



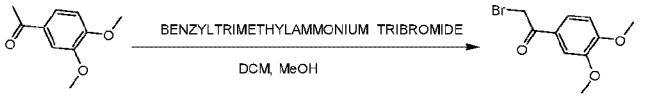
A solution of tert-butyl 4-[5-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-3-yl]piperidine-1-carboxylate (750 mg, 1.93 mmol) in hydrochloric acid / ethyl acetate (4M, 30 mL) was stirred at 20 °C for 0.5 h. The reaction mixture was concentrated under reduced pressure to give 5-(3,4-dimethoxyphenyl)-3-(4-piperidyl)-1,2,4-oxadiazole (683 mg) that was used directly without further purification.

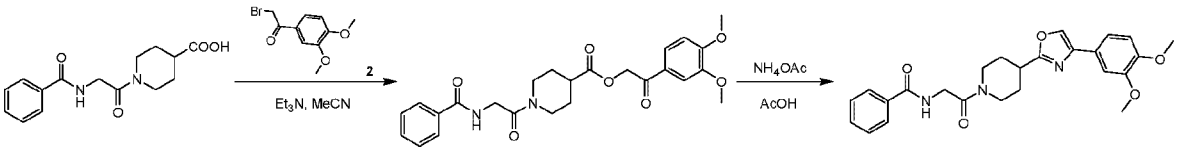
Step 4: Preparation of N-(2-(4-(5-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-3-yl)piperidin-1-yl)-2-oxoethyl)benzamide



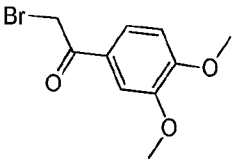
To a stirred solution of 5-(3,4-dimethoxyphenyl)-3-(4-piperidyl)-1,2,4-oxadiazole (180 mg, 622 µmol) in N,N-dimethylformamide (2 mL) were added 2-benzamidoacetic acid (111 mg, 622 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (235 mg, 622 µmol), and N-ethyl-N-(propan-2-yl)propan-2-amine (241 mg, 1.87 mmol, 325 µL). The mixture was stirred at 20 °C for 16 h. The crude product was purified by prep-HPLC (column: Waters Xbridge 150x25 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 30%-60%,12 min) to give N-[2-[4-[5-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-3-yl]-1-piperidyl]-2-oxo-ethyl]benzamide (169 mg, 376 µmol, 60 %) as a white solid. ^{1}H NMR (400MHz, DMSO-d6) δ = 8.55 (br t, J=5.4 Hz, 1H), 7.87 (br d, J=7.5 Hz, 2H), 7.70 (br d, J=8.4 Hz, 1H), 7.57 - 7.41 (m, 4H), 7.17 (br d, J=8.4 Hz, 1H), 4.34 (br d, J=12.3 Hz, 1H), 4.16 (br d, J=4.2 Hz, 2H), 3.97 (br d, J=13.0 Hz, 1H), 3.90 - 3.74 (m, 6H), 3.27 - 3.09 (m, 2H), 2.88 (br t, J=11.6 Hz, 1H), 2.03 (br t, J=11.8 Hz, 2H), 1.75 (br d, J=10.4 Hz, 1H), 1.59 (br d, J=9.9 Hz, 1H); LCMS (ESI) m/z: $[M+H]^+$ = 451.2.

Example 37: N-(2-(4-(4-(3,4-dimethoxyphenyl)oxazol-2-yl)piperidin-1-yl)-2-oxoethyl)benzamide.



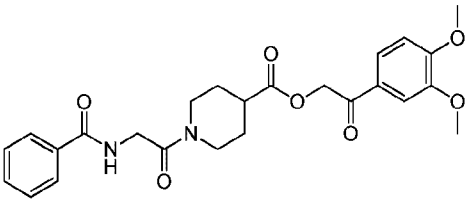


Step 1: Preparation of 2-bromo-1-(3,4-dimethoxyphenyl)ethanone.



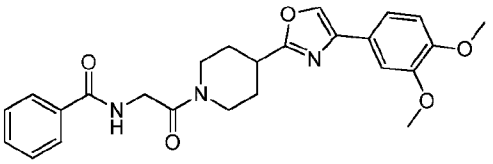
To a stirred solution of 1-(3,4-dimethoxyphenyl)ethanone (1.0 g, 5.55 mmol) in dichloromethane (6 mL) and methanol (3 mL) was added benzyltrimethylammonium tribromide (2.16 g, 5.55 mmol). After 16 h, the mixture was diluted with dichloromethane (80 mL) and water (40 mL), the organic layer was separated, and the water phase was extracted with dichloromethane (80 mL x 2). The combined organic phases were dried over anhydrous sodium sulfate, filtered, and concentrated to give 2-bromo-1-(3,4-dimethoxyphenyl)ethanone (1.20 g, 4.63 mmol, 83 %) as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (s, 1H), 7.57 (d, *J*=2.1 Hz, 1H), 6.94 (d, *J*=8.4 Hz, 1H), 4.43 (s, 2H), 3.98 (d, *J*=8.4 Hz, 6H).

Step 2: Preparation of 2-(3,4-dimethoxyphenyl)-2-oxoethyl 1-(2-benzamidoacetyl)piperidine-4-carboxylate.



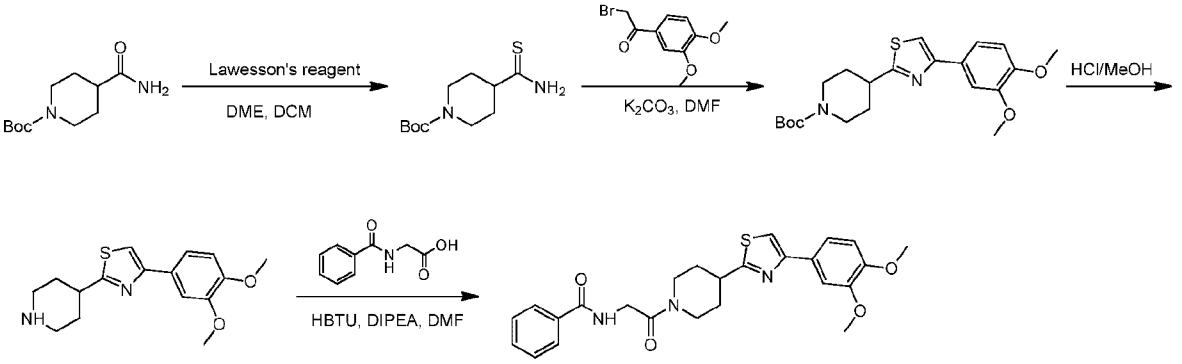
To a stirred solution of 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid (200 mg, 689 µmol) in acetonitrile (6 mL) was added 2-bromo-1-(3,4-dimethoxyphenyl)ethanone (214 mg, 826 µmol) and triethylamine (209 mg, 2.07 mmol, 286 µL) under nitrogen. The mixture was stirred at 20 °C for 2 h. The reaction mixture was concentrated in vacuo to give 2-(3,4-dimethoxyphenyl)-2-oxoethyl 1-(2-benzamidoacetyl)piperidine-4-carboxylate (233 mg, 497 µmol, 72 %) as a yellow solid. This was used directly without further purification. LCMS (ESI) m/z: $[M+H]^+$ = 469.3.

Step 3: Preparation of N-(2-(4-(4-(3,4-dimethoxyphenyl)oxazol-2-yl)piperidin-1-yl)-2-oxoethyl)benzamide.

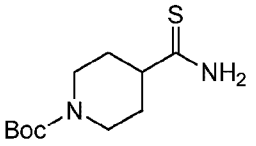


To a stirred solution of 2-(3,4-dimethoxyphenyl)-2-oxoethyl 1-(2-benzamidoacetyl)piperidine-4-carboxylate (180 mg, 384 µmol) in acetic acid (8 mL) was added ammonium acetate (148 mg, 1.92 mmol) under nitrogen, then the mixture was heated at 100 °C for 16 h. The reaction mixture was concentrated in vacuo to give crude product that was purified by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 30%-55%,12 min) to give N-(2-(4-(4-(3,4-dimethoxyphenyl)oxazol-2-yl)piperidin-1-yl)-2-oxoethyl)benzamide (55 mg, 120 µmol, 31 %) as a pink solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 - 7.84 (m, 2H), 7.80 (s, 1H), 7.58 - 7.44 (m, 3H), 7.41 - 7.35 (m, 1H), 7.28 - 7.26 (m, 2H), 6.92 (d, *J*=8.9 Hz, 1H), 4.58 - 4.47 (m, 1H), 4.32 (d, *J*=3.9 Hz, 2H), 3.99 - 3.88 (m, 7H), 3.37 - 3.06 (m, 3H), 2.28 - 2.13 (m, 2H), 2.07 - 1.89 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 450.3.

Example 38: N-(2-(4-(4-(3,4-dimethoxyphenyl)thiazol-2-yl)piperidin-1-yl)-2-oxoethyl)benzamide.

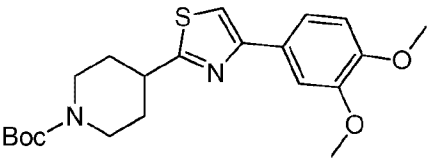


Step 1: Preparation of tert-butyl 4-carbamothioylpiperidine-1-carboxylate.



To a stirred solution of tert-butyl 4-carbamoylpiperidine-1-carboxylate (1.0 g, 4.38 mmol) in a mixture of dimethoxyethane (16 mL) and dichloromethane (8 mL) was added 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide (885 mg, 2.19 mmol). The mixture was stirred at 20 °C for 16 h, then concentrated in vacuo. The residue dissolved in ethyl acetate and washed with saturated aqueous potassium carbonate (10 mL x 2). The organic layer was separated, dried over sodium sulfate and concentrated in vacuo to give tert-butyl 4-carbamothioylpiperidine-1-carboxylate (1.0 g) as a yellow solid. This was used directly without further purification. ^{1}H NMR (400 MHz, DMSO-d6) δ 9.45 (br. s., 1H), 9.17 (br. s., 1H), 4.14-3.98 (m, 2H), 3.91-3.79 (m, 1H), 2.80-2.66 (m, 2H), 1.74-1.55 (m, 4H), 1.46 (s, 9H).

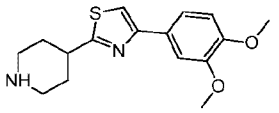
Step 2: Preparation of tert-butyl 4-(4-(3,4-dimethoxyphenyl)thiazol-2-yl)piperidine-1-carboxylate.



To a stirred solution of tert-butyl 4-carbamothioylpiperidine-1-carboxylate (200 mg, 818.5 µmol) in N,N-dimethylformamide (5 mL) was added 2-bromo-1-(3,4-dimethoxyphenyl)ethanone (212 mg, 818.50

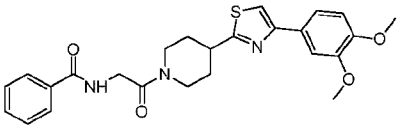
μmol) and potassium carbonate (124 mg, 900 μmol). The mixture was stirred at 110 °C for 16 h. The reaction mixture was quenched with water (10 mL) and extracted with ethyl acetate (40 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to give tert-butyl 4-(4-(3,4-dimethoxyphenyl)thiazol-2-yl)piperidine-1-carboxylate (300 mg, 742 μmol, 91 %) as a yellow solid. This was used directly without further purification. LCMS (ESI) m/z: $[M+H]^+$ = 405.3.

Step 3: Preparation of 4-(3,4-dimethoxyphenyl)-2-(piperidin-4-yl)thiazole.



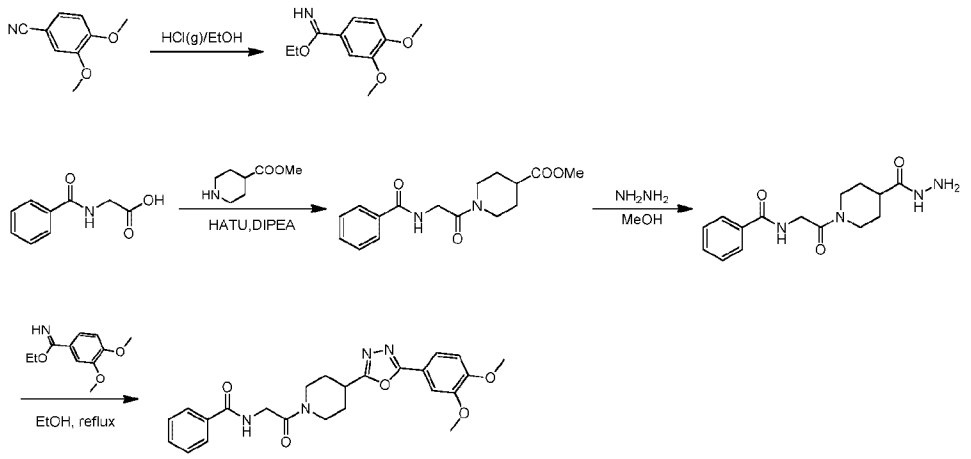
To a stirred solution of tert-butyl 4-(4-(3,4-dimethoxyphenyl)thiazol-2-yl)piperidine-1-carboxylate (300 mg, 742 μmol) in methanol (3 mL) was added methanolic hydrogen chloride solution (4M, 10 mL). The mixture was stirred at 20 °C for 1 h. The reaction mixture was concentrated under reduced pressure to provide 4-(3,4-dimethoxyphenyl)-2-(piperidin-4-yl)thiazole (260 mg) as a yellow solid. LCMS (ESI) m/z: $[M+H]^+$ = 305.1.

Step 4: Preparation of N-(2-(4-(4-(3,4-dimethoxyphenyl)thiazol-2-yl)piperidin-1-yl)-2-oxoethyl)benzamide.

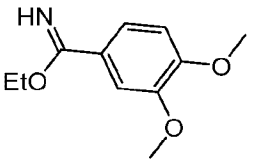


To a stirred solution of 4-(3,4-dimethoxyphenyl)-2-(piperidin-4-yl)thiazole (203 mg, 670 μmol) in N,N-dimethylformamide (4 mL) were added 2-benzamidoacetic acid (100 mg, 558 μmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (211 mg, 558 μmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (288 mg, 2.23 mmol, 389 μL). T he mixture was stirred at 20 °C for 16 h. The reaction mixture was purified directly by prep-HPLC (column: Waters Xbridge 150x2.5mm 5μm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 30%-60%, 12 min) to give N-(2-(4-(4-(3,4-dimethoxyphenyl)thiazol-2-yl)piperidin-1-yl)-2-oxoethyl)benzamide (111 mg, 239 μmol, 43 %) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91-7.85 (m, 2H), 7.57-7.42 (m, 5H), 7.39 (br. s., 1H), 6.94 (d, *J* = 8.2 Hz, 1H), 4.70 (d, *J* = 13.6 Hz, 1H), 4.40-4.26 (m, 2H), 3.97 (d, *J* = 19.7 Hz, 7H), 3.43-3.26 (m, 2H), 3.05-2.95 (m, 1H), 2.37-2.23 (m, 2H), 1.98-1.83 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 466.3.

Example 39: N-(2-(4-(5-(3,4-dimethoxyphenyl)-1,3,4-oxadiazol-2-yl)piperidin-1-yl)-2-oxoethyl)benzamide.

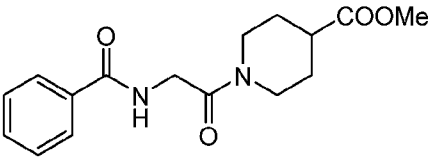


Step 1: Ethyl 3,4-dimethoxybenzimidate.



To a stirred solution of 3,4-dimethoxybenzonitrile (2.0 g, 12.3 mmol) in dry ethanol (50 mL) was added dropwise acetyl chloride (7.70 g, 98.1 mmol, 7.0 mL) at 0 ℃ , after complete addition, the mixture was warmed to 15 ℃ and stirred for 30 h. The reaction was concentrated in vacuo, and then saturated hydrochloric acid in ethanol (50 mL) was added. After 5h, the mixture was concentrated in vacuo to give crude ethyl 3,4-dimethoxybenzenecarboximidate (2.50 g) as a light yellow solid, which was used in next step directly.

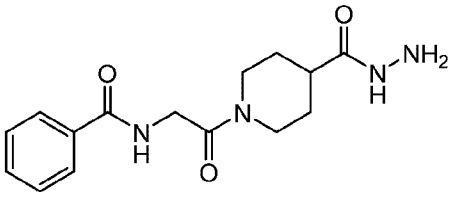
Step 2: Methyl 1-(2-benzamidoacetyl)piperidine-4-carboxylate.



To a stirred solution of 2-benzamidoacetic acid (3.0 g, 16.7 mmol) and methyl piperidine-4-carboxylate (3.60 g, 25.1 mmol) in dry N,N-dimethylformamide (50 mL) was added N-ethyl-N-(propan-2-yl)propan-2-amine (4.33 g, 33.5 mmol, 5.9 mL) and 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (7.0 g, 18.4 mmol) at 0 ℃, then the mixture was warmed to 15 ℃ and stirred for 15h. The mixture was poured into ice water (100 mL) then extracted with ethyl acetate (50 mL x 3). The combined organic phases were washed with 1N hydrochloric acid (30 mL x 2), saturated aqueous sodium carbonate (30 mL), and saturated aqueous sodium chloride solution (30 mL), then dried over anhydrous sodium sulfate, filtered and concentrated to give a crude methyl 1-(2-benzamidoacetyl)piperidine-4-carboxylate (5.30 g) as a brown oil, which was used in next step directly. ^{1}H NMR (400 MHz, Methanol-d4) δ 7.87 (d, J=7.1 Hz, 2H), 7.58 - 7.51 (m, 1H), 7.49 - 7.40 (m, 2H), 4.39 -

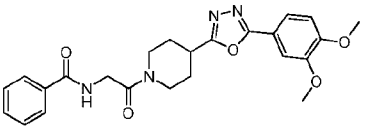
4.29 (m, 1H), 4.28 - 4.17 (m, 2H), 3.96 - 3.84 (m, 1H), 3.68 (s, 3H), 3.28 - 3.17 (m, 1H), 2.96 - 2.86 (m, 1H), 2.69 – 2.62 (m, 1H), 2.00 - 1.88 (m, 2H), 1.78 - 1.51 (m, 2H).

Step 3: N-(2-(4-(hydrazinecarbonyl)piperidin-1-yl)-2-oxoethyl)benzamide.



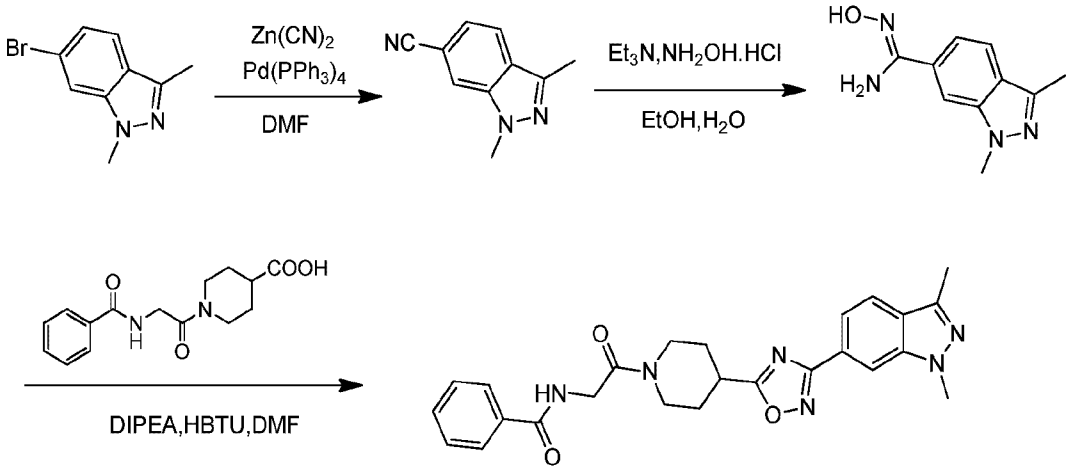
A solution of methyl 1-(2-benzamidoacetyl)piperidine-4-carboxylate (500 mg, 1.64 mmol) and hydrazine hydrate (328 mg, 6.56 mmol, 318 µL) in methanol (3 mL) was heated to 80 °C for 15 h. The mixture was concentrated in vacuo to give a crude residue that was washed with tert-butyl methyl ether (10 mL) to obtain N-[2-[4-(hydrazinecarbonyl)-1-piperidyl]-2-oxo-ethyl]benzamide (500 mg) as a light yellow solid that was used directly without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.03 (s, 1H), 8.54 (t, J=5.6 Hz, 1H), 7.94 - 7.82 (m, 2H), 7.60 - 7.43 (m, 3H), 4.41 - 4.29 (m, 1H), 4.13 (d, J=5.6 Hz, 2H), 3.93 (d, J=12.9 Hz, 1H), 3.05 (t, J=11.9 Hz, 1H), 2.68 - 2.57 (m, 1H), 2.34 (tdd, J=3.9, 7.5, 11.2 Hz, 1H), 1.73 - 1.34 (m, 4H).

Step 4: N-(2-(4-(5-(3,4-dimethoxyphenyl)-1,3,4-oxadiazol-2-yl)piperidin-1-yl)-2-oxoethyl)benzamide.

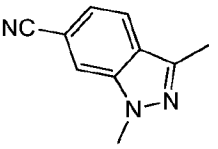


A solution of N-[2-[4-(hydrazinecarbonyl)-1-piperidyl]-2-oxo-ethyl]benzamide (200 mg, 657 µmol) and ethyl 3,4-dimethoxybenzenecarboximidate (151 mg, 723 µmol) in ethanol (4 mL) was heated to 80 °C for 15h. The mixture was concentrated to give a crude product, which was purified by prep-HPLC (column: Waters Xbridge 150x25 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 20%-35%,12 min) to give N-[2-[4-[5-(3,4-dimethoxyphenyl)-1,3,4-oxadiazol-2-yl]-1-piperidyl]-2-oxo-ethyl]benzamide (23 mg, 48 µmol, 7 %) as a white solid. ^{1}H NMR (400 MHz, Methanol-d4) δ 7.92 - 7.82 (m, 2H), 7.62 (dd, J=1.8, 8.4 Hz, 1H), 7.59 - 7.52 (m, 2H), 7.51 - 7.44 (m, 2H), 7.12 (d, J=8.4 Hz, 1H), 4.49 (d, J=13.2 Hz, 1H), 4.38 - 4.24 (m, 2H), 4.06 (d, J=13.7 Hz, 1H), 3.97 - 3.80 (m, 6H), 3.48 - 3.34 (m, 2H), 3.06 (t, J=11.2 Hz, 1H), 2.33 - 2.15 (m, 2H), 2.06 - 1.94 (m, 1H), 1.92 - 1.75 (m, 1H); LCMS (ESI) m/z: $[M+H]^+$ = 451.2.

Example 40: N-(2-(4-(3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.

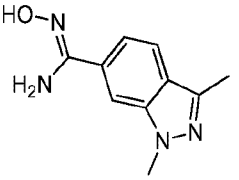


Step 1: Preparation of 1,3-dimethyl-1H-indazole-6-carbonitrile.



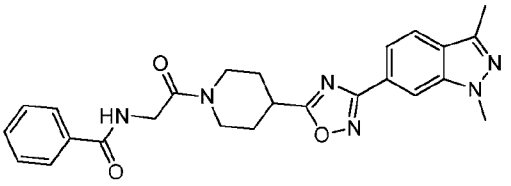
To a stirred solution of 6-bromo-1,3-dimethyl-1H-indazole (400 mg, 1.78 mmol) in N,N-dimethylformamide (5 mL) was added zinc cyanide (209 mg, 1.78 mmol, 112 µL) and tetrakis(triphenylphosphine)palladium(0) (205 mg, 178 µmol, 0.10 *eq*) under nitrogen. The mixture was heated at 100 °C for 16 h, then cooled to 20 °C, water (10 mL) added, and the resulting mixture was extracted with ethyl acetate (40 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (15 mL) and dried over anhydrous sodium sulfate. The organic phase was filtered and concentrated in vacuo to give crude product. Petroleum ether (40 mL) was added to the crude product, then the mixture was filtered, and the filter cake dried in vacuo to give 1,3-dimethyl-1H-indazole-6-carbonitrile (250 mg, 1.46 mmol, 82 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 - 7.71 (m, 2H), 7.34 (dd, *J*=1.3, 8.3 Hz, 1H), 4.07 (s, 3H), 2.61 (s, 3H).

Step 2: Preparation of (Z)-N'-hydroxy-1,3-dimethyl-1H-indazole-6-carboximidamide.



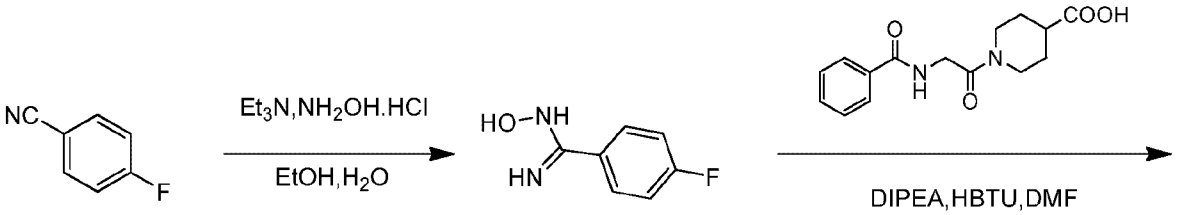
To a stirred solution of 1,3-dimethyl-1H-indazole-6-carbonitrile (100 mg, 584 µmol) in ethanol (2 mL) was added hydroxylamine hydrochloride (81 mg, 1.17 mmol), triethylamine (118 mg, 1.17 mmol, 161 µL) and water (200 µL). The mixture was heated at 75 °C for 2 h. After cooling to 20 °C, water (5 mL) was added to the solution. The mixture was extracted with dichloromethane (30 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (5 mL) and dried over anhydrous sodium sulfate, then filtered and concentrated in vacuo to give (Z)-N'-hydroxy-1,3-dimethyl-1H-indazole-6-carboximidamide (140 mg) as a white solid. LCMS (ESI) m/z: $[M+H]^+$ = 205.1.

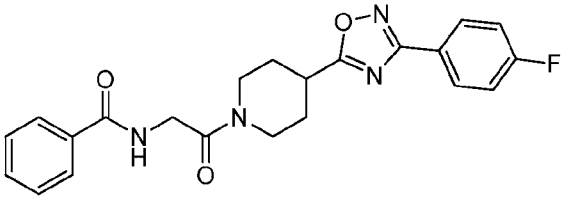
Step 3: Preparation of N-(2-(4-(3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.



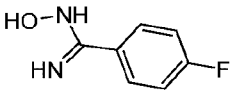
To a stirred solution of 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid (120 mg, 413 µmol) in N,N-dimethylformamide (2 mL) was added (Z)-N'-hydroxy-1,3-dimethyl-1H-indazole-6-carboximidamide (101 mg, 496 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (156 mg, 413 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (160 mg, 1.24 mmol, 216 µL). The mixture was stirred at 20 °C for 2 h, then heated at 120 °C for 2 h. The reaction mixture cooled then purified directly by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 30%-65%,12 min) to give N-(2-(4-(3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide (46 mg, 101 µmol, 25 %) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.81 - 7.73 (m, 3H), 7.66 (dd, *J*=0.6, 8.4 Hz, 1H), 7.48 - 7.42 (m, 1H), 7.42 - 7.35 (m, 2H), 7.26 (br. s., 1H), 4.46 (d, *J*=14.1 Hz, 1H), 4.24 (d, *J*=3.9 Hz, 2H), 4.01 (s, 3H), 3.86 (d, *J*=13.7 Hz, 1H), 3.29 (ddd, *J*=3.6, 10.5, 14.2 Hz, 2H), 3.13 - 3.04 (m, 1H), 2.53 (s, 3H), 2.26 - 2.15 (m, 2H), 2.04 - 1.89 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 459.3.

Example 41: N-(2-(4-(3-(4-fluorophenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.





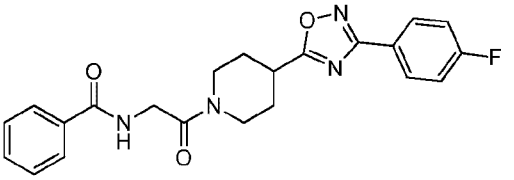
Step 1: Preparation of 4-fluoro-N-hydroxybenzimidamide.



To a stirred solution of 4-fluorobenzonitrile (1.0 g, 8.26 mmol) in ethanol (10 mL) was added hydroxylamine hydrochloride (1.15 g, 16.5 mmol), triethylamine (1.67 g, 16.52 mmol, 2.29 mL) and water (1 mL). The mixture was heated at 75 °C for 2 h. After cooling to 20 °C, water (20 mL) was added to the solution. The mixture was extracted with dichloromethane (40 mL x 4). The combined organic phases

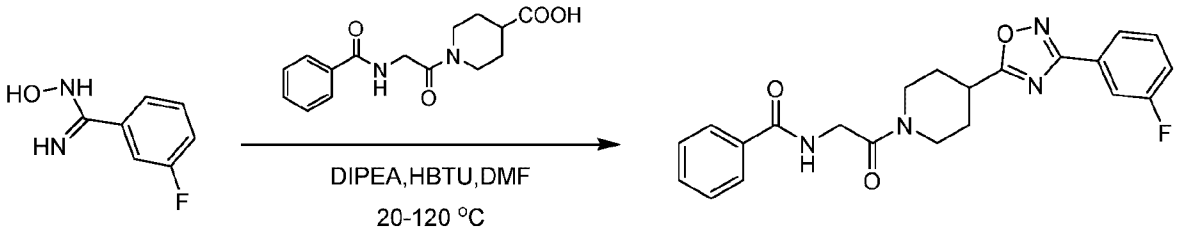
were washed with saturated aqueous sodium chloride solution (20 mL) and dried over anhydrous sodium sulfate, then filtered and concentrated in vacuo to give 4-fluoro-N-hydroxybenzimidamide (1.0 g, 6.49 mmol, 79 %) as a white solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 9.64 (s, 1H), 7.85-7.64 (m, 2H), 7.21 (t, *J* = 8.9 Hz, 2H), 5.84 (br. s., 2H).

Step 2: Preparation of N-(2-(4-(3-(4-fluorophenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.

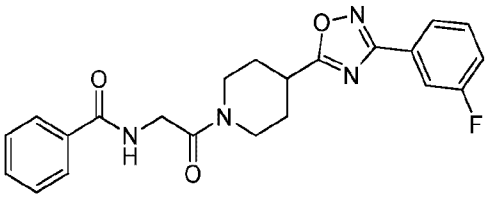


To a stirred solution of 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid (120 mg, 413 µmol) in N,N-dimethylformamide (3 mL) was added 4-fluoro-N-hydroxybenzimidamide (76 mg, 496 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (156 mg, 413 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (160 mg, 1.24 mmol, 216 µL). The mixture was stirred at 20 ℃ for 2 h, then heated at 120 ℃ for 2 h. The reaction mixture cooled then purified directly by prep-HPLC (column: Luna C18 150x2.5mm 5µm; mobile phase: [water (0.225%FA)-acetonitrile]; B%: 35%-65%,12 min) to give N-(2-(4-(3-(4-fluorophenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide (56 mg, 135 µmol, 33 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13-8.07 (m, 2H), 7.90-7.86 (m, 2H), 7.58-7.52 (m, 1H), 7.51-7.45 (m, 2H), 7.35 (br. s., 1H), 7.23-7.16 (m, 2H), 4.56-4.47 (m, 1H), 4.33 (d, *J* = 3.9 Hz, 2H), 3.93 (d, *J* = 13.9 Hz, 1H), 3.41-3.31 (m, 2H), 3.23-3.13 (m, 1H), 2.33-2.21 (m, 2H), 2.02 (ddq, *J* = 4.1, 10.5, 14.2 Hz, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 409.2.

Example 42: N-(2-(4-(3-(3-fluorophenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.



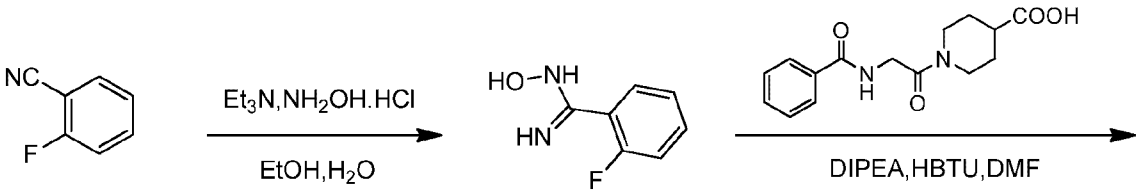
Step 1: Preparation of N-(2-(4-(3-(3-fluorophenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.

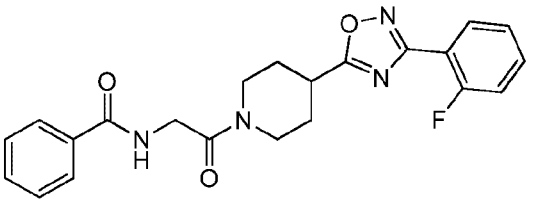


To a stirred solution of 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid (120 mg, 413 µmol) in N,N-dimethylformamide (4 mL) was added 3-fluoro-N-hydroxybenzimidamide (76 mg, 496 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (156 mg, 413 µmol) and N-ethyl-N-

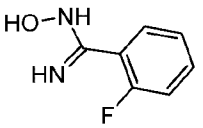
(propan-2-yl)propan-2-amine (160 mg, 1.24 mmol, 216 µL). The mixture was stirred at 20 °C for 2 h, then heated at 120 °C for 2 h. The reaction mixture was cooled then purified directly by prep-HPLC (column: Luna C8 100*30 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 35%-60%,12 min) to give N-(2-(4-(3-(3-fluorophenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide (59 mg, 145 µmol, 35 %) as a yellow solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.85-7.76 (m, 3H), 7.71 (d, *J*=9.3 Hz, 1H), 7.49-7.35 (m, 4H), 7.26 (br. s., 1H), 7.15 (s, 1H), 4.43 (d, *J*=13.7 Hz, 1H), 4.24 (d, *J*=3.5 Hz, 2H), 3.84 (d, *J*=14.1 Hz, 1H), 3.33-3.22 (m, 2H), 3.14-3.04 (m, 1H), 2.26-2.13 (m, 2H), 2.00-1.85 ppm (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 409.2.

Example 43: N-(2-(4-(3-(2-fluorophenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.



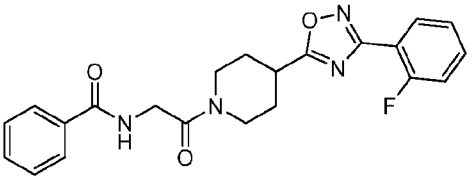


Step 1: Preparation of 2-fluoro-N-hydroxybenzimidamide.



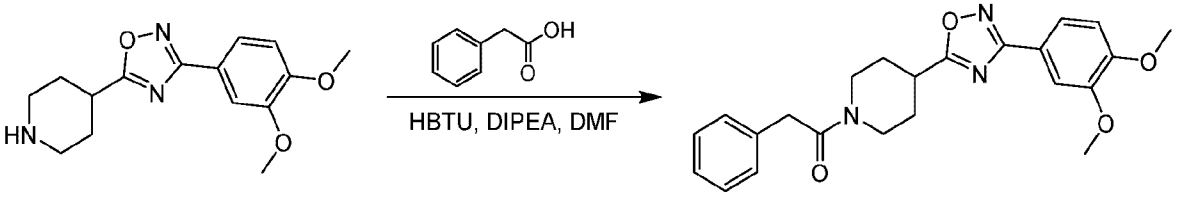
To a stirred solution of 2-fluorobenzonitrile (1.0 g, 8.26 mmol, 877 µL) in ethanol (10 mL) was added hydroxylamine hydrochloride (1.15 g, 16.5 mmol), triethylamine (1.67 g, 16.5 mmol, 2.29 mL) and water (1 mL). The mixture was heated at 75 °C for 2 h. After cooling to 20 °C, water (20 mL) was added. The mixture was extracted with dichloromethane (40 mL x 4). The combined organic phases were washed with saturated aqueous sodium chloride solution (20 mL) and dried over anhydrous sodium sulfate, then filtered and concentrated in vacuo to give 2-fluoro-N-hydroxybenzimidamide (1.20 g, 7.79 mmol, 94 %) as a white solid. LCMS (ESI) m/z: $[M+H]^+$ = 155.1.

Step 2: Preparation of N-(2-(4-(3-(2-fluorophenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.

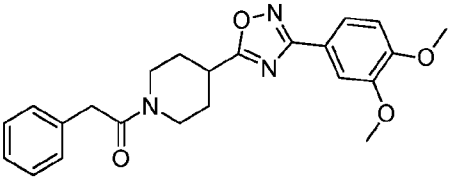


To a stirred solution of 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid (150 mg, 516.7 µmol) in N,N-dimethylformamide (4 mL) was added 2-fluoro-N-hydroxybenzimidamide (95 mg, 620 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (195 mg, 516.7 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (200 mg, 1.55 mmol, 270 µL). The mixture was stirred at 20 °C for 2 h, then heated at 120 °C for 2 h. The reaction mixture was cooled then purified directly by prep-HPLC (column: Luna C8 100*30 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 30%-60%,12 min) to give N-(2-(4-(3-(2-fluorophenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide (85 mg, 208.6 µmol, 40 %) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.81-7.75 (m, 2H), 7.48-7.34 (m, 4H), 7.28-7.20 (m, 2H), 7.16 (d, *J* = 8.5 Hz, 1H), 4.42 (d, *J* = 14.1 Hz, 1H), 4.23 (d, *J* = 3.9 Hz, 2H), 3.84 (d, *J* = 13.9 Hz, 1H), 3.29 (dt, *J* = 4.1, 10.4 Hz, 2H), 3.14-3.04 (m, 1H), 2.25-2.13 (m, 2H), 2.02-1.86 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 409.2.

Example 44: 1-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-phenylethanone.



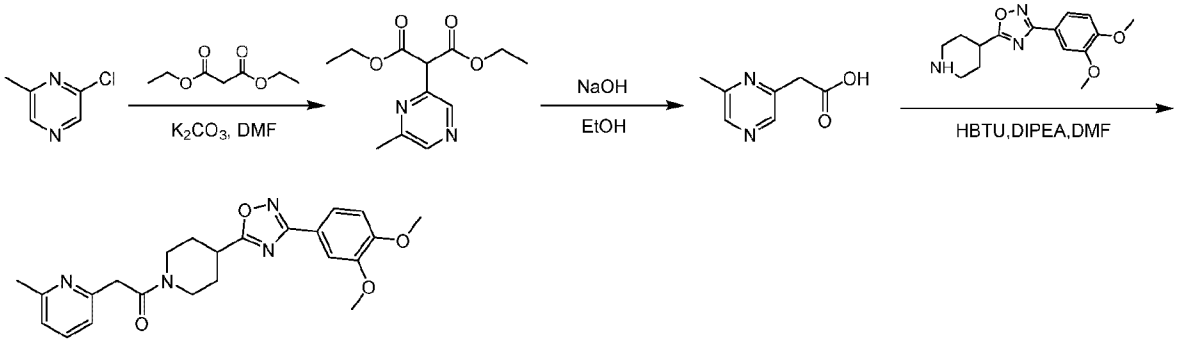
Step 1: Preparation of 1-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-phenylethanone.



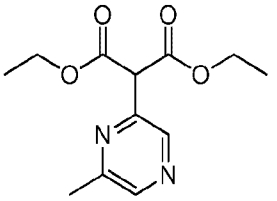
To a stirred solution of 3-(3,4-dimethoxyphenyl)-5-(4-piperidyl)-1,2,4-oxadiazole (150 mg, 518 µmol) in N,N-dimethylformamide (1.50 mL) was added (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (196 mg, 518 µmol), N-ethyl-N-(propan-2-yl)propan-2-amine (201 mg, 1.56 mmol, 271 µL) and 2-phenylacetic acid (74 mg, 544 µmol, 68 µL). The mixture was stirred at 20 °C for 16 h. The crude product was purified directly by prep-HPLC (column: Luna C8 100x30 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 35%-65%,12 min) to give 1-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-2-phenyl-ethanone (24 mg, 59 µmol, 11 %) as a white solid. ^{1}H NMR (400MHz, METHANOL-d4) δ = 7.63 (dd, J=2.0, 8.4 Hz, 1H), 7.55 (d, J=1.8 Hz, 1H), 7.39 - 7.20 (m, 5H), 7.05 (d, J=8.4 Hz, 1H), 4.49 (br d, J=13.5 Hz, 1H), 4.04 (br d, J=13.2 Hz, 1H), 3.88

(s, 6H), 3.82 (s, 2H), 3.34 (br d, J=2.6 Hz, 1H), 3.29 - 3.23 (m, 1H), 3.05 - 2.95 (m, 1H), 2.19 - 2.11 (m, 1H), 2.06 - 1.98 (m, 1H), 1.83 - 1.71 (m, 1H), 1.67 - 1.54 (m, 1H); LCMS (ESI) m/z: $[M+H]^+$ = 408.3.

Example 45: 1-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-(6-methylpyrazin-2-yl)ethanone.

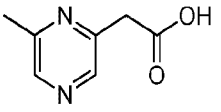


Step 1: Preparation of diethyl 2-(6-methylpyrazin-2-yl)malonate.



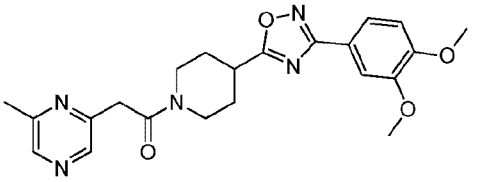
To a stirred solution of 2-chloro-6-methylpyrazine (1.0 g, 7.78 mmol) in N,N-dimethylformamide (20 mL) was added diethyl malonate (3.12 g, 19.5 mmol, 2.94 mL) and potassium carbonate (2.69 g, 19.5 mmol), then the mixture was stirred at 110 °C for 16 h. The reaction mixture was cooled to 20 °C, quenched with water (20 mL), and then extracted with ethyl acetate (60 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. Purification by chromatography (silica, petroleum ether : ethyl acetate = 50 : 1 to 10 : 1) gave diethyl 2-(6-methylpyrazin-2-yl)malonate (180 mg, 713.5 µmol, 9 %) as a green oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (s, 1H), 8.44 (s, 1H), 4.91 (s, 1H), 4.20-4.15 (q, *J* = 7.2 Hz, 4H), 2.58 (s, 3H), 1.25-1.22 (t, *J* = 7.2 Hz, 6H); LCMS (ESI) m/z: 253.1 $[M+H]^+$.

Step 2: Preparation of 2-(6-methylpyrazin-2-yl)acetic acid.



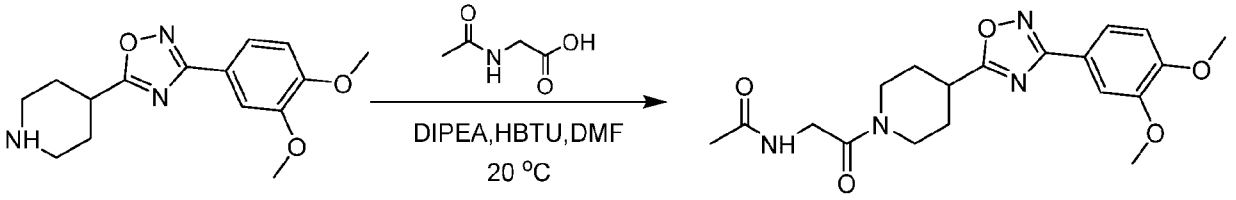
To a stirred solution of diethyl 2-(6-methylpyrazin-2-yl)malonate (180 mg, 713.5 µmol) in ethanol (10 mL) was added sodium hydroxide (2 M, 1.96 mL) and the mixture warmed at 60 °C for 2 h. The reaction was cooled to 20 °C, and acidified with 1 M hydrochloric acid (5 mL). The mixture was concentrated in vacuo to give 2-(6-methylpyrazin-2-yl) acetic acid (1.42 g) as a light yellow solid that was used directly without further purification.

Step 3: Preparation of 1-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-(6-methylpyrazin-2-yl)ethanone.



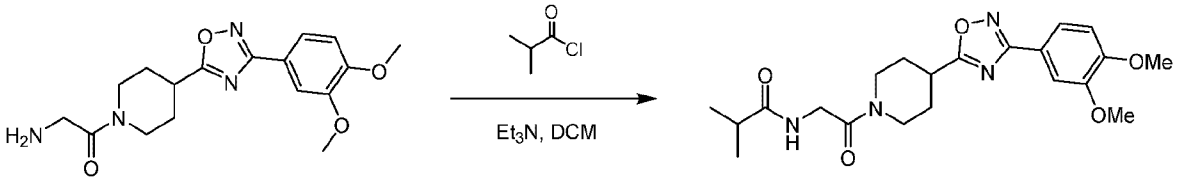
To a stirred solution of 2-(6-methylpyrazin-2-yl)acetic acid (1.05 g, 415 µmol, purity 6 %) in N,N-dimethylformamide (4 mL) was added 3-(3,4-dimethoxyphenyl)-5-(piperidin-4-yl)-1,2,4-oxadiazole (120 mg, 415 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (157 mg, 415 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (214 mg, 1.66 mmol, 289 µL). The mixture was stirred at 20 °C for 4 h. The reaction mixture was purified directly by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 25%-50%,12 min) to give 1-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-(6-methylpyrazin-2-yl)ethanone (26 mg, 62 µmol, 15 %) as a yellow solid. ^{1}H NMR (400 MHz, Methanol-d4) δ 8.41 (s, 2H), 7.68 (dd, *J*=1.9, 8.3 Hz, 1H), 7.61 (d, *J*=1.8 Hz, 1H), 7.10 (d, *J*=8.4 Hz, 1H), 4.51 (d, *J*=13.4 Hz, 1H), 4.22 (d, *J*=13.9 Hz, 1H), 4.12 - 3.93 (m, 2H), 3.92 (s, 6H), 3.52 - 3.38 (m, 2H), 3.12 - 3.02 (m, 1H), 2.57 (s, 3H), 2.28 - 2.17 (m, 2H), 2.04 - 1.80 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 424.2.

Example 46: N-(2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)acetamide.



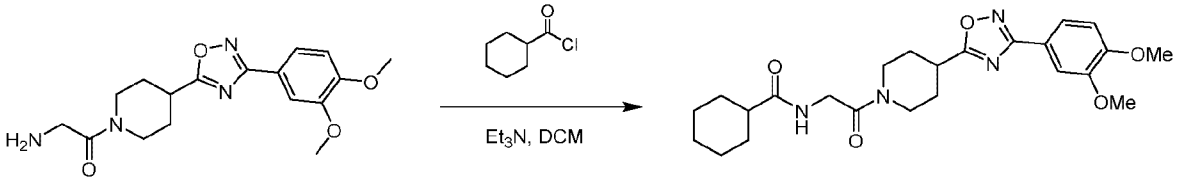
To a stirred solution of 3-(3,4-dimethoxyphenyl)-5-(4-piperidyl)-1,2,4-oxadiazole (250 mg, 864 µmol) in N,N-dimethylformamide (1.5 mL) was added (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (327 mg, 864 µmol), N-ethyl-N-(propan-2-yl)propan-2-amine (335 mg, 2.59 mmol, 452 µL) and 2-acetamidoacetic acid (106 mg, 907 µmol). The mixture was stirred at 20 °C for 16 h. The crude product was purified by prep-HPLC (column: Luna C8 100x30 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 20%-50%,12 min) to give N-[2-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-2-oxo-ethyl]acetamide (36 mg, 94 µmol, 11 %) as a white solid. ^{1}H NMR (400MHz, METHANOL-d4) δ = 7.69 (dd, J=1.9, 8.3 Hz, 1H), 7.61 (d, J=1.9 Hz, 1H), 7.10 (d, J=8.4 Hz, 1H), 4.47 (br d, J=14.2 Hz, 1H), 4.21 - 4.06 (m, 2H), 3.98 (br d, J=13.1 Hz, 1H), 3.92 (s, 6H), 3.47 - 3.38 (m, 2H), 3.13 - 3.00 (m, 1H), 2.31 - 2.16 (m, 2H), 2.05 (s, 3H), 2.00 - 1.79 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 389.2.

Example 47: N-(2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)isobutyramide.

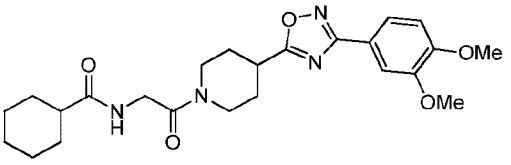


To a stirred solution of 2-amino-1-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)ethanone (150 mg, 433 µmol) in dichloromethane (3 mL) was added isobutyryl chloride (55 mg, 520 µmol, 54 µL) and triethylamine (131 mg, 1.30 mmol, 180 µL) at 0 ℃. The mixture was warmed and stirred at 20 ℃ for 1 h. The reaction mixture was concentrated in vacuo to give crude product that was purified by HPLC prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 23%-53%,12 min) to give N-(2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)isobutyramide (85 mg, 204 µmol, 47 %) as a white solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.74-7.68 (m, 1H), 7.58 (d, *J* = 1.9 Hz, 1H), 6.98 (d, *J* = 8.4 Hz, 1H), 6.63 (br. s., 1H), 4.49 (d, *J* = 13.3 Hz, 1H), 4.12 (d, *J* = 4.0 Hz, 2H), 3.98 (d, *J* = 7.3 Hz, 6H), 3.87 (d, *J* = 14.1 Hz, 1H), 3.36-3.26 (m, 2H), 3.13 (t, *J* = 10.9 Hz, 1H), 2.50 (td, *J* = 6.9, 13.8 Hz, 1H), 2.23 (br. s., 2H), 2.06-1.92 (m, 2H), 1.22 (d, *J* = 6.9 Hz, 6H); LCMS (ESI) m/z: $[M+H]^+$ = 417.3.

Example 48: N-(2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)cyclohexanecarboxamide.



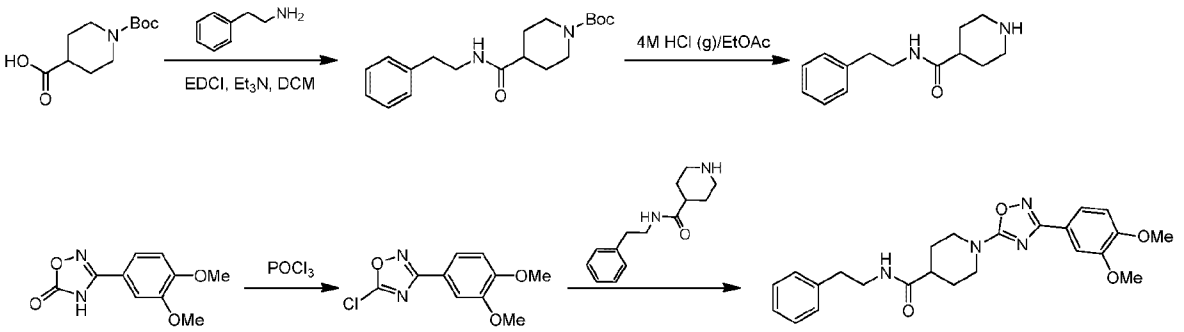
Step 1: Preparation of N-(2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)cyclohexanecarboxamide.



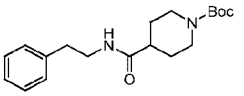
To a stirred solution of 2-amino-1-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)ethanone (150 mg, 433 µmol) in dichloromethane (3 mL) was added cyclohexanecarbonyl chloride (76 mg, 520 µmol, 69 µL) and triethylamine (131 mg, 1.30 mmol, 180 µL) at 0 ℃. The mixture was warmed and stirred at 20 ℃ for 1 h. The reaction mixture was concentrated in vacuo to give a crude product that was purified by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 23%-53%,12 min) to give N-(2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)cyclohexanecarboxamide (78 mg, 171 µmol, 39 %) as a white solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.73-7.68 (m, 1H), 7.60-7.57 (m, 1H), 6.98 (d, *J* = 8.4 Hz, 1H), 6.64-6.59 (m, 1H), 4.53-4.45 (m, 1H), 4.11 (d, *J* = 4.0 Hz, 2H), 3.98 (d, *J* = 7.2 Hz, 6H), 3.86 (d, *J* = 13.3

Hz, 1H), 3.36-3.26 (m, 2H), 3.12 (t, J = 10.7 Hz, 1H), 2.28-2.18 (m, 3H), 2.05-1.89 (m, 4H), 1.82 (d, J = 12.3 Hz, 2H), 1.71 (d, J = 10.9 Hz, 1H), 1.54-1.42 (m, 2H), 1.37-1.22 (m, 3H); LCMS (ESI) m/z: $[M+H]^+$ = 457.3.

Example 49: 1-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-N-(2-phenylethyl)piperidine-4-carboxamide.

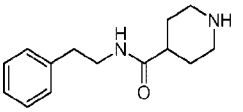


Step 1: Preparation of tert-butyl 4-(phenethylcarbamoyl)piperidine-1-carboxylate.



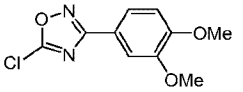
To a stirred solution of 1-tert-butoxycarbonylpiperidine-4-carboxylic acid (1.0 g, 4.36 mmol) in dichloromethane (15 mL) was added 2-phenylethanamine (528 mg, 4.36 mmol, 544 µL), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (835 mg, 4.36 mmol) and triethylamine (44 mg, 436 µmol, 60 µL). The mixture was stirred at 20 °C for 5 h. The reaction mixture was concentrated in vacuo to give a crude product that was purified by chromatography (silica, petroleum ether / ethyl acetate from 10/1 to 1/1) to give tert-butyl 4-(2-phenylethylcarbamoyl)piperidine-1-carboxylate (800 mg, 2.41 mmol, 55 %) as a white solid. LCMS (ESI) m/z: 355.2 $[M+Na]^+$.

Step 2: Preparation of N-phenethylpiperidine-4-carboxamide.



A solution of tert-butyl 4-(2-phenylethylcarbamoyl)piperidine-1-carboxylate (800 mg, 2.41 mmol) in 4N hydrochloric acid / ethyl acetate (10 mL) was stirred at 20 °C for 0.5 h. The reaction mixture was concentrated in vacuo to give N-(2-phenylethyl)piperidine-4-carboxamide (720 mg) as a hydrochloric acid salt and as a white solid.

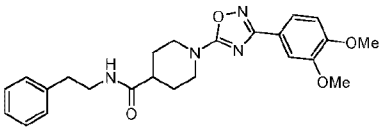
Step 3: Preparation of 5-chloro-3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazole.



3-(3,4-dimethoxyphenyl)-4H-1,2,4-oxadiazol-5-one (900 mg, 4.05 mmol) was added to a mixture of N,N-dimethylformamide (2 mL) and phosphoryl chloride (24.8 g, 161.4 mmol, 15 mL). The mixture was equipped with calcium chloride tube and the mixture was heated at 100 °C for 16 h. The mixture was

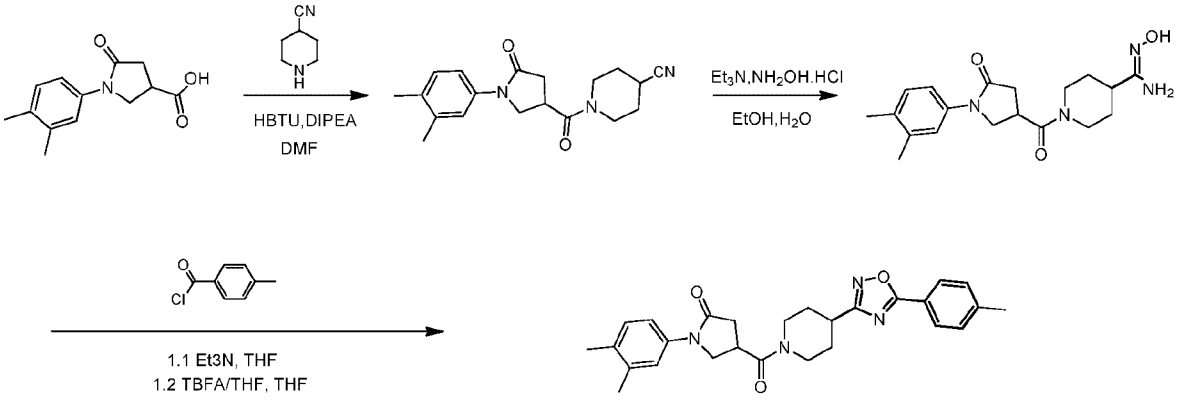
cooled to 0℃ and concentrated under reduced pressure. The residue was poured into ice-water (20 mL) and stirred for 10 min, then the aqueous phase was extracted with dichloromethane (10 mL x 5). The combined organic phases were washed with saturated aqueous sodium chloride solution (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by chromatography (silica, petroleum ether / ethyl acetate=5/1, 1/1) to give 5-chloro-3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazole (104 mg, 432 µmol, 11 %) as a white solid.

Step 4: Preparation of 1-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)-N-phenethylpiperidine-4-carboxamide.

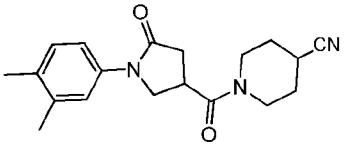


To a stirred solution of 5-chloro-3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazole (95 mg, 395 µmol) in N-methyl-2-pyrrolidone (2 mL) was added N-(2-phenylethyl)piperidine-4-carboxamide (110 mg, 474 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (102 mg, 790 µmol, 137 µL) at 20℃. Then the mixture was heated to 120 ℃ and stirred for 5 h. The crude product was purified by prep-HPLC (column: Luna C8 100x30 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 25%-65%,12 min), Compound 1-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-N-(2-phenylethyl)piperidine-4-carboxamide (117 mg, 266 µmol, 67 %) as a white solid. ^{1}H NMR (400MHz, METHANOL-d4) δ = 7.57 (dd, J=2.0, 8.4 Hz, 1H), 7.51 (d, J=1.9 Hz, 1H), 7.33 - 7.27 (m, 2H), 7.25 - 7.18 (m, 3H), 7.06 (d, J=8.4 Hz, 1H), 4.22 (br d, J=13.3 Hz, 2H), 3.90 (s, 6H), 3.44 (t, J=7.3 Hz, 2H), 3.27 - 3.17 (m, 2H), 2.82 (t, J=7.2 Hz, 2H), 2.51 - 2.40 (m, 1H), 1.92 - 1.67 (m, 4H); LCMS (ESI) m/z: $[M+H]^+$ = 437.3.

Example 50: 1-(3,4-dimethylphenyl)-4-(4-(5-(p-tolyl)-1,2,4-oxadiazol-3-yl)piperidine-1-carbonyl)pyrrolidin-2-one.

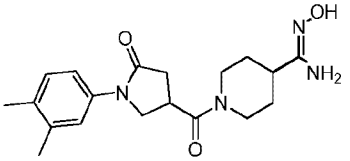


Step 1: Preparation of 1-(1-(3,4-dimethylphenyl)-5-oxopyrrolidine-3-carbonyl)piperidine-4-carbonitrile.



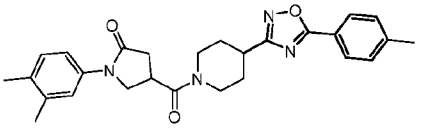
To a stirred solution of 1-(3,4-dimethylphenyl)-5-oxopyrrolidine-3-carboxylic acid (1.0 g, 4.29 mmol) in N,N-dimethylformamide (10 mL) was added piperidine-4-carbonitrile (567 mg, 5.15 mmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (1.63 g, 4.29 mmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (1.66 g, 12.87 mmol, 2.25 mL). The mixture was stirred at 20 °C for 16 h. The reaction mixture was quenched with water (10 mL), then the mixture was extracted with ethyl acetate (20 mL x 4). The combined organic phases were washed with saturated aqueous sodium chloride solution (5 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to a yellow oil (1.6 g). A portion of the crude product (0.3 g) was purified by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 20%-50%,12 min) to give 1-(1-(3,4-dimethylphenyl)-5-oxopyrrolidine-3-carbonyl)piperidine-4-carbonitrile for analysis (144 mg). The remainder of the crude product was used directly without purification. ^{1}H NMR (400 MHz, Methanol-d4) δ 7.37 (d, *J* = 2.5 Hz, 1H), 7.31-7.25 (m, 1H), 7.15 (d, *J* = 8.2 Hz, 1H), 4.08 (d, *J* = 7.0 Hz, 5H), 3.59-3.37 (m, 2H), 3.16-3.03 (m, 1H), 2.91-2.79 (m, 2H), 2.28 (d, *J* = 10.2 Hz, 6H), 2.10-1.72 (m, 4H); LCMS (ESI) m/z: $[M+H]^+$ = 326.2.

Step 2: Preparation of (Z)-1-(1-(3,4-dimethylphenyl)-5-oxopyrrolidine-3-carbonyl)-N'-hydroxypiperidine-4-carboximidamide.



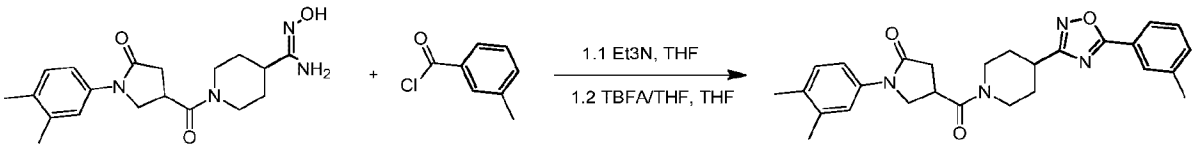
To a stirred solution of 1-(1-(3,4-dimethylphenyl)-5-oxopyrrolidine-3-carbonyl)piperidine-4-carbonitrile (1.30 g, 4.00 mmol) in ethanol (10 mL) was added hydroxylamine hydrochloride (555 mg, 8.00 mmol), triethylamine (809 mg, 8.00 mmol, 1.11 mL) and water (1 mL). The mixture was heated at 75 °C for 2 h. After cooling to 20 °C, water (20 mL) was added to the solution. The mixture was extracted with dichloromethane (40 mL x 4). The combined organic phases were washed with saturated aqueous sodium chloride solution (20 mL) and dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to give a brown solid (1.4 g). A portion of crude product (0.3 g) was purified by prep-HPLC (column: Luna C18 150x2.5mm 5µm; mobile phase: [water (0.225% TFA)-acetonitrile]; B%: 15%-40%,12 min) to give (Z)-1-(1-(3,4-dimethylphenyl)-5-oxopyrrolidine-3-carbonyl)-N'-hydroxypiperidine-4-carboximidamide. The remainder was used directly in the next step. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.86-8.77 (m, 1H), 8.15 (s, 1H), 7.45-7.33 (m, 2H), 7.12 (dd, *J* = 8.2, 2.4 Hz, 1H), 5.36 (br. s., 2H), 4.47-4.32 (m, 1H), 4.06-3.86 (m, 3H), 3.75-3.60 (m, 1H), 3.07 (br. s., 1H), 2.80-2.57 (m, 3H), 2.36-2.24 (m, 1H), 2.21 (d, *J* = 11.8 Hz, 6H), 1.83-1.67 (m, 2H), 1.56 ppm (br. s., 2H); LCMS (ESI) m/z: $[M+H]^+$ = 359.3.

Step 3: Preparation of 1-(3,4-dimethylphenyl)-4-(4-(5-(p-tolyl)-1,2,4-oxadiazol-3-yl)piperidine-1-carbonyl)pyrrolidin-2-one.



To a stirred solution of (Z)-1-(1-(3,4-dimethylphenyl)-5-oxopyrrolidine-3-carbonyl)-N'-hydroxypiperidine-4-carboximidamide (300 mg, 837 μmol) in tetrahydrofuran (8 mL) was added 4-methylbenzoyl chloride (155 mg, 1.00 mmol, 132 μL) and triethylamine (254 mg, 2.51 mmol, 348 μL) at 0 °C, then the mixture was warmed at 20 °C. After 3 h, to the reaction mixture was added ethyl acetate and water and the organic phase was separated. The organic phase was washed with water and saturated aqueous sodium chloride solution and then dried over anhydrous sodium sulfate. The mixture was filtered and concentrated under reduced pressure. To the residue were added tetrahydrofuran (8 mL) and a tetrabutylammonium fluoride in tetrahydrofuran (1 M, 2.51 mL) solution, and the mixture warmed at 50 °C for 16 h. The reaction mixture was concentrated in vacuo to give a crude product that was purified by prep-HPLC (column: Luna C18 100*30 5μm; mobile phase: [water (0.225%TFA)-acetonitrile]; B%: 45%-75%,12 min) to give the racemic of 1-(3,4-dimethylphenyl)-4-(4-(5-(p-tolyl)-1,2,4-oxadiazol-3-yl)piperidine-1-carbonyl)pyrrolidin-2-one (106 mg, 0.23 mmol, 28 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06-7.99 (m, 2H), 7.41-7.33 (m, 3H), 7.31 (d, *J* = 2.0 Hz, 1H), 7.15 (d, *J* = 8.0 Hz, 1H), 4.60 (t, *J* = 13.2 Hz, 1H), 4.30 (dd, *J* = 7.4, 9.5 Hz, 1H), 4.04-3.88 (m, 2H), 3.60 (quin, *J* = 8.5 Hz, 1H), 3.42-3.31 (m, 1H), 3.25-3.14 (m, 1H), 3.11-2.94 (m, 2H), 2.88-2.78 (m, 1H), 2.47 (s, 3H), 2.32-2.12 (m, 8H), 2.03-1.86 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 459.3.

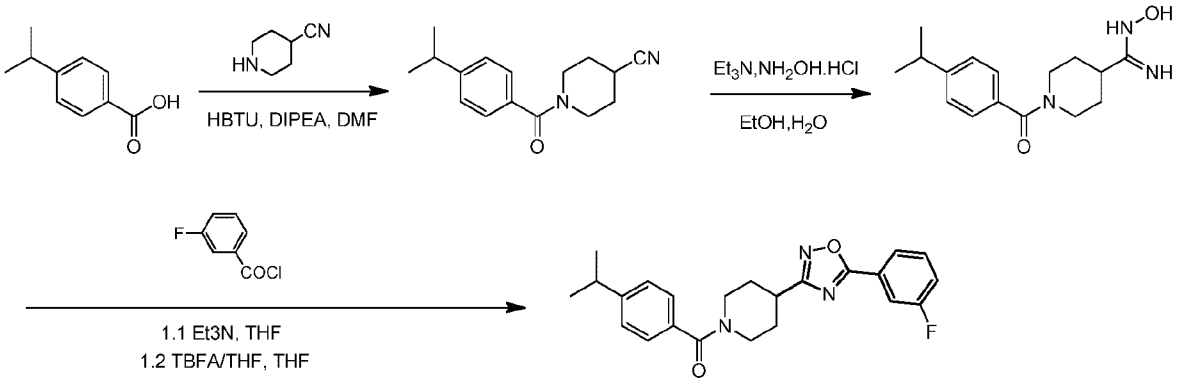
Example 51: 1-(3,4-dimethylphenyl)-4-(4-(5-(m-tolyl)-1,2,4-oxadiazol-3-yl)piperidine-1-carbonyl)pyrrolidin-2-one.



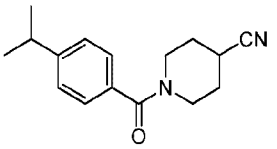
To a stirred solution of (Z)-1-(1-(3,4-dimethylphenyl)-5-oxopyrrolidine-3-carbonyl)-N'-hydroxypiperidine-4-carboximidamide (280 mg, 781 μmol) in tetrahydrofuran (8 mL) was added 3-methylbenzoyl chloride (144 mg, 937 μmol, 123 μL) and triethylamine (237 mg, 2.34 mmol, 324 μL) at 0 °C, the mixture was stirred at 20 °C for 3 h. To the reaction mixture was added ethyl acetate and water and the organic phase was separated. The organic phase was washed with water and saturated aqueous sodium chloride solution, then dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure. To the residue were addded tetrahydrofuran (8 mL) and a tetrabutylammonium fluoride in tetrahydrofuran solution (1 M, 2.34 mL). The mixture was warmed to 50 °C and stirred for 16 h. The reaction mixture was cooled and concentrated in vacuo to give a crude product that was purified by prep-HPLC (column: Luna C8 100x30 5μm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 40%-75%,12 min) to give the racemic of 1-(3,4-dimethylphenyl)-4-(4-(5-(m-tolyl)-1,2,4-oxadiazol-3-yl)piperidine-1-carbonyl)pyrrolidin-2-one (156 mg, 0.34 mmol, 44 %) as a white solid. ^{1}H NMR (400 MHz,

$CDCl_3$) δ 7.99-7.91 (m, 2H), 7.43 (d, *J* = 1.0 Hz, 3H), 7.32-7.29 (m, 1H), 7.15 (d, *J* = 8.3 Hz, 1H), 4.60 (t, *J* = 14.1 Hz, 1H), 4.30 (dd, *J* = 7.3, 9.6 Hz, 1H), 4.04-3.88 (m, 2H), 3.65-3.54 (m, 1H), 3.37 (d, *J* = 7.0 Hz, 1H), 3.21 (d, *J* = 3.5 Hz, 1H), 3.11-2.94 (m, 2H), 2.88-2.78 (m, 1H), 2.48 (s, 3H), 2.32-2.13 (m, 8H), 1.93 (d, *J* = 12.2 Hz, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 459.3.

Example 52: (4-(5-(3-fluorophenyl)-1,2,4-oxadiazol-3-yl)piperidin-1-yl)(4-isopropylphenyl)methanone.

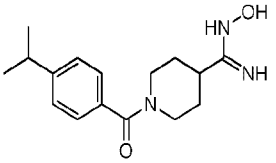


Step 1: Preparation of 1-(4-isopropylbenzoyl)piperidine-4-carbonitrile.



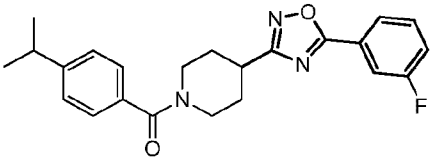
To a stirred solution of 4-isopropylbenzoic acid (1.0 g, 6.09 mmol) in N,N-dimethylformamide (10 mL) was added piperidine-4-carbonitrile (805 mg, 7.31 mmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (2.31 g, 6.09 mmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (2.36 g, 18.27 mmol, 3.19 mL). The mixture was stirred at 20 ℃ for 16 h. The reaction mixture was quenched with water (10 mL), then the mixture was extracted with ethyl acetate (40 mL x 4). The combined organic phases were washed with saturated aqueous sodium chloride solution (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give yellow oil (1.8 g). A portion of crude product (0.2 g) was purified by prep-HPLC (column: Waters Xbridge 150x2.5mm 5μm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 25%-55%,12 min) to give 1-(4-isopropylbenzoyl)piperidine-4-carbonitrile (115 mg) as a sample for analysis. The remainder was used directly. ^1H NMR (400 MHz, Methanol-d4) δ 7.37 (s, 4H), 4.16-3.40 (m, 4H), 3.15-3.07 (m, 1H), 3.02-2.93 (m, 1H), 2.10-1.76 (m, 4H), 1.31-1.26 (m, 6H); LCMS (ESI) m/z: $[M+H]^+$ = 257.2.

Step 2: Preparation of N-hydroxy-1-(4-isopropylbenzoyl)piperidine-4-carboximidamide.



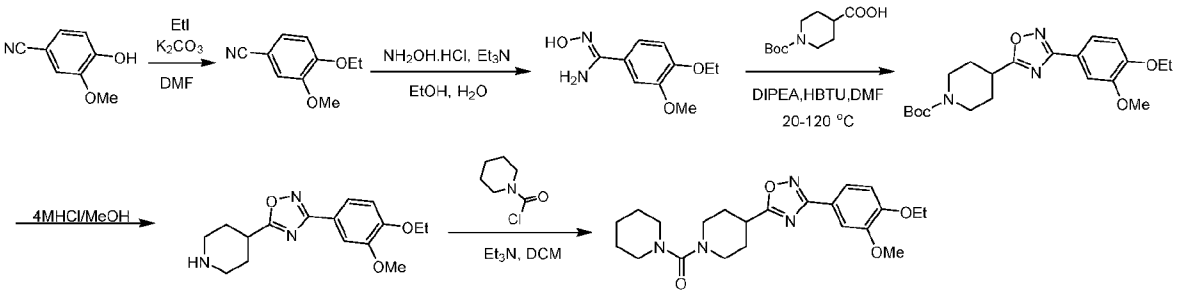
To a stirred solution of 1-(4-isopropylbenzoyl)piperidine-4-carbonitrile (1.60 g, 6.24 mmol) in ethanol (15 mL) was added hydroxylamine hydrochloride (867 mg, 12.5 mmol), triethylamine (1.26 g, 12.48 mmol, 1.73 mL) and water (1.50 mL). The mixture was heated at 75 °C for 2 h. After cooling to 20 °C, water (20 mL) was added to the solution. The mixture was extracted with dichloromethane (40 mL x 4). The combined organic phases were washed with saturated aqueous sodium chloride solution (20 mL) and dried over anhydrous sodium sulfate, then filtered and concentrated in vacuo to give N-hydroxy-1-(4-isopropylbenzoyl)piperidine-4-carboximidamide (1.60 g, 5.53 mmol, 89 %) as a white solid that was used directly without further purification. ^{1}H NMR (400 MHz, Methanol-d4) δ 7.40-7.33 (m, 4H), 4.78-4.58 (m, 1H), 3.94-3.73 (m, 1H), 3.22 (d, *J* = 7.3 Hz, 2H), 3.02-2.95 (m, 1H), 2.50-2.35 (m, 1H), 1.96-1.67 (m, 4H), 1.31-1.27 (m, 6H).

Step 3: Preparation of (4-(5-(3-fluorophenyl)-1,2,4-oxadiazol-3-yl)piperidin-1-yl)(4-isopropylphenyl)methanone.

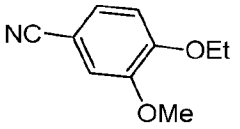


To a stirred solution of N-hydroxy-1-(4-isopropylbenzoyl)piperidine-4-carboximidamide (200 mg, 691 µmol) in tetrahydrofuran (5 mL) was added 3-fluorobenzoyl chloride (131 mg, 829 µmol, 99 µL) and triethylamine (209 mg, 2.07 mmol, 287 µL) at 0 °C. The mixture was warmed and then stirred at 20 °C for 16 h. To the reaction mixture was added ethyl acetate and water and the organic phase was separated. The organic phase was washed with water and saturated aqueous sodium chloride solution, then dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. To the obtained residue were added tetrahydrofuran (5 mL) and a solution of tetrabutylammonium fluoride in tetrahydrofuran (1 M, 2.07 mL), then the mixture was warmed at 50 °C for 16 h. The reaction mixture was concentrated in vacuo to give a crude product that was purified by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 50%-80%,12 min) to give (4-(5-(3-fluorophenyl)-1,2,4-oxadiazol-3-yl)piperidin-1-yl)(4-isopropylphenyl)methanone (76 mg, 193.5 µmol, 28 %) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 7.7 Hz, 1H), 7.78-7.72 (m, 1H), 7.45 (dt, *J* = 5.6, 8.0 Hz, 1H), 7.32-7.27 (m, 2H), 7.26-7.20 (m, 2H), 7.18 (s, 1H), 4.76-3.64 (m, 2H), 3.20-2.97 (m, 3H), 2.86 (td, *J* = 6.9, 13.8 Hz, 1H), 2.18-1.74 (m, 4H), 1.19 (d, *J* = 6.9 Hz, 6H); LCMS (ESI) m/z: $[M+H]^+$ = 394.2.

Example 53: (4-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)(piperidin-1-yl)methanone.

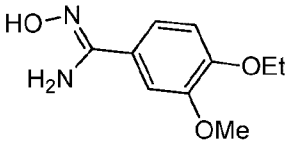


Step 1: Preparation of 4-ethoxy-3-methoxybenzonitrile.



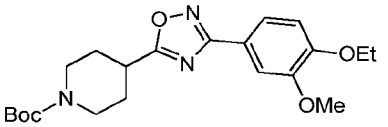
To a stirred solution of 4-hydroxy-3-methoxybenzonitrile (5.0 g, 33.5 mmol) in N,N-dimethylformamide (50 mL) was added iodoethane (6.27 g, 40.2 mmol, 3.22 mL) and potassium carbonate (9.27 g, 67.0 mmol) at 0 °C, then the reaction was warmed and stirred at 40 °C for 16 h. The reaction mixture was quenched by addition of water (50 mL) then the mixture was extracted with ethyl acetate (80 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give 4-ethoxy-3-methoxybenzonitrile (5.80 g, 32.7 mmol, 98 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20-7.16 (m, 1H), 7.00 (d, *J* = 1.9 Hz, 1H), 6.81 (d, *J* = 8.4 Hz, 1H), 4.07 (q, *J* = 6.9 Hz, 2H), 3.82 (s, 3H), 1.45-1.39 (m, 3H).

Step 2: Preparation of (Z)-4-ethoxy-N'-hydroxy-3-methoxybenzimidamide.



To a stirred solution of 4-ethoxy-3-methoxybenzonitrile (5.80 g, 32.7 mmol) in ethanol (50 mL) was added hydroxylamine hydrochloride (4.55 g, 65.5 mmol), triethylamine (6.62 g, 65.46 mmol, 9.07 mL) and water (5 mL). The mixture was heated at 75 °C for 2 h. After cooling to 20 °C, the solvents were evaporated under vacuum, and water (20 mL) was added to the solution. The mixture was extracted with dichloromethane (60 mL x 3). The combined organic extracts were washed with saturated aqueous sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, and then filtered and concentrated in vacuo to give (Z)-4-ethoxy-N'-hydroxy-3-methoxybenzimidamide (5.96 g, 28.4 mmol, 87 %) as a white solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 9.44 (br. s., 1H), 7.28-7.14 (m, 2H), 6.90 (d, *J* = 8.4 Hz, 1H), 5.73 (s, 2H), 4.00 (q, *J* = 6.9 Hz, 2H), 3.75 (s, 3H), 1.31 (t, *J* = 7.1 Hz, 3H).

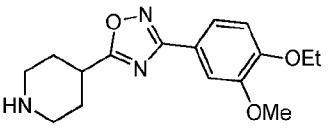
Step 3: Preparation of tert-butyl 4-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carboxylate.



To a stirred solution of (Z)-4-ethoxy-N'-hydroxy-3-methoxybenzimidamide (1.0 g, 4.76 mmol) in N,N-dimethylformamide (15 mL) was added 1-(tert-butoxycarbonyl)piperidine-4-carboxylic acid (1.09 g, 4.76 mmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (1.81 g, 4.76 mmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (1.85 g, 14.28 mmol, 2.49 mL). The mixture was stirred at 20 °C for 16 h then heated at 120 °C for 2 h. The reaction mixture was cooled then quenched by addition of water (40 mL), then the mixture was extracted with ethyl acetate (80 mL x 4). The combined organic phases were washed with saturated aqueous sodium chloride solution (30 mL), dried

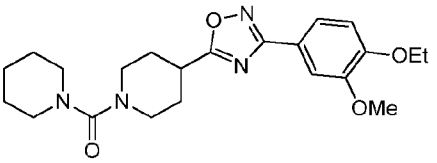
over anhydrous sodium sulfate, filtered and concentrated to give tert-butyl 4-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carboxylate (2.56 g) as a yellow oil. LCMS (ESI) m/z: $[M+H]^+$ = 404.3.

Step 4: Preparation of 3-(4-ethoxy-3-methoxyphenyl)-5-(piperidin-4-yl)-1,2,4-oxadiazole.



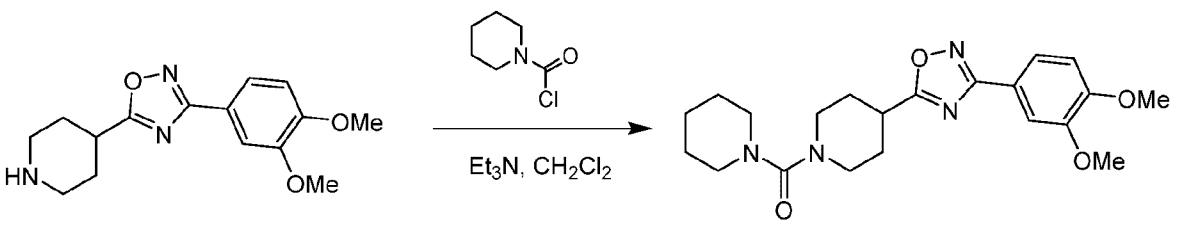
To a stirred solution of tert-butyl 4-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carboxylate (1.0 g, 2.48 mmol) in methanol (5 mL) was added 4 M methanolic hydrochloric acid (20 mL). The mixture was stirred at 20 °C for 16 h. The reaction mixture was concentrated under reduced pressure to provide the crude 3-(4-ethoxy-3-methoxyphenyl)-5-(piperidin-4-yl)-1,2,4-oxadiazole (900 mg) as a yellow solid that was used directly without further purification. LCMS (ESI) m/z: $[M+H]^+$ = 304.1

Step 5: Preparation of (4-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)(piperidin-1-yl)methanone

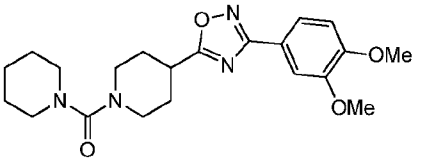


To a stirred solution of 3-(4-ethoxy-3-methoxyphenyl)-5-(piperidin-4-yl)-1,2,4-oxadiazole (200 mg, 659 µmol) in dichloromethane (3 mL) was added piperidine-1-carbonyl chloride (116 mg, 791 µmol, 98 µL) and triethylamine (200 mg, 1.98 mmol, 274 µL) at 0 °C. The mixture was stirred at 20 °C for 1 h. The reaction mixture was concentrated in vacuo to give a crude product that was purified by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 40%-70%,12 min) to give (4-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)(piperidin-1-yl)methanone (65 mg, 158 µmol, 24 %) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71-7.66 (m, 1H), 7.59 (d, J = 1.9 Hz, 1H), 6.96 (d, J = 8.4 Hz, 1H), 4.19 (q, J = 6.9 Hz, 2H), 3.98 (s, 3H), 3.75 (d, J = 13.6 Hz, 2H), 3.29-3.13 (m, 5H), 3.04-2.94 (m, 2H), 2.17 (dd, J = 3.1, 13.3 Hz, 2H), 2.05-1.93 (m, 2H), 1.60 (d, J = 8.4 Hz, 6H), 1.53 (t, J = 7.0 Hz, 3H); LCMS (ESI) m/z: $[M+H]^+$ = 415.3.

Example 54: (4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)(piperidin-1-yl)methanone.

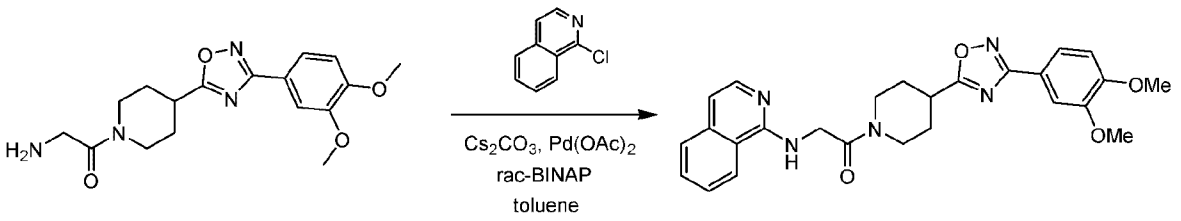


Step 1: Preparation of (4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)(piperidin-1-yl)methanone.

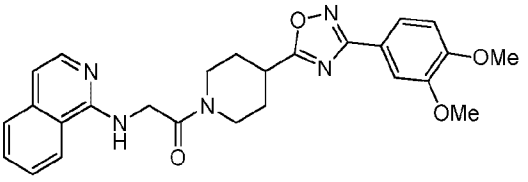


To a stirred solution of 3-(3,4-dimethoxyphenyl)-5-(piperidin-4-yl)-1,2,4-oxadiazole (100 mg, 346 µmol) in dichloromethane (3 mL) was added piperidine-1-carbonyl chloride (61 mg, 415 µmol, 51 µL) and triethylamine (104 mg, 1.04 mmol, 143 µL) at 0 ℃. The mixture was stirred at 20 ℃ for 1 h. The reaction mixture was concentrated in vacuo to give a crude product that was purified by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 35%-65%,12 min) to give (4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)(piperidin-1-yl)methanone (81 mg, 202 µmol, 58 %) as a white solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.74-7.68 (m, 1H), 7.59 (d, *J* = 1.9 Hz, 1H), 6.98 (d, *J* = 8.4 Hz, 1H), 3.98 (d, *J* = 8.4 Hz, 6H), 3.76 (d, *J* = 13.4 Hz, 2H), 3.29-3.14 (m, 5H), 3.04-2.95 (m, 2H), 2.17 (dd, *J* = 13.3, 3.4 Hz, 2H), 2.05-1.94 (m, 2H), 1.60 ppm (d, *J* = 8.5 Hz, 6H); LCMS (ESI) m/z: $[M+H]^+$ = 401.3.

Example 55: 1-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-(isoquinolin-1-ylamino)ethanone.



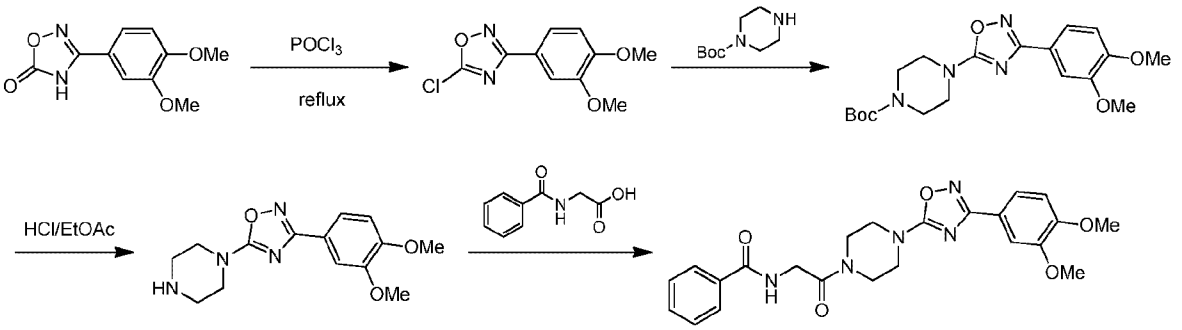
Step 1: Preparation of 1-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-(isoquinolin-1-ylamino)ethanone.



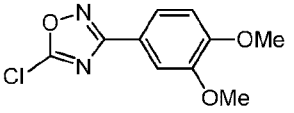
To a stirred solution of 2-amino-1-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)ethanone (150 mg, 433 µmol) in toluene (2 mL) was added 1-chloroisoquinoline (70 mg, 433 µmol), cesium carbonate (423 mg, 1.30 mmol), (±)-2,2′-bis(diphenylphosphino)-1,1′-binaphthalene (26 mg, 43 µmol, 0.10 *eq*), and palladium(II) acetate (9 mg, 43 µmol, 0.10 *eq*) under nitrogen. The mixture was stirred at 100 ℃ for 16 h. The reaction mixture was filtered through diatomaceous earth and the filtrate was concentrated in vacuo to give a crude product that was purified by prep-HPLC (column: Luna C8 100*30 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 40%-70%,12 min) to give 1-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-(isoquinolin-1-ylamino)ethanone (57 mg,

119 µmol, 27 %) as a white solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 8.04-7.96 (m, 2H), 7.75-7.50 (m, 5H), 7.03-6.95 (m, 2H), 6.66 (br. s., 1H), 4.60 (d, *J* = 13.7 Hz, 1H), 4.45 (br. s., 2H), 4.08 (d, *J* = 12.5 Hz, 1H), 3.98 (d, *J* = 7.9 Hz, 6H), 3.46-3.30 (m, 2H), 3.24-3.13 (m, 1H), 2.28 (br. s., 2H), 2.13-1.97 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 474.3.

Example 56: N-(2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperazin-1-yl)-2-oxoethyl)benzamide.

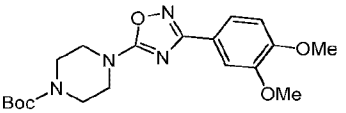


Step 1: Preparation of 5-chloro-3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazole.



To a mixture of N,N-dimethylformamide (1 mL) and phosphoryl chloride (8.25 g, 53.8 mmol, 5 mL) was added 3-(3,4-dimethoxyphenyl)-4H-1,2,4-oxadiazol-5-one (300 mg, 1.35 mmol) at 25 ℃ under calcium chloride tube. The mixture was heated to 100 ℃ and stirred for 16 h. The mixture was cooled to 25 ℃ and concentrated in vacuo carefully. The residue was poured into ice-water (20 mL) and stirred for 10 min. The aqueous phase was extracted with dichloromethane (10 mL x 5). The combined organic phases were washed with saturated aqueous sodium chloride solution (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by chromatography (petroleum ether / ethyl acetate=5/1 to 1/1) to afford 5-chloro-3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazole (99 mg, 414 µmol, 31 %) as a white solid. LCMS (ESI) m/z: 241.1 $[M+H]^+$.

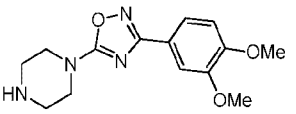
Step 2: Preparation of tert-butyl 4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperazine-1-carboxylate.



To a stirred solution of 5-chloro-3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazole (90 mg, 374 µmol) and tert-butyl piperazine-1-carboxylate (83 mg, 448.80 µmol) in N-methyl-2-pyrrolidone (1.50 mL) was added N-ethyl-N-(propan-2-yl)propan-2-amine (96 mg, 748 µmol, 130 µL). The mixture was stirred at 120 ℃ for 2 h. The mixture was cooled to 25 ℃ and concentrated in vacuo at 40 ℃. The residue was poured into water (10 mL) then the aqueous phase was extracted with ethyl acetate (10 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to afford tert-butyl 4-[3-(3,4-

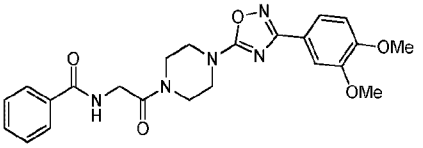
dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]piperazine-1-carboxylate (900 mg) that was used directly without further purification.

Step 3: Preparation of 3-(3,4-dimethoxyphenyl)-5-(piperazin-1-yl)-1,2,4-oxadiazole.



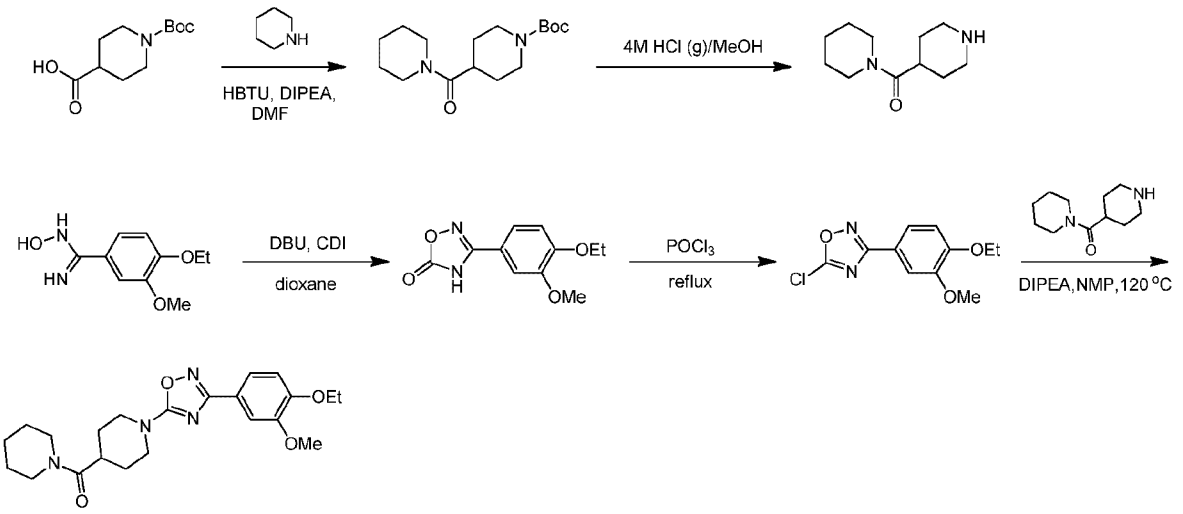
A solution of tert-butyl 4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]piperazine-1-carboxylate (146 mg, 374 µmol) in hydrochloric acid / ethyl acetate (4M, 10 mL) was stirred at 20 °C for 2 h. The reaction mixture was concentrated in vacuo to give 3-(3,4-dimethoxyphenyl)-5-piperazin-1-yl-1,2,4-oxadiazole hydrochloride (900 mg) which was used directly without further purification.

Step 4: Preparation of N-(2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperazin-1-yl)-2-oxoethyl)benzamide.

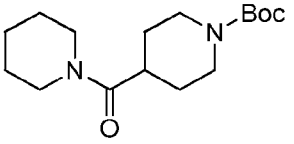


To a stirred solution of 3-(3,4-dimethoxyphenyl)-5-piperazin-1-yl-1,2,4-oxadiazole hydrochloride (667 mg, 306 µmol,) and 2-benzamidoacetic acid (137 mg, 765 µmol) in N,N-dimethylformamide (2 mL) was added (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (174 mg, 459 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (118 mg, 918.51 µmol, 160 µL) at 20 °C. The mixture was stirred at 20 °C for 5 h. The reaction mixture was purified directly by prep-HPLC (column: Waters Xbridge 150x25 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 25%-60%,12 min) to give N-[2-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]piperazin-1-yl]-2-oxo-ethyl]benzamide (55 mg, 121 µmol, 39 %) as a yellow solid. ^{1}H NMR (400MHz, DMSO-d6) δ = 8.59 (br t, J=5.6 Hz, 1H), 7.93 - 7.83 (m, 2H), 7.60 - 7.44 (m, 4H), 7.39 (d, J=1.9 Hz, 1H), 7.08 (d, J=8.5 Hz, 1H), 4.20 (d, J=5.6 Hz, 2H), 3.81 (d, J=1.1 Hz, 6H), 3.73 - 3.58 (m, 8H); LCMS (ESI) m/z: $[M+H]^+$ = 452.2.

Example 57: (1-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-4-yl)(piperidin-1-yl)methanone.

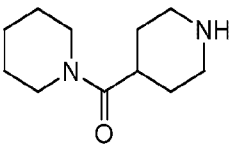


Step 1: Preparation of tert-butyl 4-(piperidine-1-carbonyl)piperidine-1-carboxylate.



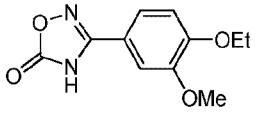
To a stirred solution of 1-(tert-butoxycarbonyl)piperidine-4-carboxylic acid (1.0 g, 4.36 mmol) in N,N-dimethylformamide (15 mL) was added piperidine (445 mg, 5.23 mmol, 518 µL), 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (1.99 g, 5.23 mmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (1.69 g, 13.1 mmol, 2.29 mL). The mixture was stirred at 20 °C for 3 h. The reaction mixture was quenched by addition of water (20 mL) then the mixture was extracted with ethyl acetate (40 mL x 4), then the combined organic phases were washed with saturated aqueous sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give tert-butyl 4-(piperidine-1-carbonyl)piperidine-1-carboxylate (1.90 g) as a yellow oil. This was used directly without further purification. LCMS (ESI) m/z: $[M+H]^+$ = 297.2

Step 2: Preparation of piperidin-1-yl(piperidin-4-yl)methanone.



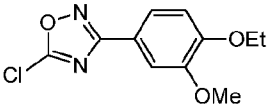
To a stirred solution of tert-butyl 4-(piperidine-1-carbonyl)piperidine-1-carboxylate (500 mg, 1.69 mmol) in methanol (5 mL) was added 4N methanolic hydrogen chloride solution (15 mL). The mixture was stirred at 20 °C for 16 h. The reaction mixture was concentrated under reduced pressure to provide piperidin-1-yl(piperidin-4-yl)methanone (400 mg) as a colorless oil. ^{1}H NMR (400 MHz, DMSO-d6) δ 3.51-3.36 (m, 4H), 3.28-3.18 (m, 2H), 2.90 (s, 4H), 1.82-1.68 (m, 4H), 1.64-1.37 (m, 6H).

Step 3: Preparation of 3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5(4H)-one.



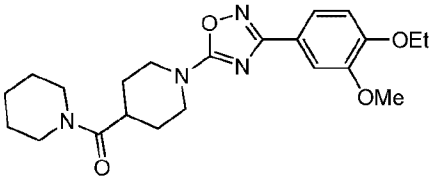
To a stirred solution of 4-ethoxy-N-hydroxy-3-methoxybenzimidamide (800 mg, 3.81 mmol) in dioxane (8 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (638 mg, 4.19 mmol, 631 µL) and 1,1'-carbonyldiimidazole (926 mg, 5.72 mmol). The mixture was stirred at 110 ℃ for 16 h. The reaction mixture was quenched with water (10 mL), then the mixture was extracted with dichloromethane (50 mL x 4). The combined organic phases were washed with saturated aqueous sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. Purification by chromatography (silica, dichloromethane : methanol = 50 :1) gave 3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5(4H)-one (1.20 g, quant.) as a yellow oil. LCMS (ESI) m/z: $[M+H]^+$ = 237.1.

Step 4: Preparation of 5-chloro-3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazole.



To a stirred mixture of 3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5(4H)-one (500 mg, 2.12 mmol) and N,N-dimethylformamide (1 mL) was equipped with calcium chloride tube and phosphoryl chloride (10 mL) was added dropwise. The mixture was heated at 110 ℃ for 16 h. The reaction mixture was cooled to 20 ℃, then poured onto ice water (100 mL), and stirred for 30 min. The mixture was extracted with dichloromethane (20 mL x 5), then the combined organic phases were washed with saturated aqueous sodium chloride solution (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give 5-chloro-3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazole (360 mg, 1.41 mmol, 67 %) as a brown solid. LCMS (ESI) m/z: $[M+H]^+$ = 255.1

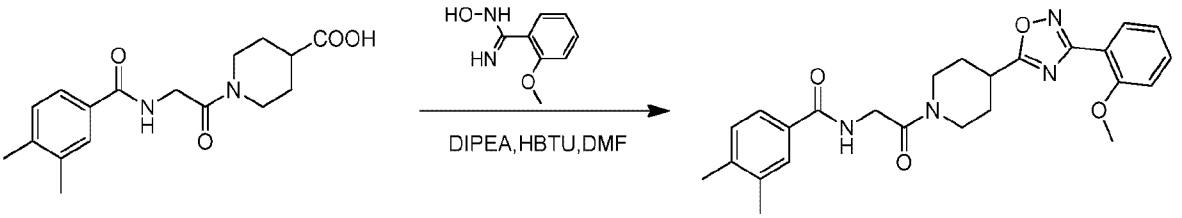
Step 5: Preparation of (1-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-4-yl)(piperidin-1-yl)methanone.



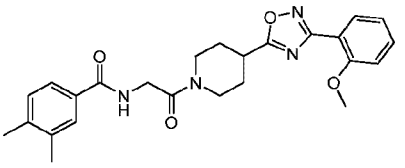
To a stirred solution of piperidin-1-yl(piperidin-4-yl)methanone (100 mg, 509 µmol) in N-methyl-2-pyrrolidone (4 mL) was added 5-chloro-3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazole (194 mg, 764 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (131 mg, 1.02 mmol, 177 µL). The mixture was stirred at 120 ℃ for 16 h. The reaction mixture was purified directly by prep-HPLC (column: Luna C8 100*30 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 35%-65%,12 min) to give (1-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-4-yl)(piperidin-1-yl)methanone (61 mg, 147.6 µmol, 29 %) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53-7.47 (m, 1H), 7.42 (d, *J* = 1.9 Hz, 1H), 6.84 (d, *J* = 8.5 Hz, 1H), 4.24-4.16 (m, 2H), 4.08 (q, *J* = 6.9 Hz, 2H), 3.87 (s, 3H), 3.50 (br. s., 2H),

3.40 (br. s., 2H), 3.19-3.09 (m, 2H), 2.69 (tt, *J* = 3.8, 10.7 Hz, 1H), 1.94-1.71 (m, 4H), 1.63-1.48 (m, 6H), 1.42 (t, *J* = 7.0 Hz, 3H); LCMS (ESI) m/z: $[M+H]^+$ = 415.3.

Example 58: N-(2-(4-(3-(2-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)-3,4-dimethylbenzamide.

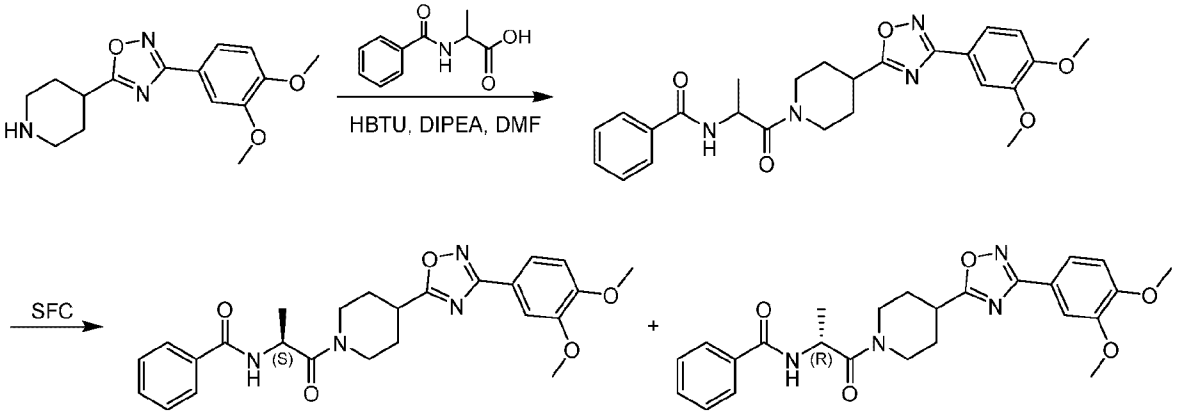


Step 1: N-(2-(4-(3-(2-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)-3,4-dimethylbenzamide.

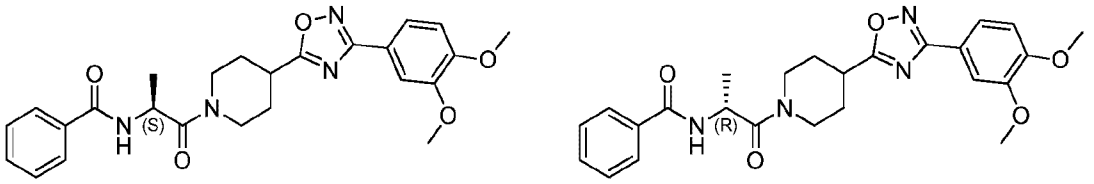


To a stirred solution of 1-(2-(3,4-dimethylbenzamido)acetyl)piperidine-4-carboxylic acid (150 mg, 471 µmol) and N-hydroxy-2-methoxybenzimidamide (78 mg, 471 µmol) in N,N-dimethylformamide (2 mL) was added N-ethyl-N-(propan-2-yl)propan-2-amine (121 mg, 942 µmol, 164 µL) and (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (178 mg, 471 µmol) at 15 ℃. The mixture was stirred for 15 h, then the mixture was heated to 110 ℃ and stirred for 5 h. The mixture was cooled and then purified by prep-HPLC (column: Waters Xbridge 150x25 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 37%-67%,12 min) to obtain N-(2-(4-(3-(2-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)-3,4-dimethylbenzamide (110 mg, 244 µmol, 52 %) as yellow solid. ^{1}H NMR (400 MHz, Methanol-d4) δ7.96 (dd, J=1.5, 7.7 Hz, 1H), 7.66 (s, 1H), 7.60 (d, J=7.9 Hz, 1H), 7.56 - 7.49 (m, 1H), 7.23 (d, J=7.5 Hz, 1H), 7.18 (d, J=8.4 Hz, 1H), 7.09 (t, J=7.5 Hz, 1H), 4.47 (d, J=12.8 Hz, 1H), 4.35 - 4.23 (m, 2H), 4.04 (d, J=13.7 Hz, 1H), 3.92 (s, 3H), 3.49 - 3.35 (m, 2H), 3.07 (t, J=11.0 Hz, 1H), 2.32 (s, 6H), 2.27 - 2.10 (m, 2H), 2.06 - 1.83 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 449.3.

Example 59: N-[2-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-1-methyl-2-oxo-ethyl]benzamide, Enantiomer 1 and Example 60: N-[2-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-1-methyl-2-oxo-ethyl]benzamide, Enantiomer 2



Step 1: Preparation of N-[(R)-2-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-1-methyl-2-oxo-ethyl]benzamide and N-[(S)- 2-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-1-methyl-2-oxo-ethyl]benzamide.



To a stirred solution of 3-(3,4-dimethoxyphenyl)-5-(4-piperidyl)-1,2,4-oxadiazole (150 mg, 518 µmol) and 2-benzamidopropanoic acid (105 mg, 544 µmol) in N,N-dimethylformamide (2 mL) was added (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (196 mg, 518 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (201 mg, 1.56 mmol, 271 µL). The mixture was stirred at 20 °C for 5 h. The crude product was purified by prep-HPLC (column: Luna C18 150x25 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 35%-65%,12 min) to give rac-N-(1-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-1-oxopropan-2-yl)benzamide then the product purified by SFC separation (column: AD(250x30mm, 5µm); mobile phase: [Neu-IPA]; B%: 42%-42%,min) to give N-[2-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-1-methyl-2-oxo-ethyl]benzamide, Enantiomer 1 (63 mg, 134.93 µmol, 26 %) as a white solid and N-[2-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-1-methyl-2-oxo-ethyl]benzamide, Enantiomer 2 (56 mg, 120 µmol, 23% as a white solid.

N-[2-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-1-methyl-2-oxo-ethyl]benzamide, Enantiomer 1:

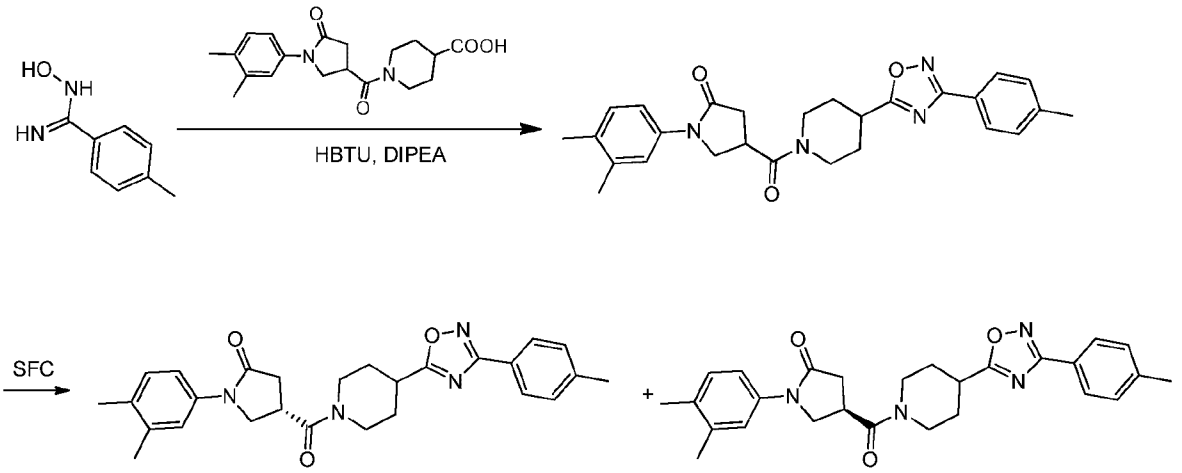
^{1}H NMR (400MHz, DMSO-d_6) δ = 8.63 (br dd, *J*=7.3, 16.1 Hz, 1H), 7.88 (br d, *J*=7.5 Hz, 2H), 7.62 - 7.41 (m, 5H), 7.11 (br d, *J*=8.2 Hz, 1H), 4.97 (br d, *J*=6.4 Hz, 1H), 4.43 - 4.24 (m, 1H), 4.10 - 3.95 (m, 1H),

3.82 (s, 6H), 3.42 (br t, *J*=10.8 Hz, 1H), 3.30 - 3.21 (m, 1H), 2.99 - 2.83 (m, 1H), 2.09 (br d, *J*=11.9 Hz, 2H), 1.83 - 1.60 (m, 2H), 1.30 (br s, 3H); LCMS (ESI) m/z: $[M+H]^+$ = 465.3. ee = 100%.

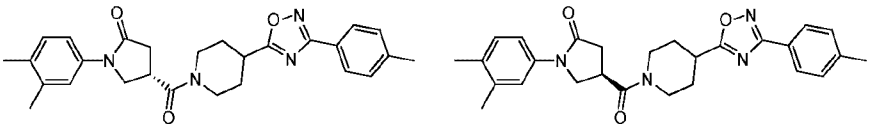
N-[2-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-1-methyl-2-oxo-ethyl]benzamide, Enantiomer 2:

^{1}H NMR (400MHz, DMSO-d_6) δ = 8.65 (br dd, *J*=7.6, 16.1 Hz, 1H), 7.98 - 7.86 (m, 2H), 7.70 - 7.41 (m, 5H), 7.13 (br d, *J*=8.2 Hz, 1H), 5.00 (br d, *J*=5.5 Hz, 1H), 4.49 - 4.24 (m, 1H), 4.12 - 3.96 (m, 1H), 3.85 (s, 6H), 3.45 (br t, *J*=10.7 Hz, 1H), 3.27 (br s, 1H), 3.05 - 2.83 (m, 1H), 2.12 (br d, *J*=12.5 Hz, 2H), 1.89 - 1.61 (m, 2H), 1.32 (br s, 3H); LCMS (ESI) m/z: $[M+H]^+$ = 465.3. ee = 99.6

Example 61: (2-methyl-4-(2-oxo-4-(4-(3-(p-tolyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)pyrrolidin-1-yl)phenyl)methylium, Enantiomer 1 and Example 62: (2-methyl-4-(2-oxo-4-(4-(3-(p-tolyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)pyrrolidin-1-yl)phenyl)methylium, Enantiomer 2



Step 1: Preparation of (2-methyl-4-(2-oxo-4-(4-(3-(p-tolyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)pyrrolidin-1-yl)phenyl)methylium, Enantiomer 1 and (2-methyl-4-(2-oxo-4-(4-(3-(p-tolyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)pyrrolidin-1-yl)phenyl)methylium, Enantiomer 2



To a stirred solution of N-hydroxy-4-methylbenzimidamide (300 mg, 2.0 mmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (834 mg, 2.20 mmol) and 1-(1-(3,4-dimethylphenyl)-5-oxopyrrolidine-3-carbonyl)piperidine-4-carboxylic acid (688 mg, 2.00 mmol) in N,N-dimethylformamide (10 mL) were added N-ethyl-N-(propan-2-yl)propan-2-amine (516 mg, 4.00 mmol, 698 µL) at 0 °C. Then the reaction was warmed to 25 °C. After 17 h, the reaction was warmed to 90 °C. After 3 h, the mixture was cooled, diluted with water (10 mL), and extracted with ethyl acetate (30 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (40 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give a crude residue that was purified by prep-HPLC (column: Phenomenex luna(2) C18 250x50 10µm; mobile phase: [water (0.1%TFA)-acetonitrile]; B%: 40%-70%,20min) to give the racemic of 1-(3,4-dimethylphenyl)-4-(4-(3-(p-tolyl)-1,2,4-

oxadiazol-5-yl)piperidine-1-carbonyl)pyrrolidin-2-one (600 mg, 1.31 mmol, 65 %). This was purified by SFC (column: AS(250x30mm, 5µm); mobile phase: [CO_2 base-methanol]; B%: 40%-40%) to give (2-methyl-4-(2-oxo-4-(4-(3-(p-tolyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)pyrrolidin-1-yl)phenyl)methylium, Enantiomer 1 (193 mg, 421 µmol, 21%) as a white solid, and (2-methyl-4-(2-oxo-4-(4-(3-(p-tolyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)pyrrolidin-1-yl)phenyl)methylium, Enantiomer 2 (199 mg, 433 µmol, 22 %) as a white solid.

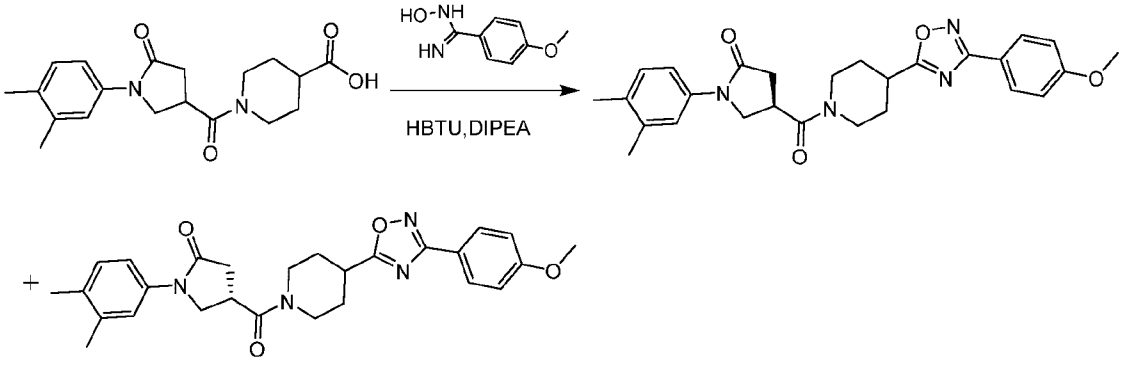
(2-methyl-4-(2-oxo-4-(4-(3-(p-tolyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)pyrrolidin-1-yl)phenyl)methylium, Enantiomer 1:

^{1}H NMR (400MHz, DMSO-d6) δ = 7.91 (br d, J=6.9 Hz, 2H), 7.43 (br s, 1H), 7.38 (br d, J=8.0 Hz, 3H), 7.12 (br d, J=6.3 Hz, 1H), 4.35 (br s, 1H), 4.09 - 3.98 (m, 2H), 3.92 (td, J=5.0, 10.0 Hz, 1H), 3.80 - 3.63 (m, 1H), 3.45 (br t, J=10.8 Hz, 1H), 3.36 (br s, 1H), 3.00 - 2.90 (m, 1H), 2.82 - 2.65 (m, 2H), 2.39 (s, 3H), 2.27 - 2.10 (m, 8H), 1.91 - 1.61 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 459.3; ee = 98.6

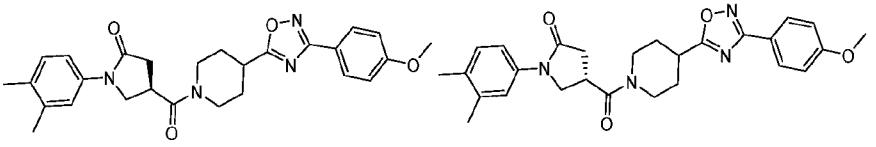
(2-methyl-4-(2-oxo-4-(4-(3-(p-tolyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)pyrrolidin-1-yl)phenyl)methylium, Enantiomer 2:

^{1}H NMR (400MHz, DMSO-d6) δ = 7.91 (br d, J=6.9 Hz, 2H), 7.43 (br s, 1H), 7.38 (br d, J=8.0 Hz, 3H), 7.12 (br d, J=6.4 Hz, 1H), 4.35 (br s, 1H), 4.11 - 3.97 (m, 2H), 3.92 (td, J=5.0, 9.9 Hz, 1H), 3.81 - 3.68 (m, 1H), 3.53 - 3.37 (m, 1H), 3.36 (br s, 1H), 3.02 - 2.90 (m, 1H), 2.82 - 2.65 (m, 2H), 2.39 (s, 3H), 2.25 - 2.09 (m, 8H), 1.89 - 1.62 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 459.3; ee = 99%.

Example 63: 1-(3,4-dimethylphenyl)-4-(4-(3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)pyrrolidin-2-one, Enantiomer 1 and Example 64: 1-(3,4-dimethylphenyl)-4-(4-(3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)pyrrolidin-2-one, Enantiomer 2



Step 1: Preparation of 1-(3,4-dimethylphenyl)-4-(4-(3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)pyrrolidin-2-one, Enantiomer 1 and 1-(3,4-dimethylphenyl)-4-(4-(3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)pyrrolidin-2-one, Enantiomer 2



To a stirred solution of 1-(1-(3,4-dimethylphenyl)-5-oxopyrrolidine-3-carbonyl)piperidine-4-carboxylic acid (350 mg, 1.02 mmol) and N-hydroxy-4-methoxybenzimidamide (168 mg, 1.02 mmol) in N,N-dimethylformamide (3 mL) was added N-ethyl-N-(propan-2-yl)propan-2-amine (262 mg, 2.03 mmol,

354 µL) and (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (385 mg, 1.02 mmol), then the mixture was stirred for 15 h at 15 °C. The the mixture was then heated to 110 °C and stirred for 5 h. The mixture was cooled and purified by prep-HPLC (column: Waters Xbridge 150x25 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 37%-67%, 12 min) to give racemic 1-(3,4-dimethylphenyl)-4-(4-(3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)pyrrolidin-2-one (0.2 g) as a white solid. This was purified by SFC separation: (column: OJ(250x30mm,10µm); mobile phase: [CO_2 base-ethanol]; B%: 45%-45%) to give ((1-(3,4-dimethylphenyl)-4-(4-(3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)pyrrolidin-2-one, Enantiomer 1 (84 mg, 177 µmol, 17 %) as a white solid and 1-(3,4-dimethylphenyl)-4-(4-(3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)pyrrolidin-2-one, Enantiomer 2 (96 mg, 198 µmol, 19 %) as a yellow solid

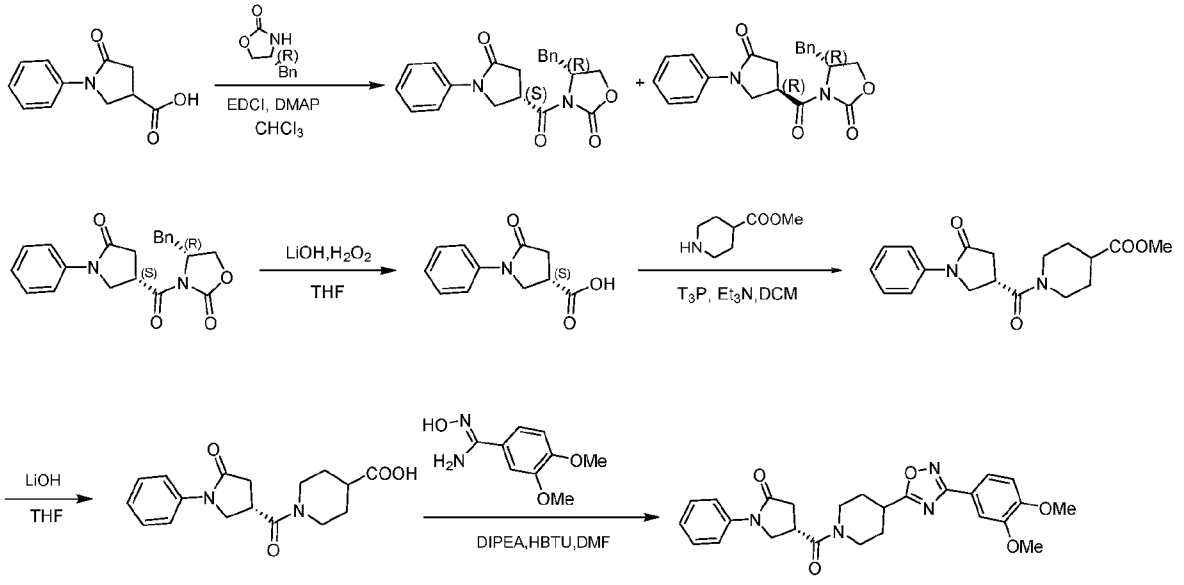
1-(3,4-dimethylphenyl)-4-(4-(3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)pyrrolidin-2-one, Enantiomer 1:

^{1}H NMR (400 MHz, Methanol-d4) δ 7.98 (dd, J=2.2, 8.8 Hz, 2H), 7.36 (s, 1H), 7.27 (d, J=7.9 Hz, 1H), 7.13 (d, J=8.4 Hz, 1H), 7.04 (d, J=7.1 Hz, 2H), 4.53 - 4.43 (m, 1H), 4.18 - 3.99 (m, 3H), 3.95 - 3.73 (m, 4H), 3.49 - 3.36 (m, 2H), 3.14 - 3.01 (m, 1H), 2.93 - 2.77 (m, 2H), 2.47 - 2.04 (m, 8H), 2.01 - 1.80 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 475.3; ee = 100 %.

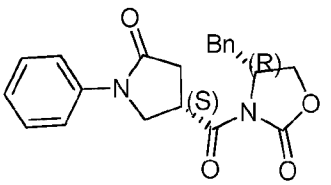
1-(3,4-dimethylphenyl)-4-(4-(3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)pyrrolidin-2-one, Enantiomer 2:

^{1}H NMR (400 MHz, Methanol-d4) δ 7.98 (dd, J=2.4, 9.0 Hz, 2H), 7.36 (s, 1H), 7.27 (d, J=8.4 Hz, 1H), 7.13 (d, J=8.4 Hz, 1H), 7.04 (d, J=7.1 Hz, 2H), 4.48 (d, J=7.5 Hz, 1H), 4.16 - 4.00 (m, 3H), 3.92 - 3.74 (m, 4H), 3.49 - 3.37 (m, 2H), 3.13 - 3.03 (m, 1H), 2.91 - 2.80 (m, 2H), 2.34 - 2.11 (m, 8H), 1.98 - 1.83 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 475.3; ee = 100 %.

Example 65: (4S)-4-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]piperidine-1-carbonyl]-1-phenyl-pyrrolidin-2-one

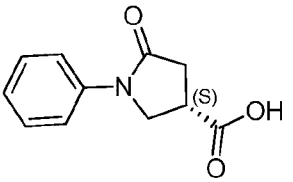


Step 1: (4R)-4-benzyl-3-[(3S)-5-oxo-1-phenyl-pyrrolidine-3-carbonyl]oxazolidin-2-one



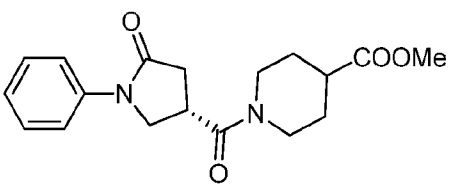
To a stirred solution of 5-oxo-1-phenyl-pyrrolidine-3-carboxylic acid (20.0 g, 97.5 mmol) in chloroform (100 mL) was added (4R)-4-benzyloxazolidin-2-one (20.72 g, 117 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (20.74 g, 108.2 mmol) and DMAP (6.43 g, 52.6 mmol) at 0 ℃. After addition, the mixture was stirred for 15 min, then warmed and stirred at 20 ℃ for 18 h. The residue was purified by chromatography (silica, petroleum ether / ethyl acetate=1/1 to 1:9) to give (4R)-4-benzyl-3-[(3S)-5-oxo-1-phenyl-pyrrolidine-3-carbonyl]oxazolidin-2-one (10.0 g, 27.4 mmol, 28 %) and (4R)-4-benzyl-3-[(3R)-5-oxo-1-phenyl-pyrrolidine-3-carbonyl]oxazolidin-2-one (10.0 g, 27 mmol, 28 %) each as a white solid. LCMS (ESI) m/z: 365.1 $[M+H]^+$.

Step 2: (3S)-5-oxo-1-phenyl-pyrrolidine-3-carboxylic acid



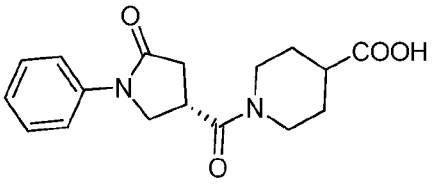
To a stirred solution of lithium hydroxide monohydrate (2.63 g, 62.8 mmol) in water (30 mL) was added dropwise hydrogen peroxide (15.5 g, 456.6 mmol, 13.2 mL) at 0℃. The mixture was stirred for 30 min. To the mixture was then added tetrahydrofuran (80 mL), water (30 mL) followed by a solution of 3-[(3S)-5-oxo-1-phenyl-pyrrolidine-3-carbonyl]-4-phenyl-oxazolidin-2-one (10.0 g, 28.5 mmol) in tetrahydrofuran (80 mL) dropwise. The mixture was stirred at 0 ℃ for 1h, quenched by addition of a sodium sulfate solution in water (10 mL) at 0 ℃, and made basic (pH 11) by addition of an aqueous sodium carbonate solution. The mixture was extracted with ethyl acetate (100 mL), acidified to pH 2 using 1M HCl, and extracted again with ethyl acetate (100 mL). The organic layers were washed with a saturated aqueous sodium chloride solution (100 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to give (3S)-5-oxo-1-phenyl-pyrrolidine-3-carboxylic acid (4.80 g, 23.39 mmol, 82 %) as a white solid. ^{1}H NMR (400MHz, CHLOROFORM-d) δ 7.57 (dd, J=0.9, 8.6 Hz, 2H), 7.40 - 7.34 (m, 2H), 7.20 - 7.15 (m, 1H), 4.18 - 4.13 (m, 1H), 4.10 - 4.04 (m, 1H), 3.45 - 3.35 (m, 1H), 3.03 - 2.86 (m, 2H).

Step 3: methyl 1-[(3S)-5-oxo-1-phenyl-pyrrolidine-3-carbonyl]piperidine-4-carboxylate



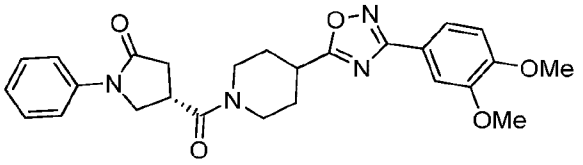
A mixture of (3S)-5-oxo-1-phenyl-pyrrolidine-3-carboxylic acid (4.50 g, 21.93 mmol), methyl piperidine-4-carboxylate (3.77 g, 26.32 mmol), 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphinane 2,4,6-trioxide in ethyl acetate (27.91 g, 43.86 mmol, 26.08 mL, 50% purity), triethylamine (44.38 g, 438.60 mmol, 60 mL) in dichloromethane (60 mL) was degassed, purged with nitrogen 3 times, and then the mixture was stirred at 20 °C for 16 h under a nitrogen atmosphere. The reaction mixture was diluted with water (30 mL) and extracted with dichloromethane (50 mL). The organic layers were washed with saturated aqueous sodium chloride solution (50 mL), dried over Na_2SO_4, filtered, concentrated under reduced pressure and purified by chromatography (silica, petroleum ether / ethyl acetate=1:1) to give methyl 1-[(3S)-5-oxo-1-phenyl-pyrrolidine-3-carbonyl]piperidine-4-carboxylate (4.70 g, 14.2 mmol, 65 %) as a white solid. ^{1}H NMR (400MHz, CHLOROFORM-d) δ 7.56 (d, J=7.7 Hz, 2H), 7.35 (t, J=7.5 Hz, 2H), 7.16 - 7.11 (m, 1H), 4.47 - 4.34 (m, 1H), 4.24 (dd, J=7.3, 9.5 Hz, 1H), 3.91 - 3.81 (m, 2H), 3.69 (s, 3H), 3.52 (quin, J=8.5 Hz, 1H), 3.24 - 3.12 (m, 1H), 2.98 - 2.87 (m, 2H), 2.80 - 2.73 (m, 1H), 2.64 - 2.52 (m, 1H), 1.97 (br dd, J=4.3, 8.3 Hz, 2H), 1.73 - 1.63 (m, 2H).

Step 4: 1-[(3S)-5-oxo-1-phenyl-pyrrolidine-3-carbonyl]piperidine-4-carboxylic acid.



To a stirred solution of methyl 1-[(3S)-5-oxo-1-phenyl-pyrrolidine-3-carbonyl]piperidine-4-carboxylate (3.00 g, 9.08 mmol) in tetrahydrofuran (60 mL) was added a solution of lithium hydroxide monohydrate (0.5 M, 21.79 mL) in water. The mixture was then stirred at 0 °C for 2 h. The mixture was acidified to pH 4-5 using 1M HCl, and then extracted with dichloromethane (60 mL; 30 mL x 2). The combined organic phases were washed with saturated aqueous sodium chloride solution 40 mL; 20 mL x 2), dried over sodium sulfate, filtered and concentrated under reduced pressure to give 1-[(3S)-5-oxo-1-phenyl-pyrrolidine-3-carbonyl]piperidine-4-carboxylic acid (2.70 g, 8.53 mmol, 94 %) as a white solid.

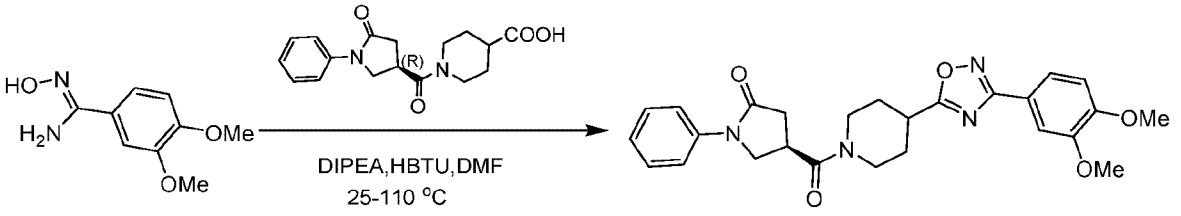
Step 5: (4S)-4-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]piperidine-1-carbonyl]-1-phenyl-pyrrolidin-2-one



A mixture of N'-hydroxy-3,4-dimethoxy-benzamidine (1.04 g, 5.32 mmol), 1-[(3S)-5-oxo-1-phenyl-pyrrolidine-3-carbonyl]piperidine-4-carboxylic acid (1.40 g, 4.43 mmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (2.18 g, 5.76 mmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (1.72 g, 13.29 mmol, 2.32 mL) in N,N-dimethylformamide (8.00 mL), was stirred at 20°C for 15h and at 110°C for 1h. The mixture was cooled to room temperature, concentrated under reduced pressure to give a residue purified by prep-HPLC [column: Phenomenex luna C18 250x50mmx10 μm; mobile phase: water / ammonium carbonate (10mM) / acetonitrile]; B%: 30%-60%,30 min. The desired

compound (4S)-4-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]piperidine-1-carbonyl]-1-phenyl-pyrrolidin-2-one was isolated as a light yellow solid (608 mg, 1.28 mmol, 29 %). ^{1}H NMR (400MHz, CHLOROFORM-d) δ 7.68 (br d, J=8.2 Hz, 1H), 7.61 - 7.53 (m, 3H), 7.40 - 7.33 (m, 2H), 7.18 - 7.12 (m, 1H), 6.95 (d, J=8.4 Hz, 1H), 4.61 - 4.46 (m, 1H), 4.30 (dd, J=7.2, 9.6 Hz, 1H), 4.01 - 3.92 (m, 8H), 3.57 (quin, J=8.4 Hz, 1H), 3.43 - 3.26 (m, 2H), 3.14 - 2.91 (m, 2H), 2.86 - 2.80 (m, 1H), 2.23 (br t, J=13.1 Hz, 2H), 2.02 - 1.93 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 477.3.

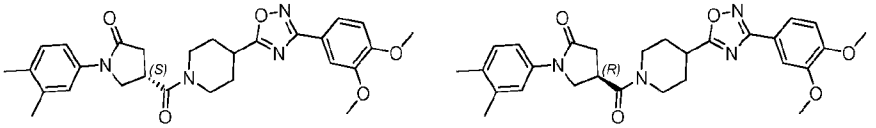
Example 66 [(4R)-4-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]piperidine-1-carbonyl]-1-phenyl-pyrrolidin-2-one]



To a stirred solution of 1-[(3R)-5-oxo-1-phenyl-pyrrolidine-3-carbonyl]piperidine-4-carboxylic acid (115 mg, 363.52 µmol) and N'-hydroxy-3,4-dimethoxy-benzamidine (71 mg, 363.52 µmol) in N,N-dimethylformamide (500 µL) was added (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (137 mg, 363.52 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (93 mg, 727 µmol, 126 µL) at 25℃. The mixture was then stirred at 25 ℃ for 2 h, and at 110 ℃ for 2h. The mixture was concentrated under reduced pressure and the resulting crude product was purified by chromatography (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: water / ammonium carbonate (10mM) / acetonitrile]; B%: 25%-60%,12 min to give (4R)-4-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]piperidine-1-carbonyl]-1-phenyl-pyrrolidin-2-one (32 mg, 67.45 µmol, 19 %) as a yellow solid. ^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.68 (br d, *J*=8.2 Hz, 1H), 7.61 - 7.55 (t, 3H), 7.37 (t, *J*=7.8 Hz, 2H), 7.19 - 7.14 (t, 1H), 6.95 (d, *J*=8.4 Hz, 1H), 4.60 - 4.46 (m, 1H), 4.31 (dd, *J*=7.2, 9.6 Hz, 1H), 3.98 - 3.94 (m, 7H), 3.98 - 3.92 (m, 1H), 3.58 (quin, *J*=8.5 Hz, 1H), 3.43 - 3.26 (m, 2H), 3.16 - 2.91 (m, 2H), 2.88 - 2.79 (m, 1H), 2.24 (br t, *J*=13.3 Hz, 2H), 2.06 - 1.88 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 477.3.

Examples 67: 4-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)-1-(3,4-dimethylphenyl)pyrrolidin-2-one, Enantiomer 1 and Example 68: 4-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)-1-(3,4-dimethylphenyl)pyrrolidin-2-one, Enantiomer 2.

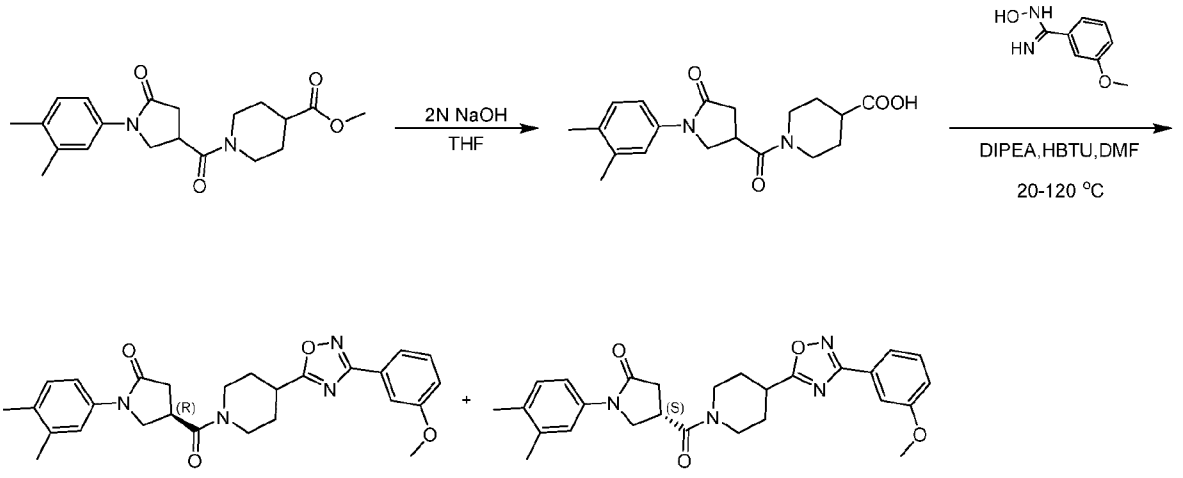
Step 1: Preparation of 4-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)-1-(3,4-dimethylphenyl)pyrrolidin-2-one



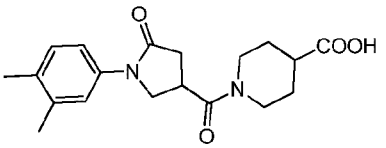
To a stirred solution of 1-[1-(3,4-dimethylphenyl)-5-oxo-pyrrolidine-3-carbonyl]piperidine-4-carboxylic acid (351 mg, 1.02 mmol) in N,N-dimethylformamide (1.50 mL) was added (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (386 mg, 1.02 mmol), N-ethyl-N-(propan-2-yl)propan-2-amine (395 mg, 3.06 mmol, 534 µL) and N-hydroxy-3,4-dimethoxy-benzamidine (200 mg,

1.02 mmol). The mixture was stirred at 20 °C for 12 h. The reaction mixture was then diluted with water (5mL) and extracted with ethyl acetate (10 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (10 mL x 2), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. N,N-dimethylformamide (2 mL) was added to the residue and the resulting mixture was heated at 120 °C for 5 h. The mixture was cooled to 25 °C, diluted by addition of water (5mL) and extracted with ethyl acetate (10 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (10 mL x 2), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue that was purified by prep-HPLC (column: Waters Xbridge 150x25 μm; mobile phase: water / ammonium carbonate (10mM) / acetonitrile]; B%: 33%-63%,12 min) to give racemic 4-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)-1-(3,4-dimethylphenyl)pyrrolidin-2-one. This was separated by chiral-SFC (column: AS(250x30mm, 10μm); mobile phase: [CO_2 base-methanol]; B%: 40%-40%,min) to give firstly 4-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]piperidine-1-carbonyl]-1-(3,4-dimethylphenyl)pyrrolidin-2-one, Enantiomer 1 (51 mg, 102 μmol, 10 %) as a white solid. ^{1}H NMR (400MHz, DMSO-d6) δ = 7.61 (br d, J=8.4 Hz, 1H), 7.48 (s, 1H), 7.43 (br s, 1H), 7.38 (br d, J=7.5 Hz, 1H), 7.16 - 7.10 (m, 2H), 4.37 (br s, 1H), 4.08 - 3.99 (m, 2H), 3.96 - 3.88 (m, 1H), 3.85 (s, 6H), 3.79 - 3.67 (m, 1H), 3.45 (br t, J=10.8 Hz, 1H), 3.32 - 3.28 (m, 1H), 3.02 - 2.87 (m, 1H), 2.82 - 2.70 (m, 2H), 2.24 - 2.18 (m, 6H), 2.18 - 2.10 (m, 2H), 1.91 - 1.61 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 505.4 and secondly 4-[4-[3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl]piperidine-1-carbonyl]-1-(3,4-dimethylphenyl)pyrrolidin-2-one, Enantiomer 2 (48 mg, 95 μmol, 9 %) also as a white solid. ^{1}H NMR (400MHz, DMSO-d6) δ = 7.61 (br d, J=8.4 Hz, 1H), 7.48 (s, 1H), 7.43 (br s, 1H), 7.41 - 7.35 (m, 1H), 7.17 - 7.10 (m, 2H), 4.37 (br s, 1H), 4.09 - 3.99 (m, 2H), 3.98 - 3.89 (m, 1H), 3.85 (s, 6H), 3.78 - 3.68 (m, 1H), 3.50 - 3.39 (m, 1H), 3.35 (br s, 1H), 3.00 - 2.88 (m, 1H), 2.81 - 2.70 (m, 2H), 2.26 - 2.19 (m, 6H), 2.17 - 2.09 (m, 2H), 1.88 - 1.63 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 505.4

Example 69 1-(3,4-dimethylphenyl)-4-(4-(3-(3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)pyrrolidin-2-one, Enantiomer 1 and Example 70 1-(3,4-dimethylphenyl)-4-(4-(3-(3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)pyrrolidin-2-one, Enantiomer 2

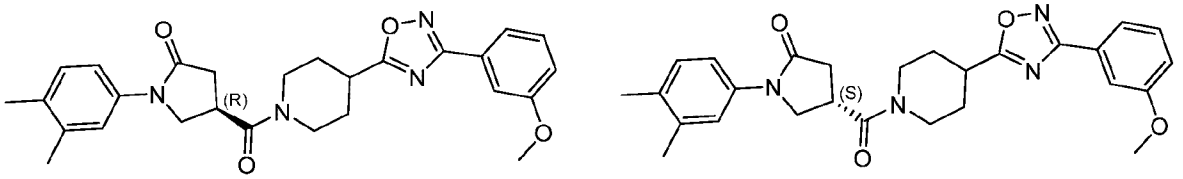


Step 1: Preparation of 1-(1-(3,4-dimethylphenyl)-5-oxopyrrolidine-3-carbonyl)piperidine-4-carboxylic acid



To a stirred solution of methyl 1-(1-(3,4-dimethylphenyl)-5-oxopyrrolidine-3-carbonyl)piperidine-4-carboxylate (470 mg, 1.31 mmol) in tetrahydrofuran (5 mL) was added sodium hydroxide (2 M, 1.31 mL). The mixture was stirred at 20 ℃ for 16 h. The mixture was acidified with concentrated hydrochloric acid until pH = 1. The mixture was extracted with dichloromethane (20 mL x 4). The organic layers were combined and washed with saturated aqueous sodium chloride solution (5 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give 1-(1-(3,4-dimethylphenyl)-5-oxopyrrolidine-3-carbonyl)piperidine-4-carboxylic acid (300 mg) as a brown solid. LCMS (ESI) m/z: $[M+H]^+$ = 345.2.

Step 2: Preparation of 1-(3,4-dimethylphenyl)-4-(4-(3-(3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)pyrrolidin-2-one, Enantiomer 1 and 1-(3,4-dimethylphenyl)-4-(4-(3-(3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)pyrrolidin-2-one, Enantiomer 2



To a stirred solution of 1-(1-(3,4-dimethylphenyl)-5-oxopyrrolidine-3-carbonyl)piperidine-4-carboxylic acid (300 mg, 871 μmol) in N,N-dimethylformamide (4 mL) was added N-hydroxy-3-methoxy-benzamidine (173 mg, 1.05 mmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (330 mg, 871 μmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (337 mg, 2.61 mmol, 456 μL). The mixture was stirred at 20℃ for 2 h and then at 120 ℃ for 2 h. The reaction mixture was cooled, concentrated under reduced pressure and purified directly by preparative HPLC (column: Luna C8 100*30 5μm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 45%-65%,12 min) to give (rac)- 1-(3,4-dimethylphenyl)-4-(4-(3-(3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl) pyrrolidin-2-one that was was purified by chiral-SFC (column: AD(250mm*30mm,5mm); mobile phase: [Base-isopropanol]; B%: 42%-42%,min) to give firstly 1-(3,4-dimethylphenyl)-4-(4-(3-(3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl) yrrolidin-2-one, Enantiomer 1 (75 mg, 158.7 μmol, 18 %, ee 100 %) as a white solid, then 1-(3,4-dimethylphenyl)-4-(4-(3-(3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)pyrrolidin-2-one, Enantiomer 2 (75 mg, 160 μmol, 18 %, ee 99.7 %) as a yellow solid.

1-(3,4-dimethylphenyl)-4-(4-(3-(3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl) pyrrolidin-2-one, Enantiomer 1.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63-7.57 (m, 1H), 7.55-7.50 (m, 1H), 7.31 (d, *J* = 12.3 Hz, 2H), 7.22-7.19 (m, 1H), 7.05 (d, *J* = 8.2 Hz, 1H), 7.00 (d, *J* = 1.8 Hz, 1H), 4.53-4.37 (m, 1H), 4.21 (dd, *J* = 7.3, 9.6 Hz, 1H), 3.95-3.77 (m, 5H), 3.49 (td, *J* = 8.6, 16.9 Hz, 1H), 3.36-3.20 (m, 2H), 3.12-2.96 (m, 1H), 2.89 (td, *J* =

8.3, 16.9 Hz, 1H), 2.79-2.70 (m, 1H), 2.18 (d, *J* = 13.1 Hz, 8H), 1.99-1.83 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 475.1.

1-(3,4-dimethylphenyl)-4-(4-(3-(3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)pyrrolidin-2-one, Enantiomer 2.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63-7.57 (m, 1H), 7.53 (s, 1H), 7.36-7.27 (m, 2H), 7.21 (d, *J* = 2.0 Hz, 1H), 7.05 (d, *J* = 8.0 Hz, 1H), 7.00 (d, *J* = 2.0 Hz, 1H), 4.53-4.37 (m, 1H), 4.21 (dd, *J* = 7.3, 9.5 Hz, 1H), 3.96-3.77 (m, 5H), 3.55-3.44 (m, 1H), 3.37-3.19 (m, 2H), 3.12-2.82 (m, 2H), 2.76 (d, *J* = 9.4 Hz, 1H), 2.18 (d, *J* = 13.1 Hz, 8H), 1.92 (br. s., 2H); LCMS (ESI) m/z: $[M+H]^+$ = 475.1.

Example 71 (1-(3,4-dimethylphenyl)-4-(4-(5-(p-tolyl)-1,2,4-oxadiazol-3-yl)piperidine-1-carbonyl)pyrrolidin-2-one), Enantiomer 1 and Example 72 (1-(3,4-dimethylphenyl)-4-(4-(5-(p-tolyl)-1,2,4-oxadiazol-3-yl)piperidine-1-carbonyl)pyrrolidin-2-one), Enantiomer 2

Racemic 1-(3,4-dimethylphenyl)-4-(4-(5-(p-tolyl)-1,2,4-oxadiazol-3-yl)piperidine-1-carbonyl)pyrrolidin-2-one (80 mg) was purified by SFC separation (column: AD (250x30mm,5μm); mobile phase: [CO_2 base-isopropanol]; B%: 50%-50%,min) to give firstly 1-(3,4-dimethylphenyl)-4-(4-(5-(p-tolyl)-1,2,4-oxadiazol-3-yl)piperidine-1-carbonyl)pyrrolidin-2-one, Enantiomer 1 (26 mg, 59 μmol, 7 %) as a white solid and secondly 1-(3,4-dimethylphenyl)-4-(4-(5-(p-tolyl)-1,2,4-oxadiazol-3-yl)piperidine-1-carbonyl)pyrrolidin-2-one, Enantiomer 2 as a white solid (23 mg, 52 μmol, 6 %).

1-(3,4-dimethylphenyl)-4-(4-(5-(p-tolyl)-1,2,4-oxadiazol-3-yl)piperidine-1-carbonyl)pyrrolidin-2-one, Enantiomer 1.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06-8.00 (m, 2H), 7.41-7.33 (m, 3H), 7.32-7.29 (m, 1H), 7.15 (d, *J* = 8.3 Hz, 1H), 4.66-4.54 (m, 1H), 4.30 (dd, *J* = 7.4, 9.5 Hz, 1H), 4.05-3.88 (m, 2H), 3.65-3.55 (m, 1H), 3.43-3.30 (m, 1H), 3.20 (d, *J* = 3.4 Hz, 1H), 3.12-2.94 (m, 2H), 2.85 (d, *J* = 9.7 Hz, 1H), 2.47 (s, 3H), 2.32-2.14 (m, 8H), 1.94 (br. s., 2H); LCMS (ESI) m/z: $[M+H]^+$ = 459.3.

1-(3,4-dimethylphenyl)-4-(4-(5-(p-tolyl)-1,2,4-oxadiazol-3-yl)piperidine-1-carbonyl)pyrrolidin-2-one, Enantiomer 2.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96-7.90 (m, 2H), 7.32-7.24 (m, 3H), 7.22-7.19 (m, 1H), 7.05 (d, J=8.2 Hz, 1H), 4.58-4.43 (m, 1H), 4.20 (s, 1H), 3.94-3.79 (m, 2H), 3.50 (quin, J = 8.5 Hz, 1H), 3.28 (br. s., 1H), 3.10 (d, J = 3.9 Hz, 1H), 3.02-2.84 (m, 2H), 2.78-2.68 (m, 1H), 2.38 (s, 3H), 2.23-2.03 (m, 8H), 1.83 (d, J = 10.8 Hz, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 459.3

Examples 73 1-(3,4-dimethylphenyl)-4-(4-(5-(m-tolyl)-1,2,4-oxadiazol-3-yl)piperidine-1-carbonyl)pyrrolidin-2-one, Enantiomer 1 and Example 74 1-(3,4-dimethylphenyl)-4-(4-(5-(m-tolyl)-1,2,4-oxadiazol-3-yl)piperidine-1-carbonyl)pyrrolidin-2-one, Enantiomer 2

Racemic 1-(3,4-dimethylphenyl)-4-(4-(5-(m-tolyl)-1,2,4-oxadiazol-3-yl)piperidine-1-carbonyl)pyrrolidin-2-one (120 mg) was purified by SFC separation (column: OJ(250mmX30mm,5mm); mobile phase: [CO_2 base-ethanol]; B%: 30%-30%,min) to give firstly 1-(3,4-dimethylphenyl)-4-(4-(5-(m-tolyl)-1,2,4-oxadiazol-3-yl)piperidine-1-carbonyl)pyrrolidin-2-one, Enantiomer 1 (39 mg, 86.7 μmol, 11 %) as a pink solid and secondly 1-(3,4-dimethylphenyl)-4-(4-(5-(m-tolyl)-1,2,4-oxadiazol-3-yl)piperidine-1-carbonyl)pyrrolidin-2-one, Enantiomer 2 (36 mg, 77.9 μmol, 10 %) as a pink solid.

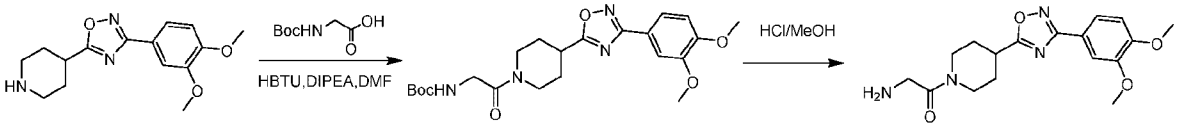
1-(3,4-dimethylphenyl)-4-(4-(5-(m-tolyl)-1,2,4-oxadiazol-3-yl)piperidine-1-carbonyl)pyrrolidin-2-one, Enantiomer 1:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (br. s., 2H), 7.39 (d, *J* = 15.0 Hz, 3H), 7.29 (br. s., 1H), 7.12 (d, *J* = 8.4 Hz, 1H), 4.58 (t, *J* = 13.9 Hz, 1H), 4.28 (*t*, *J* = 8.6 Hz, 1H), 4.01-3.87 (m, 2H), 3.62-3.53 (m, 1H), 3.35 (br. s., 1H), 3.19 (br. s., 1H), 3.08-2.93 (m, 2H), 2.86-2.76 (m, 1H), 2.45 (s, 3H), 2.32-2.11 (m, 8H), 1.90 (d, *J* = 13.7 Hz, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 459.3.

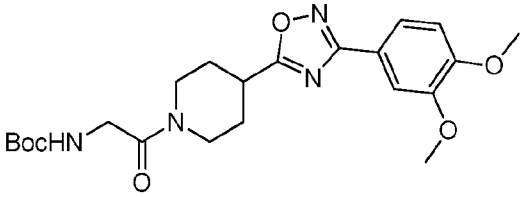
1-(3,4-dimethylphenyl)-4-(4-(5-(m-tolyl)-1,2,4-oxadiazol-3-yl)piperidine-1-carbonyl)pyrrolidin-2-one, Enantiomer 2:

^{1}H NMR (400 MHz, Methanol-d4) δ8.00-7.90 (m, 2H), 7.53-7.45 (m, 2H), 7.41-7.37 (m, 1H), 7.32-7.27 (m, 1H), 7.19-7.13 (m, 1H), 4.53 (dd, *J*=3.5, 13.2 Hz, 1H), 4.19-4.03 (m, 3H), 3.90-3.80 (m, 1H), 3.49-3.39 (m, 1H), 3.30-3.20 (m, 1H), 3.12-3.00 (m, 1H), 2.94-2.82 (m, 2H), 2.47 (s, 3H), 2.35-2.11 (m, 8H), 1.99-1.77 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 459.3.

Example 75: (2-amino-1-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)ethanone).

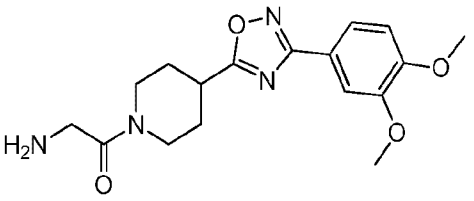


Step 1: Preparation of tert-butyl (2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)carbamate.



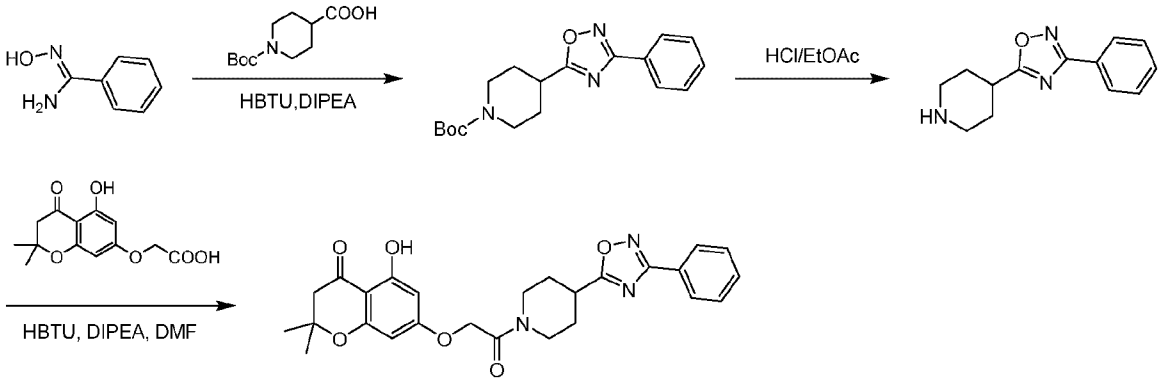
To a stirred solution of 3-(3,4-dimethoxyphenyl)-5-(piperidin-4-yl)-1,2,4-oxadiazole (2.0 g, 6.91 mmol) in N,N-dimethylformamide (20 mL) was added 2-(tert-butoxycarbonylamino)acetic acid (1.21 g, 6.91 mmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (2.62 g, 6.91 mmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (2.68 g, 20.7 mmol, 3.62 mL). The mixture was stirred at 15 ℃ for 2 h. The reaction mixture was quenched by addition of water (20 mL) then the mixture was extracted with ethyl acetate (60 mL x 4). The combined organic phases were washed with saturated aqueous sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give a crude material that was purified by chromatography (silica, petroleum ether : ethyl acetate = 5:1 to 1:1) to give tert-butyl (2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)carbamate (2.60 g, 5.82 mmol, 84 %) as a brown solid. LCMS (ESI) m/z: $[M+H]^+$ = 447.2.

Step 2: Preparation of 2-amino-1-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)ethanone

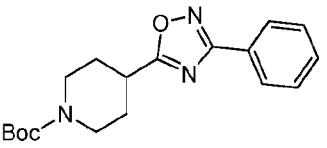


To a stirred solution of tert-butyl (2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)carbamate (2.50 g, 5.60 mmol) in methanol (10 mL) was added methanolic hydrogen chloride solution (30 mL). The mixture was stirred at 20 °C for 1 h and then concentrated to give 2-amino-1-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)ethanone (1.90 g, 5.49 mmol, 97.95 %), isolated as a brown solid and used for the next step without further purification. A small amount (0.1g) of the crude product was purified by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 20%-50%,12 min) to give a pure sample for analysis: 2-amino-1-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)ethanone (32 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73-7.67 (m, 1H), 7.58 (d, J = 1.5 Hz, 1H), 6.98 (d, J = 8.4 Hz, 1H), 4.54 (d, J = 12.2 Hz, 1H), 3.98 (d, J = 7.2 Hz, 6H), 3.84 (d, J = 12.0 Hz, 1H), 3.54 (s, 2H), 3.34-3.21 (m, 2H), 3.08 (d, J = 12.3 Hz, 1H), 2.21 (d, J = 13.1 Hz, 2H), 1.98 (d, J = 9.4 Hz, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 347.1.

Example 76: (5-hydroxy-2,2-dimethyl-7-(2-oxo-2-(4-(3-phenyl-1,2,4-oxadiazol-5-yl)piperidin-1-yl)ethoxy)choman-4-one).



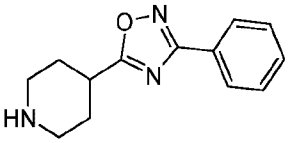
Step 1: Preparation of tert-butyl 4-(3-phenyl-1,2,4-oxadiazol-5-yl)piperidine-1-carboxylate



To a stirred solution of (Z)-N'-hydroxybenzimidamide (214 mg, 1.57 mmol) in N,N-dimethylformamide (5 mL) was added 1-(tert-butoxycarbonyl)piperidine-4-carboxylic acid (300 mg, 1.31 mmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (496 mg, 1.31 mmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (507 mg, 3.93 mmol, 686 µL). The mixture was stirred at 20 °C for 2 h, and then heated at 120 °C for 2 h. The reaction mixture was quenched with water (10 mL),

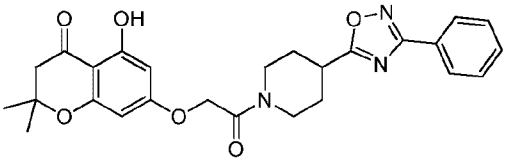
then the mixture was extracted with ethyl acetate (30 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product. The crude product was extracted with petroleum ether (30 mL x 2). The combined organic extracts were concentrated under reduced pressure to give tert-butyl 4-(3-phenyl-1,2,4-oxadiazol-5-yl)piperidine-1-carboxylate (310 mg, 941 µmol, 72 %) as a yellow oil. This product was used in the next step without further purification.

Step 2: Preparation of 3-phenyl-5-(piperidin-4-yl)-1,2,4-oxadiazole



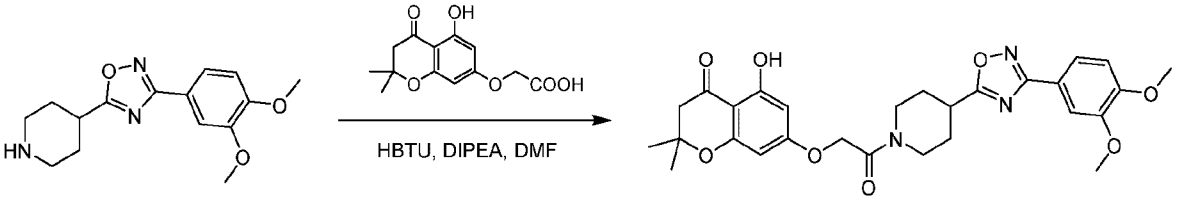
To a stirred solution of tert-butyl 4-(3-phenyl-1,2,4-oxadiazol-5-yl)piperidine-1-carboxylate (310 mg, 941 µmol) in ethyl acetate (2 mL) was added an anhydrous solution of hydrochloric acid in ethyl acetate (20 mL). The mixture was stirred at 20 °C for 1 h. The reaction mixture was concentrated under reduced pressure to provide the crude 3-phenyl-5-(piperidin-4-yl)-1,2,4-oxadiazole (233 mg) as a yellow solid that was used for the next step without further purification. LCMS (ESI) m/z: $[M+H]^+$ = 230.2.

Step 3: Preparation of 5-hydroxy-2,2-dimethyl-7-(2-oxo-2-(4-(3-phenyl-1,2,4-oxadiazol-5-yl)piperidin-1-yl)ethoxy)choman-4-one



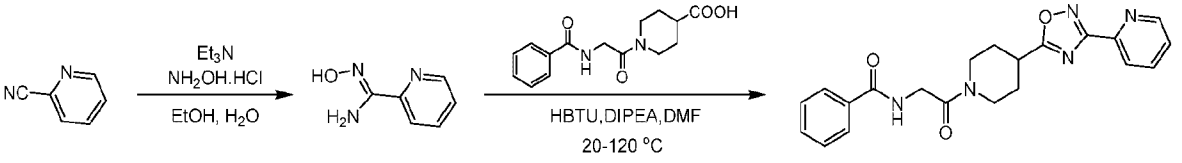
To a stirred solution of 2-((5-hydroxy-2,2-dimethyl-4-oxochoman-7-yl)oxy)acetic acid (150 mg, 563 µmol) in N,N-dimethylformamide (2 mL) was added 3-phenyl-5-(piperidin-4-yl)-1,2,4-oxadiazole (142 mg, 620 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (213 mg, 563 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (291 mg, 2.25 mmol, 393 µL). The mixture was stirred at 20 °C for 2 h. The reaction mixture was concentrated under reduced pressure and the resulting residue purified by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 45%-75%,12 min) to give 5-hydroxy-2,2-dimethyl-7-(2-oxo-2-(4-(3-phenyl-1,2,4-oxadiazol-5-yl)piperidin-1-yl)ethoxy)choman-4-one (120 mg, 250.6 µmol, 44 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.00 (s, 1H), 8.12 - 8.07 (m, 2H), 7.56 - 7.48 (m, 3H), 6.07 (d, *J*=2.4 Hz, 1H), 6.04 (d, *J*=2.3 Hz, 1H), 4.74 (s, 2H), 4.46 (d, *J*=13.8 Hz, 1H), 3.98 (d, *J*=13.1 Hz, 1H), 3.42 - 3.28 (m, 2H), 3.13 (t, *J*=11.1 Hz, 1H), 2.71 (s, 2H), 2.23 (br. s., 2H), 2.07 - 1.92 (m, 2H), 1.49 - 1.46 (m, 6H); LCMS (ESI) m/z: $[M+H]^+$ = 478.2.

Example 77 (7-(2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethoxy)-5-hydroxy-2,2-dimethylchoman-4-one).

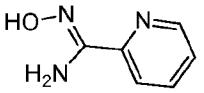


To a stirred solution of 2-((5-hydroxy-2,2-dimethyl-4-oxochoman-7-yl)oxy)acetic acid (150 mg, 563 µmol) in N,N-dimethylformamide (2 mL) was added 3-(3,4-dimethoxyphenyl)-5-(piperidin-4-yl)-1,2,4-oxadiazole (195 mg, 676 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (213 mg, 563 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (291 mg, 2.25 mmol, 393 µL). The mixture was stirred at 20 °C for 2 h. The reaction mixture was concentrated under reduced pressure. The resulting residue was purified by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 40%-70%,12 min) to give 7-(2-(4-(3-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethoxy)-5-hydroxy-2,2-dimethylchoman-4-one (133 mg, 245.66 µmol, 44 %) as a white solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 12.00 (s, 1H), 7.71 (dd, *J*=1.9, 8.3 Hz, 1H), 7.58 (d, *J*=1.9 Hz, 1H), 6.98 (d, *J*=8.4 Hz, 1H), 6.06 (d, *J*=2.4 Hz, 1H), 6.03 (d, *J*=2.4 Hz, 1H), 4.74 (s, 2H), 4.47 (d, *J*=14.2 Hz, 1H), 4.01 - 3.94 (m, 7H), 3.41 - 3.26 (m, 2H), 3.11 (t, *J*=11.0 Hz, 1H), 2.71 (s, 2H), 2.22 (br. s., 2H), 2.06 - 1.93 (m, 2H), 1.47 (s, 6H); LCMS (ESI) m/z: $[M+H]^+$ = 538.3.

Example 78: (N-(2-oxo-2-(4-(3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)ethyl)benzamide.

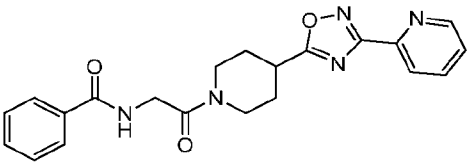


Step 1: Preparation of (Z)-N'-hydroxypicolinimidamide.



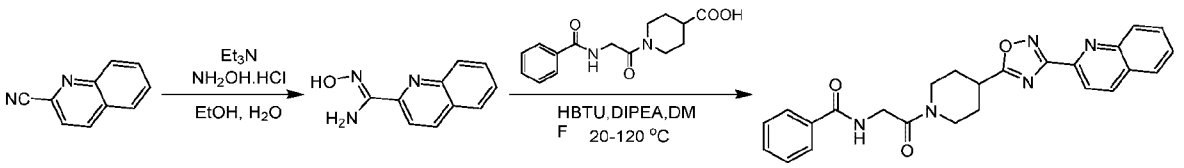
To a stirred solution of picolinonitrile (3.0 g, 28.8 mmol, 2.78 mL) in ethanol (30 mL) was added hydroxylamine hydrochloride (4.01 g, 57.6 mmol), triethylamine (5.83 g, 57.6 mmol, 8.0 mL) and water (5 mL). The mixture was heated at 75 °C for 5 h. The mixture was then concentrated to give a residue. The solid residue was triturated with water (30 mL), filtered, and dried under reduced pressure to give (Z)-N'-hydroxypicolinimidamide (2.0 g, 14.6 mmol, 51 %) as a white solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 9.93 (s, 1H), 8.57 (d, *J*=4.5 Hz, 1H), 7.92 - 7.75 (m, 2H), 7.47 - 7.35 (m, 1H), 5.85 (br. s., 2H).

Step 2: Preparation of N-(2-oxo-2-(4-(3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)ethyl)benzamide

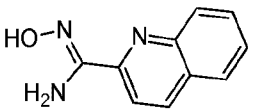


To a stirred solution of 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid (120 mg, 413 µmol) in N,N-dimethylformamide (2 mL) was added (Z)-N'-hydroxypicolinimidamide (56 mg, 413 µmol), N-ethyl-N-(propan-2-yl)propan-2-amine (160 mg, 1.24 mmol, 216 µL) and (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (156 mg, 413 µmol). The mixture was stirred at 20 °C for 2 h, then heated at 120 °C for 2 h. The reaction mixture was cooled, concentrated under reduced pressure and the resulting residue was purified by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 20%-55%,12 min) to give N-(2-oxo-2-(4-(3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)ethyl)benzamide (75 mg, 192 µmol, 47 %) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (td, *J*=0.8, 4.0 Hz, 1H), 8.18 - 8.12 (m, 1H), 7.93 - 7.84 (m, 3H), 7.58 - 7.43 (m, 4H), 7.35 (br. s., 1H), 4.53 (d, *J*=13.6 Hz, 1H), 4.32 (t, *J*=3.5 Hz, 2H), 3.93 (d, *J*=14.1 Hz, 1H), 3.45 - 3.31 (m, 2H), 3.21 - 3.10 (m, 1H), 2.37 - 2.24 (m, 2H), 2.15 - 1.98 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 392.2.

Example 79: N-(2-oxo-2-(4-(3-(quinolin-2-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)ethyl)benzamide

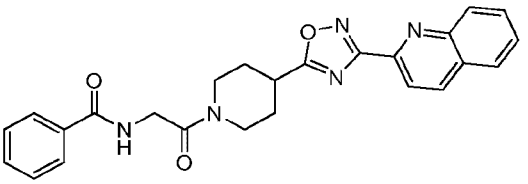


Step 1: Preparation of (Z)-N'-hydroxyquinoline-2-carboximidamide.



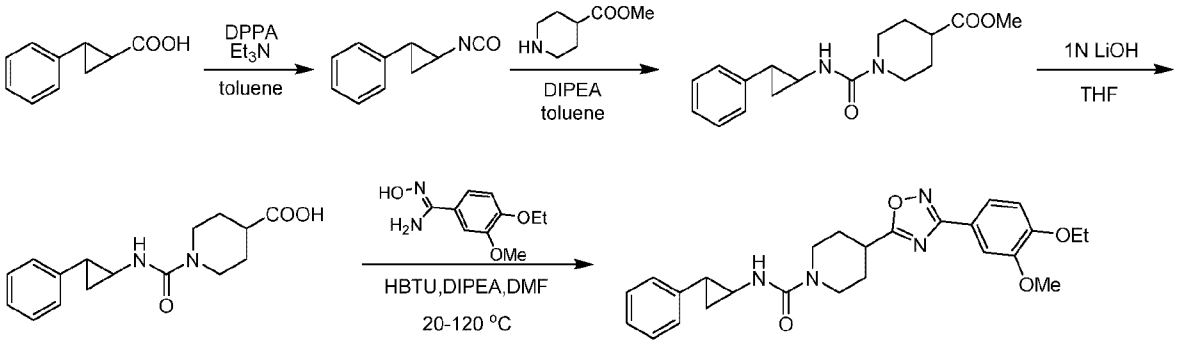
To a stirred solution of quinoline-2-carbonitrile (900 mg, 5.84 mmol) in ethanol (10 mL) was added hydroxylamine hydrochloride (811 mg, 11.7 mmol), triethylamine (1.18 g, 11.7 mmol, 1.6 mL) and water (1 mL). The mixture was heated at 75 °C for 5 h. The reaction mixture was cooled and filtered, and the filter cake dried in vacuo to give (Z)-N'-hydroxyquinoline-2-carboximidamide (1.0 g, 5.34 mmol, 91 %) as a light yellow solid. This was used directly without further purification. ^{1}H NMR (400 MHz, DMSO-d6) δ 10.23 (s, 1H), 8.34 (d, *J*=8.7 Hz, 1H), 8.10 - 7.93 (m, 3H), 7.80 (s, 1H), 7.67 - 7.59 (m, 1H), 6.02 (br. s., 2H).

Step 2: Preparation of N-(2-oxo-2-(4-(3-(quinolin-2-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)ethyl)benzamide

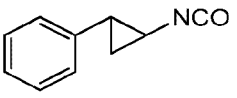


To a stirred solution of 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid (120 mg, 413 µmol) in N,N-dimethylformamide (2 mL) was added (Z)-N'-hydroxyquinoline-2-carboximidamide (77 mg, 413 µmol), N-ethyl-N-(propan-2-yl)propan-2-amine (160 mg, 1.24 mmol, 216 µL) and (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (156 mg, 413 µmol). The mixture was stirred at 20 °C for 2 h firstly, then heated at 120 °C for 2 h. The reaction mixture was cooled and purified directly by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%:30%-60%,12 min) to give N-(2-oxo-2-(4-(3-(quinolin-2-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)ethyl)benzamide (66 mg, 150 µmol, 36 %) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (dd, *J*=2.1, 8.5 Hz, 2H), 8.14 (d, *J*=8.5 Hz, 1H), 7.86 - 7.77 (m, 3H), 7.72 (dt, *J*=1.3, 7.7 Hz, 1H), 7.61 - 7.53 (m, 1H), 7.49 - 7.34 (m, 3H), 7.27 (br. s., 1H), 4.50 (d, *J*=13.8 Hz, 1H), 4.24 (d, *J*=3.6 Hz, 2H), 3.87 (d, *J*=13.8 Hz, 1H), 3.42 - 3.22 (m, 2H), 3.09 - 2.98 (m, 1H), 2.31 - 2.16 (m, 2H), 2.10 - 1.91 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 442.2.

Example 80: 4-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)-N-(2-phenylcyclopropyl)piperidine-1-carboxamide

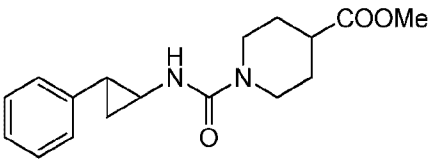


Step 1: (2-isocyanatocyclopropyl)benzene.



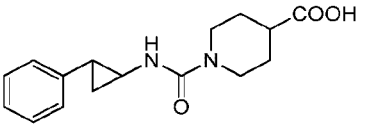
To a stirred solution of 2-phenylcyclopropanecarboxylic acid (1.0 g, 6.17 mmol) in toluene (10 mL) was added diphenylphosphoryl azide (2.04 g, 7.40 mmol, 1.60 mL) and triethylamine (935 mg, 9.25 mmol, 1.28 mL) under nitrogen. The mixture was stirred at 120 °C for 2 h. The reaction mixture was cooled then concentrated in vacuo to give (2-isocyanatocyclopropyl)benzene (2.0 g) as a yellow oil that was used directly without purification.

Step 2: Preparation of methyl 1-((2-phenylcyclopropyl)carbamoyl)piperidine-4-carboxylate.



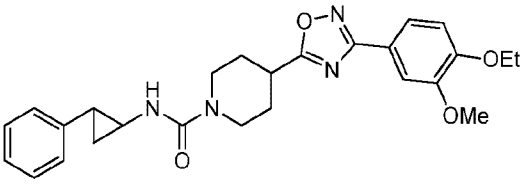
To a stirred solution of methyl piperidine-4-carboxylate (800 mg, 5.59 mmol) in toluene (10 mL) was added (2-isocyanatocyclopropyl)benzene (2.0 g, 12.58 mmol, 2.25 *eq*) and N-ethyl-N-(propan-2-yl)propan-2-amine (722 mg, 5.59 mmol, 975 µL). After 16 h, the reaction mixture was quenched with water (10 mL). The mixture was extracted with ethyl acetate (50 mL x 3), then the combined organic phases were washed with saturated aqueous sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated to a residue which was purified by chromatography (silica, petroleum ether : ethyl acetate = 50 : 1 to 2 :1) to give methyl 1-((2-phenylcyclopropyl)carbamoyl)piperidine-4-carboxylate (820 mg, 2.71 mmol, 48 %) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 - 7.19 (m, 1H), 7.17 (s, 1H), 7.10 (d, *J*=7.4 Hz, 3H), 4.75 (br. s., 1H), 3.79 (d, *J*=13.3 Hz, 2H), 3.63 (s, 3H), 2.89 - 2.73 (m, 3H), 2.47 - 2.33 (m, 1H), 2.02 - 1.78 (m, 3H), 1.61 (dd, *J*=2.1, 13.1 Hz, 2H), 1.16 - 1.11 (m, 1H), 1.08 - 1.03 (m, 1H).

Step 3: Preparation of 1-((2-phenylcyclopropyl)carbamoyl)piperidine-4-carboxylic acid.



To a stirred solution of methyl 1-((2-phenylcyclopropyl)carbamoyl)piperidine-4-carboxylate (770 mg, 2.55 mmol) in tetrahydrofuran (10 mL) was added lithium hydroxide (1 M, 5.10 mL). After 2 h, the reaction was acidified with 1 M hydrochloric acid (8 mL). The mixture was extracted with dichloromethane (40 mL x 3). The organic phases were combined and washed with saturated aqueous sodium chloride solution (10 mL), then dried over anhydrous sodium sulfate, filtered, and concentrated to give 1-((2-phenylcyclopropyl)carbamoyl)piperidine-4-carboxylic acid (660 mg, 2.29 mmol, 90 %) as a yellow solid that was used directly without further purification. ^{1}H NMR (400 MHz, DMSO-d6) δ 12.22 (s, 1H), 7.33 - 7.01 (m, 5H), 6.78 (d, *J*=2.5 Hz, 1H), 3.85 (d, *J*=13.3 Hz, 2H), 2.81 - 2.66 (m, 3H), 2.40 (br. s., 1H), 1.95 - 1.69 (m, 3H), 1.39 (d, *J*=12.0 Hz, 2H), 1.21 - 1.13 (m, 1H), 1.10 - 1.04 (m, 1H).

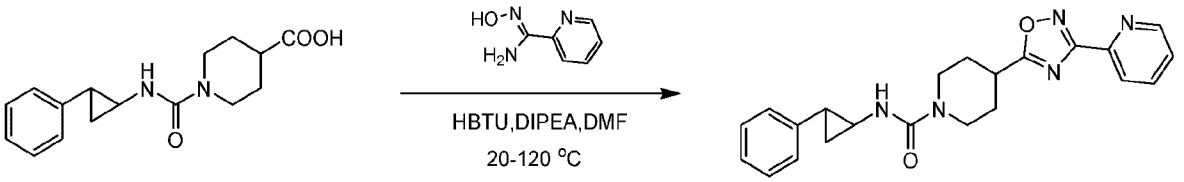
Step 4: Preparation of 4-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)-N-(2-phenylcyclopropyl)piperidine-1-carboxamide.



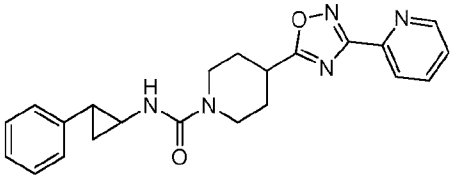
To a stirred solution of 1-((2-phenylcyclopropyl)carbamoyl)piperidine-4-carboxylic acid (100 mg, 347 µmol) in N,N-dimethylformamide (2 mL) was added (Z)-4-ethoxy-N'-hydroxy-3-methoxybenzimidamide (72 mg, 347 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium

hexafluorophosphate) (131 mg, 347 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (134 mg, 1.04 mmol, 181 µL). The mixture was stirred at 20 °C for 2 h, then heated at 120 °C for 2 h. The reaction mixture was cooled then purified by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 40 %-75 %,12 min) to give 4-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)-N-(2-phenylcyclopropyl)piperidine-1-carboxamide (81 mg, 173 µmol, 50 %) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 - 7.66 (m, 1H), 7.58 (d, *J*=1.9 Hz, 1H), 7.31 (s, 1H), 7.27 (s, 1H), 7.23 - 7.17 (m, 3H), 6.97 (d, *J*=8.5 Hz, 1H), 4.91 (s, 1H), 4.19 (q, *J*=7.0 Hz, 2H), 3.98 (s, 5H), 3.25 - 3.16 (m, 1H), 3.13 - 3.03 (m, 2H), 2.91 - 2.85 (m, 1H), 2.18 (dd, *J*=3.5, 13.4 Hz, 2H), 2.07 (ddd, *J*=3.3, 6.2, 9.5 Hz, 1H), 2.03 - 1.91 (m, 2H), 1.53 (t, *J*=7.0 Hz, 3H), 1.28 - 1.22 (m, 1H), 1.17 (td, *J*=5.0, 9.7 Hz, 1H); LCMS (ESI) m/z: $[M+H]^+$ = 463.2.

Example 81: N-(2-phenylcyclopropyl)-4-(3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl)piperidine-1-carboxamide.

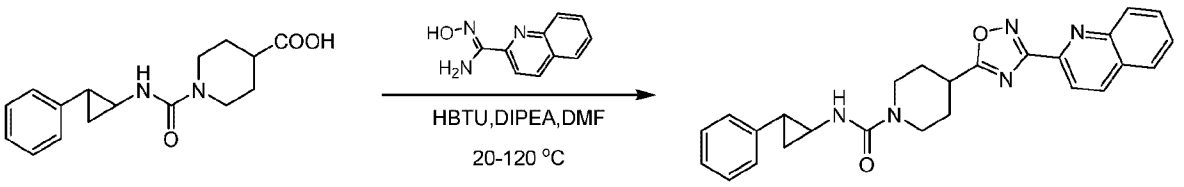


Step 1: Preparation of N-(2-phenylcyclopropyl)-4-(3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl)piperidine-1-carboxamide.

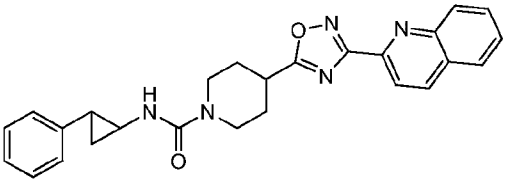


To a stirred solution of 1-((2-phenylcyclopropyl)carbamoyl)piperidine-4-carboxylic acid (130 mg, 451 µmol) in N,N-dimethylformamide (1 mL) was added (Z)-N'-hydroxypicolinimidamide (74 mg, 541 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (170 mg, 451 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (174 mg, 1.35 mmol, 236 µL). The mixture was stirred at 20 °C for 2 h, then heated at 110 °C for 2 h. The reaction mixture was cooled then purified by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 30%-60%,12 min) to give N-(2-phenylcyclopropyl)-4-(3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl)piperidine-1-carboxamide (47 mg, 121.6 µmol, 27 %) as a yellow solid. ^{1}H NMR (400MHz, DMSO-d6) δ 8.76 (d, *J*=4.0 Hz, 1H), 8.12 - 7.97 (m, 2H), 7.65 - 7.55 (m, 1H), 7.30 - 7.19 (m, 2H), 7.18 - 7.05 (m, 3H), 6.87 (br. s., 1H), 3.96 (d, *J*=13.2 Hz, 2H), 2.93 (t, *J*=11.7 Hz, 2H), 2.71 (d, *J*=3.1 Hz, 1H), 2.06 (d, *J*=11.5 Hz, 2H), 1.89 (br. s., 1H), 1.68 (d, *J*=11.9 Hz, 3H), 1.20 - 1.04 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 390.1.

Example 82: N-(2-phenylcyclopropyl)-4-(3-(quinolin-2-yl)-1,2,4-oxadiazol-5-yl)piperidine-1-carboxamide

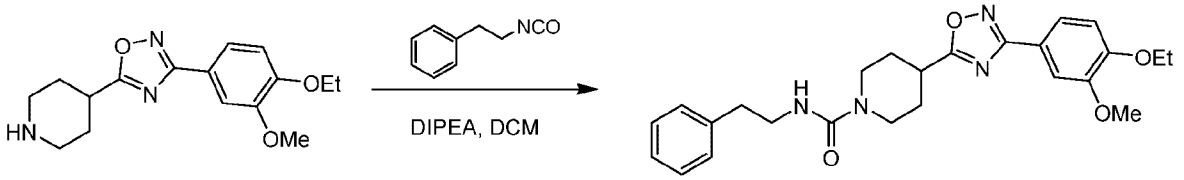


Step 1: Preparation of N-(2-phenylcyclopropyl)-4-(3-(quinolin-2-yl)-1,2,4-oxadiazol-5-yl)piperidine-1-carboxamide.

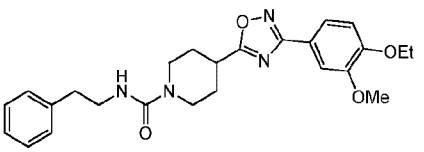


To a stirred solution of 1-[(2-phenylcyclopropyl)carbamoyl]piperidine-4-carboxylic acid (130 mg, 451 µmol) in N,N-dimethylformamide (2 mL) was added (Z)-N'-hydroxyquinoline-2-carboximidamide (101 mg, 541 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (170 mg, 451 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (174 mg, 1.35 mmol, 236 µL). The mixture was stirred at 20 ℃ for 2 h, and then heated at 120 ℃ for 2 h. The reaction mixture was cooled then purified by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 40%-70%,12 min) to give N-(2-phenylcyclopropyl)-4-(3-(quinolin-2-yl)-1,2,4-oxadiazol-5-yl)piperidine-1-carboxamide (34 mg, 77 µmol, 17 %) as a yellow solid. ^{1}H NMR (400MHz, DMSO-d6) δ 8.60 (s, 1H), 8.22 - 8.07 (m, 3H), 7.88 (br. s., 1H), 7.74 (d, *J*=7.5 Hz, 1H), 7.30 - 7.20 (m, 2H), 7.18 - 7.06 (m, 3H), 6.89 (br. s., 1H), 3.99 (d, *J*=13.7 Hz, 2H), 3.45 - 3.37 (m, 1H), 2.94 (t, *J*=11.7 Hz, 2H), 2.72 (d, *J*=3.5 Hz, 1H), 2.10 (d, *J*=11.0 Hz, 2H), 1.89 (br. s., 1H), 1.72 (d, *J*=11.5 Hz, 2H), 1.18 (td, *J*=4.6, 9.3 Hz, 1H), 1.11 - 1.05 (m, 1H); LCMS (ESI) m/z: $[M+H]^+$ = 440.1.

Example 83: 4-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)-N-phenethylpiperidine-1-carboxamide.

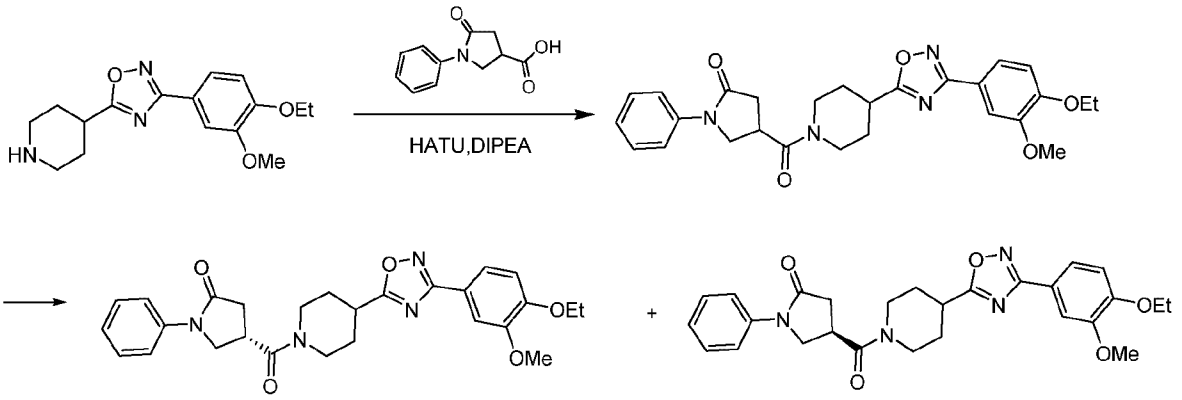


Step 1: Preparation of 4-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)-N-phenethylpiperidine-1-carboxamide.

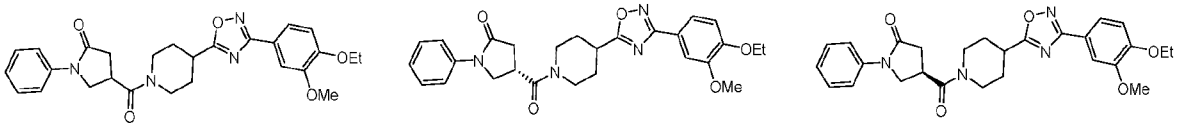


To a stirred solution of (2-isocyanatoethyl)benzene (72 mg, 494 µmol, 68 µL) in toluene (2 mL) was added 3-(4-ethoxy-3-methoxyphenyl)-5-(piperidin-4-yl)-1,2,4-oxadiazole (150 mg, 494 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (63 mg, 494 µmol, 86 µL). Then mixture was stirred at 20 °C for 16 h. The reaction mixture was concentrated in vacuo to give a crude product that was purified by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 35%-60%,12 min) to give 4-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)-N-phenethylpiperidine-1-carboxamide (58 mg, 130 µmol, 26 %) as a white solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.59 (dd, *J*=2.0, 8.4 Hz, 1H), 7.49 (d, *J*=1.9 Hz, 1H), 7.28 - 7.22 (m, 2H), 7.18 - 7.12 (m, 3H), 6.87 (d, *J*=8.4 Hz, 1H), 4.40 (br. s., 1H), 4.10 (q, *J*=7.0 Hz, 2H), 3.88 (s, 3H), 3.86 - 3.80 (m, 2H), 3.48 - 3.41 (m, 2H), 3.14 - 3.05 (m, 1H), 2.97 - 2.88 (m, 2H), 2.78 (t, *J*=6.8 Hz, 2H), 2.04 (dd, *J*=3.2, 13.1 Hz, 2H), 1.89 - 1.77 (m, 2H), 1.43 (t, *J*=7.0 Hz, 3H); LCMS (ESI) m/z: $[M+H]^+$ = 451.3.

Example 84: 4-(4-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)-1-phenylpyrrolidin-2-one, Example 85: (R)-4-(4-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)-1-phenylpyrrolidin-2-one, and Example 86: (S)-4-(4-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)-1-phenylpyrrolidin-2-one.



Step 1: Preparation of 4-(4-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)-1-phenylpyrrolidin-2-one, (S)-4-(4-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)-1-phenylpyrrolidin-2-one, and (R)-4-(4-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)-1-phenylpyrrolidin-2-one



To a stirred solution of 5-oxo-1-phenyl-pyrrolidine-3-carboxylic acid (200 mg, 975 µmol) in N,N-dimethylformamide (4 mL) was added 3-(4-ethoxy-3-methoxy-phenyl)-5-(4-piperidyl)-1,2,4-oxadiazole (295 mg, 975 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (369 mg, 975 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (377 mg, 2.92 mmol, 510 µL). The mixture was stirred at 20 °C for 1 h. The reaction mixture was purified by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 40%-70%,12

min) to give racemic 4-(4-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)-1-phenylpyrrolidin-2-one (151 mg, 31 %). A portion of this racemic mixture (140 mg) underwent SFC separation (column: OJ(250x30mm, 5µm);mobile phase: [CO_2 base-isopropanol]; B%: 45%-45%, min]) to give (R)-4-(4-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)-1-phenylpyrrolidin-2-one (64 mg, 132 µmol, 14 %, 99.7% purity) as a white solid then (S)-4-(4-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)-1-phenylpyrrolidin-2-one (65 mg, 133.9 µmol, 14 %, 99.58% purity) also as a white solid.

4-(4-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)-1-phenylpyrrolidin-2-one:

^{1}H NMR (400 MHz, DMSO-d6) δ 7.68 (d, *J*=8.0 Hz, 2H), 7.62 - 7.56 (m, 1H), 7.48 (s, 1H), 7.39 (t, *J*=6.7 Hz, 2H), 7.19 - 7.09 (m, 2H), 4.38 (d, *J*=13.8 Hz, 1H), 4.14 - 3.93 (m, 5H), 3.85 (s, 3H), 3.80 - 3.71 (m, 1H), 3.51 - 3.40 (m, 1H), 3.30 (br. s., 1H), 3.00 - 2.89 (m, 1H), 2.83 - 2.73 (m, 2H), 2.22 - 2.09 (m, 2H), 1.90 - 1.64 (m, 2H), 1.37 (t, *J*=7.0 Hz, 3H); LCMS (ESI) m/z: $[M+H]^+$ = 491.2.

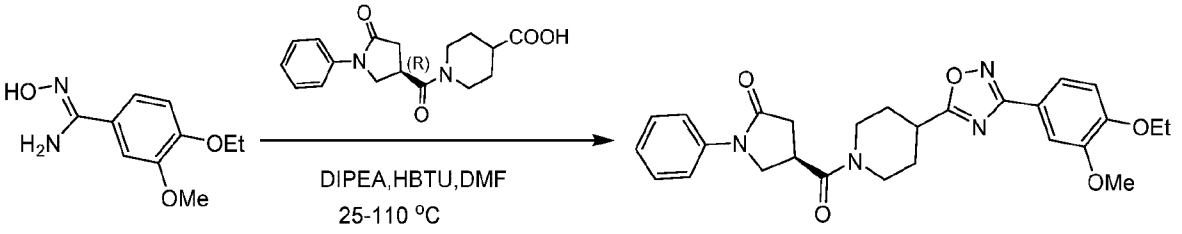
(R)-4-(4-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)-1-phenylpyrrolidin-2-one:

^{1}H NMR (400 MHz, DMSO-d6) δ 7.68 (d, *J*=7.9 Hz, 2H), 7.62 - 7.56 (m, 1H), 7.51 - 7.46 (m, 1H), 7.39 (t, *J*=6.7 Hz, 2H), 7.19 - 7.09 (m, 2H), 4.38 (d, *J*=13.4 Hz, 1H), 4.13 - 3.95 (m, 5H), 3.85 (s, 3H), 3.80 - 3.71 (m, 1H), 3.44 (d, *J*=10.0 Hz, 2H), 2.94 (br. s., 1H), 2.81 - 2.74 (m, 2H), 2.16 (t, *J*=13.6 Hz, 2H), 1.91 - 1.64 (m, 2H), 1.37 (t, *J*=6.9 Hz, 3H); LCMS (ESI) m/z: $[M+H]^+$ = 491.1.

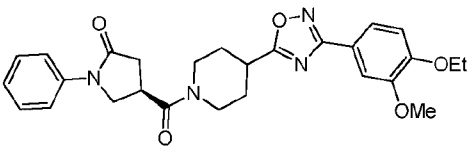
(S)-4-(4-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)-1-phenylpyrrolidin-2-one.

^{1}H NMR (400 MHz, DMSO-d6) δ 7.66 (d, *J*=6.6 Hz, 2H), 7.57 (d, *J*=8.4 Hz, 1H), 7.46 (s, 1H), 7.41 - 7.33 (m, 2H), 7.17 - 7.07 (m, 2H), 4.37 (d, *J*=12.8 Hz, 1H), 4.12 - 3.92 (m, 5H), 3.83 (s, 3H), 3.78 - 3.69 (m, 1H), 3.43 (t, *J*=10.6 Hz, 1H), 3.28 (br. s., 1H), 2.92 (t, *J*=13.0 Hz, 1H), 2.81 - 2.70 (m, 2H), 2.14 (t, *J*=13.5 Hz, 2H), 1.88 - 1.78 (m, 1H), 1.74 - 1.64 (m, 1H), 1.35 (t, *J*=7.1 Hz, 3H); LCMS (ESI) m/z: C27H30N4O5 $[M+H]^+$ = 491.1

Alternatively, Example 85: (4R)-4-[4-[3-(4-ethoxy-3-methoxy-phenyl)-1,2,4-oxadiazol-5-yl]piperidine-1-carbonyl]-1-phenyl-pyrrolidin-2-one can be prepared in an enantioselective fashion as follows:

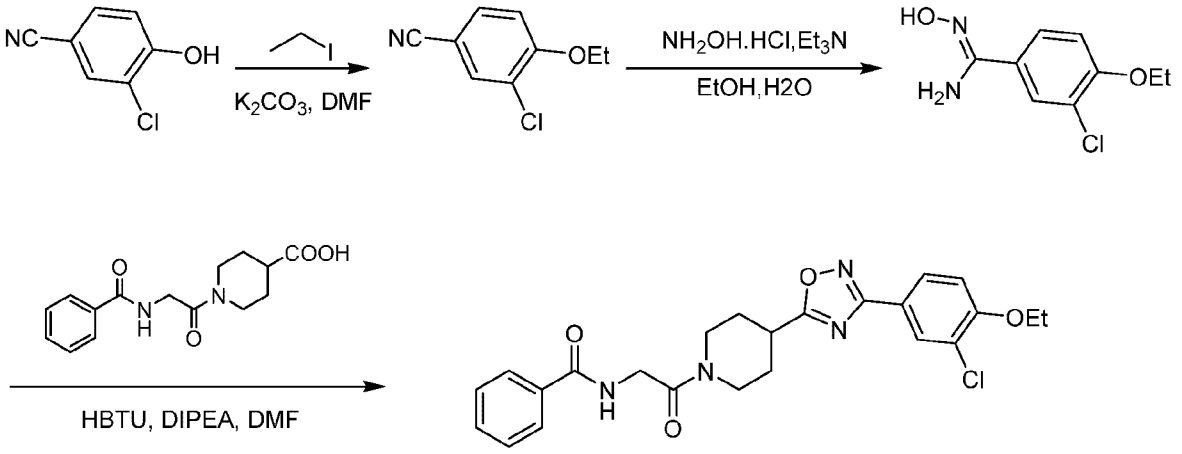


Step 1: Preparation of (4R)-4-[4-[3-(4-ethoxy-3-methoxy-phenyl)-1,2,4-oxadiazol-5-yl]piperidine-1-carbonyl]-1-phenyl-pyrrolidin-2-one.

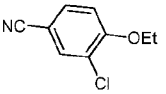


To a stirred solution of 1-[(3R)-5-oxo-1-phenyl-pyrrolidine-3-carbonyl]piperidine-4-carboxylic acid (100 mg, 316 µmol) and 4-ethoxy-N'-hydroxy-3-methoxy-benzamidine (66 mg, 316 µmol) in DMF (1.50 mL) was added (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (119 mg, 316 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (81 mg, 632 µmol, 110 µL) at 25℃. After 12h, the mixture was heated and stirred at 110 ℃ for 1 h. The mixture was cooled then purified by prep_HPLC (Waters Xbridge 150x25 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 25%-65%,12 min) to give (4R)-4-[4-[3-(4-ethoxy-3-methoxy-phenyl)-1,2,4-oxadiazol-5-yl]piperidine-1-carbonyl]-1-phenyl-pyrrolidin-2-one (59 mg,122 µmol, 39 %) as a pink solid. ^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.66 (br d, *J*=8.2 Hz, 1H), 7.61 - 7.54 (m, 3H), 7.37 (m, *J*=7.9 Hz, 2H), 7.19 - 7.14 (m, 1H), 6.94 (d, *J*=8.4 Hz, 1H), 4.59 - 4.46 (m, 1H), 4.31 (dd, *J*=7.3, 9.7 Hz, 1H), 4.17 (q, *J*=7.0 Hz, 2H), 3.99 - 3.90 (m, 5H), 3.58 (quin, *J*=8.4 Hz, 1H), 3.43 - 3.26 (m, 2H), 3.16 - 2.92 (m, 2H), 2.88 - 2.79 (m, 1H), 2.24 (br t, *J*=12.9 Hz, 2H), 2.05 - 1.89 (m, 2H), 1.50 (t, *J*=6.9 Hz, 3H); LCMS (ESI) m/z: $[M+H]^+$ = 491.3.

Example 87: N-(2-(4-(3-(3-chloro-4-ethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.



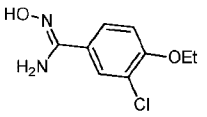
Step 1: Preparation of 3-chloro-4-ethoxybenzonitrile.



To a stirred solution of 3-chloro-4-hydroxybenzonitrile (2.0 g, 13.0 mmol) in N,N-dimethylformamide (20 mL) was added iodoethane (2.44 g, 15.6 mmol, 1.25 mL) and potassium carbonate (3.60 g, 26.1 mmol) at 0 ℃. The reaction was warmed to 40 ℃. After 16 h, the reaction mixture was quenched by addition of water (30 mL) then the mixture was extracted with ethyl acetate (60

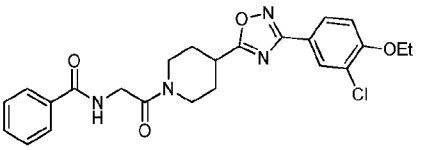
mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to give crude 3-chloro-4-ethoxybenzonitrile (2.50 g) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J*=1.9 Hz, 1H), 7.45 (dd, *J*=2.0, 8.7 Hz, 1H), 6.88 (d, *J*=8.5 Hz, 1H), 4.10 (q, *J*=7.0 Hz, 2H), 1.43 (t, *J*=7.0 Hz, 3H).

Step 2: Preparation of (Z)-3-chloro-4-ethoxy-N'-hydroxybenzimidamide.



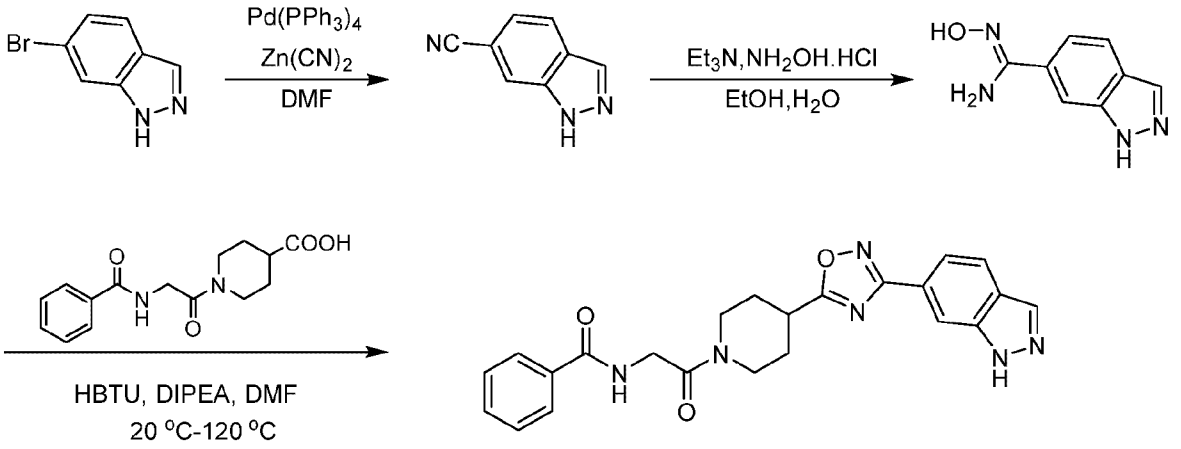
To a stirred solution of 3-chloro-4-ethoxybenzonitrile (2.40 g, 13.2 mmol) in ethanol (30 mL) was added hydroxylamine hydrochloride (1.84 g, 26.4 mmol), triethylamine (2.67 g, 26.4 mmol, 3.66 mL) and water (3 mL). The mixture was heated at 80 °C for 2 h. The reaction mixture was filtered and the filter cake dried in vacuo to give (Z)-3-chloro-4-ethoxy-N'-hydroxybenzimidamide (700 mg, 3.62 mmol, 69 %) as a brown oil. ^{1}H NMR (400 MHz, DMSO-d6) δ 9.59 (s, 1H), 7.72 (d, *J*=2.0 Hz, 2H), 7.14 (d, *J*=8.8 Hz, 1H), 5.83 (s, 2H), 4.14 (q, *J*=6.9 Hz, 2H), 1.45 - 1.30 (m, 3H).

Step 3: Preparation of N-(2-(4-(3-(3-chloro-4-ethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide

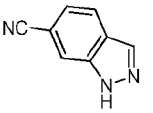


To a stirred solution of 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid (120 mg, 413 µmol) in N,N-dimethylformamide (2 mL) was added (Z)-3-chloro-4-ethoxy-N'-hydroxybenzimidamide (97 mg, 455 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (156 mg, 413 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (160 mg, 1.24 mmol, 216 µL). The mixture was stirred at 20 °C for 2 h, then heated at 120 °C for 2 h. The reaction mixture was cooled then purified by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 45%-80%,12 min) to give N-(2-(4-(3-(3-chloro-4-ethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide (104 mg, 223 µmol, 54 %) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J*=2.0 Hz, 1H), 7.95 (dd, *J*=2.1, 8.6 Hz, 1H), 7.91 - 7.86 (m, 2H), 7.58 - 7.44 (m, 3H), 7.35 (br. s., 1H), 7.02 (d, *J*=8.7 Hz, 1H), 4.51 (d, *J*=13.7 Hz, 1H), 4.33 (d, *J*=3.9 Hz, 2H), 4.21 (q, *J*=7.0 Hz, 2H), 3.93 (d, *J*=13.9 Hz, 1H), 3.41 - 3.29 (m, 2H), 3.18 (t, *J*=10.8 Hz, 1H), 2.33 - 2.20 (m, 2H), 2.09 - 1.93 (m, 2H), 1.53 (t, *J*=7.0 Hz, 3H); LCMS (ESI) m/z: $[M+H]^+$ = 469.3.

Example 88: N-(2-(4-(3-(1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide

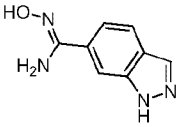


Step 1: Preparation of 1H-indazole-6-carbonitrile



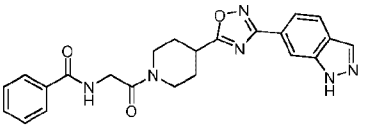
To a stirred solution of 6-bromo-1H-indazole (1.0 g, 5.08 mmol) in N,N-dimethylformamide (12 mL) was added zinc cyanide (595 mg, 5.08 mmol, 322 µL) and tetrakis(triphenylphosphine)palladium(0) (586 mg, 508 µmol), and the mixture was degassed with nitrogen three times. The mixture heated at 100 °C for 4 h under nitrogen. The reaction cooled to 20 °C, water (15 mL) was added, and the reaction mixture was extracted with ethyl acetate (40 mL x 3). The combined organic extracts were washed with saturated aqueous sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to give crude product. This was triturated with petroleum ether (30 mL) and dichloromethane (5 mL), and the mixture filtered. The filter cake was dried in vacuo to give 1H-indazole-6-carbonitrile (880 mg) as a yellow solid that was used directly without further purification. ^{1}H NMR (400 MHz, DMSO-d6) δ 13.65 (br. s., 1H), 8.33 - 8.12 (m, 2H), 7.99 (d, *J*=8.4 Hz, 1H), 7.88 - 7.80 (m, 1H).

Step 2: Preparation of (Z)-N'-hydroxy-1H-indazole-6-carboximidamide.



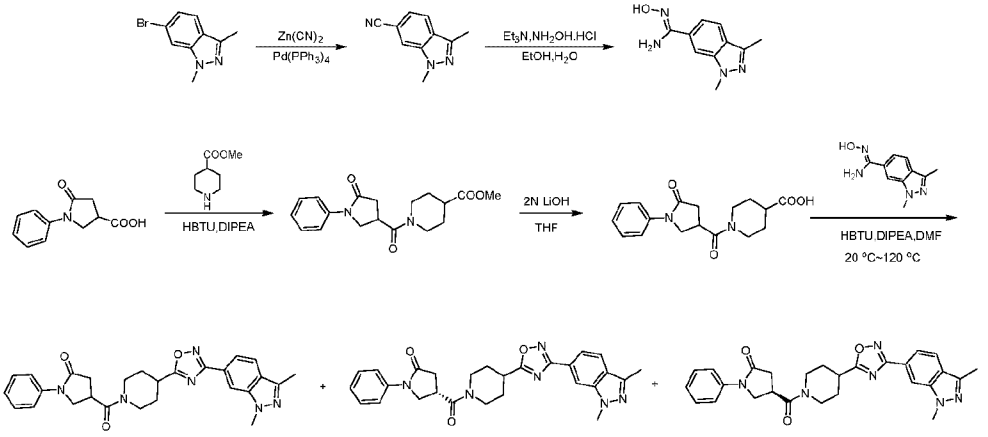
To a stirred solution of 1H-indazole-6-carbonitrile (800 mg, 5.59 mmol) in ethanol (1 mL) was added hydroxylamine hydrochloride (776 mg, 11.18 mmol), triethylamine (1.13 g, 11.18 mmol, 1.55 mL) and water (100 µL). The mixture was heated at 80 °C for 2 h. The reaction mixture was cooled, concentrated under reduced pressure, and then diluted with water (5 mL). The solid that formed was filtered and the filter cake was dried under reduced pressure to give (Z)-N'-hydroxy-1H-indazole-6-carboximidamide (500 mg, 2.84 mmol, 51 %) as a yellow solid that was used directly without further purification. ^{1}H NMR (400 MHz, DMSO-d6) δ 13.22 - 13.10 (m, 1H), 9.68 (br. s., 1H), 8.04 (s, 1H), 7.78 (s, 1H), 7.70 - 7.66 (m, 1H), 7.47 - 7.42 (m, 1H), 5.87 (br. s., 2H).

Step 3: Preparation of N-(2-(4-(3-(1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.

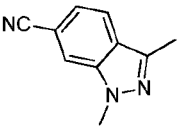


To a stirred solution of 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid (120 mg, 413 µmol) in N,N-dimethylformamide (2 mL) was added (Z)-N'-hydroxy-1H-indazole-6-carboximidamide (94 mg, 537 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (156 mg, 413 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (160 mg, 1.24 mmol, 216 µL). The mixture was stirred at 20 ℃ for 1 h, then heated at 110 ℃ for 1 h. The reaction mixture was purified directly by prep-HPLC (column: Luna C18 100*30 5µm; mobile phase: [water (0.225%TFA)-acetonitrile]; B%: 30%-55%,12 min) to give N-(2-(4-(3-(1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide (21 mg, 44 µmol, 11 %) as a brown solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 13.34 (br s, 1H), 8.55 (t, *J*=5.6 Hz, 1H), 8.18 - 8.16 (m, 1H), 7.94 - 7.89 (m, 1H), 7.88 - 7.83 (m, 2H), 7.72 (dd, *J*=1.1, 8.4 Hz, 1H), 7.54 - 7.41 (m, 3H), 4.36 - 4.27 (m, 1H), 4.16 (d, *J*=5.7 Hz, 2H), 3.97 (br d, *J*=14.1 Hz, 1H), 3.59 (br s, 1H), 3.47 (s, 1H), 3.34 - 3.24 (m, 1H), 2.98 - 2.88 (m, 1H), 2.20 - 2.08 (m, 2H), 1.89 - 1.77 (m, 1H), 1.66 (br d, *J*=11.5 Hz, 1H); LCMS (ESI) m/z: $[M+H]^+$ = 431.1.

Example 89: 4-(4-(3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)-1-phenylpyrrolidin-2-one, example 90: 4-(4-(3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)-1-phenylpyrrolidin-2-one, Enantiomer 1 and Example 91: (R)-4-(4-(3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)-1-phenylpyrrolidin-2-one, Enantiomer 2.



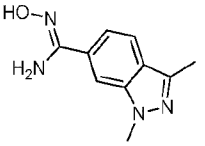
Step 1: Preparation of 1,3-dimethyl-1H-indazole-6-carbonitrile.



To a stirred solution of 6-bromo-1,3-dimethyl-1H-indazole (480 mg, 2.13 mmol) in N,N-dimethylformamide (5 mL) was added zinc cyanide (250 mg, 2.13 mmol) and

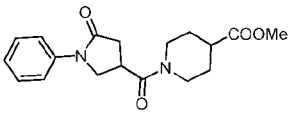
tetrakis(triphenylphosphine)palladium(0) (246 mg, 213 µmol) under nitrogen, then the mixture was heated to 100 °C. After 16 h, the reaction was cooled to 20 °C, water (10 mL) was added, and the reaction mixture extracted with ethyl acetate (40 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (15 mL), dried over anhydrous sodium sulfate, filtered and then concentrated in vacuo to give crude product. The residue was triturated with petroleum ether (30 mL), then filtered and the filter cake dried in vacuo to give 1,3-dimethyl-1H-indazole-6-carbonitrile (300 mg, 1.75 mmol, 82 %) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 - 7.71 (m, 2H), 7.38 - 7.31 (m, 1H), 4.08 (s, 3H), 2.61 (s, 3H).

Step 2: Preparation of (Z)-N'-hydroxy-1,3-dimethyl-1H-indazole-6-carboximidamide.



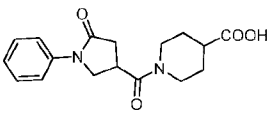
To a stirred solution of 1,3-dimethyl-1H-indazole-6-carbonitrile (300 mg, 1.75 mmol) in ethanol (5 mL) was added hydroxylamine hydrochloride (243 mg, 3.50 mmol), triethylamine (354 mg, 3.50 mmol, 485 µL) and water (500 µL). The mixture was heated at 80 °C for 5 h, then cooled and filtered, and the filter cake was dried in vacuo to give (Z)-N'-hydroxy-1,3-dimethyl-1H-indazole-6-carboximidamide (290 mg, 1.42 mmol, 81 %) as a white solid that was used directly without further purification. ^{1}H NMR (400 MHz, DMSO-d6) δ 9.71 (s, 1H), 7.86 (s, 1H), 7.65 (d, *J*=8.5 Hz, 1H), 7.49 (d, *J*=8.5 Hz, 1H), 5.90 (s, 2H), 3.97 (s, 3H), 2.47 (s, 3H).

Step 3: Preparation of methyl 1-(5-oxo-1-phenylpyrrolidine-3-carbonyl)piperidine-4-carboxylate.



To a stirred solution of 5-oxo-1-phenylpyrrolidine-3-carboxylic acid (500 mg, 2.44 mmol) in N,N-dimethylformamide (10 mL) was added methyl piperidine-4-carboxylate (349 mg, 2.44 mmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (925 mg, 2.44 mmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (946 mg, 7.32 mmol, 1.28 mL). The mixture was stirred at 20 °C for 2 h. The reaction mixture was quenched by addition of water (20 mL) then extracted with ethyl acetate (40 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. Purification by chromatography (silica, petroleum ether : ethyl acetate = 20 : 1 to 1 : 1) gave methyl 1-(5-oxo-1-phenylpyrrolidine-3-carbonyl)piperidine-4-carboxylate (940 mg) as a yellow oil.

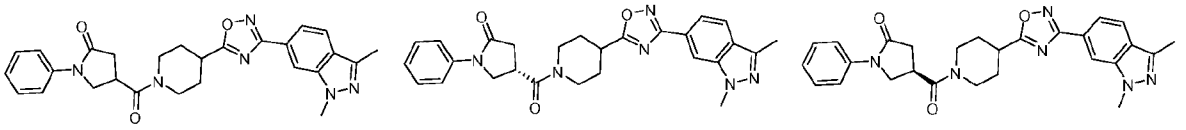
Step 4: Preparation of 1-(5-oxo-1-phenylpyrrolidine-3-carbonyl)piperidine-4-carboxylic acid



To a stirred solution of methyl 1-(5-oxo-1-phenylpyrrolidine-3-carbonyl)piperidine-4-carboxylate (900 mg, 2.72 mmol) in tetrahydrofuran (10 mL) was added lithium hydroxide (2 M, 2.72 mL). Afterr 2 h,

the reaction mixture was acidified to pH 1 with 1 M hydrochloric acid (6 mL). The mixture was extracted with ethyl acetate (40 mL x 3). The organic extracts were combined and washed with saturated aqueous sodium chloride solution (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to give 1-(5-oxo-1-phenylpyrrolidine-3-carbonyl)piperidine-4-carboxylic acid (600 mg, 1.90 mmol, 70 %) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 12.37 - 12.17 (m, 1H), 7.66 (dd, *J*=5.8, 7.2 Hz, 2H), 7.38 (t, *J*=7.9 Hz, 2H), 7.19 - 7.09 (m, 1H), 4.28 - 4.19 (m, 1H), 4.04 (s, 1H), 3.93 (br. s., 2H), 3.76 - 3.66 (m, 1H), 3.18 (br. s., 1H), 2.86 - 2.67 (m, 4H), 1.87 (t, *J*=13.2 Hz, 2H), 1.61 - 1.35 (m, 2H).

Step 5: Preparation of 4-(4-(3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)-1-phenylpyrrolidin-2-one, 4-(4-(3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)-1-phenylpyrrolidin-2-one, Enantiomer 1 and 4-(4-(3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)-1-phenylpyrrolidin-2-one, Enantiomer 2.



To a stirred solution of 1-(5-oxo-1-phenyl-pyrrolidine-3-carbonyl)piperidine-4-carboxylic acid (150 mg, 474 µmol) in N,N-dimethylformamide (2 mL) was added N'-hydroxy-1,3-dimethyl-indazole-6-carboxamidine (96 mg, 474 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (179 mg, 474 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (183 mg, 1.42 mmol, 248 µL). The mixture was stirred at 20 °C for 2 h, then heated at 120 °C for 1 h. The reaction mixture was cooled then purified by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 30%-55%,12 min) to give the racemic of 4-(4-(3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)-1-phenylpyrrolidin-2-one (85 mg) as a white solid. A portion (25 mg, 53 µmol, 11 %, 99.83% purity) was retained for analysis. The remainder (60 mg) was purified by SFC (column: OJ (250x30mm, 5µm); mobile phase: [CO_2 base-methanol]; B%: 45%-45%,min) to give 4-(4-(3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)-1-phenylpyrrolidin-2-one, Enatiomer 1 (27 mg, 56 µmol, 12 %) as a brown solid then 4-(4-(3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)-1-phenylpyrrolidin-2-one, Enantiomer 2 (26 mg, 55 µmol, 12 %) as a white solid.

4-(4-(3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)-1-phenylpyrrolidin-2-one:

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 - 8.07 (m, 1H), 7.83 (s, 1H), 7.78 - 7.72 (m, 1H), 7.61 (d, *J*=8.0 Hz, 2H), 7.39 (t, *J*=7.9 Hz, 2H), 7.18 (s, 1H), 4.65 - 4.50 (m, 1H), 4.34 (t, *J*=7.3 Hz, 1H), 4.09 (d, *J*=3.3 Hz, 3H), 4.05 - 3.92 (m, 2H), 3.60 (quin, *J*=8.4 Hz, 1H), 3.46 - 3.32 (m, 2H), 2.98 (d, *J*=6.7 Hz, 2H), 2.91 - 2.81 (m, 1H), 2.61 (s, 3H), 2.35 - 2.22 (m, 2H), 2.02 (d, *J*=6.1 Hz, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 485.2.

4-(4-(3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)-1-phenylpyrrolidin-2-one, Enantiomer 1:

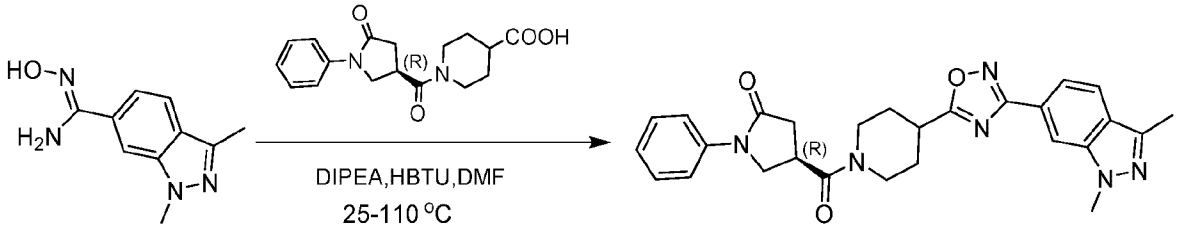
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J*=4.1 Hz, 1H), 7.86 (br d, *J*=8.5 Hz, 1H), 7.80 - 7.74 (m, 1H), 7.63 (d, *J*=7.9 Hz, 2H), 7.41 (t, *J*=8.0 Hz, 2H), 7.23 - 7.18 (m, 1H), 4.67 - 4.52 (m, 1H), 4.36 (br t, *J*=7.0 Hz, 1H), 4.11 (d, *J*=3.4 Hz, 3H), 4.07 - 3.94 (m, 2H), 3.62 (quin, *J*=8.5 Hz, 1H), 3.49 - 3.35 (m, 2H), 3.22 -

2.96 (m, 2H), 2.93 - 2.81 (m, 1H), 2.63 (s, 3H), 2.37 - 2.25 (m, 2H), 2.11 - 1.97 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 485.3.

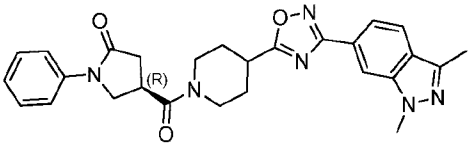
4-(4-(3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperidine-1-carbonyl)-1-phenylpyrrolidin-2-one, Enantiomer 2:

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J*=3.9 Hz, 1H), 7.86 (d, *J*=8.4 Hz, 1H), 7.80 - 7.74 (m, 1H), 7.63 (d, *J*=8.3 Hz, 2H), 7.41 (t, *J*=8.0 Hz, 2H), 7.24 - 7.18 (m, 1H), 4.66 - 4.53 (m, 1H), 4.36 (br t, *J*=7.3 Hz, 1H), 4.11 (d, *J*=3.5 Hz, 3H), 4.07 - 3.94 (m, 2H), 3.62 (quin, *J*=8.5 Hz, 1H), 3.48 - 3.36 (m, 2H), 3.21 - 2.96 (m, 2H), 2.93 - 2.81 (m, 1H), 2.63 (s, 3H), 2.36 - 2.26 (m, 2H), 2.06 (br d, *J*=13.4 Hz, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 485.3.

Examples 90 and 91 can be synthesized in an enantiospecific fashion using appropriate enantiopure starting materials, following the representative procedure below:

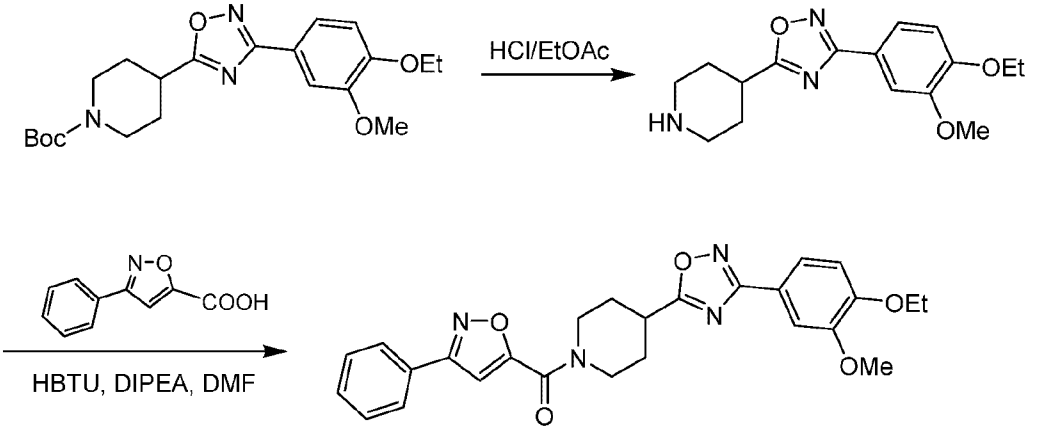


Preparation of (4R)-4-[4-[3-(1,3-dimethylindazol-6-yl)-1,2,4-oxadiazol-5-yl]piperidine-1-carbonyl]-1-phenyl-pyrrolidin-2-one.

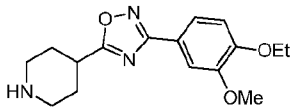


To a stirred solution of 1-[(3R)-5-oxo-1-phenyl-pyrrolidine-3-carbonyl]piperidine-4-carboxylic acid (115 mg, 363.52 µmol) and N'-hydroxy-1,3-dimethyl-indazole-6-carboxamidine (74 mg, 364 µmol) in DMF (1.50 mL) was added (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (137 mg, 364 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (93 mg, 727 µmol, 126 µL) at 25 °C. After 3 h, the mixture was warmed to 110 °C. After 1h, the mixture was purified by chromatography (Waters Xbridge 150x25 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 25%-60%,12 min) to give (4R)-4-[4-[3-(1,3-dimethylindazol-6-yl)-1,2,4-oxadiazol-5-yl]piperidine-1-carbonyl]-1-phenyl-pyrrolidin-2-one (64 mg,133 µmol, 37 %) as a pink solid. ^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.09 (d, *J*=4.0 Hz, 1H), 7.84 - 7.80 (d, 1H), 7.75 - 7.71 (d, 1H), 7.59 (d, *J*=7.9 Hz, 2H), 7.38 (t, *J*=7.9 Hz, 2H), 7.20 - 7.14 (t, 1H), 4.62 - 4.49 (m, 1H), 4.36 - 4.29 (m, 1H), 4.07 (d, *J*=3.3 Hz, 3H), 4.04 - 3.89 (m, 2H), 3.58 (quin, *J*=8.4 Hz, 1H), 3.45 - 3.30 (m, 2H), 3.18 - 2.92 (m, 2H), 2.90 - 2.80 (m, 1H), 2.59 (s, 3H), 2.27 (br t, *J*=13.2 Hz, 2H), 2.09 - 1.91 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 485.3.

Example 92: (4-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)(3-phenylisoxazol-5-yl)methanone.

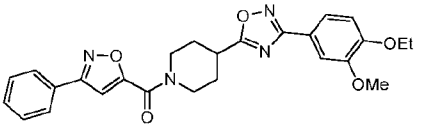


Step 1: Preparation of 3-(4-ethoxy-3-methoxyphenyl)-5-(piperidin-4-yl)-1,2,4-oxadiazole.



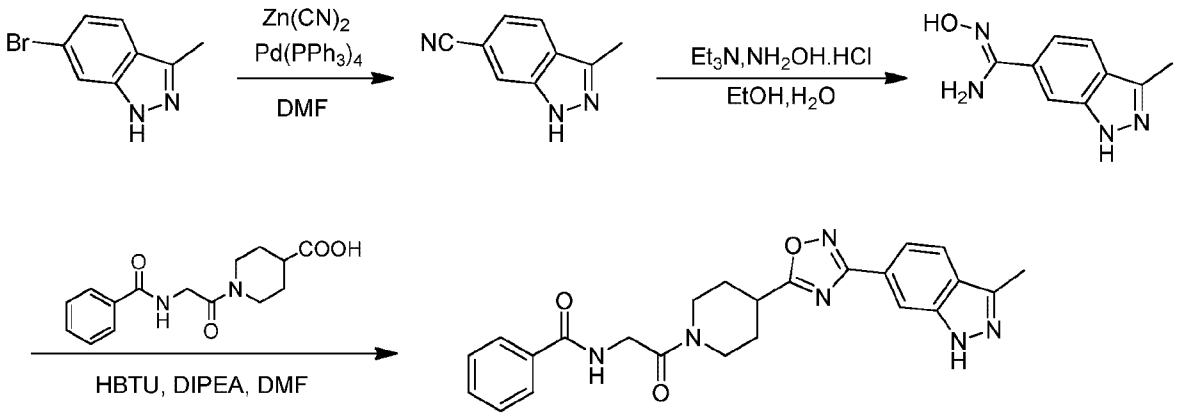
To a stirred solution of tert-butyl 4-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carboxylate (800 mg, 1.98 mmol) in ethyl acetate (5 mL) was added 4M hydrochloric acid / ethyl acetate (20 mL). The mixture was stirred at 20 °C for 0.5 h. The reaction mixture was filtered and the filter cake was dried in vacuo to give 3-(4-ethoxy-3-methoxyphenyl)-5-(piperidin-4-yl)-1,2,4-oxadiazole (450 mg, 1.48 mmol, 75 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (dd, *J*=1.6, 8.3 Hz, 1H), 7.60 - 7.54 (m, 1H), 6.97 (d, *J*=8.4 Hz, 1H), 4.24 - 4.13 (m, 2H), 3.98 (s, 3H), 3.56 (br s, 2H), 3.39 (br s, 1H), 3.33 - 3.15 (m, 2H), 2.51 (br s, 2H), 2.48 - 2.33 (m, 2H), 2.19 - 1.83 (m, 1H), 1.53 (t, *J*=7.0 Hz, 3H).

Step 2: Preparation of (4-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)(3-phenylisoxazol-5-yl)methanone.

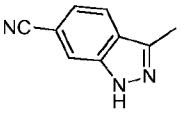


To a stirred solution of 3-phenylisoxazole-5-carboxylic acid (75 mg, 396 µmol) in N,N-dimethylformamide (2 mL) was added 3-(4-ethoxy-3-methoxyphenyl)-5-(piperidin-4-yl)-1,2,4-oxadiazole (120 mg, 396 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (150 mg, 396 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (153 mg, 1.19 mmol, 207 µL). The mixture was stirred at 20 °C for 2 h. The reaction mixture was then purified by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%:40%-70%,12 min) to give (4-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)(3-phenylisoxazol-5-yl)methanone (41 mg, 87 µmol, 22 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (br s, 2H), 7.70 (br d, *J*=7.8 Hz, 1H), 7.60 (br s, 1H), 7.53 (br s, 3H), 7.14 (s, 1H), 6.99 (br d, *J*=7.5 Hz, 1H), 4.59 (br s, 1H), 4.36 (br d, *J*=12.5 Hz, 1H), 4.21 (br d, *J*=6.4 Hz, 2H), 4.00 (s, 3H), 3.55 (br s, 1H), 3.46 - 3.25 (m, 2H), 2.32 (br s, 2H), 2.15 (br s, 2H), 1.54 (br t, *J*=6.8 Hz, 3H); LCMS (ESI) m/z: $[M+H]^+$ = 475.2.

Example 93: N-(2-(4-(3-(3-methyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.

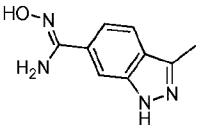


Step 1: Preparation of 3-methyl-1H-indazole-6-carbonitrile.



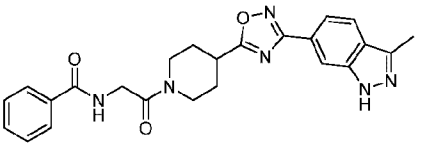
To a stirred solution of 6-bromo-3-methyl-1H-indazole (440 mg, 2.08 mmol) in N,N-dimethylformamide (5 mL) was added zinc cyanide (244 mg, 2.08 mmol) and tetrakis(triphenylphosphine)palladium(0) (240 mg, 208 µmol), then the mixture was degassed with nitrogen three times. The mixture stirred at 100 °C for 4 h under nitrogen, then cooled to 20 °C, water (10 mL) added, and the reaction mixture was extracted with ethyl acetate (40 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (15 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to give crude product. Petroleum ether (20 mL) was added to the crude product, then the mixture was filtered and the filter cake dried in vacuo to give 3-methyl-1H-indazole-6-carbonitrile (220 mg, 1.40 mmol, 67 %) as a brown solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 13.29 - 13.09 (m, 1H), 8.09 - 8.05 (m, 1H), 7.96 - 7.90 (m, 1H), 7.41 (d, *J*=8.3 Hz, 1H), 2.54 (s, 3H).

Step 2: Preparation of (Z)-N'-hydroxy-3-methyl-1H-indazole-6-carboximidamide.



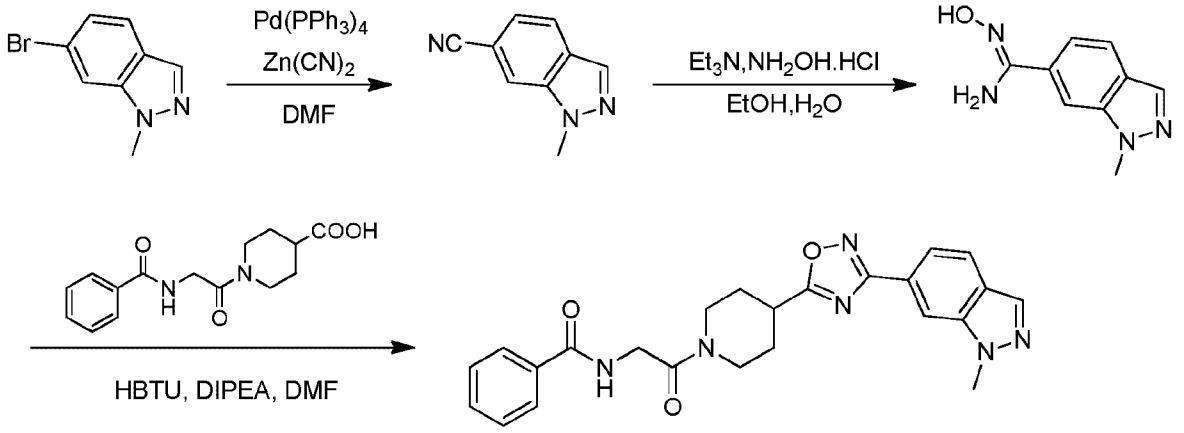
To a stirred solution of 3-methyl-1H-indazole-6-carbonitrile (200 mg, 1.27 mmol) in ethanol (1 mL) was added hydroxylamine hydrochloride (176 mg, 2.55 mmol), triethylamine (257 mg, 2.55 mmol, 352 µL) and water (100 µL). The mixture was stirred at 80 °C for 2 h. The reaction mixture was cooled and then concentrated under reduced pressure to remove ethanol. The residue was diluted with water (5 mL), filtered and the filter cake was dried under reduced pressure to give (Z)-N'-hydroxy-3-methyl-1H-indazole-6-carboximidamide (150 mg, 789 µmol, 62 %) as a white solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 12.73 (s, 1H), 9.67 (s, 1H), 7.73 (s, 1H), 7.65 (d, *J*=8.5 Hz, 1H), 7.45 (d, *J*=8.5 Hz, 1H), 5.86 (s, 2H), 2.49 (s, 3H).

Step 3: Preparation of N-(2-(4-(3-(3-methyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.

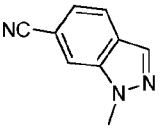


To a stirred solution of 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid (120 mg, 413 µmol) in N,N-dimethylformamide (2 mL) was added (Z)-N'-hydroxy-3-methyl-1H-indazole-6-carboximidamide (78 mg, 413 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (156 mg, 413 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (160 mg, 1.24 mmol, 216 µL). The mixture was stirred at 20 °C for 2 h, then heated at 110 °C for 1 h. The reaction mixture was cooled then purified directly by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 20%-55%,12 min) to give N-(2-(4-(3-(3-methyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide (93 mg, 209 µmol, 51 %) as a white solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 12.92 (s, 1H), 8.59 - 8.53 (m, 1H), 8.08 (s, 1H), 7.86 (d, *J*=8.4 Hz, 3H), 7.71 - 7.65 (m, 1H), 7.55 - 7.42 (m, 3H), 4.30 (d, *J*=13.2 Hz, 1H), 4.16 (d, *J*=5.7 Hz, 2H), 3.97 (d, *J*=14.6 Hz, 1H), 3.49 - 3.43 (m, 1H), 3.29 - 3.24 (m, 1H), 2.92 (t, *J*=11.2 Hz, 1H), 2.50 (s, 3H), 2.14 (t, *J*=13.0 Hz, 2H), 1.88 - 1.78 (m, 1H), 1.66 (d, *J*=9.7 Hz, 1H); LCMS (ESI) m/z: $[M+H]^+$ = 445.3.

Example 94: N-(2-(4-(3-(1-methyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.



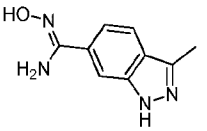
Step 1: Preparation of 1-methyl-1H-indazole-6-carbonitrile.



To a stirred solution of 6-bromo-1-methyl-1H-indazole (500 mg, 2.37 mmol) in N,N-dimethylformamide (8 mL) was added zinc cyanide (278 mg, 2.37 mmol) and tetrakis(triphenylphosphine)palladium(0) (273 mg, 236.90 µmol), the mixture was degassed with nitrogen three times. The mixture was stirred at 100 °C for 4 h under nitrogen, then cooled to 20 °C, water (10 mL)

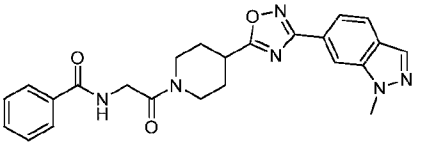
added, and the reaction mixture extracted with ethyl acetate (40 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (15 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to give crude product. The mixture was triturated with petroleum ether (20 mL) and dichloromethane (3 mL), then filtered and dried in vacuo to give 1-methyl-1H-indazole-6-carbonitrile (300 mg, 1.91 mmol, 81 %) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.88 - 7.83 (m, 1H), 7.82 (s, 1H), 7.39 (dd, *J*=1.1, 8.3 Hz, 1H), 4.16 (s, 3H).

Step 2: Preparation of (Z)-N'-hydroxy-1-methyl-1H-indazole-6-carboximidamide.



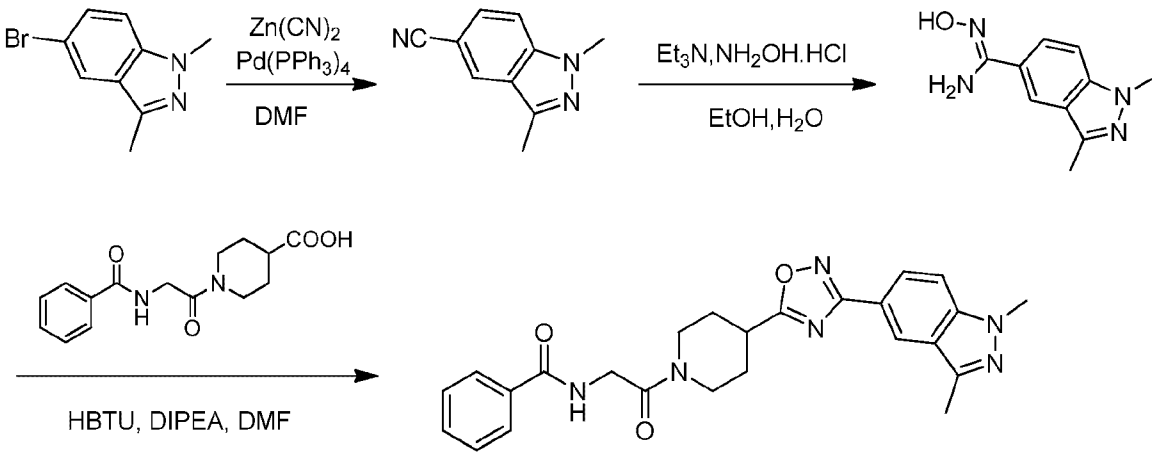
To a stirred solution of 1-methyl-1H-indazole-6-carbonitrile (250 mg, 1.59 mmol) in ethanol (1 mL) was added hydroxylamine hydrochloride (221 mg, 3.18 mmol), triethylamine (321 mg, 3.18 mmol, 440 µL) and water (100 µL). The mixture was heated at 80 ℃ for 2 h. The reaction mixture was concentrated under reduced pressure and the residue then triturated with water (4 mL), filtered and the filter cake was dried under reduced pressure to give (Z)-N'-hydroxy-1-methyl-1H-indazole-6-carboximidamide (500 mg) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 10.65 (br. s., 2H), 9.65-9.84 (m, 1H), 7.98 (d, *J*=18.1 Hz, 2H), 7.67 (d, *J*=8.8 Hz, 1H), 7.46-7.52 (m, 1H), 4.03 ppm (s, 3H).

Step 3: Preparation of N-(2-(4-(3-(1-methyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.

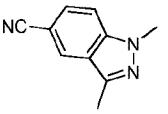


To a stirred solution of 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid (120 mg, 413 µmol) in N,N-dimethylformamide (2 mL) was added (Z)-N'-hydroxy-1-methyl-1H-indazole-6-carboximidamide (125 mg, 661 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (156 mg, 413 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (160 mg, 1.24 mmol, 216 µL). The mixture was stirred at 20 ℃ for 1 h, then heated at 110 ℃ for 1 h. The reaction mixture was cooled then purified by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 33%-63%,12 min) to give N-(2-(4-(3-(1-methyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide (29 mg, 64 µmol, 15 %) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1H), 8.06 (s, 1H), 7.92 - 7.82 (m, 4H), 7.58 - 7.45 (m, 3H), 7.36 (br. s., 1H), 4.56 (d, *J*=14.2 Hz, 1H), 4.34 (d, *J*=3.9 Hz, 2H), 4.19 (s, 3H), 4.00 - 3.92 (m, 1H), 3.44 - 3.34 (m, 2H), 3.19 (t, *J*=10.9 Hz, 1H), 2.36 - 2.26 (m, 2H), 2.14 - 1.98 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 445.2.

Example 95: N-(2-(4-(3-(1,3-dimethyl-1H-indazol-5-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.

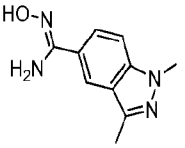


Step 1: Preparation of 1,3-dimethyl-1H-indazole-5-carbonitrile.



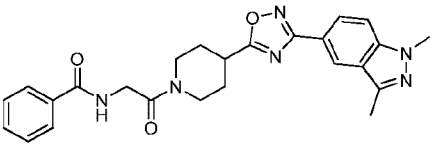
To a stirred solution of 5-bromo-1,3-dimethyl-1H-indazole (600 mg, 2.67 mmol) in N,N-dimethylformamide (10 mL) was added zinc cyanide (313 mg, 2.67 mmol, 169 µL) and tetrakis(triphenylphosphine)palladium(0) (308 mg, 267 µmol) under nitrogen. The mixture was stirred at 100 °C for 16 h, then cooled to 20 °C, and diluted with water (15 mL). The reaction mixture was extracted with ethyl acetate (40 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to give crude product. This was triturated with petroleum ether (30 mL) and dichloromethane (5 mL), filtered and the filter cake dried in vacuo to give 1,3-dimethyl-1H-indazole-5-carbonitrile (340 mg, 1.99 mmol, 74 %) as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.54 (d, *J*=8.8 Hz, 1H), 7.37 (d, *J*=8.8 Hz, 1H), 4.02 (s, 3H), 2.57 (s, 3H).

Step 2: Preparation of (Z)-N'-hydroxy-1,3-dimethyl-1H-indazole-5-carboximidamide.



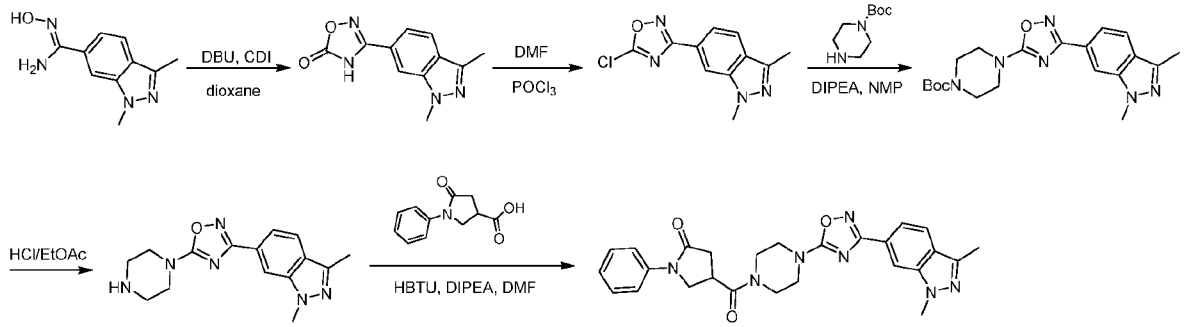
To a stirred solution of 1,3-dimethyl-1H-indazole-5-carbonitrile (340 mg, 1.99 mmol) in ethanol (6 mL) was added hydroxylamine hydrochloride (276 mg, 3.97 mmol), triethylamine (401 mg, 3.97 mmol, 550 µL) and water (600 µL). The mixture was stirred at 80 °C for 2 h. The reaction mixture was cooled and then concentrated under reduced pressure. The residue was triturated with water (4 mL), filtered and the filter cake was dried under reduced pressure to give (Z)-N'-hydroxy-1,3-dimethyl-1H-indazole-5-carboximidamide (250 mg, 1.22 mmol, 62 %) as a white solid.^{1}H NMR (400 MHz, DMSO-d6) δ 9.50 (s, 1H), 7.99 (s, 1H), 7.72 (dd, *J*=1.5, 9.0 Hz, 1H), 7.48 (d, *J*=8.8 Hz, 1H), 5.82 (s, 2H), 3.92 (s, 3H), 2.46 (s, 3H).

Step 3: Preparation of N-(2-(4-(3-(1,3-dimethyl-1H-indazol-5-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.

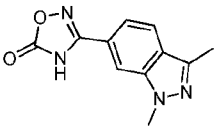


To a stirred solution of 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid (120 mg, 413 µmol) in N,N-dimethylformamide (2 mL) was added N'-hydroxy-1,3-dimethyl-indazole-5-carboxamidine (84 mg, 413 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (156 mg, 413 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (160 mg, 1.24 mmol, 216 µL). The mixture was stirred at 20 °C for 2 h, and then heated at 110 °C for 2 h. The reaction mixture was cooled then purified by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 35%-64%,12 min) to give N-(2-(4-(3-(1,3-dimethyl-1H-indazol-5-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide (54 mg, 118 µmol, 29 %) as a white solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.55 (t, *J*=5.5 Hz, 1H), 8.34 (s, 1H), 7.96 (dd, *J*=1.3, 8.8 Hz, 1H), 7.86 (d, *J*=7.1 Hz, 2H), 7.70 (d, *J*=8.8 Hz, 1H), 7.55 - 7.42 (m, 3H), 4.31 (d, *J*=13.2 Hz, 1H), 4.16 (dd, *J*=2.2, 5.3 Hz, 2H), 4.03 - 3.92 (m, 4H), 3.49 - 3.40 (m, 1H), 3.34 - 3.30 (m, 1H), 2.92 (t, *J*=11.5 Hz, 1H), 2.52 (s, 3H), 2.14 (t, *J*=13.0 Hz, 2H), 1.83 (d, *J*=10.1 Hz, 1H), 1.71 - 1.62 (m, 1H); LCMS (ESI) m/z: $[M+H]^+$ = 459.3.

Example 96: 4-(4-(3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperazine-1-carbonyl)-1-phenylpyrrolidin-2-one.



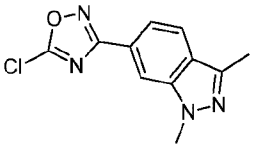
Step 1: Preparation of 3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5(4H)-one.



To a stirred solution of (Z)-N'-hydroxy-1,3-dimethyl-1H-indazole-6-carboximidamide (180 mg, 881 µmol) in dioxane (3 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (147 mg, 970 µmol, 146 µL) and 1,1'-carbonyldiimidazole (214 mg, 1.32 mmol). The mixture was stirred at 110 °C for 16 h. The reaction mixture was concentrated in vacuo then purified by chromatography (silica, dichloromethane : methanol = 50 :1) to give 3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5(4H)-one (220 mg) as a yellow solid. ^{1}H

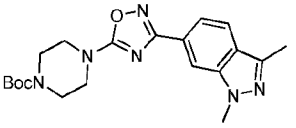
NMR (400 MHz, Methanol-d4) δ 7.97 - 7.93 (m, 1H), 7.82 - 7.77 (m, 1H), 7.62 (d, *J*=1.1 Hz, 1H), 4.05 (s, 3H), 2.57 (s, 3H).

Step 2: Preparation of 5-chloro-3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazole



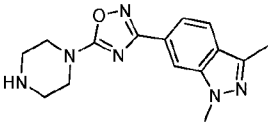
A flask 3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5(4H)-one (220 mg, 956 µmol) was charged with N,N-dimethylformamide (1 mL) then phosphoryl chloride (10 mL) was added dropwise. The mixture was heated at 110 °C for 16 h, then cooled and concentrated under reduced pressure, poured onto ice water (10 mL), and stirred for 10 min. The mixture was extracted with dichloromethane (20 mL x 3), then the combined organic phases were washed with saturated aqueous sodium chloride solution (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give 5-chloro-3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazole (100 mg) as a brown solid.

Step 3: Preparation of tert-butyl 4-(3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperazine-1-carboxylate



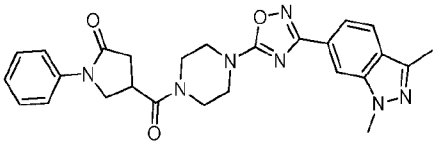
To a stirred solution of 5-chloro-3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazole (100 mg, 402.1 µµmol) in N-methyl-2-pyrrolidone (3 mL) was added tert-butyl piperazine-1-carboxylate (74 mg, 402 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (103 mg, 804 µmol, 140 µL). The mixture was stirred at 120 °C for 16 h. The reaction mixture was cooled, quenched by addition of water (5 mL) then the mixture was extracted with ethyl acetate (20 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. Purification by prep-TLC (silica, petroleum ether : ethyl acetate = 1:1) gave tert-butyl 4-(3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperazine-1-carboxylate (65 mg, 163 µmol, 41 %) as a brown solid.

Step 4: Preparation of 3-(1,3-dimethyl-1H-indazol-6-yl)-5-(piperazin-1-yl)-1,2,4-oxadiazole



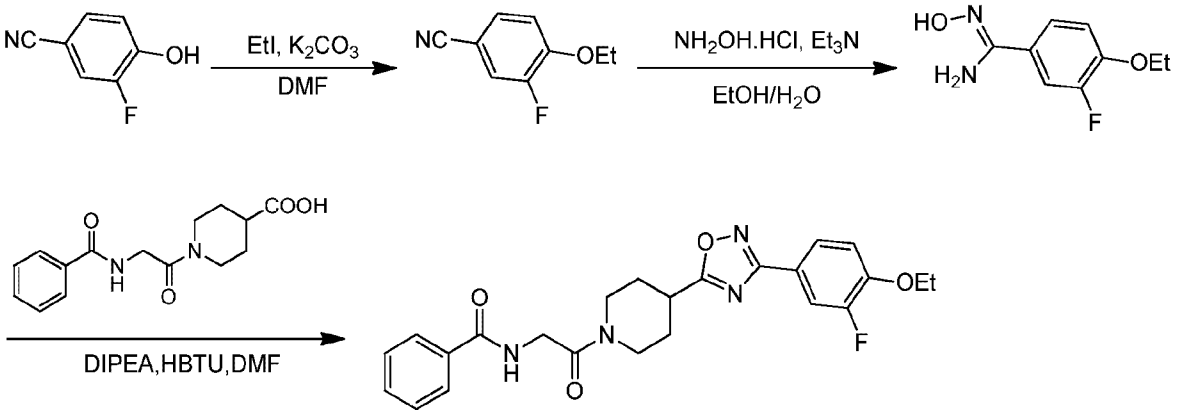
To a stirred solution of tert-butyl 4-[3-(1,3-dimethylindazol-6-yl)-1,2,4-oxadiazol-5-yl]piperazine-1-carboxylate (65 mg, 163 µmol) in ethyl acetate (1 mL) was added hydrochloric acid / ethyl acetate (4M, 5 mL). The mixture was stirred at 20 °C for 0.5 h. The reaction mixture was concentrated under reduced pressure to give 3-(1,3-dimethyl-1H-indazol-6-yl)-5-(piperazin-1-yl)-1,2,4-oxadiazole (40 mg, 134 µmol, 82 %) as a white solid. LCMS (ESI) m/z: $[M+H]^+$ = 299.1.

Step 5: Preparation of 4-(4-(3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperazine-1-carbonyl)-1-phenylpyrrolidin-2-one

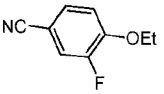


To a stirred solution of 3-(1,3-dimethyl-1H-indazol-6-yl)-5-(piperazin-1-yl)-1,2,4-oxadiazole (35 mg, 117 μmol) in N,N-dimethylformamide (1 mL) was added 5-oxo-1-phenylpyrrolidine-3-carboxylic acid (24 mg, 117 μmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (44 mg, 117 μmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (45 mg, 352 μmol, 61 μL). The mixture was stirred at 20 °C for 1 h. The reaction mixture was purified directly by prep-HPLC (column: Waters Xbridge 150x2.5mm 5μm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 30%-60%,12 min) to give 4-(4-(3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperazine-1-carbonyl)-1-phenylpyrrolidin-2-one (26 mg, 54.58 μmol, 47 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.83 - 7.69 (m, 2H), 7.63 (br d, *J*=7.5 Hz, 2H), 7.42 (br t, *J*=7.5 Hz, 2H), 7.22 (br d, *J*=7.9 Hz, 1H), 4.37 (br t, *J*=8.0 Hz, 1H), 4.09 (s, 3H), 4.03 - 3.96 (m, 1H), 3.93 - 3.72 (m, 8H), 3.63 (br d, *J*=9.7 Hz, 1H), 3.04 - 2.85 (m, 2H), 2.62 (s, 3H); LCMS (ESI) m/z: $[M+H]^+$ = 486.3.

Example 97: N-(2-(4-(3-(4-ethoxy-3-fluorophenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide



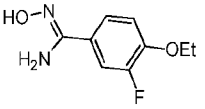
Step 1: Preparation of 4-ethoxy-3-fluorobenzonitrile



To a stirred solution of 3-fluoro-4-hydroxybenzonitrile (800 mg, 5.83 mmol) in N,N-dimethylformamide (10 mL) was added iodoethane (1.09 g, 7.00 mmol, 559 μL) and potassium carbonate (1.61 g, 11.7 mmol) at 0 °C. The reaction was warmed at 40 °C for 16 h. The reaction mixture was quenched with water (10 mL), then the mixture was extracted with ethyl acetate (40 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give crude 4-ethoxy-3-fluorobenzonitrile (750

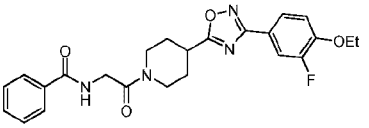
mg, 4.54 mmol, 78 %) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 - 7.30 (m, 2H), 6.98 (t, *J*=8.3 Hz, 1H), 4.15 (q, *J*=7.0 Hz, 2H), 1.47 (tt, *J*=1.2, 7.0 Hz, 3H).

Step 2: Preparation of (Z)-4-ethoxy-3-fluoro-N'-hydroxybenzimidamide



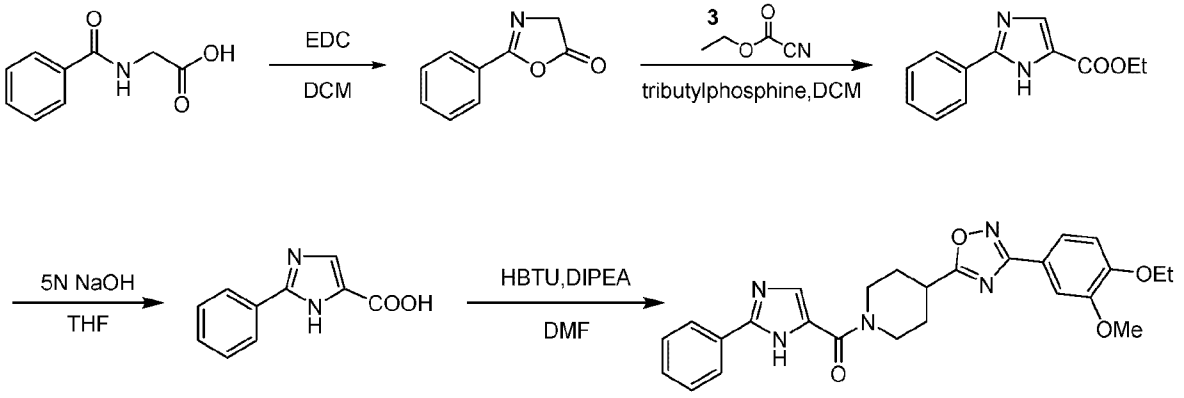
To a stirred solution of 4-ethoxy-3-fluorobenzonitrile (400 mg, 2.42 mmol) in ethanol (6 mL) was added hydroxylamine hydrochloride (336 mg, 4.84 mmol), triethylamine (490 mg, 4.84 mmol, 671 µL) and water (600 µL). The mixture was stirred at 80 °C for 2 h. The reaction mixture was cooled then concentrated under reduced pressure. The residue was triturated with water (5 mL), filtered and the filter cake was dried under reduced pressure to give (Z)-4-ethoxy-3-fluoro-N'-hydroxybenzimidamide (300 mg, 1.51 mmol, 63 %) as a white solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 9.57 (s, 1H), 7.47 - 7.39 (m, 2H), 7.12 (t, *J*=8.9 Hz, 1H), 5.80 (s, 2H), 4.13 - 4.06 (m, 2H), 1.34 - 1.29 (m, 3H).

Step 3: Preparation of N-(2-(4-(3-(4-ethoxy-3-fluorophenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide

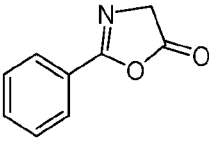


To a stirred solution of 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid (100 mg, 344 µmol) in N,N-dimethylformamide (2 mL) was added (Z)-4-ethoxy-3-fluoro-N'-hydroxybenzimidamide (68 mg, 344 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (130 mg, 344 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (133 mg, 1.03 mmol, 180 µL). The mixture was stirred at 20 °C for 1 h, then heated at 110 °C for 1 h. The reaction mixture was cooled then purified by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 40%-70%,12 min) to give N-(2-(4-(3-(4-ethoxy-3-fluorophenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide (43 mg, 96 µmol, 28 %) as a pink solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J*=7.0 Hz, 2H), 7.85 - 7.79 (m, 2H), 7.58 - 7.44 (m, 3H), 7.35 (br s, 1H), 7.05 (t, *J*=8.5 Hz, 1H), 4.51 (br d, *J*=13.6 Hz, 1H), 4.33 (d, *J*=3.8 Hz, 2H), 4.20 (q, *J*=7.0 Hz, 2H), 3.93 (br d, *J*=13.7 Hz, 1H), 3.41 - 3.29 (m, 2H), 3.23 - 3.13 (m, 1H), 2.32 - 2.20 (m, 2H), 2.08 - 1.93 (m, 2H), 1.51 (t, *J*=7.0 Hz, 3H); LCMS (ESI) m/z: $[M+H]^+$ = 453.1.

Example 98: [4-[3-(4-ethoxy-3-methoxy-phenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-(2-phenyl-1H-imidazol-5-yl)methanone

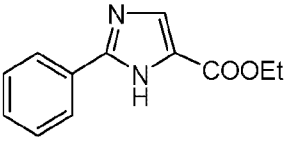


Step 1: Preparation of 2-phenyl-4H-oxazol-5-one



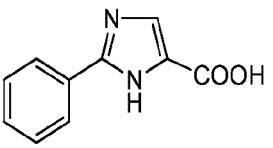
A mixture of 2-benzamidoacetic acid (1.0 g, 5.58 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (953 mg, 6.14 mmol, 1.08 mL) in dichloromethane (25 mL) was degassed and purged with nitrogen 3 times, and then the mixture was stirred at 20 °C for 6h under a nitrogen atmosphere. The mixture was concentrated in vacuum to get a crude product. The crude product, 2-phenyl-4H-oxazol-5-one (1.20 g) was used directly without further purification.

Step 2: Ethyl 2-phenyl-1H-imidazole-5-carboxylate



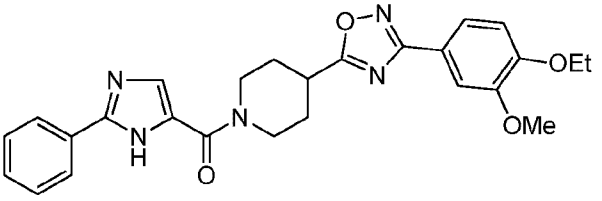
A mixture of 2-phenyl-4H-oxazol-5-one (1.0 g, 6.21 mmol), ethyl cyanoformate (676 mg, 6.83 mmol, 669 µL) and tributylphosphine (753 mg, 3.72 mmol, 918 µL) in dichloromethane (3 mL) was degassed and purged with nitrogen 3 times, and then the mixture was stirred at 20 °C for 6h under a nitrogen atmosphere. The reaction mixture was quenched by addition of water (3 mL), then extracted with dichloromethane (10 mL x 2). The combined organic phases were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue that was purified by chromatography (silica, petroleum ether / ethyl acetate = 2:1) to give ethyl 2-phenyl-1H-imidazole-5-carboxylate (480 mg, 2.22 mmol, 36 %) as a white solid.

Step 3: 2-phenyl-1H-imidazole-5-carboxylic acid



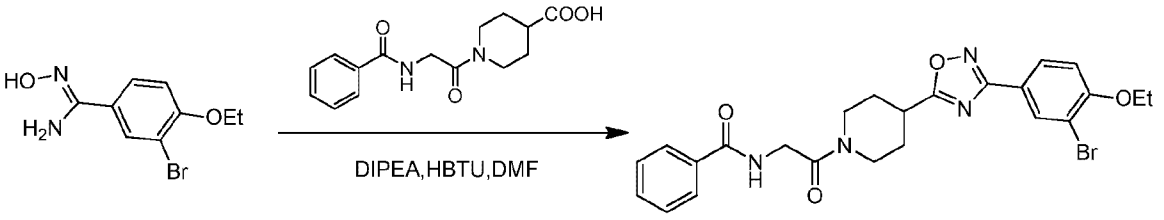
A mixture of ethyl 2-phenyl-1H-imidazole-5-carboxylate (300 mg, 1.39 mmol) and sodium hydroxide (166 mg, 4.17 mmol) in tetrahydrofuran (3 mL) and water (1.50 mL) was stirred at 20 °C for 2 h. The reaction mixture was extracted with dichloromethane (10 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (5 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give 2-phenyl-1H-imidazole-5-carboxylic acid (200 mg) that was used directly without further purification.

Step 4: [4-[3-(4-ethoxy-3-methoxy-phenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-(2-phenyl-1H-imidazol-5-yl)methanone

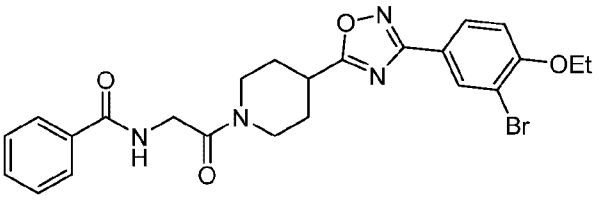


A mixture of 2-phenyl-1H-imidazole-5-carboxylic acid (62 mg, 330 µmol), 3-(4-ethoxy-3-methoxy-phenyl)-5-(4-piperidyl)-1,2,4-oxadiazole (100 mg, 330 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (125 mg, 330 µmol) and diisopropylethylamine (85 mg, 659 µmol, 115 µL) in N,N-dimethylformamide (3 mL) was degassed and purged with nitrogen 3 times, and then the mixture was stirred at 20 °C for 2 h under a nitrogen atmosphere. The mixture was purified by prep-HPLC (column: Waters Xbridge 150x25 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 40%-65%,12 min) to give [4-[3-(4-ethoxy-3-methoxy-phenyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-(2-phenyl-1H-imidazol-5-yl)methanone (25 mg, 105 µmol, 16 %) as a white solid. ^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.95 (br d, J=7.7 Hz, 2H), 7.65 (dd, J=1.8, 8.4 Hz, 1H), 7.54 (s, 2H), 7.47 - 7.32 (m, 3H), 6.92 (d, J=8.4 Hz, 1H), 5.56 - 5.27 (m, 1H), 4.77 - 4.46 (m, 1H), 4.14 (q, J=6.8 Hz, 2H), 3.99 - 3.88 (m, 3H), 3.66 - 3.09 (m, 3H), 2.24 (br d, J=9.7 Hz, 2H), 2.07 (br s, 1H), 1.84 (br s, 1H), 1.47 (t, J=6.8 Hz, 3H); LCMS(ESI) m/z: $[M+H]^+$ = 474.3.

Example 99: N-(2-(4-(3-(3-bromo-4-ethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide

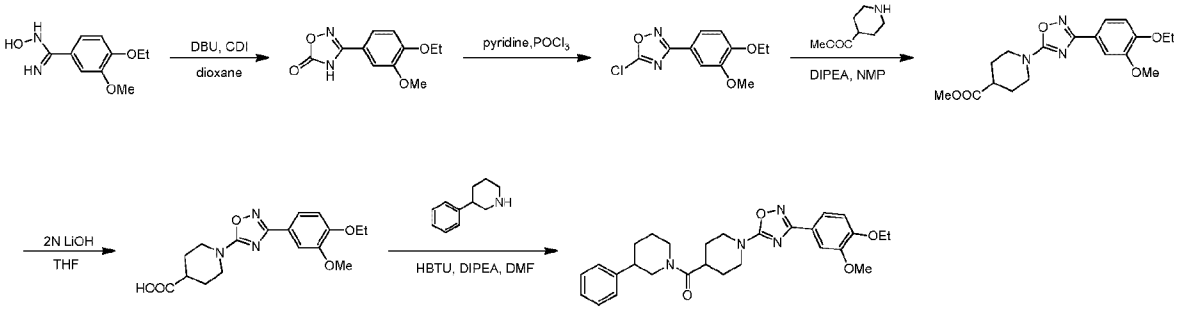


Step 1: Preparation of N-(2-(4-(3-(3-bromo-4-ethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide

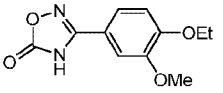


To a stirred solution of 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid (100 mg, 344 µmol) in N,N-dimethylformamide (2 mL) was added (Z)-3-bromo-4-ethoxy-N'-hydroxybenzimidamide (89 mg, 344 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (130 mg, 344 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (133 mg, 1.03 mmol, 180 µL). The mixture was stirred at 20 °C for 1 h, then heated at 110 °C for 1 h. The reaction mixture was purified directly by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 45%-75%,12 min) to give N-(2-(4-(3-(3-bromo-4-ethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide (43 mg, 83 µmol, 24 %) as a yellow solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 8.30 (d, *J*=2.1 Hz, 1H), 8.00 (dd, *J*=2.1, 8.6 Hz, 1H), 7.91 - 7.85 (m, 2H), 7.58 - 7.44 (m, 3H), 7.35 (br s, 1H), 6.98 (d, *J*=8.7 Hz, 1H), 4.50 (br d, *J*=14.1 Hz, 1H), 4.33 (d, *J*=3.9 Hz, 2H), 4.20 (q, *J*=6.9 Hz, 2H), 3.93 (br d, *J*=13.8 Hz, 1H), 3.41 - 3.29 (m, 2H), 3.18 (br t, *J*=10.6 Hz, 1H), 2.32 - 2.20 (m, 2H), 2.09 - 1.93 (m, 2H), 1.53 (t, *J*=7.0 Hz, 3H); LCMS (ESI) m/z: $[M+H]^+$ = 513.2.

Example 100: (1-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-4-yl)(3-phenylpiperidin-1-yl)methanone.



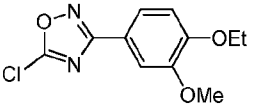
Step 1: Preparation of 3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5(4H)-one



To a stirred solution of 4-ethoxy-N-hydroxy-3-methoxybenzimidamide (1.0 g, 4.76 mmol) in dioxane (10 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (796 mg, 5.24 mmol, 788 µL) and 1,1'-carbonyldiimidazole (1.16 g, 7.14 mmol). The mixture was heated at 110 °C for 16 h. The reaction mixture was cooled, quenched with water (10 mL), and then extracted with dichloromethane (50 mL x 3). The combined organic phases were washed with 1M aqueous hydrochloric acid (5 mL x 2), then with saturated aqueous sodium chloride solution (10 mL), filtered and dried over anhydrous sodium sulfate. The organic layer was concentrated to give 3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5(4H)-one

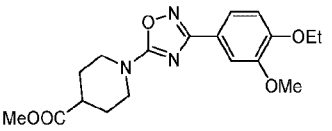
(1.02 g, 4.32 mmol, 91 %) as a brown solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 12.78 (br s, 1H), 7.38 - 7.28 (m, 2H), 7.08 (d, *J*=8.4 Hz, 1H), 4.05 (q, *J*=7.1 Hz, 2H), 3.77 (s, 3H), 1.30 (t, *J*=6.9 Hz, 3H).

Step 2: Preparation of 5-chloro-3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazole.



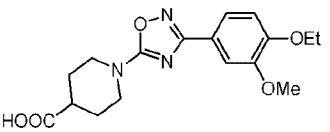
A flask 3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5(4H)-one (1.02 g, 4.32 mmol) was equipped with calcium chloride tube, then phosphoryl chloride (12 mL) and pyridine (170 mg, 2.16 mmol, 174 µL) were added dropwise and the mixture was heated at 110 °C for 16 h. The reaction mixture was cooled then concentrated under reduced pressure to remove phosphoryl chloride, and the residue added to ice water (20 mL) and stirred for 10 min. The mixture was extracted with dichloromethane (40 mL x 3), then the combined organic phases were washed with saturated aqueous sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give crude 5-chloro-3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazole (910 mg) as a yellow solid.

Step 3: Preparation of methyl 1-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-4-carboxylate.



To a stirred solution of 5-chloro-3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazole (600 mg, 2.36 mmol) in N-methyl-2-pyrrolidone (8 mL) was added methyl piperidine-4-carboxylate (337 mg, 2.36 mmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (610 mg, 4.72 mmol, 824 µL). The mixture was stirred at 120 °C for 16 h. The reaction mixture was quenched with water (10 mL), then the mixture was extracted with ethyl acetate (40 mL x 3), then the combined organic phases were washed with saturated aqueous sodium chloride solution (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give a residue that was purified by chromatography (silica, petroleum ether : ethyl acetate = 50 : 1 to 10:1) to give methyl 1-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-4-carboxylate (510 mg, 1.41 mmol, 60 %) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 7.47 (dd, *J*=1.9, 8.3 Hz, 1H), 7.38 (d, *J*=2.0 Hz, 1H), 7.06 (d, *J*=8.4 Hz, 1H), 4.08 (q, *J*=7.0 Hz, 2H), 4.00 (td, *J*=3.5, 13.2 Hz, 2H), 3.82 (s, 3H), 3.64 (s, 3H), 3.31 - 3.24 (m, 2H), 2.68 (tt, *J*=3.9, 10.9 Hz, 1H), 1.98 (br dd, *J*=3.2, 13.5 Hz, 2H), 1.70 - 1.58 (m, 2H), 1.36 (t, *J*=7.0 Hz, 3H).

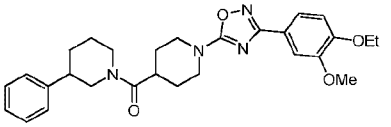
Step 4: Preparation of 1-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-4-carboxylic acid.



To a stirred solution of methyl 1-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-4-carboxylate (490 mg, 1.36 mmol) in tetrahydrofuran (10 mL) was added lithium hydroxide (2 M, 2.04 mL). The mixture was stirred at 20 °C for 16 h. The reaction mixture was concentrated under reduced

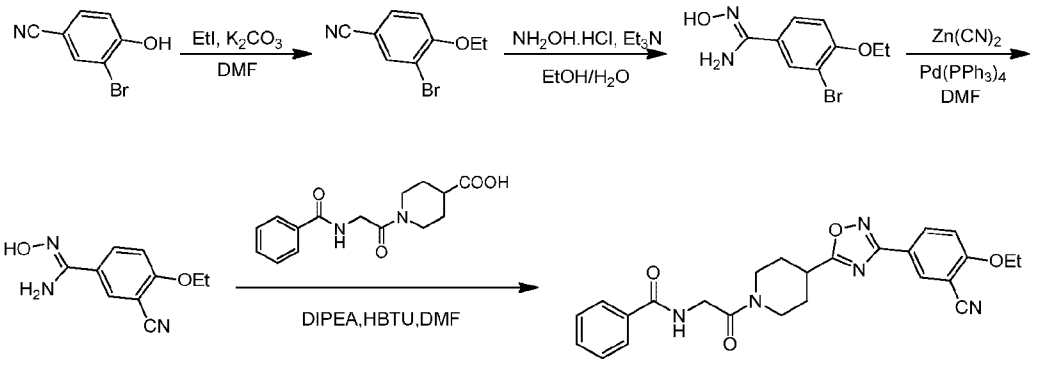
pressure to remove tetrahydrofuran, then the mixture was acidified with concentrated hydrochloric acid until pH 1. The mixture was extracted with dichloromethane (40 mL x 3). The organic layer was washed with saturated aqueous sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give crude 1-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-4-carboxylic acid (400 mg, 1.15 mmol, 85 %) as a white solid. ^{1}H NMR (400 MHz, Methanol-d4) δ 7.52 - 7.45 (m, 2H), 6.99 (d, *J*=8.4 Hz, 1H), 4.15 - 4.05 (m, 4H), 3.86 (s, 3H), 3.32 (br d, *J*=3.1 Hz, 1H), 3.28 - 3.25 (m, 1H), 2.61 (tt, *J*=3.8, 10.8 Hz, 1H), 2.07 - 1.98 (m, 2H), 1.80 - 1.68 (m, 2H), 1.41 (t, *J*=6.9 Hz, 3H).

Step 5: Preparation of (1-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-4-yl)(3-phenylpiperidin-1-yl)methanone.

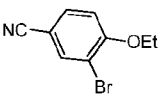


To a stirred solution of 1-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-4-carboxylic acid (100 mg, 288 µmol) in N,N-dimethylformamide (500 µL) was added 3-phenylpiperidine (46 mg, 288 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (109 mg, 288 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (111 mg, 863.66 µmol, 150 µL). The mixture was stirred at 20 °C for 2 h. The reaction mixture was then purified by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 35%-60%,12 min) to give (1-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-4-yl)(3-phenylpiperidin-1-yl)methanone (80 mg, 162 µmol, 56 %) as a white solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 7.45 - 7.40 (m, 1H), 7.36 - 7.16 (m, 6H), 7.02 (d, *J*=8.4 Hz, 1H), 4.49 - 4.36 (m, 1H), 4.09 - 3.92 (m, 5H), 3.78 (s, 3H), 3.28 - 2.92 (m, 4H), 2.70 - 2.50 (m, 2H), 1.89 (br d, *J*=11.7 Hz, 1H), 1.82 - 1.44 (m, 7H), 1.31 (t, *J*=6.9 Hz, 3H); LCMS (ESI) m/z: $[M+H]^+$ = 491.3.

Example 101: N-(2-(4-(3-(3-cyano-4-ethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.



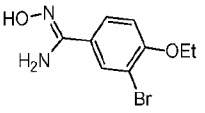
Step 1: Preparation of 3-bromo-4-ethoxybenzonitrile.



To a stirred solution of 3-bromo-4-hydroxybenzonitrile (1.0 g, 5.05 mmol) in N,N-dimethylformamide (10 mL) was added iodoethane (945 mg, 6.06 mmol, 484 µL) and potassium

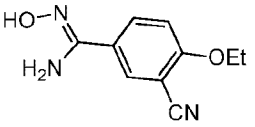
carbonate (1.40 g, 10.1 mmol) at 0 °C. The reaction was warmed at 40 °C for 16 h. The reaction mixture was quenched by addition of water (15 mL), then the mixture was extracted with ethyl acetate (40 mL x 3), then the combined organic phases were washed with saturated aqueous sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to give 3-bromo-4-ethoxybenzonitrile (1.20 g) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J*=2.0 Hz, 1H), 7.55 (dd, *J*=2.0, 8.6 Hz, 1H), 6.89 (d, *J*=8.6 Hz, 1H), 4.14 (q, *J*=7.0 Hz, 2H), 1.49 (t, *J*=6.9 Hz, 3H).

Step 2: Preparation of (Z)-3-bromo-4-ethoxy-N'-hydroxybenzimidamide.



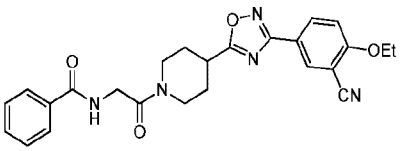
To a stirred solution of 3-bromo-4-ethoxybenzonitrile (1.15 g, 5.09 mmol) in ethanol (10 mL) was added hydroxylamine hydrochloride (706 mg, 10.2 mmol), triethylamine (1.03 g, 10.2 mmol, 1.41 mL) and water (1 mL). The mixture was heated at 80 °C for 1 h, then cooled and concentrated under reduced pressure to remove ethanol. The residue was triturated with water (5 mL) and filtered, and the filter cake was dried under reduced pressure to give (Z)-3-bromo-4-ethoxy-N'-hydroxybenzimidamide (1.31 g, 5.06 mmol, 99 %) as a white solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 9.55 (br s, 1H), 7.82 (d, *J*=2.2 Hz, 1H), 7.60 (dd, *J*=2.2, 8.6 Hz, 1H), 7.05 (d, *J*=8.8 Hz, 1H), 5.79 (s, 2H), 4.12 - 4.05 (m, 2H), 1.31 (t, *J*=7.1 Hz, 3H).

Step 3: Preparation of (Z)-3-cyano-4-ethoxy-N'-hydroxybenzimidamide.



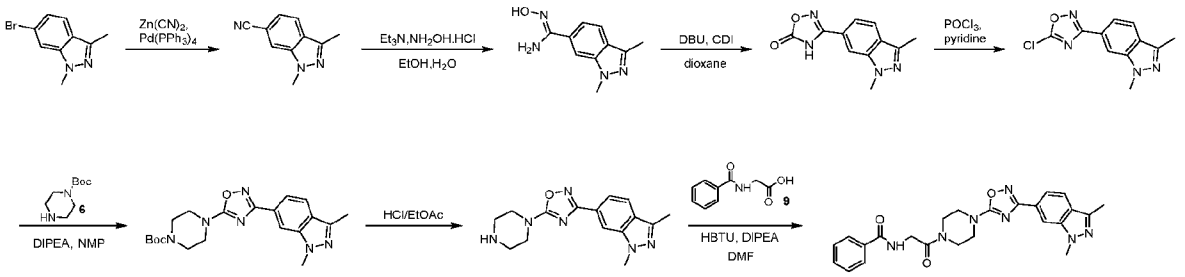
To a stirred solution of zinc cyanide (226 mg, 1.93 mmol, 122 µL) in N,N-dimethylformamide (10 mL) was added (Z)-3-bromo-4-ethoxy-N'-hydroxybenzimidamide (500 mg, 1.93 mmol) and tetrakis(triphenylphosphine)palladium(0) (222 mg, 193 µmol), then the mixture was degassed with nitrogen three times. The mixture was heated at 110 °C for 16 h under nitrogen then cooled to 20 °C, water (10 mL) was added, and the reaction mixture extracted with ethyl acetate (40 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (15 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to give a residue that was purified by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 13%-43%,12 min) to give (Z)-3-cyano-4-ethoxy-N'-hydroxybenzimidamide (60 mg, 292 µmol, 15 %) as a white solid.

Step 4: Preparation of N-(2-(4-(3-(3-cyano-4-ethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.

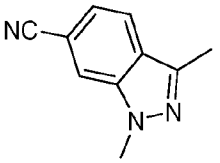


To a stirred solution of 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid (70 mg, 241 µmol) in N,N-dimethylformamide (1 mL) was added (Z)-3-cyano-4-ethoxy-N'-hydroxybenzimidamide (49 mg, 241 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (91 mg, 241 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (93 mg, 723 µmol, 126 µL). The mixture was stirred at 20 °C for 1 h, then heated at 110 °C for 1 h. The reaction mixture was cooled then purified by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 40%-65%,12 min) to give N-(2-(4-(3-(3-cyano-4-ethoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide (20 mg, 43 µmol, 18 %) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.55 (t, *J*=5.5 Hz, 1H), 8.26 - 8.17 (m, 2H), 7.84 (dd, *J*=1.2, 8.3 Hz, 2H), 7.57 - 7.34 (m, 4H), 4.26 (q, *J*=6.9 Hz, 3H), 4.14 (br d, *J*=5.5 Hz, 2H), 3.94 (br d, *J*=14.6 Hz, 1H), 3.48 - 3.40 (m, 1H), 3.29 - 3.22 (m, 1H), 2.90 (br t, *J*=11.4 Hz, 1H), 2.10 (br t, *J*=12.8 Hz, 2H), 1.87 - 1.72 (m, 1H), 1.68 - 1.55 (m, 1H), 1.37 (t, *J*=6.9 Hz, 3H); LCMS (ESI) m/z: $[M+H]^+$ = 460.2.

Example 102: N-(2-(4-(3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperazin-1-yl)-2-oxoethyl)benzamide

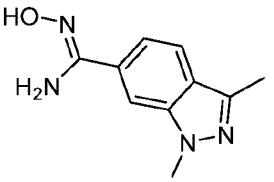


Step 1: Preparation of 1,3-dimethyl-1H-indazole-6-carbonitrile.



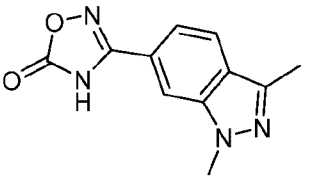
To a stirred solution of 6-bromo-1,3-dimethyl-1H-indazole (1.0 g, 4.44 mmol) in N,N-dimethylformamide (10 mL) was added zinc cyanide (521 mg, 4.44 mmol, 281 µL) and tetrakis(triphenylphosphine)palladium(0) (513 mg, 444 µmol), then the mixture was degassed with nitrogen three times. The mixture was stirred at 100 °C for 16 h under nitrogen, then cooled to 20 °C, water (10 mL) added, and the reaction mixture extracted with ethyl acetate (40 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (15 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to give a residue that was purified by chromatography (silica, petroleum ether : ethyl acetate = 50 : 1 to 10:1) to give 1,3-dimethyl-1H-indazole-6-carbonitrile (660 mg, 3.86 mmol, 87 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 - 7.66 (m, 2H), 7.30 (d, *J*=8.4 Hz, 1H), 4.03 (s, 3H), 2.57 (s, 3H).

Step 2: Preparation of (Z)-N'-hydroxy-1,3-dimethyl-1H-indazole-6-carboximidamide.



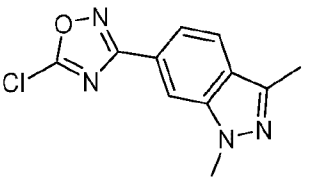
To a stirred solution of 1,3-dimethyl-1H-indazole-6-carbonitrile (660 mg, 3.86 mmol) in ethanol (8 mL) was added hydroxylamine hydrochloride (536 mg, 7.72 mmol), triethylamine (781 mg, 7.72 mmol, 1.07 mL) and water (800 µL). The mixture was heated at 80 °C for 2 h, then cooled and concentrated under reduced pressure. The residue was triturated with water (5 mL), filtered and the filter cake was dried under reduced pressure to give (Z)-N'-hydroxy-1,3-dimethyl-1H-indazole-6-carboximidamide (650 mg, 3.18 mmol, 82 %) as a white solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 9.72 (br. s., 1H), 7.86 (s, 1H), 7.65 (d, *J*=8.5 Hz, 1H), 7.49 (dd, *J*=1.1, 8.5 Hz, 1H), 5.91 (s, 2H), 3.97 (s, 3H), 2.47 (s, 3H).

Step 3: Preparation of 3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5(4H)-one.



To a stirred solution of (Z)-N'-hydroxy-1,3-dimethyl-1H-indazole-6-carboximidamide (510 mg, 2.50 mmol) in dioxane (8 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (418 mg, 2.75 mmol, 414 µL) and 1,1'-carbonyldiimidazole (608 mg, 3.75 mmol). The mixture was stirred at 110 °C for 16 h. The reaction mixture was cooled, quenched with water (10 mL), and then extracted with dichloromethane (50 mL x 3). The combined organic layers were washed with 1M hydrochloric acid (5 mL x 2), then washed with saturated aqueous sodium chloride solution (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give 3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5(4H)-one (430 mg, 1.87 mmol, 75 %) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 13.29 - 12.78 (m, 1H), 8.03 (s, 1H), 7.87 (d, *J*=8.4 Hz, 1H), 7.48 (dd, *J*=1.1, 8.4 Hz, 1H), 3.98 (s, 3H), 2.48 (br s, 3H).

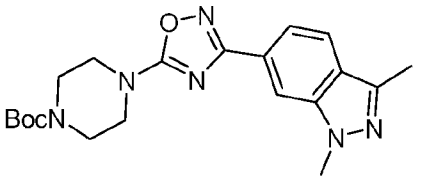
Step 4: Preparation of 5-chloro-3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazole.



A flask 3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5(4H)-one (180 mg, 781.86 µmol) was equipped with calcium chloride tube then pyridine (123 mg, 1.56 mmol, 126 µL) and phosphoryl chloride (5 mL) were added dropwise. The mixture was heated at 110 °C for 16 h, then cooled and concentrated under reduced pressure to remove phosphoryl chloride, and then added to ice water (20 mL). The mixture was extracted with dichloromethane (40 mL x 3), then the combined organic phases were washed with saturated aqueous sodium chloride solution (10 mL), dried over anhydrous sodium sulfate, filtered and

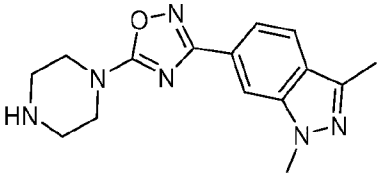
concentrated to give 5-chloro-3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazole (250 mg) as a brown solid.

Step 5: Preparation of tert-butyl 4-(3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperazine-1-carboxylate.



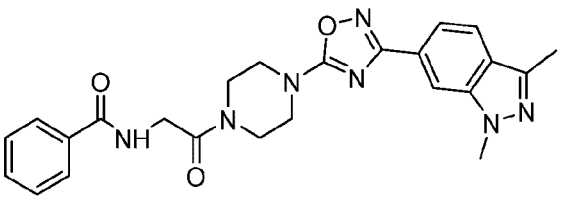
To a stirred solution of 5-chloro-3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazole (230 mg, 925 µmol) in N-methyl-2-pyrrolidone (3 mL) was added tert-butyl piperazine-1-carboxylate (172 mg, 925 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (239 mg, 1.85 mmol, 323 µL). The mixture was heated at 120 °C for 2 h. The reaction mixture was cooled, quenched by addition of water (5 mL), then the mixture was extracted with ethyl acetate (20 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. Purification by prep-TLC (silica, petroleum ether : ethyl acetate = 1:1) gave tert-butyl 4-(3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperazine-1-carboxylate (150 mg, 376 µmol, 41 %) as a pink solid.

Step 6: Preparation of 3-(1,3-dimethyl-1H-indazol-6-yl)-5-(piperazin-1-yl)-1,2,4-oxadiazole.



To a stirred solution of tert-butyl 4-(3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperazine-1-carboxylate (150 mg, 376 µmol) in ethyl acetate (1 mL) was added hydrochloric acid / ethyl acetate (4M, 5 mL). The mixture was stirred at 20 °C for 2 h. The reaction mixture was concentrated under reduced pressure to give 3-(1,3-dimethyl-1H-indazol-6-yl)-5-(piperazin-1-yl)-1,2,4-oxadiazole (110 mg, 369 µmol, 98 %) as a pink solid. LCMS (ESI) m/z: $[M+H]^+$ = 299.2.

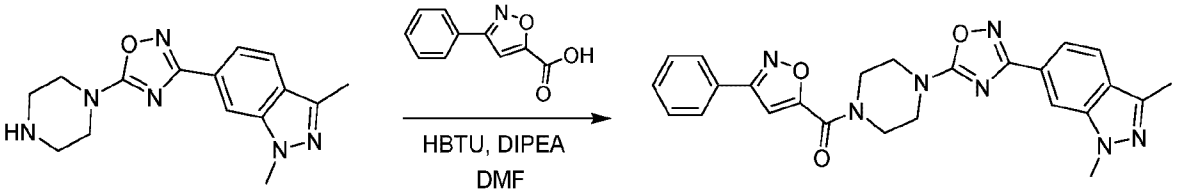
Step 7: Preparation of N-(2-(4-(3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperazin-1-yl)-2-oxoethyl)benzamide.



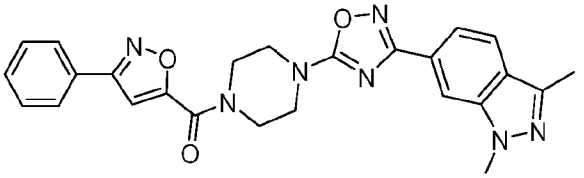
To a stirred solution of 3-(1,3-dimethyl-1H-indazol-6-yl)-5-(piperazin-1-yl)-1,2,4-oxadiazole (50 mg, 168 µmol) in N,N-dimethylformamide (1 mL) was added 2-benzamidoacetic acid (30 mg, 168 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (63 mg, 168 µmol) and N-

ethyl-N-(propan-2-yl)propan-2-amine (64 mg, 503 µmol, 87 µL). The mixture was stirred at 20 ℃ for 1 h. The reaction mixture was purified directly by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 30%-60%,12 min) to give N-(2-(4-(3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperazin-1-yl)-2-oxoethyl)benzamide (29 mg, 64 µmol, 38 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.84 (d, *J*=7.7 Hz, 2H), 7.76 - 7.66 (m, 2H), 7.55 - 7.41 (m, 3H), 7.27 - 7.25 (m, 1H), 4.33 (d, *J*=3.7 Hz, 2H), 4.05 (s, 3H), 3.89 - 3.75 (m, 6H), 3.66 (br d, *J*=5.1 Hz, 2H), 2.57 (s, 3H); LCMS (ESI) m/z: $[M+H]^+$ = 460.3.

Example 103: (4-(3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperazin-1-yl)(3-phenylisoxazol-5-yl)methanone.

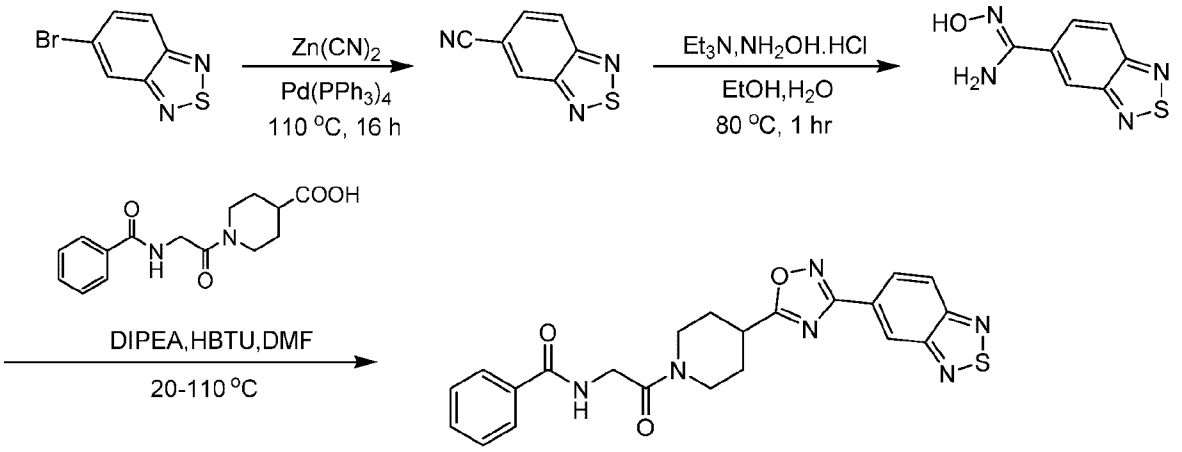


Step 1: Preparation of (4-(3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperazin-1-yl)(3-phenylisoxazol-5-yl)methanone.

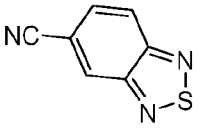


To a stirred solution of 3-(1,3-dimethyl-1H-indazol-6-yl)-5-(piperazin-1-yl)-1,2,4-oxadiazole (50 mg, 168 µmol) in N,N-dimethylformamide (1 mL) was added 3-phenylisoxazole-5-carboxylic acid (31 mg, 168 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (63 mg, 168 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (64 mg, 502.8 µmol, 87 µL). The mixture was stirred at 20 ℃ for 1 h. The reaction mixture was purified directly by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 35%-75%,12 min) to give (4-(3-(1,3-dimethyl-1H-indazol-6-yl)-1,2,4-oxadiazol-5-yl)piperazin-1-yl)(3-phenylisoxazol-5-yl)methanone (26 mg, 56.9 µmol, 34 %) as a white solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.83 (td, *J*=2.8, 4.1 Hz, 2H), 7.76 - 7.73 (m, 1H), 7.71 - 7.67 (m, 1H), 7.51 - 7.47 (m, 3H), 7.18 (s, 1H), 4.05 (s, 3H), 4.03 - 3.93 (m, 4H), 3.89 - 3.84 (m, 4H), 2.57 (s, 3H); LCMS (ESI) m/z: $[M+H]^+$ = 470.3.

Example 104: N-(2-(4-(3-(benzo[c][1,2,5]thiadiazol-5-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.

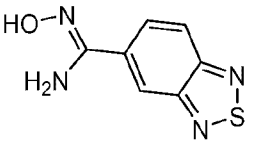


Step 1: Preparation of benzo[c][1,2,5]thiadiazole-5-carbonitrile.



To a stirred solution of 5-bromobenzo[c][1,2,5]thiadiazole (200 mg, 930 µmol) in N,N-dimethylformamide (2 mL) was added zinc cyanide (109 mg, 930 µmol, 59 µL) and tetrakis(triphenylphosphine)palladium(0) (107 mg, 93 µmol), the mixture was degassed with nitrogen three times. The mixture was heated at 110 °C for 16 h under nitrogen. After cooling to 20 °C, water (5 mL) was added to the reaction, and the mixture extracted with ethyl acetate (20 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to give crude product. The mixture was triturated with petroleum ether (20 mL) and dichloromethane (2 mL), then the mixture was filtered, and the filter cake dried in vacuo to give benzo[c][1,2,5]thiadiazole-5-carbonitrile (100 mg, 620 µmol, 67 %) as a red solid. LCMS (ESI) m/z: $[M+H]^+$ = 162.0.

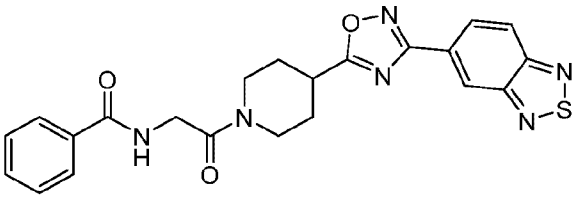
Step 2: Preparation of (Z)-N'-hydroxybenzo[c][1,2,5]thiadiazole-5-carboximidamide.



To a stirred solution of benzo[c][1,2,5]thiadiazole-5-carbonitrile (100 mg, 620 µmol) in ethanol (2 mL) was added hydroxylamine hydrochloride (86 mg, 1.24 mmol), triethylamine (125 mg, 1.24 mmol, 172 µL) and water (200 µL). The mixture was heated at 80 °C for 1 h. The reaction mixture was cooled and then concentrated under reduced pressure to remove ethanol. The residue was triturated with water (5 mL), filtered and the filter cake was dried under reduced pressure to give (Z)-N'-hydroxybenzo[c][1,2,5]thiadiazole-5-carboximidamide (70 mg, 360 µmol, 58 %) as a brown solid. ^{1}H NMR

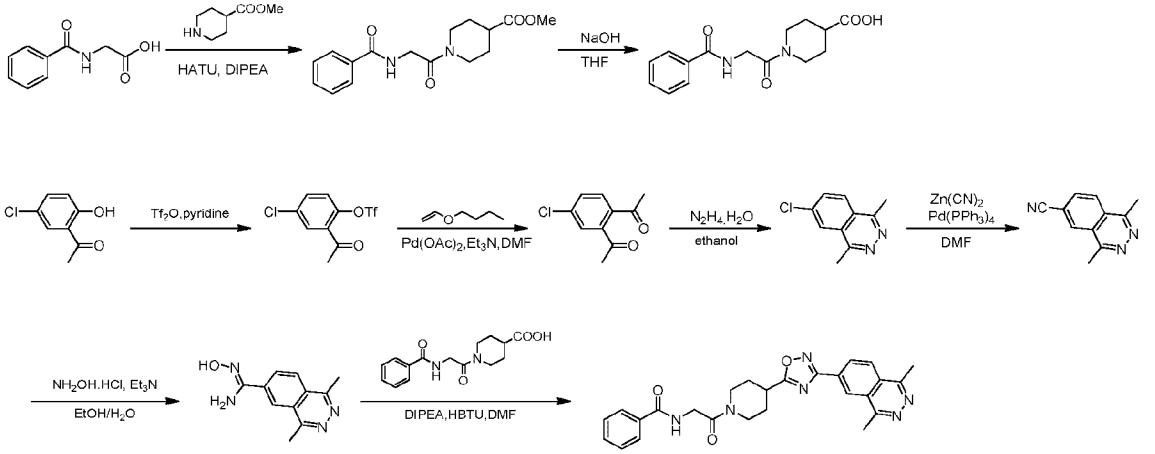
(400 MHz, DMSO-d6) δ 10.13 (s, 1H), 8.35 (d, *J*=0.9 Hz, 1H), 8.10 (dd, *J*=1.5, 9.3 Hz, 1H), 8.01 - 7.96 (m, 1H), 6.08 (s, 2H).

Step 3: Preparation of N-(2-(4-(3-(benzo[c][1,2,5]thiadiazol-5-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.

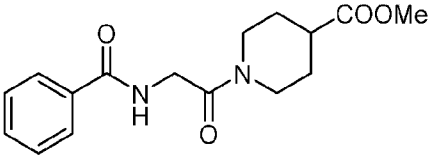


To a stirred solution of 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid (80 mg, 276 µmol) in N,N-dimethylformamide (2 mL) was added (Z)-N'-hydroxybenzo[c][1,2,5]thiadiazole-5-carboximidamide (53 mg, 276 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (104 mg, 276 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (106 mg, 827 µmol, 144 µL). The mixture was stirred at 20 °C for 1 h, then heated at 110 °C for 1 h. The reaction mixture was purified directly by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 45%-65%,12 min) to give N-(2-(4-(3-(benzo[c][1,2,5]thiadiazol-5-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide (30 mg, 67 µmol, 24 %) as a brown solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.66 (t, *J*=1.2 Hz, 1H), 8.55 (t, *J*=5.7 Hz, 1H), 8.28 - 8.22 (m, 2H), 7.87 - 7.83 (m, 2H), 7.54 - 7.42 (m, 3H), 4.31 (br d, *J*=13.0 Hz, 1H), 4.16 (dd, *J*=1.5, 5.7 Hz, 2H), 3.98 (br d, *J*=13.5 Hz, 1H), 3.54 - 3.51 (m, 1H), 3.29 (br t, *J*=11.5 Hz, 1H), 2.93 (br t, *J*=11.2 Hz, 1H), 2.16 (br t, *J*=13.2 Hz, 2H), 1.90 - 1.78 (m, 1H), 1.73 - 1.62 (m, 1H); LCMS (ESI) m/z: $[M+H]^+$ = 449.2.

Example 105: N-(2-(4-(3-(1,4-dimethylphthalazin-6-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.

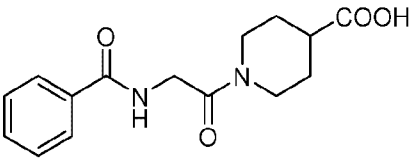


Step 1: Preparation of methyl 1-(2-benzamidoacetyl)piperidine-4-carboxylate.



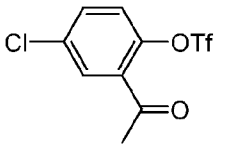
To a stirred solution of 2-benzamidoacetic acid (5.0 g, 27.9 mmol) in N,N-dimethylformamide (50 mL) was added methyl piperidine-4-carboxylate (4.40 g, 30.7 mmol), 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (10.6 g, 27.9 mmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (10.8 g, 83.7 mmol, 14.6 mL). The mixture was stirred at 20 °C for 2 h, then quenched by addition of water (50 mL). The mixture was extracted with ethyl acetate (100 mL x 3), then the combined organic phases were washed with saturated aqueous sodium chloride solution (40 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give a residue that was purified by chromatography (silica, petroleum ether : ethyl acetate = 5:1 to 1:1) to give methyl 1-(2-benzamidoacetyl)piperidine-4-carboxylate (9.17 g) as a yellow solid. ^{1}H NMR (400 MHz, Methanol-d4) δ 7.88 - 7.83 (m, 2H), 7.55 - 7.49 (m, 1H), 7.48 - 7.41 (m, 2H), 4.35 - 4.28 (m, 1H), 4.24 (d, *J*=5.3 Hz, 2H), 3.88 (d, *J*=14.1 Hz, 1H), 3.66 (s, 3H), 3.20 (d, *J*=2.2 Hz, 1H), 2.92 - 2.84 (m, 1H), 2.65 (tt, *J*=4.0, 10.8 Hz, 1H), 1.99 - 1.87 (m, 2H), 1.74 - 1.64 (m, 1H), 1.62 - 1.51 (m, 1H).

Step 2: Preparation of 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid.



To a stirred solution of methyl 1-(2-benzamidoacetyl)piperidine-4-carboxylate (9.17 g, 30.1 mmol) in tetrahydrofuran (90 mL) was added sodium hydroxide (2 M, 30.1 mL). The mixture was stirred at 20 °C for 2 h. The reaction mixture was concentrated under reduced pressure then acidified with concentrated hydrochloric acid until pH 1. The mixture was extracted with dichloromethane (80 mL x 4). The organic phases were combined and then washed with saturated aqueous sodium chloride solution (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give a crude residue (8.85 g). A portion of crude product (2.5 g) was purified by prep-HPLC (column: Daiso 250*50mm, 10μm; mobile phase: [water (0.1%TFA)-acetonitrile]; B%: 1%-30%, 20 min) to provide 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid (0.95 g). The remaining crude product was used directly without purification. ^{1}H NMR (400 MHz, Methanol-d4) δ 7.87 - 7.83 (m, 2H), 7.55 - 7.50 (m, 1H), 7.48 - 7.42 (m, 2H), 4.36 (td, *J*=3.2, 13.2 Hz, 1H), 4.25 (d, *J*=3.3 Hz, 2H), 3.94 - 3.86 (m, 1H), 3.22 - 3.14 (m, 1H), 2.89 - 2.80 (m, 1H), 2.46 (tt, *J*=3.9, 11.0 Hz, 1H), 2.00 - 1.87 (m, 2H), 1.74 - 1.52 (m, 2H).

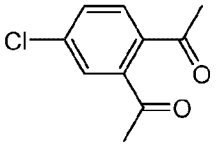
Step 3: Preparation of 2-acetyl-4-chlorophenyl trifluoromethanesulfonate.



Triflic anhydride (9.92 g, 35.2 mmol, 5.80 mL) was added dropwise at 0° C to a stirred solution of 1-(5-chloro-2-hydroxy-phenyl)ethanone (5.0 g, 29.3 mmol) in pyridine (50 mL) The reaction was warmed slowly to 15 °C and stirred for 15 h. The reaction solution was diluted with dichloromethane (100 mL), then poured into 1N aqueous hydrochloric acid (100 mL) at 0 °C and the phases separated. The organic phase was washed with 1N hydrochloric acid (50 mL x 2), saturated aqueous sodium chloride solution

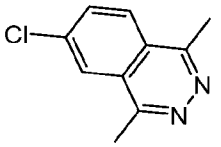
(50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to give a crude residue. Purification by chromatography (silica, petroleum ether : ethyl acetate from 100/1 to 30/1) gave 2-acetyl-4-chlorophenyl trifluoromethanesulfonate (7.50 g, 24.8 mmol, 85 %) as a yellow liquid.

Step 4: Preparation of 1,1'-(4-chloro-1,2-phenylene)diethanone.



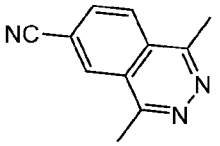
To a stirred solution of 2-acetyl-4-chlorophenyl trifluoromethanesulfonate (3.0 g, 9.91 mmol) in N,N-dimethylformamide (30 mL) was added 1-vinyloxybutane (4.96 g, 49.6 mmol, 6.36 mL), palladium(II) acetate(111 mg, 495.5 µmol), 3-diphenylphosphanylpropyl(diphenyl)phosphane (245 mg, 594.6 µmol) and TEA (1.20 g, 11.9 mmol, 1.65 mL), then the mixture was degassed with nitrogen three times. The mixture was heated at 80 °C for 16 h under nitrogen. After cooling to 20 °C, 2M hydrochloric acid (20 mL) was added and the solution stirred at 20 °C for 2 h. Water (30 mL) was added and the mixture was extracted with ethyl acetate (80 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to give a crude residue that was purified by chromatography (silica, petroleum ether : ethyl acetate = 50 : 1 to 10:1) to give 1,1'-(4-chloro-1,2-phenylene)diethanone (800 mg, 4.07 mmol, 41 %) as a red oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 - 7.54 (m, 1H), 7.51 - 7.47 (m, 1H), 7.43 (t, *J*=1.9 Hz, 1H), 2.52 (d, *J*=2.0 Hz, 3H), 2.50 (d, *J*=2.0 Hz, 3H).

Step 5: Preparation of 6-chloro-1,4-dimethylphthalazine.



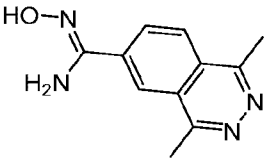
1,1'-(4-chloro-1,2-phenylene)diethanone (800 mg, 4.07 mmol) in ethanol (15 mL) was added to hydrazine hydrate (224 mg, 4.48 mmol, 217 µL) in ethanol (15 mL) at 0 °C over a period of 5 min under argon. The mixture was stirred at 20 °C for 18 h. The reaction mixture was concentrated under reduced pressure to ~15 mL, then extracted with dichloromethane (50 mL x 3). The combined organic phases were washed water (20 mL x 2), then the separated organic layer was washed saturated aqueous sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give 6-chloro-1,4-dimethylphthalazine (662 mg, 3.44 mmol, 84 %) as a red solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 - 7.93 (m, 2H), 7.75 (dd, *J*=2.1, 8.8 Hz, 1H), 2.88 (d, *J*=5.1 Hz, 6H).

Step 6: Preparation of 1,4-dimethylphthalazine-6-carbonitrile.



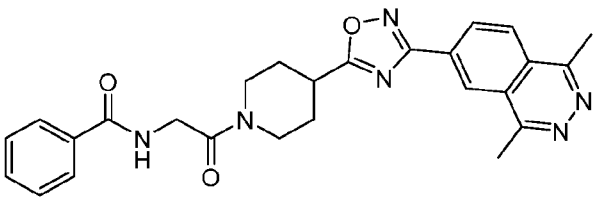
To a stirred solution of 6-chloro-1,4-dimethylphthalazine (640 mg, 3.32 mmol) in N,N-dimethylformamide (10 mL) was added zinc cyanide (390 mg, 3.32 mmol, 210 µL) and tetrakis(triphenylphosphine)palladium(0) (383 mg, 332 µmol) under nitrogen. The mixture was heated at 110 °C for 16 h, then cooled to 20 °C. Water (15 mL) was added then the reaction mixture was extracted with ethyl acetate (40 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to give a crude product. Trituration with petroleum ether (30 mL) and dichloromethane (5 mL) followed by filtration and drying the filter cake in vacuo gave 1,4-dimethylphthalazine-6-carbonitrile (400 mg, 2.18 mmol, 66 %) as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1H), 8.21 (d, *J*=8.5 Hz, 1H), 8.09 (dd, *J*=1.4, 8.5 Hz, 1H), 3.04 (s, 6H).

Step 7: Preparation of (Z)-N'-hydroxy-1,4-dimethylphthalazine-6-carboximidamide.



To a stirred solution of 1,4-dimethylphthalazine-6-carbonitrile (380 mg, 2.07 mmol) in ethanol (1 mL) was added hydroxylamine hydrochloride (288 mg, 4.15 mmol), triethylamine (419 mg, 4.15 mmol, 575 µL) and water (100 µL). The mixture was heated at 80 °C for 1 h. The reaction mixture was cooled then concentrated under reduced pressure. The residue was triturated with water (5 mL), filtered and the filter cake was dried under reduced pressure to give (Z)-N'-hydroxy-1,4-dimethylphthalazine-6-carboximidamide (330 mg, 1.53 mmol, 74 %) as a brown solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 10.06 (s, 1H), 8.38 (d, *J*=1.3 Hz, 1H), 8.28 (dd, *J*=1.7, 8.7 Hz, 1H), 8.12 (d, *J*=8.8 Hz, 1H), 6.19 (s, 2H), 2.85 (d, *J*=17.0 Hz, 6H).

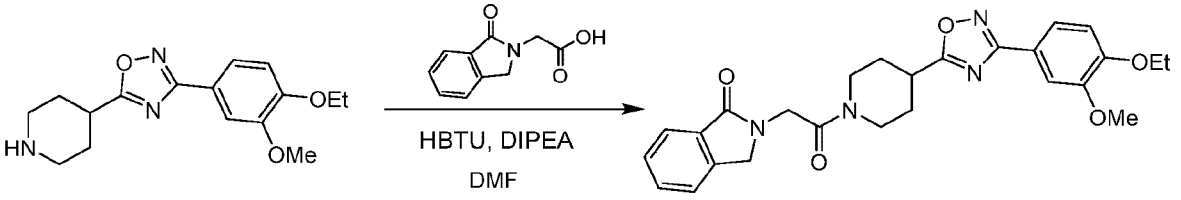
Step 8: Preparation of N-(2-(4-(3-(1,4-dimethylphthalazin-6-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.



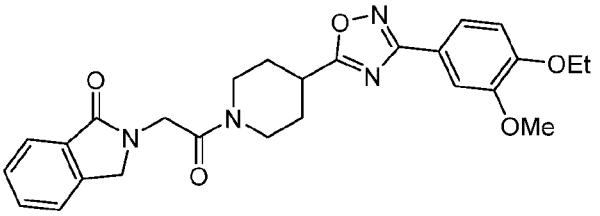
To a stirred solution of 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid (100 mg, 344 µmol) in N,N-dimethylformamide (2 mL) was added N'-hydroxy-1,4-dimethyl-phthalazine-6-carboxamidine (74 mg, 344 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (130 mg, 344 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (133 mg, 1.03 mmol, 180 µL). The mixture was stirred

at 20 °C for 1 h, then heated at 110 °C for 1 h. The reaction mixture was cooled, then purified by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 25%-55%,12 min) to give N-(2-(4-(3-(1,4-dimethylphthalazin-6-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide (37 mg, 77 µmol, 22 %) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.71 (d, *J*=1.5 Hz, 1H), 8.59 (t, *J*=5.6 Hz, 1H), 8.54 (dd, *J*=1.5, 8.6 Hz, 1H), 8.39 (d, *J*=8.6 Hz, 1H), 7.90 - 7.86 (m, 2H), 7.57 - 7.45 (m, 3H), 4.37 (br d, *J*=13.2 Hz, 1H), 4.25 - 4.13 (m, 2H), 4.02 (br d, *J*=13.5 Hz, 1H), 3.55 (tt, *J*=3.8, 11.1 Hz, 1H), 3.32 - 3.27 (m, 1H), 2.96 (s, 3H), 2.98 - 2.91 (m, 1H), 2.93 (s, 3H), 2.20 (br t, *J*=13.7 Hz, 2H), 1.95 - 1.82 (m, 1H), 1.77 - 1.65 (m, 1H); LCMS (ESI) m/z: $[M+H]^+$ = 471.3.

Example 106: 2-(2-(4-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)isoindolin-1-one.

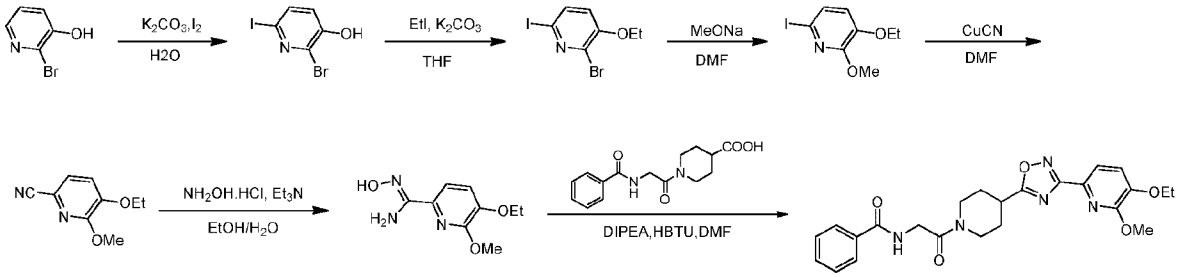


Step 1: Preparation of 2-(2-(4-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)isoindolin-1-one.

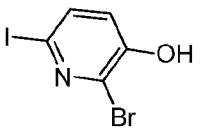


To a stirred solution of 3-(4-ethoxy-3-methoxyphenyl)-5-(piperidin-4-yl)-1,2,4-oxadiazole (50 mg, 165 µmol) in N,N-dimethylformamide (1 mL) was added 2-(1-oxoisoindolin-2-yl)acetic acid (31 mg, 165 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (62 mg, 165 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (63 mg, 494 µmol, 86 µL). The mixture was stirred at 20 °C for 1 h, then the reaction mixture was cooled then purified by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 30%-60%,12 min) to give 2-(2-(4-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)isoindolin-1-one (41 mg, 86 µmol, 52 %) as a gray solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.88 (d, *J*=8.2 Hz, 1H), 7.66 (dd, *J*=1.9, 8.3 Hz, 1H), 7.59 - 7.54 (m, 2H), 7.48 (t, *J*=6.4 Hz, 2H), 6.95 (d, *J*=8.4 Hz, 1H), 4.59 (d, *J*=3.4 Hz, 2H), 4.53 - 4.40 (m, 3H), 4.18 (q, *J*=7.0 Hz, 2H), 4.08 (br d, *J*=13.7 Hz, 1H), 3.96 (s, 3H), 3.43 - 3.24 (m, 2H), 3.11 - 3.02 (m, 1H), 2.28 - 2.15 (m, 2H), 2.05 - 1.90 (m, 2H), 1.51 (t, *J*=7.0 Hz, 3H); LCMS (ESI) m/z: $[M+H]^+$ = 477.3.

Example 107: N-[2-[4-[3-(5-ethoxy-6-methoxy-2-pyridyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-2-oxo-ethyl]benzamide.

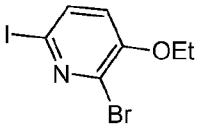


Step 1: 2-bromo-6-iodo-pyridin-3-ol.



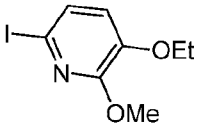
A mixture of 2-bromopyridin-3-ol (5.0 g, 28.7 mmol), iodine (8.02 g, 31.6 mmol, 6.37 mL), and potassium carbonate (7.94 g, 57.5 mmol) in water (66 mL) was degassed and purged with nitrogen 3 times, and then the mixture was stirred at 20 °C for 16 h under a nitrogen atmosphere. Excess iodine was quenched by addition of solid sodium bisulfite. The pH of the solution was adjusted to 5-6 using glacial acetic acid, and the solid formed was collected by filtration and dried in vacuum to give 2-bromo-6-iodo-pyridin-3-ol (10.0 g) that was used directly without further purification.

Step 2: 2-bromo-3-ethoxy-6-iodo-pyridine.



To a stirred solution of 2-bromo-6-iodo-pyridin-3-ol (10.0 g, 33.4 mmol) in tetrahydrofuran (200 mL) was added potassium carbonate (6.91 g, 50.0 mmol) and the mixture was stirred for 10 min at 0 °C in an ice bath. Iodoethane (6.24 g, 40.0 mmol, 3.20 mL) was added dropwise, then the reaction mixture was warmed to 40 °C. After 16 h, the reaction mixture was quenched by addition of water (10 mL), and then extracted with ethyl acetate (10 mL x 2). The combined organic phases were washed with saturated aqueous sodium chloride solution (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give 2-bromo-3-ethoxy-6-iodo-pyridine (7.50 g, 22.9 mmol, 69 %) that was used directly without further purification.

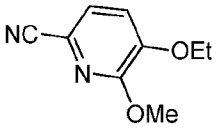
Step 3: 3-ethoxy-6-iodo-2-methoxy-pyridine.



A mixture of 2-bromo-3-ethoxy-6-iodo-pyridine (7.0 g, 21.4 mmol) and sodium methoxide (1.73 g, 32.0 mmol) in N,N-dimethylformamide (3 mL) was degassed and purged with nitrogen 3 times, and then the mixture was heated at 100 °C for 16 h under a nitrogen atmosphere. The reaction mixture was

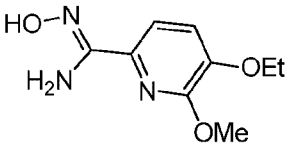
quenched by addition of water (20 mL), then extracted with ethyl acetate (20 mL x 3). The organic layer phases were combined and then washed with saturated aqueous sodium chloride solution (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give 3-ethoxy-6-iodo-2-methoxy-pyridine (5.0 g, 17.9 mmol). This was used directly without further purification.

Step 4: 5-ethoxy-6-methoxy-pyridine-2-carbonitrile.



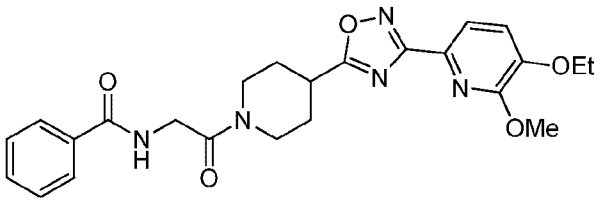
A mixture of 3-ethoxy-6-iodo-2-methoxy-pyridine (2.50 g, 8.96 mmol) and coper(I) cyanide (962 mg, 10.75 mmol, 2.35 mL) in N,N-dimethylformamide (10 mL) was degassed and purged with nitrogen 3 times, and then the mixture was heated at 100 °C for 16 h under a nitrogen atmosphere. The reaction mixture was quenched by addition of water (20 mL), then extracted with ethyl acetate (20 mL x 3). The organic extracts were combined, washed with saturated aqueous sodium chloride solution (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give 5-ethoxy-6-methoxy-pyridine-2-carbonitrile (1.40 g). This was used directly without further purification.

Step 5: 5-ethoxy-6-methoxy-pyridine-2-carbonitrile.



A mixture of 5-ethoxy-6-methoxy-pyridine-2-carbonitrile (1.0 g, 5.61 mmol), hydroxylamine hydrochloride (857 mg, 12.34 mmol) and triethylamine (1.25 g, 12.34 mmol, 1.71 mL) in ethanol (10 mL) was heated at 75 °C for 16 h under a nitrogen atmosphere. The reaction mixture was cooled, diluted with water (10 mL), and filtered. The filter cake was dried in vacuo to give 5-ethoxy-N'-hydroxy-6-methoxy-pyridine-2-carboxamidine (950 mg, 4.50 mmol, 80 %) as a yellow solid. ^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.40 (d, J=8.2 Hz, 1H), 6.99 (d, J=8.2 Hz, 1H), 5.45 (br s, 2H), 4.05 (q, J=6.9 Hz, 2H), 3.98 (s, 3H), 1.41 (t, J=7.0 Hz, 3H).

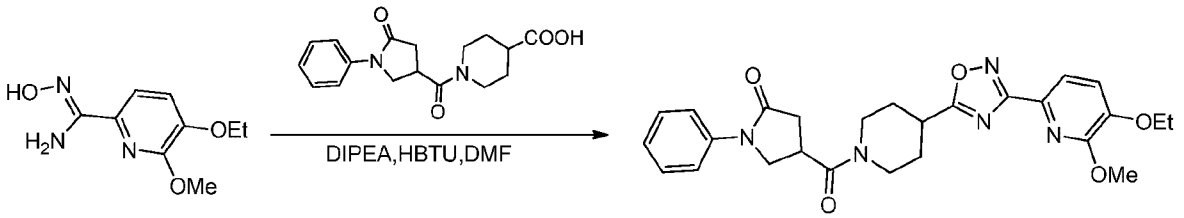
Step 6: N-[2-[4-[3-(5-ethoxy-6-methoxy-2-pyridyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-2-oxo-ethyl]benzamide.



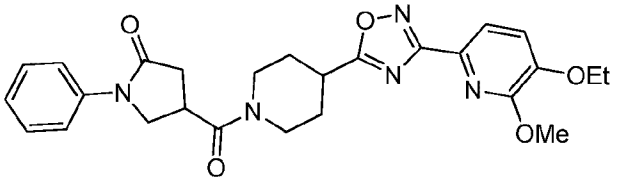
To a stirred solution of 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid (100 mg, 344 µmol) in N,N-dimethylformamide (2 mL) was added 5-ethoxy-N'-hydroxy-6-methoxy-pyridine-2-carboxamidine (72 mg, 344 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (156 mg, 413 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (133 mg, 1.03 mmol, 180 µL). The mixture was stirred

at 20 °C for 1 h, then heated at 110 °C for 1 h. The crude product was purified by prep-HPLC (column: Waters Xbridge 150x25 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 30%-60%,12 min) to give N-[2-[4-[3-(5-ethoxy-6-methoxy-2-pyridyl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-2-oxo-ethyl]benzamide (37 mg, 79.9 µmol, 23 %) as a yellow solid. ^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.91 - 7.85 (m, 2H), 7.70 (d, J=8.0 Hz, 1H), 7.57 - 7.52 (m, 1H), 7.51 - 7.44 (m, 2H), 7.36 (br s, 1H), 7.13 (d, J=8.2 Hz, 1H), 4.57 - 4.48 (m, 1H), 4.32 (d, J=3.9 Hz, 2H), 4.23 - 4.12 (m, 5H), 4.06 - 3.90 (m, 1H), 3.42 - 3.32 (m, 2H), 3.20 - 3.11 (m, 1H), 2.32 - 2.20 (m, 2H), 2.08 - 1.95 (m, 2H), 1.54 (t, J=7.0 Hz, 3H); LCMS(ESI) m/z: $[M+H]^+$ = 466.3.

Example 108: 4-[4-[3-(5-ethoxy-6-methoxy-2-pyridyl)-1,2,4-oxadiazol-5-yl]piperidine-1-carbonyl]-1-phenyl-pyrrolidin-2-one.

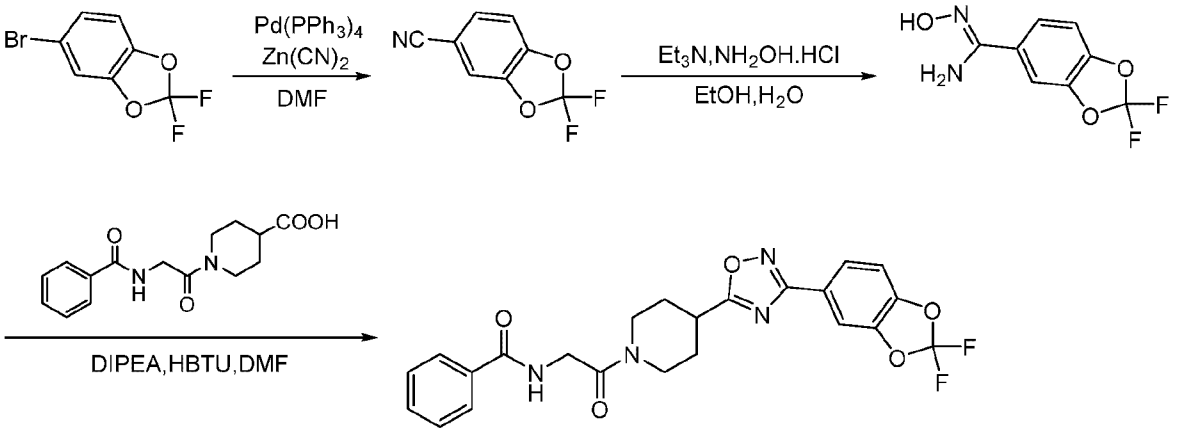


Step 1: 4-[4-[3-(5-ethoxy-6-methoxy-2-pyridyl)-1,2,4-oxadiazol-5-yl]piperidine-1-carbonyl]-1-phenyl-pyrrolidin-2-one.

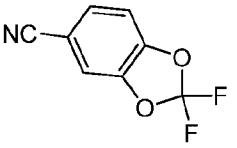


To a stirred solution of 5-ethoxy-N'-hydroxy-6-methoxy-pyridine-2-carboxamidine (66 mg, 316 µmol) in N,N-dimethylformamide (2 mL) was added 1-(5-oxo-1-phenyl-pyrrolidine-3-carbonyl)piperidine-4-carboxylic acid (100 mg, 316 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (143 mg, 379 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (122 mg, 948 µmol, 165 µL). The mixture was stirred at 20 °C for 1 h, then heated at 110 °C for 1 h. The mixture was cooled and the crude product was purified by prep-HPLC (column: Waters Xbridge 150x25 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 30%-70%,12 min) to give 4-[4-[3-(5-ethoxy-6-methoxy-2-pyridyl)-1,2,4-oxadiazol-5-yl]piperidine-1-carbonyl]-1-phenyl-pyrrolidin-2-one (47 mg, 96 µmol, 3 %) as a yellow solid. ^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.71 (dd, J=4.6, 8.0 Hz, 1H), 7.62 (dd, J=1.1, 8.7 Hz, 2H), 7.43 - 7.38 (m, 2H), 7.22 - 7.17 (m, 1H), 7.13 (d, J=7.8 Hz, 1H), 4.63 - 4.48 (m, 1H), 4.34 (t, J=7.9 Hz, 1H), 4.22 - 4.15 (m, 5H), 4.03 - 3.93 (m, 2H), 3.60 (m, 1H), 3.46 - 3.33 (m, 2H), 3.15 - 2.95 (m, 2H), 2.91 - 2.82 (m, 1H), 2.27 (m, 2H), 2.08 - 1.94 (m, 2H), 1.54 (t, J=7.0 Hz, 3H); LCMS(ESI) m/z: $[M+H]^+$ = 492.3.

Example 109: N-[2-[4-[3-(2,2-difluoro-1,3-benzodioxol-5-yl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-2-oxo-ethyl]benzamide

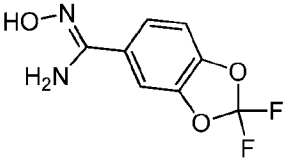


Step 1: 2,2-difluoro-1,3-benzodioxole-5-carbonitrile.



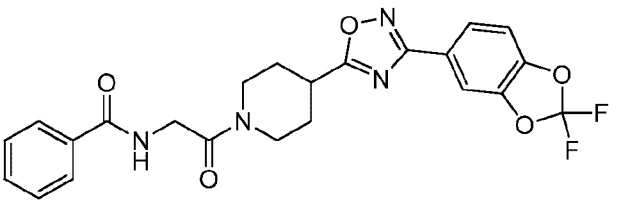
A mixture of 5-bromo-2,2-difluoro-1,3-benzodioxole (500 mg, 2.11 mmol), zinc cyanide (247 mg, 2.11 mmol, 133 µL) and tetrakis(triphenylphosphine)palladium(0) (243 mg, 211 µmol) in N,N-dimethylformamide (4 mL) was degassed and purged with nitrogen 3 times, and then the mixture was heated at 100 ℃ for 16 h under a nitrogen atmosphere. The reaction mixture was cooled, diluted with water (5 mL), and extracted with ethyl acetate (10 mL x 2). The combined organic phases were washed with saturated aqueous sodium chloride solution (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give 2,2-difluoro-1,3-benzodioxole-5-carbonitrile (300 mg, 1.64 mmol, 78 %) as a solid. ^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.38 (dd, J=1.5, 8.3 Hz, 1H), 7.27 (d, J=1.5 Hz, 1H), 7.08 (d, J=8.3 Hz, 1H).

Step 2: 2,2-difluoro-N'-hydroxy-1,3-benzodioxole-5-carboxamidine.



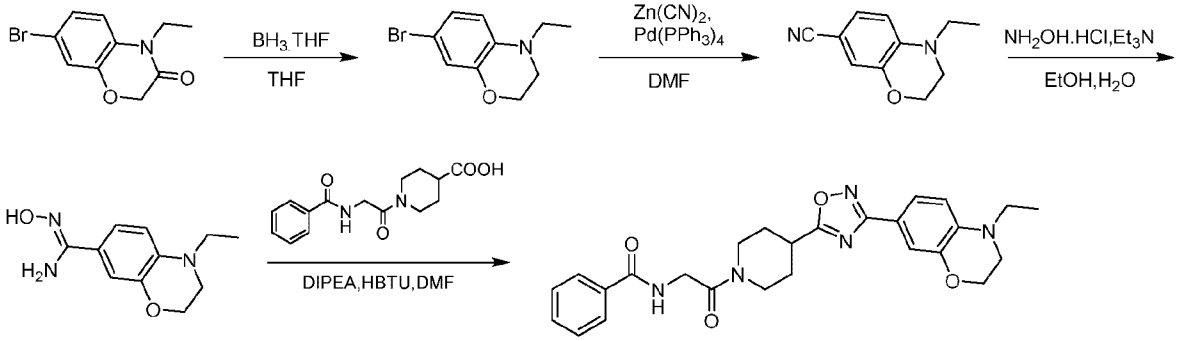
A mixture of 2,2-difluoro-1,3-benzodioxole-5-carbonitrile (300 mg, 1.64 mmol), triethylamine (331 mg, 3.28 mmol, 454 µL) and hydroxylamine hydrochloride (227 mg, 3.28 mmol) in water (500 µL) and ethanol (5 mL) was heated at 70 ℃ for 16 h. The reaction mixture was cooled, diluted with water (10 mL) and filtered. The collected solid was dried in vacuo to give 2,2-difluoro-N'-hydroxy-1,3-benzodioxole-5-carboxamidine (210 mg) as a solid.

Step 3: N-[2-[4-[3-(2,2-difluoro-1,3-benzodioxol-5-yl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-2-oxo-ethyl]benzamide,

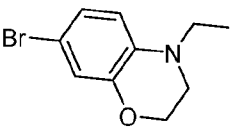


A mixture of 2,2-difluoro-N'-hydroxy-1,3-benzodioxole-5-carboxamidine (74 mg, 344 µmol), 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid (100 mg, 344 µmol), N-ethyl-N-(propan-2-yl)propan-2-amine (133 mg, 1.03 mmol, 180 µL) and (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (156 mg, 413 µmol) in N,N-dimethylformamide (2 mL) was stirred at 20 °C for 1 h under a nitrogen atmosphere. The mixture was heated at 120°C for 1 h, then cooled and purified by prep-HPLC (column: Waters Xbridge 150x25 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 40%-70%,12 min) to give N-[2-[4-[3-(2,2-difluoro-1,3-benzodioxol-5-yl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-2-oxo-ethyl]benzamide (58 mg, 124 µmol, 36 %) as a white solid. ^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.85 - 7.76 (m, 3H), 7.72 (d, J=1.5 Hz, 1H), 7.48 - 7.42 (m, 1H), 7.41 - 7.35 (m, 2H), 7.26 (br s, 1H), 7.10 (d, J=8.4 Hz, 1H), 4.53 - 4.37 (m, 1H), 4.23 (d, J=4.0 Hz, 2H), 3.84 (br d, J=13.9 Hz, 1H), 3.35 - 3.21 (m, 2H), 3.12 - 3.02 (m, 1H), 2.26 - 2.10 (m, 2H), 1.98 - 1.85 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$:471.2.

Example 110: N-(2-(4-(3-(4-ethyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.



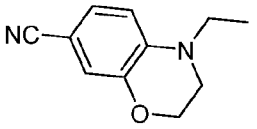
Step 1: Preparation of 7-bromo-4-ethyl-3,4-dihydro-2H-benzo[b][1,4]oxazine



To a stirred solution of 7-bromo-4-ethyl-2H-benzo[b][1,4]oxazin-3(4H)-one (900 mg, 3.51 mmol) in tetrahydrofuran (10 mL) was added a solution of borane in tetrahydrofuran (1 M, 12.28 mL), and the mixture was stirred 20 °C for 1 h, then heated at 80 °C for 2 h. The reaction mixture was cooled then quenched by addition of methanol (15 mL). The mixture was concentrated under reduced pressure, then diluted with water (20 mL), extracted with ethyl acetate (60 mL x 2), and the combined organic phases

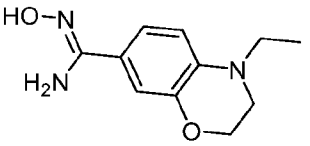
washed with saturated aqueous sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give 7-bromo-4-ethyl-3,4-dihydro-2H-benzo[b][1,4]oxazine (750 mg, 3.10 mmol, 88 %) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.86 - 6.80 (m, 2H), 6.45 (d, *J*=8.3 Hz, 1H), 4.19 - 4.13 (m, 2H), 3.28 - 3.18 (m, 4H), 1.06 (t, *J*=7.1 Hz, 3H).

Step 2: Preparation of 4-ethyl-3,4-dihydro-2H-benzo[b][1,4]oxazine-7-carbonitrile.



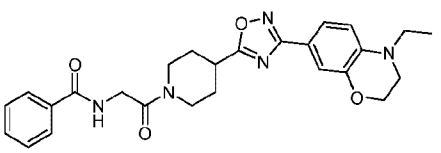
To a stirred solution of 7-bromo-4-ethyl-3,4-dihydro-2H-benzo[b][1,4]oxazine (80 mg, 330 µmol) in N,N-dimethylformamide (1 mL) was added zinc cyanide (38 mg, 330 µmol) and tetrakis(triphenylphosphine)palladium(0) (38 mg, 33 µmol), then the mixture was degassed with nitrogen three times. The mixture was heated at 110 °C for 16 h under nitrogen, then cooled to 20 °C, and water (3 mL) added. The reaction mixture was extracted with ethyl acetate (20 mL x 2). The combined organic phases were washed with saturated aqueous sodium chloride solution (5 mL), dried over anhydrous sodium sulfate, filtered and then concentrated in vacuo to give a crude residue that was purified by prep-TLC (petroleum ether : ethyl acetate=2:1) to give 4-ethyl-3,4-dihydro-2H-benzo[b][1,4]oxazine-7-carbonitrile (60 mg, 319 µmol, 96 %) as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (td, *J*=1.4, 8.5 Hz, 1H), 7.00 - 6.92 (m, 1H), 6.59 (d, *J*=8.4 Hz, 1H), 4.20 (dt, *J*=0.9, 4.5 Hz, 2H), 3.42 - 3.33 (m, 4H), 1.16 (dt, *J*=0.9, 7.2 Hz, 3H).

Step 3: Preparation of (Z)-4-ethyl-N'-hydroxy-3,4-dihydro-2H-benzo[b][1,4]oxazine-7-carboximidamide.



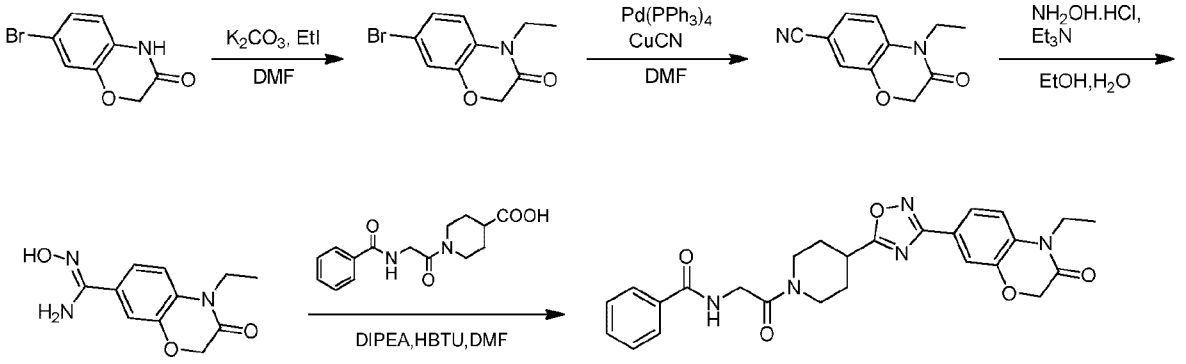
To a stirred solution of 4-ethyl-3,4-dihydro-2H-benzo[b][1,4]oxazine-7-carbonitrile (60 mg, 319 µmol) in ethanol (1 mL) was added hydroxylamine hydrochloride (44 mg, 638 µmol), triethylamine (64 mg, 638 µmol, 88 µL) and water (100 µL). The mixture was stirred at 80 °C for 5 h. The reaction mixture was cooled, concentrated under reduced pressure, and then diluted with water (5 mL). The mixture was extracted with ethyl acetate (20 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to give crude (Z)-4-ethyl-N'-hydroxy-3,4-dihydro-2H-benzo[b][1,4]oxazine-7-carboximidamide (60 mg, 271 µmol, 85 %) as a white solid.

Step 4: Preparation of N-(2-(4-(3-(4-ethyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.

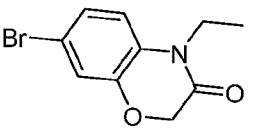


To a stirred solution of 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid (60 mg, 207 µmol) in N,N-dimethylformamide (1 mL) was added (Z)-4-ethyl-N'-hydroxy-3,4-dihydro-2H-benzo[b][1,4]oxazine-7-carboximidamide (45 mg, 207 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (78 mg, 207 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (80 mg, 620 µmol, 108 µL). The mixture was stirred at 20 °C for 1 h, then heated at 110 °C for 1 h. The reaction mixture was purified directly by prep-HPLC (column: Luna C18 150x2.5mm 5µm; mobile phase: [water (0.225% TFA)-acetonitrile]; B%: 40%-65%,16 min) to give N-(2-(4-(3-(4-ethyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide (17 mg, 35.8 µmol, 17 %) as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 - 7.84 (m, 2H), 7.58 - 7.43 (m, 5H), 7.35 (br s, 1H), 6.72 (d, *J*=8.5 Hz, 1H), 4.45 (br d, *J*=13.8 Hz, 1H), 4.33 - 4.24 (m, 4H), 3.89 (br d, *J*=14.1 Hz, 1H), 3.45 - 3.25 (m, 6H), 3.18 (br t, *J*=10.4 Hz, 1H), 2.28 - 2.18 (m, 2H), 2.07 - 1.92 (m, 2H), 1.20 (t, *J*=7.2 Hz, 3H); LCMS (ESI) m/z: $[M+H]^+$ = 476.3.

Example 111: N-(2-(4-(3-(4-ethyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.

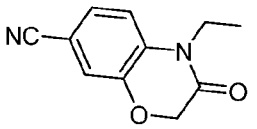


Step 1: Preparation of 7-bromo-4-ethyl-2H-benzo[b][1,4]oxazin-3(4H)-one.



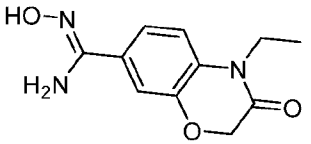
To a stirred solution of 7-bromo-4H-1,4-benzoxazin-3-one (2.0 g, 8.77 mmol) in N,N-dimethylformamide (20 mL) was added iodoethane (1.64 g, 10.52 mmol, 841 µL) and potassium carbonate (3.64 g, 26.3 mmol) at 0 °C. The reaction was warmed at 40 °C for 2 h. The reaction mixture was cooled then quenched by addition of water (30 mL), and then the mixture was extracted with ethyl acetate (60 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give 7-bromo-4-ethyl-2H-benzo[b][1,4]oxazin-3(4H)-one (2.06 g, 8.04 mmol, 92 %) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 - 7.05 (m, 2H), 6.78 (d, *J*=8.9 Hz, 1H), 4.52 (s, 2H), 3.89 (q, *J*=7.2 Hz, 2H), 1.20 (t, *J*=7.2 Hz, 3H).

Step 2: Preparation of 4-ethyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-7-carbonitrile.



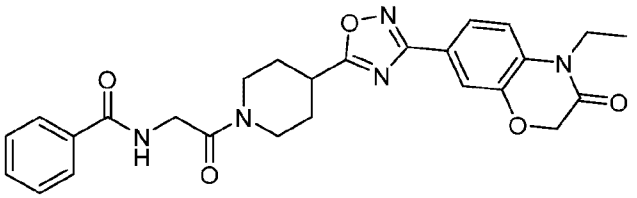
To a stirred solution of 7-bromo-4-ethyl-2H-benzo[b][1,4]oxazin-3(4H)-one (800 mg, 3.12 mmol) in N,N-dimethylformamide (10 mL) was added copper(I) cyanide (559 mg, 6.25 mmol, 1.36 mL) and tetrakis(triphenylphosphine)palladium(0) (360 mg, 312 µmol). The mixture was degassed with nitrogen, then heated at 110 °C for 16 h under nitrogen. The reaction mixture was cooled to 20 °C, then water (15 mL) was added and the reaction mixture extracted with ethyl acetate (40 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, filetered and concentrated in vacuo to give a crude residue that was purified by chromatography (silica, petroleum ether : ethyl acetate = 1:0 to 5:1) to give 4-ethyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-7-carbonitrile (70 mg, 346 µmol, 11 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (dd, *J*=1.9, 8.4 Hz, 1H), 7.30 - 7.29 (m, 1H), 7.08 (d, *J*=8.3 Hz, 1H), 4.68 (s, 2H), 4.04 (q, *J*=7.2 Hz, 2H), 1.32 (t, *J*=7.2 Hz, 3H).

Step 3: Preparation of (Z)-4-ethyl-N'-hydroxy-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-7-carboximidamide.



To a stirred solution of 4-ethyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-7-carbonitrile (70 mg, 346 µmol) in ethanol (1 mL) was added hydroxylamine hydrochloride (48 mg, 692 µmol), triethylamine (70 mg, 692 µmol, 95 µL) and water (100 µL). The mixture was heated at 80 °C for 5 h. The reaction mixture was cooled then concentrated under reduced pressure. The residue was diluted with water (5 mL), then the reaction mixture was extracted with ethyl acetate (20 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to give (Z)-4-ethyl-N'-hydroxy-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-7-carboximidamide (60 mg, 255 µmol, 74 %) as a white solid.

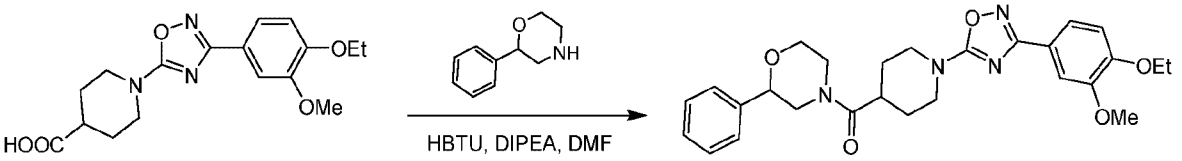
Step 4: Preparation of N-(2-(4-(3-(4-ethyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.



To a stirred solution of 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid (60 mg, 206.7 µmol) in N,N-dimethylformamide (1 mL) was added (Z)-4-ethyl-N'-hydroxy-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-7-carboximidamide (48 mg, 206.7 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-

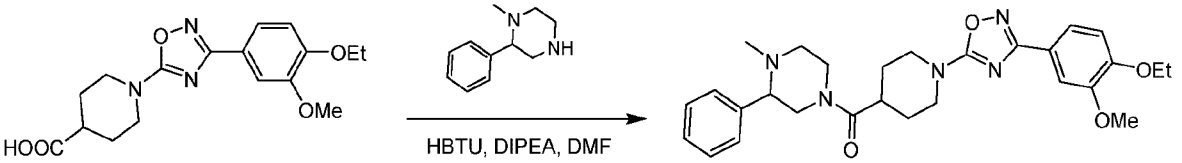
tetramethyluronium hexafluorophosphate) (78 mg, 206.7 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (80 mg, 620 µmol, 108 µL). The mixture was stirred at 20 °C for 1 h, then heated at 110 °C for 1 h. The reaction mixture was cooled then purified by prep-HPLC (column: Luna C18 100x30 5µm; mobile phase: [water (0.1%TFA)-methanol]; B%: 38%-68%,12 min) to give N-(2-(4-(3-(4-ethyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide (6 mg, 13 µmol, 6 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J*=7.2 Hz, 2H), 7.77 (dd, *J*=1.8, 8.5 Hz, 1H), 7.71 (d, *J*=1.8 Hz, 1H), 7.56 - 7.43 (m, 3H), 7.34 (br s, 1H), 7.10 (d, *J*=8.4 Hz, 1H), 4.66 (s, 2H), 4.50 (br d, *J*=13.7 Hz, 1H), 4.31 (d, *J*=3.8 Hz, 2H), 4.04 (q, *J*=7.1 Hz, 2H), 3.92 (br d, *J*=14.7 Hz, 1H), 3.40 - 3.29 (m, 2H), 3.17 (br t, *J*=10.7 Hz, 1H), 2.31 - 2.19 (m, 2H), 2.00 (br t, *J*=13.4 Hz, 2H), 1.32 (t, *J*=7.2 Hz, 3H); LCMS (ESI) m/z: $[M+H]^+$ = 490.2.

Example 112: (1-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-4-yl)(2-phenylmorpholino)methanone.

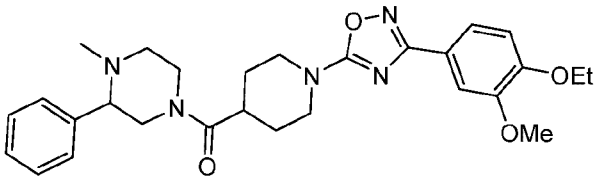


To a stirred solution of 1-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-4-carboxylic acid (80 mg, 230 µmol) in N,N-dimethylformamide (1 mL) was added 2-phenylmorpholine (37 mg, 230 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (87 mg, 230 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (89 mg, 690.93 µmol, 120 µL). The mixture was stirred at 20 °C for 1 h. The reaction mixture was purified by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 30%-70%,12 min) to give (1-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-4-yl)(2-phenylmorpholino)methanone (94 mg, 191.6 µmol, 83 %) as a yellow oil. ^{1}H NMR (400MHz, Methanol-d4) δ 7.55 - 7.41 (m, 3H), 7.40 - 7.26 (m, 4H), 6.99 (d, *J*=8.4 Hz, 1H), 4.51 - 4.36 (m, 2H), 4.26 - 4.13 (m, 2H), 4.12 - 3.98 (m, 4H), 3.86 (s, 3H), 3.75 - 3.58 (m, 1H), 3.46 - 3.30 (m, 1H), 3.28 - 3.17 (m, 2H), 3.04 (br s, 1H), 2.95 - 2.64 (m, 1H), 1.93 - 1.68 (m, 4H), 1.40 (t, *J*=6.9 Hz, 3H); LCMS (ESI) m/z: $[M+H]^+$ = 493.3.

Example 113: (1-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-4-yl)(4-methyl-3-phenylpiperazin-1-yl)methanone.

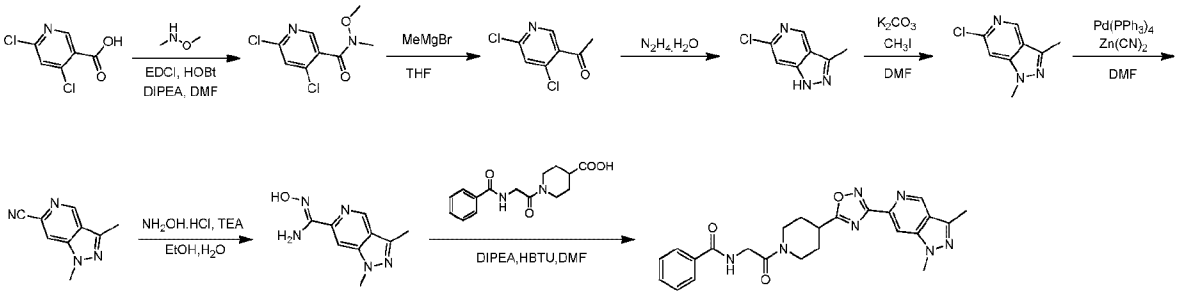


Step 1: Preparation of (1-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-4-yl)(4-methyl-3-phenylpiperazin-1-yl)methanone.

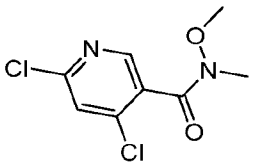


To a stirred solution of 1-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidine-4-carboxylic acid (70 mg, 201.5 µmol) in N,N-dimethylformamide (1 mL) was added 1-methyl-2-phenylpiperazine dihydrochloride (50 mg, 201.5 µmol,), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (76 mg, 201.5 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (78 mg, 604.6 µmol, 105 µL). The mixture was stirred at 20 °C for 1 h. The reaction mixture was purified directly by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 38%-68%,12 min) to give (1-(3-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)piperidin-4-yl)(4-methyl-3-phenylpiperazin-1-yl)methanone (60 mg, 117 µmol, 58 %) as a yellow solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.57 (br d, *J*=7.9 Hz, 1H), 7.50 (br s, 1H), 7.45 - 7.29 (m, 5H), 6.91 (d, *J*=8.3 Hz, 1H), 4.68 - 4.48 (m, 1H), 4.35 - 4.11 (m, 4H), 3.94 (s, 3H), 3.92 - 3.69 (m, 1H), 3.52 - 3.10 (m, 3H), 3.09 - 2.60 (m, 4H), 2.33 - 2.17 (m, 1H), 2.07 (br d, *J*=4.9 Hz, 3H), 2.04 - 1.73 (m, 4H), 1.49 (t, *J*=7.0 Hz, 3H); LCMS (ESI) m/z: $[M+H]^+$ = 506.4.

Example 114: N-(2-(4-(3-(1,3-dimethyl-1H-pyrazolo[4,3-c]pyridin-6-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.



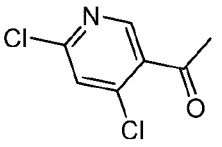
Step 1: Preparation of 4,6-dichloro-N-methoxy-N-methylnicotinamide.



To a stirred solution of 4,6-dichloronicotinic acid (1.0 g, 5.21 mmol) in N,N-dimethylformamide (15 mL) was added N,O-dimethylhydroxylamine (1.02 g, 10.42 mmol), hydroxybenzotriazole (1.41 g, 10.4 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (2.0 g, 10.4 mmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (2.02 g, 15.6 mmol, 2.73 mL). The mixture was stirred at 20 °C for 48 h. The reaction mixture was quenched by addition of water (20 mL) then the mixture was extracted with ethyl acetate (50 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give a crude residue that was

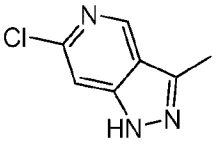
purified by chromatography (silica, petroleum ether : ethyl acetate = 50 : 1 to 5:1 to give 4,6-dichloro-N-methoxy-N-methylnicotinamide (660 mg, 2.81 mmol, 54 %) as a yellow oil.^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1H), 7.45 (s, 1H), 3.51 (br s, 3H), 3.40 (br s, 3H).

Step 2: Preparation of 1-(4,6-dichloropyridin-3-yl)ethanone.



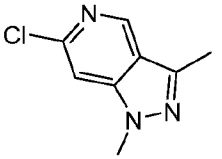
To a stirred solution of 4,6-dichloro-N-methoxy-N-methylnicotinamide (600 mg, 2.55 mmol) in tetrahydrofuran (10 mL) was added methylmagnesium bromide (3 M, 2.16 mL) at 0 °C, then the mixture was stirred at 0 °C for 2 h. After addition of saturated aqueous ammonium chloride (20 mL), the mixture was concentrated to ~20 mL and the residue that remained was extracted with dichloromethane (40 mL x 3). The combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give 1-(4,6-dichloropyridin-3-yl)ethanone (430 mg, 2.26 mmol, 89 %) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (s, 1H), 7.48 (s, 1H), 2.70 (s, 3H).

Step 3: Preparation of 6-chloro-3-methyl-1H-pyrazolo[4,3-c]pyridine.



1-(4,6-dichloropyridin-3-yl)ethanone (430 mg, 2.26 mmol) in hydrazine hydrate (10 mL) was stirred at 20 °C for 4 h. The reaction mixture was diluted with water (10 mL), then the mixture was extracted with dichloromethane (40 mL x 3). The combined organic phases were washed with water (10 mL x 2), then saturated aqueous sodium chloride solution (20 mL), then dried over anhydrous sodium sulfate, filtered and concentrated to give crude 6-chloro-3-methyl-1H-pyrazolo[4,3-c]pyridine (370 mg, 2.21 mmol, 98 %) as a yellow solid.^{1}H NMR (400 MHz, DMSO-d6) δ 13.23 (br s, 1H), 8.95 (br s, 1H), 7.59 (s, 1H), 2.61 (br s, 3H).

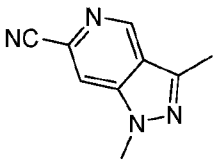
Step 4: Preparation of 6-chloro-1,3-dimethyl-1H-pyrazolo[4,3-c]pyridine.



To a stirred solution of 6-chloro-3-methyl-1H-pyrazolo[4,3-c]pyridine (330 mg, 1.97 mmol) in N,N-dimethylformamide (5 mL) was added iodomethane (558 mg, 3.94 mmol, 245 µL) and potassium carbonate (816 mg, 5.91 mmol) at 0 °C. The reaction was heated at 60 °C for 2 h. The reaction mixture was cooled then quenched with water (10 mL), and the mixture was extracted with ethyl acetate (20 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give a crude residue that was purified

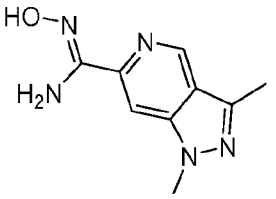
by prep-TLC (Petroleum ether : ethyl acetate=1:1) to give 6-chloro-1,3-dimethyl-1H-pyrazolo[4,3-c]pyridine (120 mg, 661 µmol, 34 %) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (s, 1H), 7.29 - 7.27 (m, 1H), 3.98 (s, 3H), 2.63 (s, 3H).

Step 5: Preparation of 1,3-dimethyl-1H-pyrazolo[4,3-c]pyridine-6-carbonitrile.



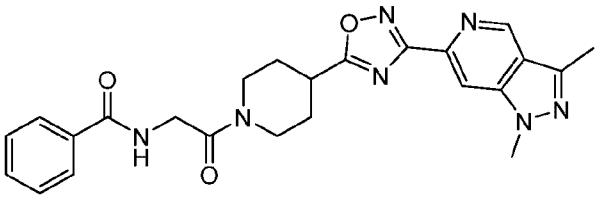
To a stirred solution of 6-chloro-1,3-dimethyl-1H-pyrazolo[4,3-c]pyridine (100 mg, 551 µmol) in N,N-dimethylformamide (2 mL) was added zinc cyanide (64 mg, 551 µmol) and tetrakis(triphenylphosphine)palladium(0) (63 mg, 55 µmol), then the mixture was degassed with nitrogen three times. The mixture was stirred at 110 °C for 16 h under nitrogen. The reaction was cooled to 20 °C, then water (3 mL) was added and the mixture was extracted with ethyl acetate (20 mL x 2). The combined organic phases were washed with saturated aqueous sodium chloride solution (5 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to give a crude residue that was purified by prep-TLC (silica, petroleum ether : ethyl acetate = 1:1). 1,3-dimethyl-1H-pyrazolo[4,3-c]pyridine-6-carbonitrile (50 mg, 290 µmol, 53 %) as a white solid. LCMS (ESI) m/z: $[M+H]^+$ = 173.1.

Step 6: Preparation of (Z)-N'-hydroxy-1,3-dimethyl-1H-pyrazolo[4,3-c]pyridine-6-carboximidamide.



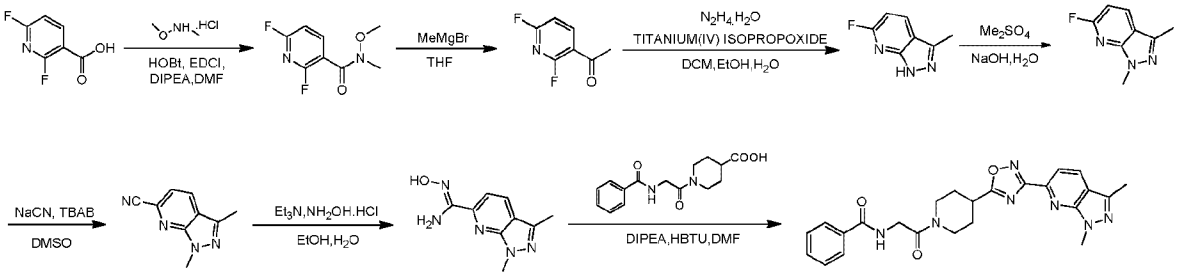
To a stirred solution of 1,3-dimethyl-1H-pyrazolo[4,3-c]pyridine-6-carbonitrile (50 mg, 290 µmol) in ethanol (1 mL) was added hydroxylamine hydrochloride (40 mg, 580.76 µmol), triethylamine (58 mg, 580.76 µmol, 80 µL) and water (100 µL). The mixture was stirred at 80 °C for 2 h. The reaction mixture was concentrated under reduced pressure then diluted with water (5 mL). The reaction mixture was extracted with ethyl acetate (20 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to give crude (Z)-N'-hydroxy-1,3-dimethyl-1H-pyrazolo[4,3-c]pyridine-6-carboximidamide (60 mg) as a white solid. LCMS (ESI) m/z: $[M+H]^+$ = 206.2.

Step 7: Preparation of N-(2-(4-(3-(1,3-dimethyl-1H-pyrazolo[4,3-c]pyridin-6-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide.

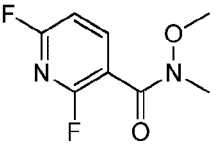


To a stirred solution of 1-(2-benzamidoacetyl)piperidine-4-carboxylic acid (35 mg, 120.6 µmol) in N,N-dimethylformamide (1 mL) was added (Z)-N'-hydroxy-1,3-dimethyl-1H-pyrazolo[4,3-c]pyridine-6-carboximidamide (24 mg, 120.6 µmol), (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (45 mg, 120.6 µmol) and N-ethyl-N-(propan-2-yl)propan-2-amine (46 mg, 361.7 µmol, 63 µL). The mixture was stirred at 20 °C for 1 h, then heated at 110 °C for 1 h. The reaction mixture was cooled then purified by prep-HPLC (column: Waters Xbridge 150x2.5mm 5µm; mobile phase: [water (10mM ammonium carbonate)-acetonitrile]; B%: 20%-50%,12 min) to give N-(2-(4-(3-(1,3-dimethyl-1H-pyrazolo[4,3-c]pyridin-6-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-2-oxoethyl)benzamide (5 mg, 11 µmol, 9 %) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.13 (d, *J*=1.1 Hz, 1H), 8.12 (d, *J*=1.0 Hz, 1H), 7.89 - 7.84 (m, 2H), 7.56 - 7.43 (m, 3H), 7.34 (br s, 1H), 4.55 (br d, *J*=13.7 Hz, 1H), 4.32 (d, *J*=3.9 Hz, 2H), 4.09 (s, 3H), 3.94 (br d, *J*=13.8 Hz, 1H), 3.44 - 3.32 (m, 2H), 3.14 (br t, *J*=10.9 Hz, 1H), 2.68 (s, 3H), 2.37 - 2.24 (m, 2H), 2.16 - 1.96 (m, 2H); LCMS (ESI) m/z: $[M+H]^+$ = 460.1.

Example 115: N-[2-[4-[3-(1,3-dimethylpyrazolo[3,4-b]pyridin-6-yl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-2-oxo-ethyl]benzamide.



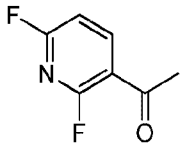
Step 1: 2,6-difluoro-N-methoxy-N-methyl-pyridine-3-carboxamide.



A mixture of 2,6-difluoropyridine-3-carboxylic acid (3.0 g, 18.9 mmol), N-methoxymethanamine hydrochloride (12.9 g, 132.0 mmol) hydroxybenzotriazole (10.2 g, 75.4 mmol), diisopropylethylamine (3.70 g, 28.7 mmol, 5.01 mL) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (7.20 g, 37.5 mmol) in N,N-dimethylformamide (50 mL) was stirred at 20 °C for 16 h under a nitrogen atmosphere. The reaction mixture was diluted with water (30 mL) and extracted with dichloromethane (20 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (20 mL x 3), dried over

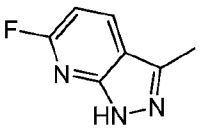
anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give 2,6-difluoro-N-methoxy-N-methyl-pyridine-3-carboxamide (2.80 g, 13.9 mmol, 73 %) as a solid.

Step 2: 1-(2,6-difluoro-3-pyridyl)ethanone.



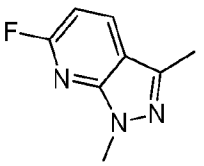
To a stirred solution of 2,6-difluoro-N-methoxy-N-methyl-pyridine-3-carboxamide (3.0 g, 14.8 mmol) in tetrahydrofuran (60 mL) was added dropwise methylmagnesium bromide (1.77 g, 14.84 mmol) at 0℃. The resulting mixture was stirred at 0℃ for 2 h, and then quenched by water at 0 ℃. The mixture was diluted with ethyl acetate (60 mL) and extracted with ethyl acetate (50 mL x 2). The combined organic phases were washed with saturated aqueous sodium chloride solution (25 mL x 2), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. Purification by chromatography (silica, petroleum ether / ethyl acetate=2:1) gave 1-(2,6-difluoro-3-pyridyl)ethanone (2.20 g, 14.0 mmol, 94 %) as a white solid.

Step 3: 3-ethoxy-6-iodo-2-methoxy-pyridine.



A solution of 1-(2,6-difluoro-3-pyridyl)ethanone (1.50 g, 9.55 mmol) in dichloromethane (55 mL) was treated with titanium(IV) isopropoxide (10.37 g, 36.48 mmol, 10.80 mL) at room temperature. The resulting mixture was stirred for 15 min, then hydrazine hydrate (2.06 g, 41.16 mmol, 2 mL) was added. Stirring continued for an additional 1.5 h, then water (5 mL) was added, and the resulting thick mixture was stirred vigorously for 20 min. The reaction mixture was filtered, and the solids were washed with dichloromethane (10 mL). The filtrate was concentrated in vacuo to provide the crude hydrazone intermediate as an oil. The crude hydrazine was dissolved in ethanol (15 mL), and the solution was heated at 80 ℃ for 24 h. The reaction mixture was quenched by addition of water (10 mL) at 20℃, and then extracted with dichloromethane (10 mL x 3). The combined organic phases were washed with saturated aqueous sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give 6-fluoro-3-methyl-1H-pyrazolo[3,4-b]pyridine (1.20 g) which was used directly without further purification.

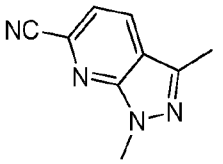
Step 4: 6-fluoro-1,3-dimethyl-pyrazolo[3,4-b]pyridine.



A mixture of 6-fluoro-3-methyl-1H-pyrazolo[3,4-b]pyridine (1.20 g, 7.94 mmol), dimethylsulfate (1.20 g, 9.53 mmol, 903 µL), sodium hydroxide (952 mg, 23.82 mmol) in water (30 mL) was degassed

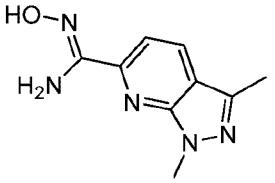
and purged with nitrogen 3 times, and then the mixture was stirred at 70 ℃ for 2 h under a nitrogen atmosphere. The reaction mixture was cooled, extracted with ethyl acetate (50 mL x 2), then the combined organic phases were washed with saturated aqueous sodium chloride solution (20 mL x 2), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by chromatography (silica, petroleum ether / ethyl acetate=2:1) to give 6-fluoro-1,3-dimethyl-pyrazolo[3,4-b]pyridine (400 mg, 2.42 mmol, 3 %) as a yellow solid.

Step 5: 1,3-dimethylpyrazolo[3,4-b]pyridine-6-carbonitrile.



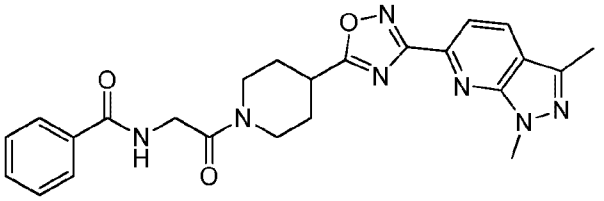
A mixture of 6-fluoro-1,3-dimethyl-pyrazolo[3,4-b]pyridine (350 mg, 2.12 mmol), tetra-n-butylammonium bromide (1.37 g, 4.24 mmol) and sodium cyanide (727 mg, 14.84 mmol) in dimethylsulfoxide (10 mL) was degassed and purged with nitrogen 3 times, and then the mixture was heated at 150 ℃ for 2 h under a nitrogen atmosphere. The reaction mixture was cooled then extracted with ethyl acetate (5 mL x 2). The combined organic phases were washed with saturated aqueous sodium chloride solution (10 mL), dried over anhydrous sodium sulfate, then filtered and concentrated under reduced pressure to give a residue. The residue was purified by chromatography (silica, petroleum ether / ethyl acetate=2:1) to give 1,3-dimethylpyrazolo[3,4-b]pyridine-6-carbonitrile (150 mg, 871 μmol, 41 %) as a yellow solid.

Step 6: N'-hydroxy-1,3-dimethyl-pyrazolo[3,4-b]pyridine-6-carboxamidine



A mixture of 1,3-dimethylpyrazolo[3,4-b]pyridine-6-carbonitrile (150 mg, 871 μmol), hydroxylamine hydrochloride (121 mg, 1.74 mmol) and triethylamine (176 mg, 1.74 mmol, 241 μL) in ethanol (3 mL) and water (300 μL) was degassed and purged with nitrogen 3 times, and then the mixture was stirred at 70 ℃ for 5 h under a nitrogen atmosphere. The reaction mixture was filtered and concentrated under reduced pressure to give N'-hydroxy-1,3-dimethyl-pyrazolo[3,4-b]pyridine-6-carboxamidine (120 mg, 584.7 μmol, 67 %) as a yellow solid.

Step 7: N-[2-[4-[3-(1,3-dimethylpyrazolo[3,4-b]pyridin-6-yl)-1,2,4-oxadiazol-5-yl]-1-piperidyl]-2-oxo-ethyl]benzamide



What is claimed is:

CLAIMS

1. A compound, or pharmaceutically acceptable salt thereof, having the structure of any one of compounds 747-966 in Table 2A, compounds 967-1195 in Table 2B, or compounds 1196-1313 in Table 2C.

2. A pharmaceutical composition comprising a compound, or pharmaceutically acceptable salt thereof, of claim 1, and a pharmaceutically acceptable excipient.

3. A method of treating a neurological disorder in a subject in need thereof, the method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, of claim 1 or a pharmaceutical composition of claim 2.

4. A method of inhibiting toxicity in a cell related to a protein, the method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, of claim 1 or a pharmaceutical composition of claim 2.

5. The method of claim 4, wherein the toxicity is α-synuclein-related toxicity.

6. The method of claim 4, wherein the toxicity is ApoE4-related toxicity.

7. The method of any one of claims 4 to 6, wherein the cell is a mammalian neural cell.

8. A method of treating a stearoyl-CoA desaturase (SCD)-associated disorder in a subject in need thereof, the method comprising administering an effective amount of a compound, or pharmaceutically acceptable salt thereof, of claim 1 or a pharmaceutical composition of claim 2.

FIG. 1A

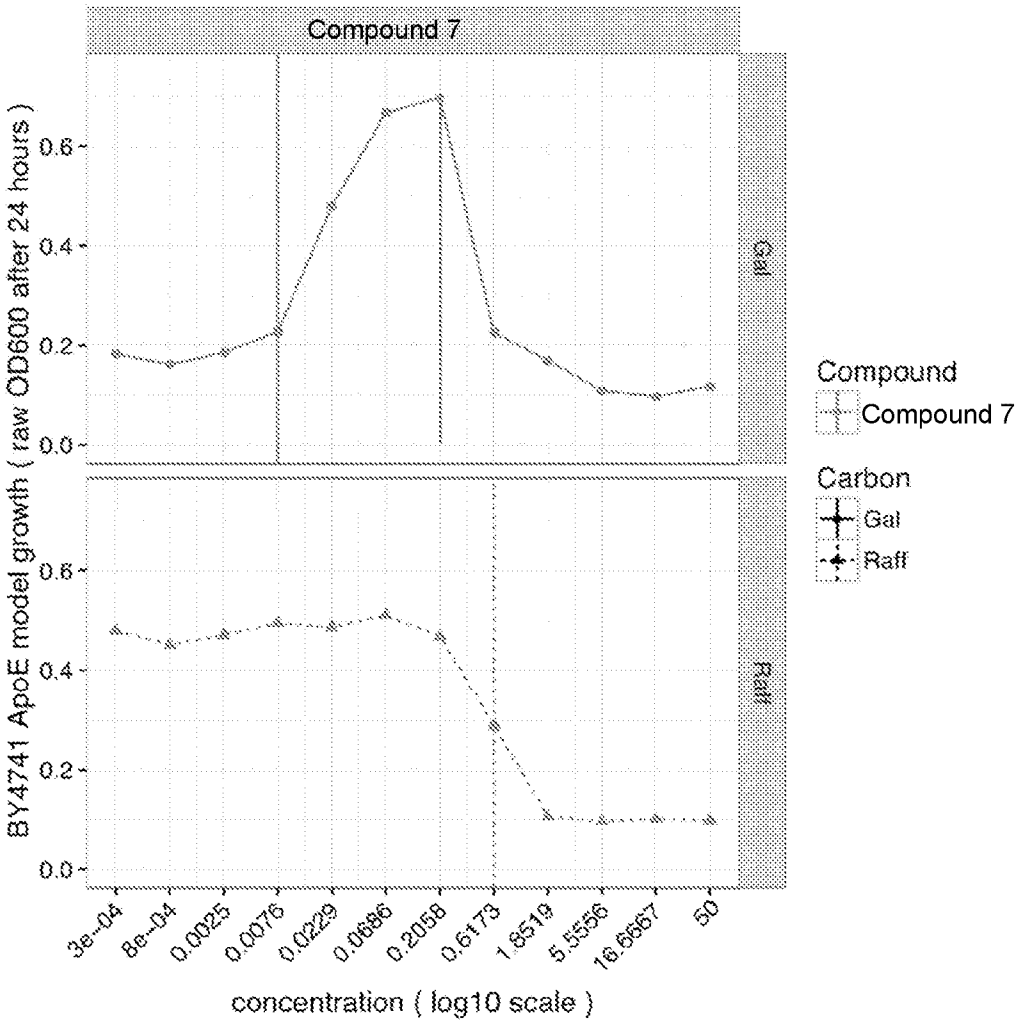

Compound 7
Gal
Raff
BY4741 ApoE model growth (raw OD600 after 24 hours)
0.0
0.2
0.4
0.6
3e−04
8e−04
0.0025
0.0076
0.0229
0.0686
0.2058
0.6173
1.8519
5.5556
16.6667
50
concentration (log10 scale)
Compound
Compound 7
Carbon
Gal
Raff

FIG. 1B

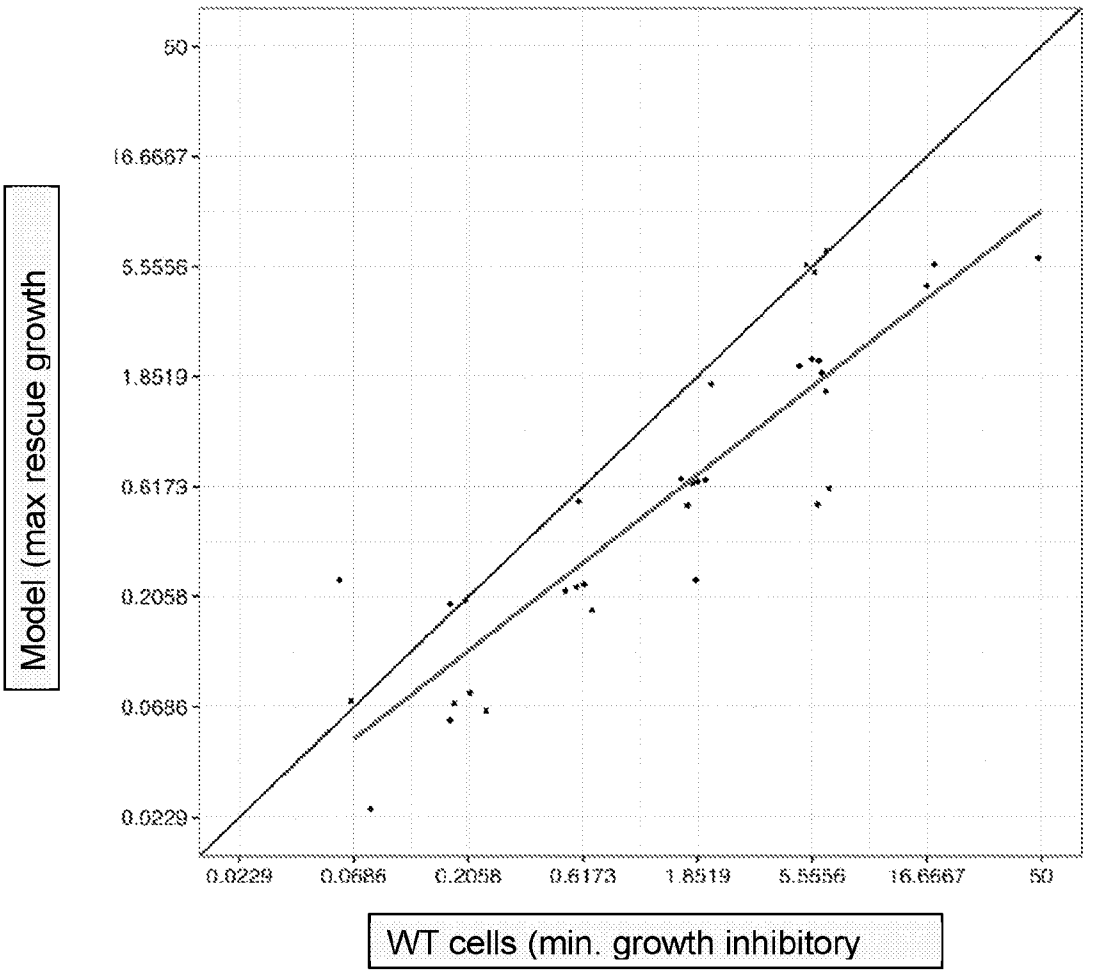

Model (max rescue growth
50
16.6667
5.5556
1.8519
0.6173
0.2058
0.0686
0.0229
0.0229
0.0686
0.2058
0.6173
1.8519
5.5556
16.6667
50
WT cells (min. growth inhibitory

FIG. 2A

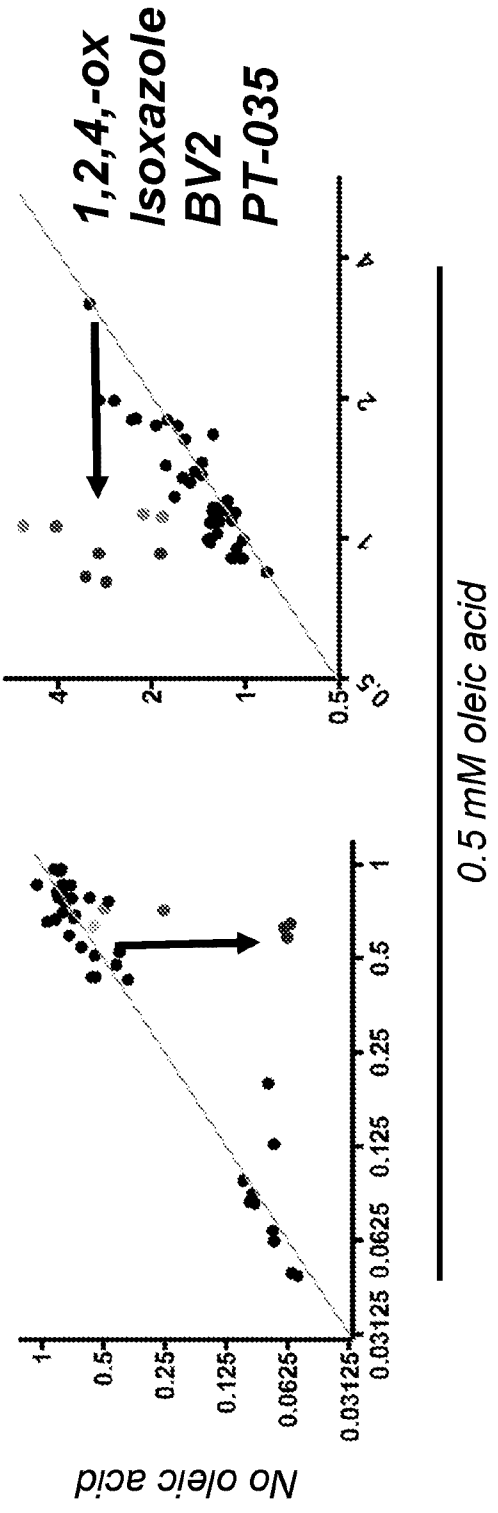

Growth Inhibition
Rescue (aSyn)
1,2,4,-ox
Isoxazole
BV2
PT-035
No oleic acid
0.5 mM oleic acid
1
0.5
0.25
0.125
0.0625
0.03125
0.03125
0.0625
0.125
0.25
0.5
1
0.5
1
2
4

FIG. 2B

FIG. 3A

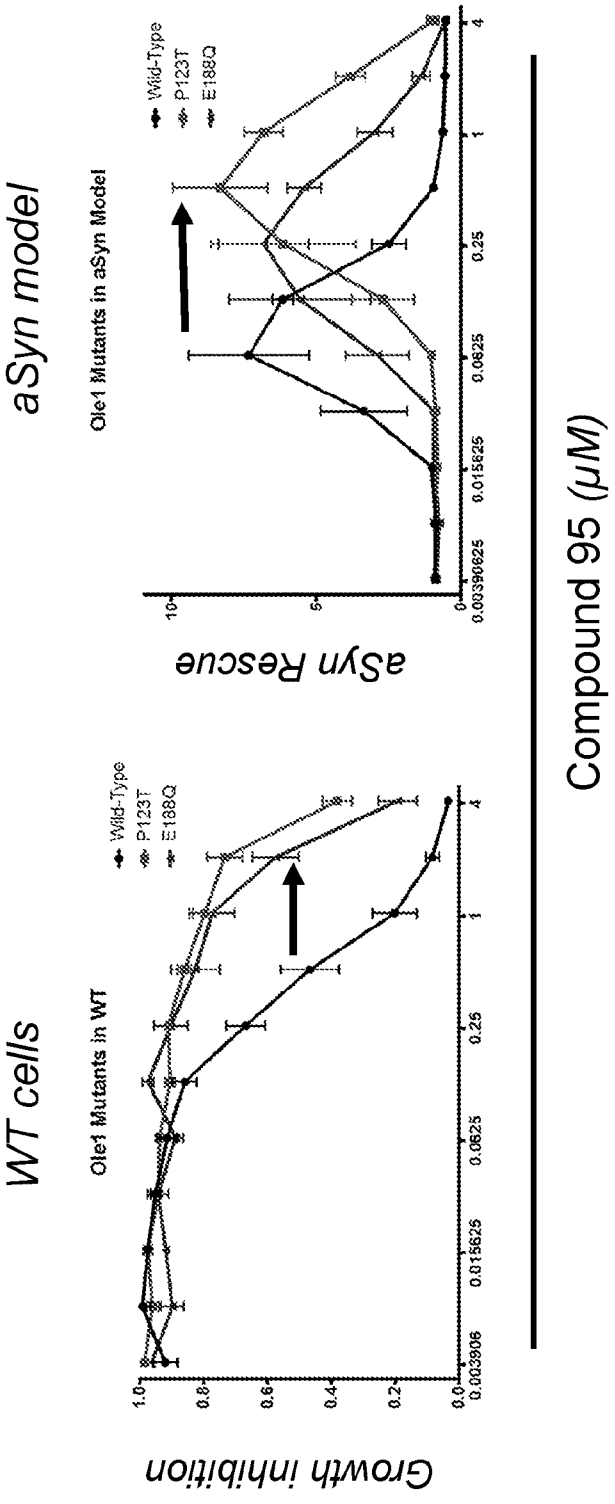

WT cells
aSyn model
Ole1 Mutants in WT
Ole1 Mutants in aSyn Model
Wild-Type
P123T
E188Q
Growth inhibition
aSyn Rescue
Compound 95 (μM)

FIG. 3B

FIG. 4

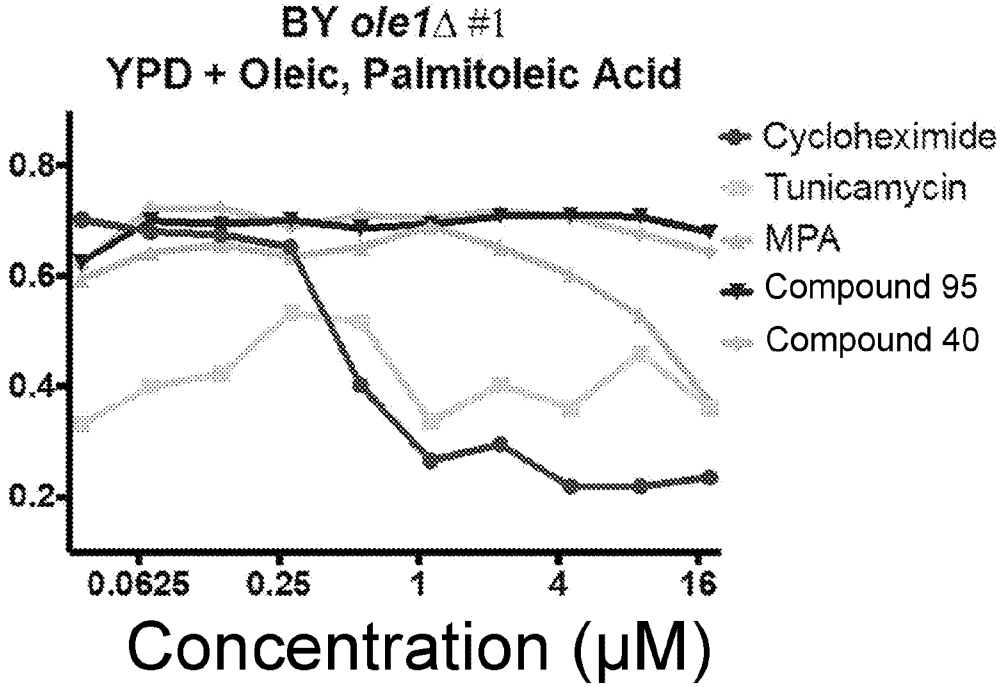

BY ole1Δ #1
YPD + Oleic, Palmitoleic Acid
Cycloheximide
Tunicamycin
MPA
Compound 95
Compound 40
0.8
0.6
0.4
0.2
0.0625
0.25
1
4
16
Concentration (μM)

FIG. 5

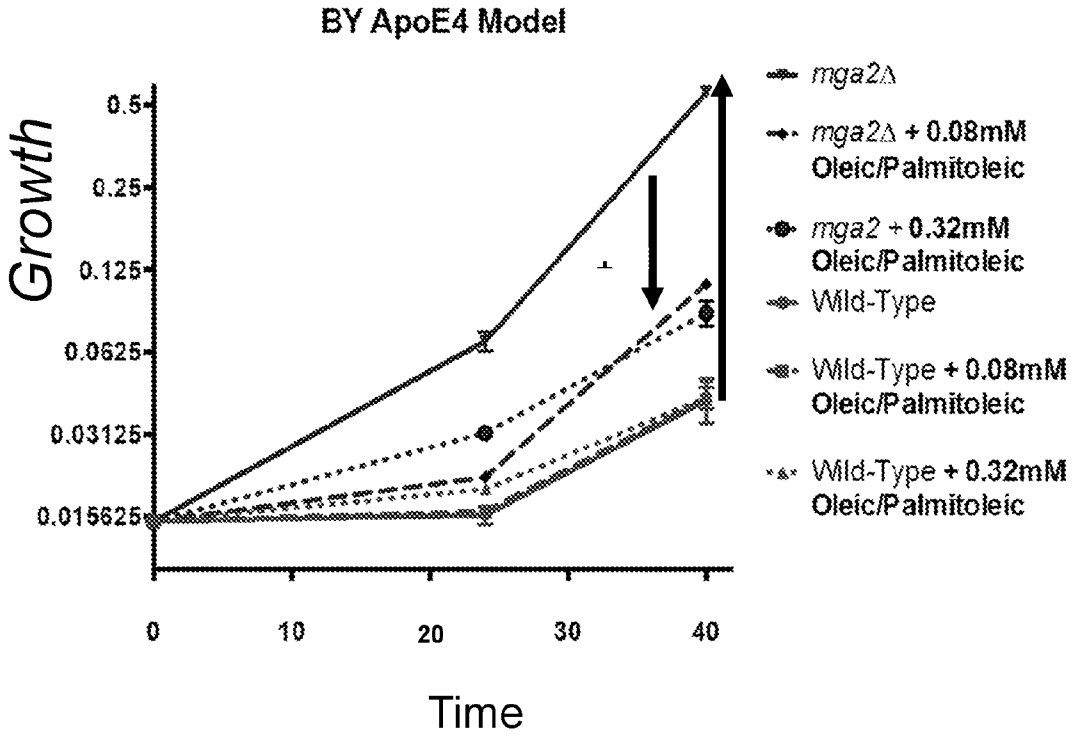

BY ApoE4 Model
Growth
0.5
0.25
0.125
0.0625
0.03125
0.015625
0
10
20
30
40
Time
mga2Δ
mga2Δ + 0.08mM Oleic/Palmitoleic
mga2 + 0.32mM Oleic/Palmitoleic
Wild-Type
Wild-Type + 0.08mM Oleic/Palmitoleic
Wild-Type + 0.32mM Oleic/Palmitoleic

FIG. 6

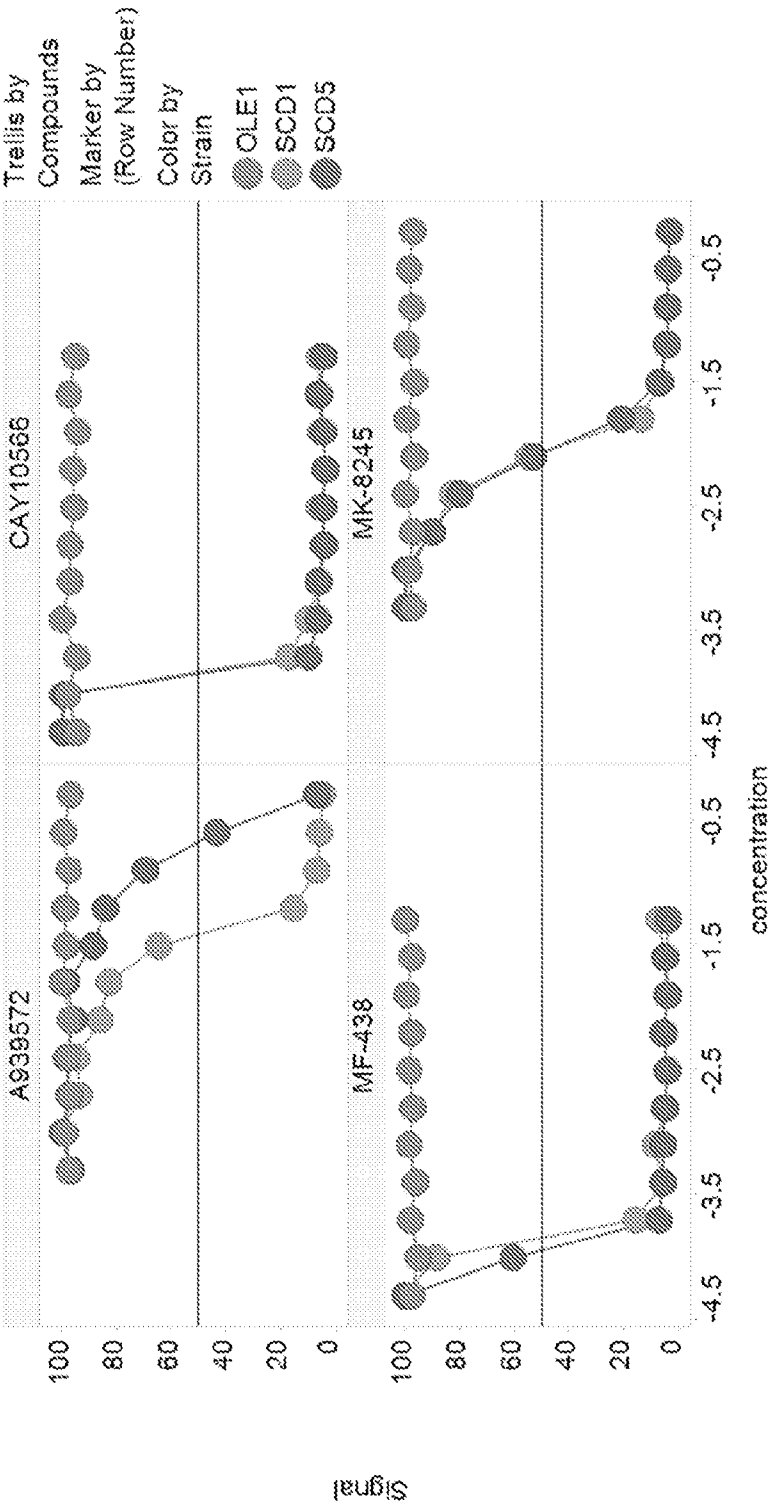

Trellis by
Compounds
Marker by
(Row Number)
Color by
Strain
OLE1
SCD1
SCD5
A939572
CAY10566
MF-438
MK-8245
Signal
concentration
100
80
60
40
20
0
-4.5
-3.5
-2.5
-1.5
-0.5

FIG. 7

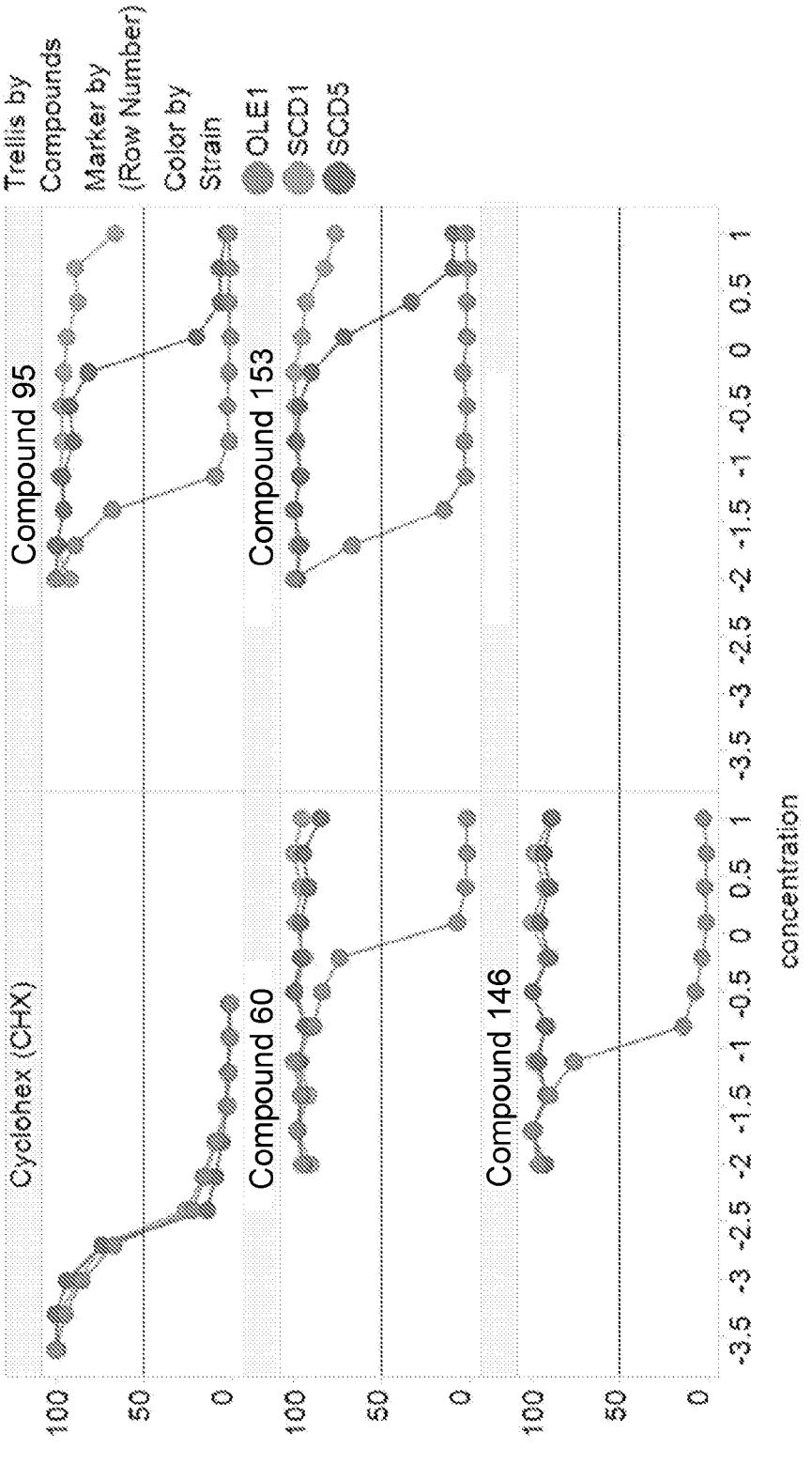

Trellis by
Compounds
Marker by
(Row Number)
Color by
Strain
OLE1
SCD1
SCD5
Cyclohex (CHX)
Compound 95
Compound 153
Compound 60
Compound 146
100
50
0
-3.5 -3 -2.5 -2 -1.5 -1 -0.5 0 0.5 1
concentration

Fig. 8A

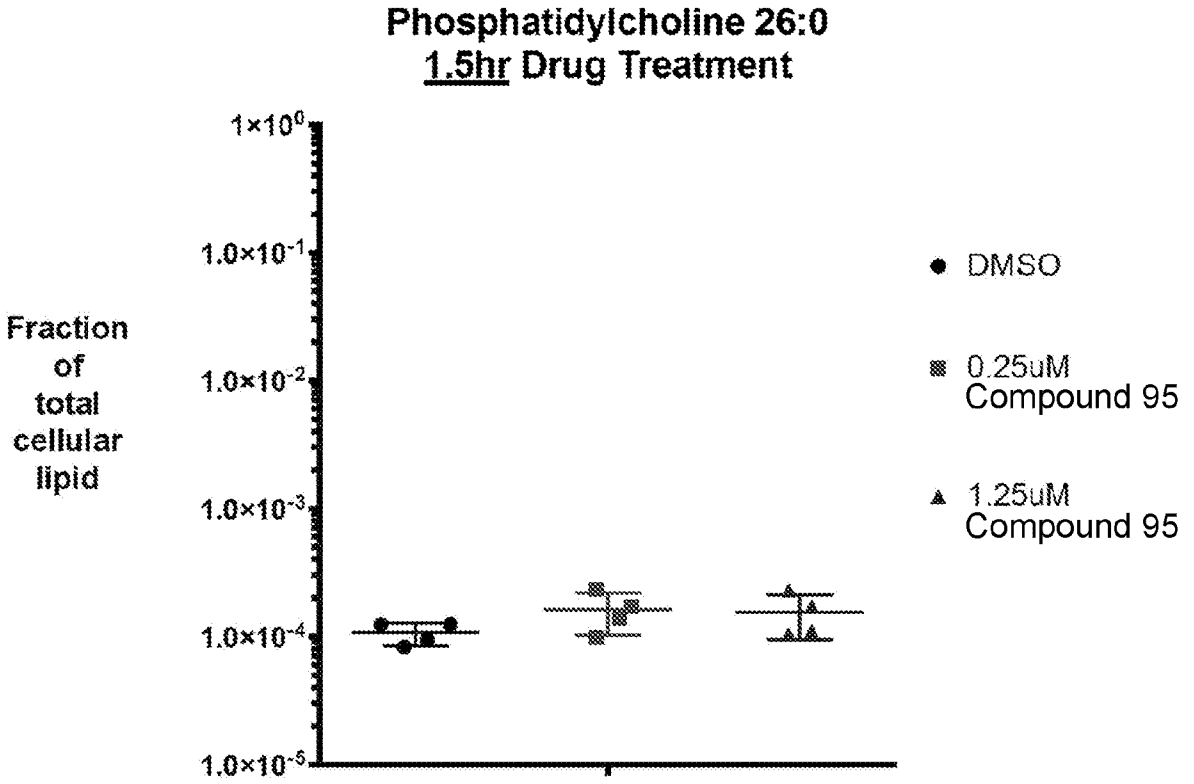

Phosphatidylcholine 26:0
1.5hr Drug Treatment
Fraction of total cellular lipid
1×10^0
1.0×10^-1
1.0×10^-2
1.0×10^-3
1.0×10^-4
1.0×10^-5
DMSO
0.25uM Compound 95
1.25uM Compound 95

Fig. 8B

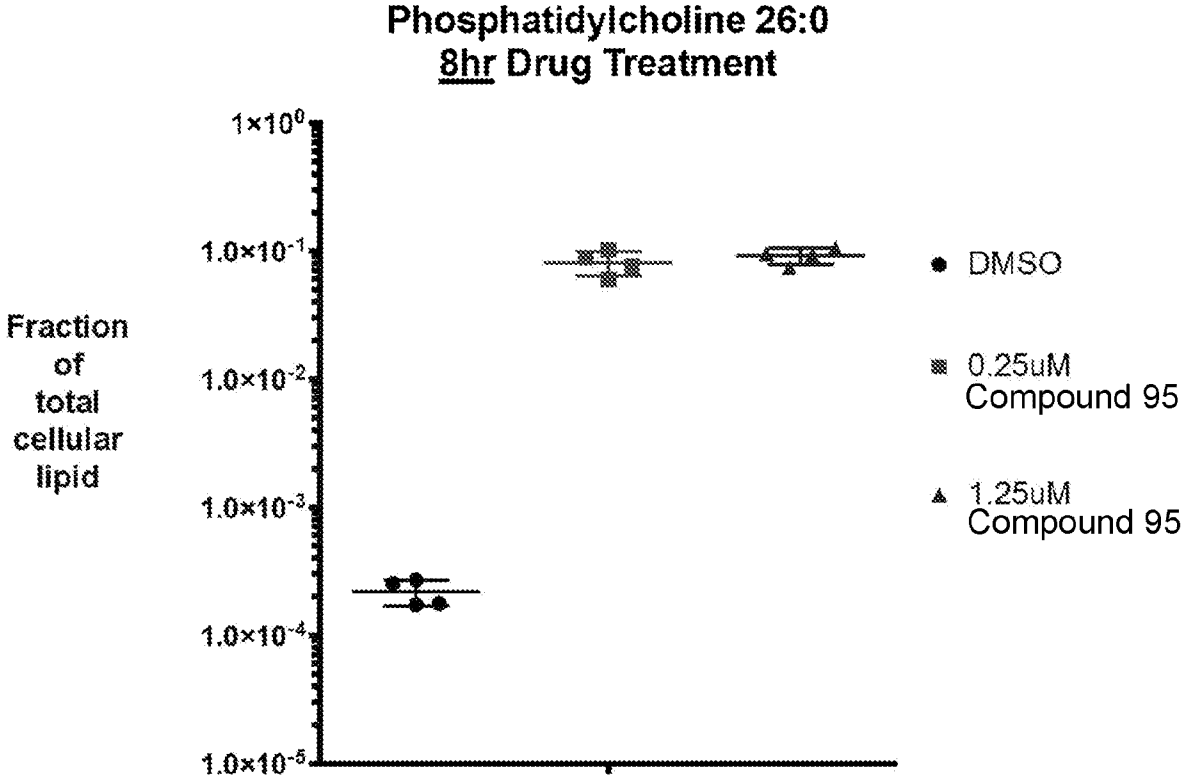

Phosphatidylcholine 26:0
8hr Drug Treatment
Fraction of total cellular lipid
1×10^0
1.0×10^-1
1.0×10^-2
1.0×10^-3
1.0×10^-4
1.0×10^-5
DMSO
0.25uM Compound 95
1.25uM Compound 95

Fig. 8C

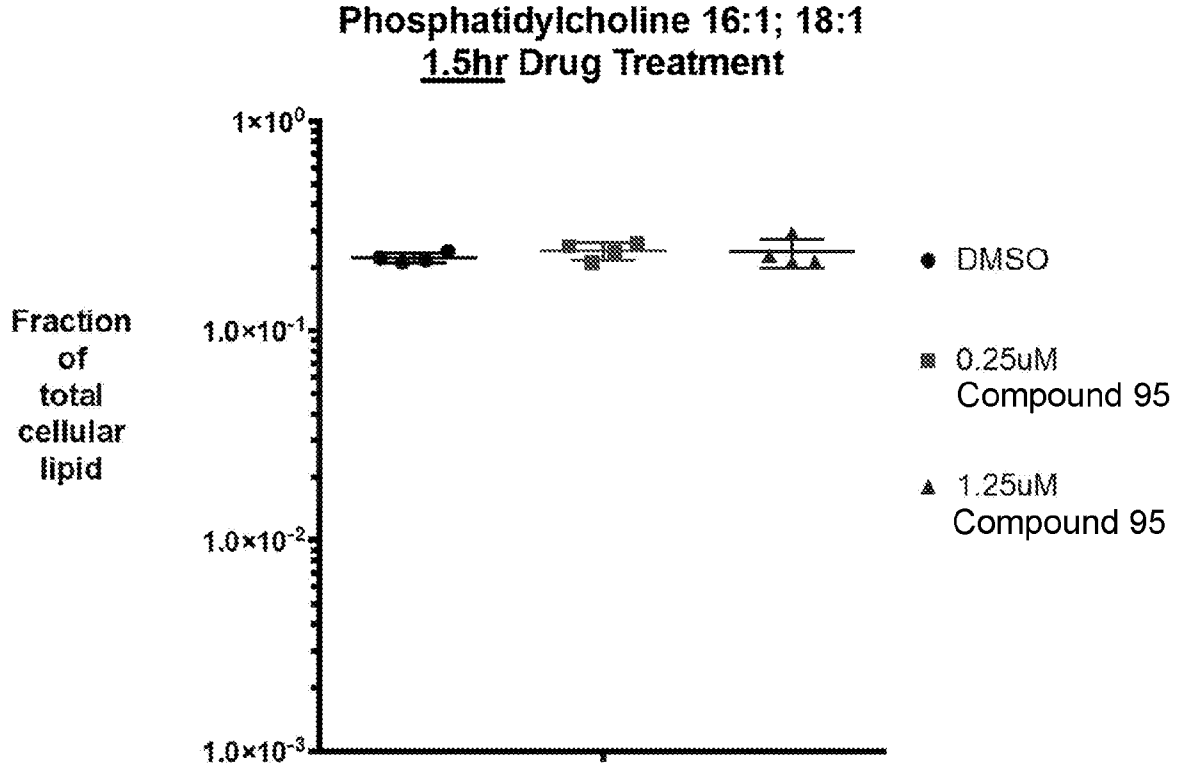

Phosphatidylcholine 16:1; 18:1
1.5hr Drug Treatment
Fraction of total cellular lipid
1×10^0
1.0×10^-1
1.0×10^-2
1.0×10^-3
DMSO
0.25uM Compound 95
1.25uM Compound 95

Fig. 8D

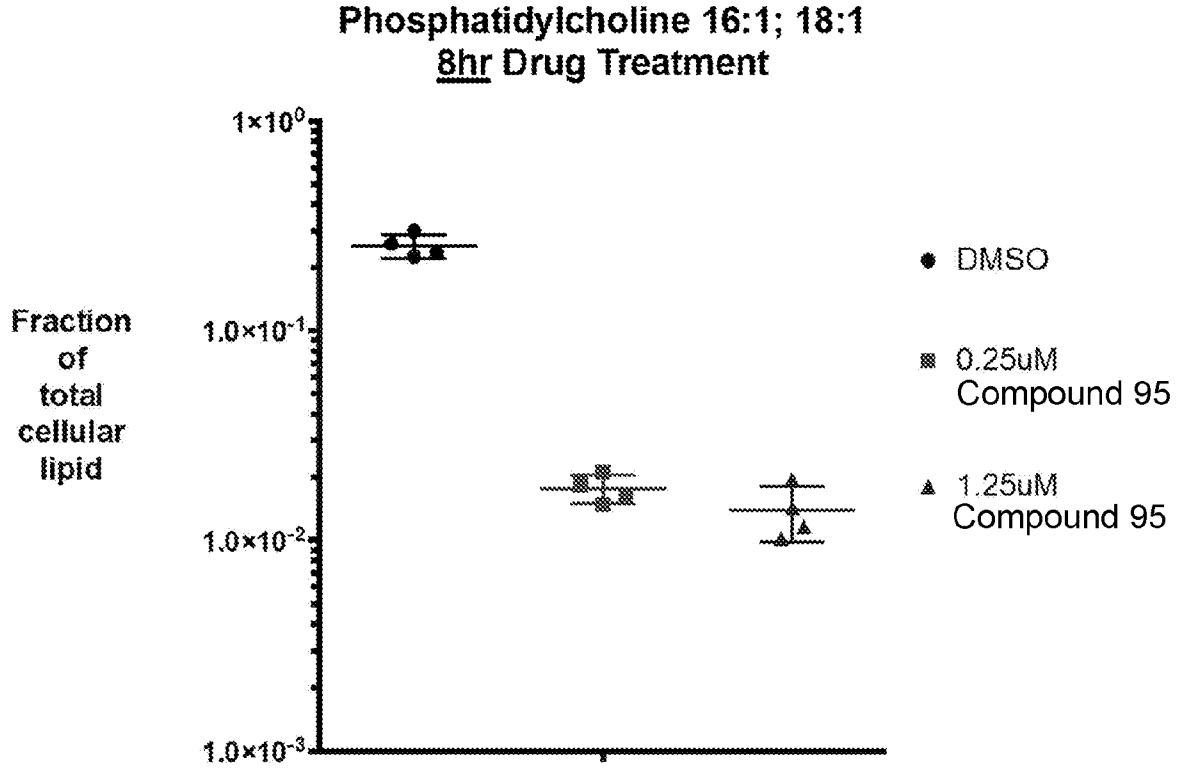
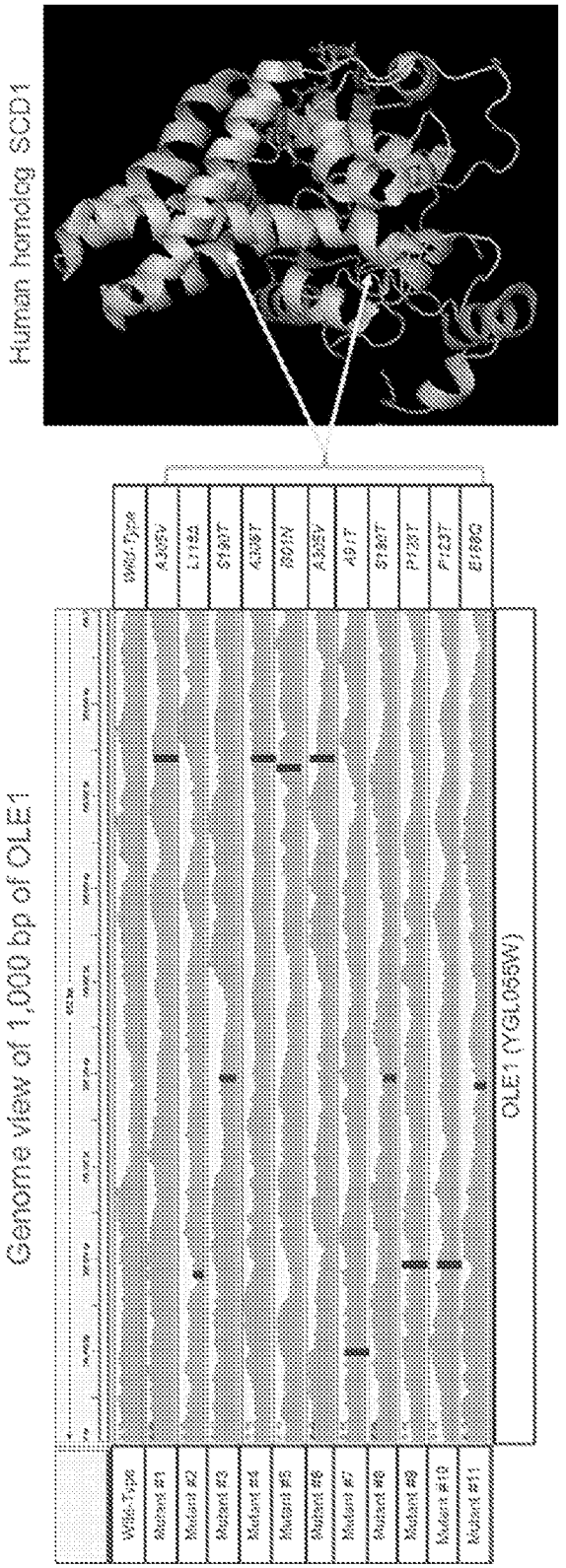

Phosphatidylcholine 16:1; 18:1
8hr Drug Treatment
Fraction of total cellular lipid
1×10^0
1.0×10^-1
1.0×10^-2
1.0×10^-3
DMSO
0.25uM Compound 95
1.25uM Compound 95

FIG. 9


Human homolog SCD1
Genome view of 1,000 bp of OLE1
Wild-Type
A305V
L119S
S180T
A305T
I301N
A305V
A91T
S180T
P128T
P128T
E166G
Wild-Type
Mutant #1
Mutant #2
Mutant #3
Mutant #4
Mutant #5
Mutant #6
Mutant #7
Mutant #8
Mutant #9
Mutant #10
Mutant #11
OLE1 (YGL055W)