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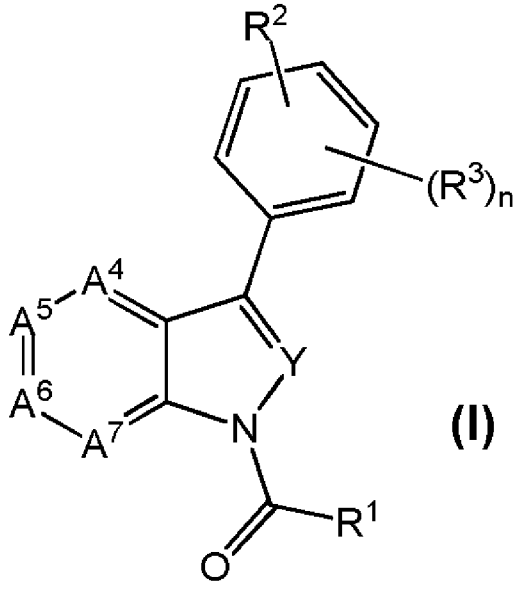
[Continued on next page]

(54) Title: 4-HETEROARYL SUBSTITUTED BENZOIC ACID COMPOUNDS AS RORGAMMAT INHIBITORS AND USES THEREOF

(57) Abstract: Provided are compounds according to Formula I or a pharmaceutically acceptable salt or solvate thereof. Such compounds can be used in the treatment of RORgammaT-mediated diseases or conditions.



(I)

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4-HETEROARYL SUBSTITUTED BENZOIC ACID COMPOUNDS AS RORgammaT INHIBITORS AND USES THEREOF

BACKGROUND OF THE INVENTION

Upon activation by antigen-presenting cells naïve T helper cells undergo clonal expansion and will ultimately differentiate in cytokine secreting effector T cells, such as Th1 and Th2 subtypes. A third and distinct effector subset has been identified, which plays a key role in providing immunity to bacteria and fungi at mucosal surfaces (Kastelein et al., *Annu. Rev. Immunol.* 25: 221-242, 2007). This effector T helper cell subset can be distinguished based on its ability to produce large quantities of IL-17/F, IL-21 and IL-22, and is named Th17 (Miossec et al., *New Eng. J. Med.* 2361: 888-898, 2009).

Different T helper subsets are characterized by the expression of lineage specific master transcription factors. Th1 and Th2 effector cells express Tbet and GATA3, respectively. A Thymocyte/T cell specific variant of Retinoic Acid Receptor-related Orphan Receptor (ROR), RORgammaT, is highly expressed in Th17 cells (He et al., *Immunity* 9: 797-806, 1998). RORgammaT belongs to the nuclear hormone receptor superfamily (Hirose et al., *Biochem. Biophys. Res. Comm.* 205: 1976-1983, 1994). RORgammaT is a truncated form of RORgamma, lacking the first N-terminal 21 amino acids and is, in contrast to RORgamma which is expressed in multiple tissues (heart, brain, kidney, lung, liver and muscle), exclusively expressed in cells of the lymphoid lineage and embryonic lymphoid tissue inducers (Sun et al., *Science* 288: 2369-2372, 2000; Eberl et al., *Nat Immunol.* 5: 64-73, 2004).

Studies using heterozygous knock-in mice replacing the RORgammaT open reading frame with GFP, revealed a constitutive expression of GFP in approximately 10% of the CD4+ T cells in the small intestinal lamina propria (LP), co-expressing the Th17 cytokines IL-17/F and IL-22 (Ivanov et al., *Cell* 126: 1121-1133, 2006). In mice deficient for RORgammaT, the number of Th17 cells was markedly decreased in the LP and in vitro stimulation of CD4+ T cells, under Th17 polarizing conditions resulted in a drastic decrease of IL-17 expression. These results were further substantiated via forced expression of RORgammaT in naïve CD4+ T cells, which resulted in an induction of IL-17/F and IL-22

(Ivanov et al., *Cell* 126: 1121-1133, 2006). Taken together demonstrating the importance of RORgammaT in differentiation and stabilization of the Th17 lineage. In addition, a ROR family member, RORalpha has been demonstrated to be involved in Th17 differentiation and stabilization (Yang et al., *Immunity* 28: 29-39, 2008).

Recently, RORgammaT was shown to play a crucial role in non-Th17 lymphoid cells. In these studies, RORgammaT was critically important in innate lymphoid cells expressing Thy1, SCA-1 and IL-23R proteins. Genetic disruption of RORgamma in a mouse colitis model dependent on these innate lymphoid cells, prevented colitis development (Buonocore et al., *Nature* 464: 1371-1375, 2010). In addition, RORgammaT was shown to play a crucial role in other non-Th17 cells, such as mast cells (Hueber et al., *J. Immunol.* 184: 3336-3340, 2010). Finally, RORgammaT expression and secretion of Th17-type of cytokines was reported for Lymphoid Tissue Inducer cells, NK T-cells, NK cells (Eberl et al., *Nat. Immunol.* 5: 64-73, 2004) and gamma-delta T-cells (Sutton et al., *Nat. Immunol.* 31: 331-341, 2009; Louten et al., *J. Allergy Clin. Immunol.* 123: 1004-1011, 2009), suggesting an important function for RORgammaT in these subtypes of cells.

Based on the role of IL-17 producing cells (either Th17 or non-Th17 cells) RORgammaT has been identified as a key mediator in the pathogenesis of several diseases (Louten et al., *J. Allergy Clin. Immunol.* 123: 1004-1011, 2009; Annuziato et al., *Nat. Rev. Rheumatol.* 5: 325-331, 2009). This was confirmed using several disease models representative of autoimmune diseases. Genetic ablation of the RORgamma gene in mice prevented the development of experimental autoimmune diseases, such as experimental autoimmune encephalomyelitis (EAE) and colitis (Ivanov et al., *Cell* 126:1121-33, 2006; Buonocore et al., *Nature* 464: 1371-1375, 2010).

Being a critical mediator in Th17-cells and other non-Th17 cells, antagonism of the transcriptional activity of RORgammaT is expected to have a beneficial effect on autoimmune diseases, such as, but not limited to rheumatoid arthritis, psoriasis, multiple sclerosis, inflammatory bowel disease, Crohn's disease, and asthma (Annunziato et al., *Nat. Rev. Immunol.* 5: 325-331, 2009; Louten et al., *J. Allergy Clin. Immunol.* 123: 1004-1011, 2009). Antagonism of RORgammaT may also be beneficial in other diseases, which are characterized by increased levels of Th17 cells and/or elevated levels of Th17 hallmark cytokines such as IL-17, IL-22 and IL-23. Examples of such diseases are Kawasaki Disease (Jia et al., *Clin. Exp. Immunol.* 162: 131-137, 2010) and Hashimoto's thyroiditis (Figueroa-

Vega et al., *J. Clin. Endocrinol. Metab.* 95: 953-62, 2010). Another example includes infectious diseases, such as, but not limited to, mucosal leishmaniasis (Boaventura et al., *Eur. J. Immunol.* 40: 2830-2836, 2010). In each of the above examples the inhibition may be enhanced by simultaneous inhibition of RORalpha.

Compounds modulating RORgammaT have been reported. Examples of agonists include T0901317 and SR1078 (Wang et al., *ACS Chem. Biol.* 5:1029-1034, 2010). In addition, antagonist have been reported such as 7-oxygenated sterols (Wang et al., *J. Biol. Chem.* 285: 5013-5025, 2009) and compounds described in EP2181710 A1.

Numerous immune and inflammatory disorders continue to afflict millions of patients worldwide. Although significant advances have been made in treating these disorders, current therapies do not provide satisfactory results for all patients due to, for example, detrimental side effects or insufficient efficacy. One exemplary immue disorder in need of better therapy is psoriasis. Various therapeutics have been developed in an attempt to treat psoriasis. However, the traditional therapies for psoriasis often have toxic adverse effects. An exemplary inflammatory disorder in need of better treatment is rheumatoid arthritis. Numerous therapeutics have been developed in an attempt to treat this disorder. However, some patients develop resistance to current therapies.

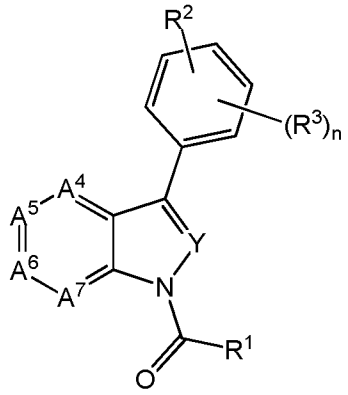
Accordingly, a need exists for improved treatments for immune disorders and inflammatory disorders. The present invention addresses this need and provides other related advantages.

SUMMARY OF THE INVENTION

The present invention provides compounds which alter the interaction of coregulator proteins with RORgammaT and thereby antagonize RORgammaT-mediated transcriptional ativity, their use for the treatment of RORgammaT-mediated diseases or conditions, in particular autoimmune diseases and inflammatory diseases, as well as pharmaceutical compositions comprising such compounds and pharmaceutical carriers.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a compound according to Formula I



I

or a pharmaceutically acceptable salt or solvate thereof wherein,

Y is CH, CR^a, or N;

n = 0, 1, 2, 3 or 4;

A^4 is CR^4 or N,

A^5 is CR^5 or N,

A^6 is CR^6 or N,

A^7 is CR^7 or N,

with the proviso that no more than one or two of A^4-A^7 can be N;

R^a is (C_{1-4})alkyl or (C_{3-7})cycloalkyl;

R^1 is

(i) (C_{3-12})carbocyclyl(C_{0-4})alkyl;

(ii) a 4- to 12-membered heterocyclyl(C_{0-4})alkyl, or

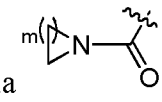
(iii) (C_{1-4})alkoxy,

each optionally substituted with one, two, three, four or five R^8;

R^2 is hydroxycarbonyl, hydroxycarbonyl(C_{1-10})alkyl, (C_{1-10})alkylsulfoxyaminocarbonyl, or carbamoyl;

R^3 is hydrogen, halogen, cyano, nitro, hydroxy, (C_{1-4})alkylcarbonyloxy, (C_{1-4}) alkylsulfonylamino, (C_{1-4}) alkylcarbonylamino, (C_{0-4}) alkylamino, (C_{1-4})alkyl, or $(C_{1-}$

$_4$)alkoxy, wherein (C_{1-4})alkyl and (C_{1-4})alkoxy are optionally substituted with one or more halogen;

R^4-R^7 independently are hydrogen, halogen, amino, cyano, hydroxy, (C_{1-3})alkoxy, (C_{1-4})alkyl, (C_{0-10})alkylaminocarbonyl, (C_{0-6})alkyoxycarbonylamino, (di)(C_{1-6})alkylaminocarbonyl, (C_{1-6})alkylcarbonylamino, (C_{1-4})alkylamino, amino(C_{1-4})alkyl or formaldehyde, wherein (C_{1-3})alkoxy, (C_{1-4})alkyl, (C_{0-10})alkyl)aminocarbonyl, (di)(C_{1-6})alkylaminocarbonyl, (C_{1-4})alkylamino and amino(C_{1-4})alkyl are optionally substituted with one or more halogen, hydroxyl or (C_{1-3})alkoxy; or a group having the formula  , optionally substituted with one or more of the following: (C_{1-10})alkyl, halogen, amino, cyano, hydroxy, (C_{1-3})alkoxy, and wherein m is 1, 2, 3, or 4;

R^6 is, additionally,

(i) (C_{3-7})cycloalkyl or (C_{3-5})heterocycloalkyl, both optionally substituted with one or more groups selected from halogen, amino, amino(C_{1-4})alkyl, cyano, nitro, hydroxyl, oxo (=O), $H_2NC(O)$, (C_{1-3})alkoxycarbonyl, (di)(C_{1-6})alkylaminocarbonyl, (C_{1-4})alkyl or (C_{1-3})alkoxy, wherein (C_{1-3})alkoxycarbonyl, (di)(C_{1-6})alkylaminocarbonyl, (C_{1-4})alkyl and (C_{1-3})alkoxy are optionally substituted with one or more halogen, amino or hydroxyl;

(ii) (C_{2-9})heteroaryl, optionally substituted with one or more groups selected from halogen, amino, amino(C_{1-4})alkyl, cyano, nitro, hydroxyl, oxo (=O), $H_2NC(O)$, (C_{1-3})alkoxycarbonyl, (di)(C_{1-6})alkylaminocarbonyl, (C_{1-4})alkyl or (C_{1-3})alkoxy, wherein (C_{1-3})alkoxycarbonyl, (di)(C_{1-6})alkylaminocarbonyl, (C_{1-4})alkyl and (C_{1-3})alkoxy are optionally substituted with one or more halogen, amino or hydroxyl;

(iii) (C_{6-14})aryl, optionally substituted with one or more groups selected from halogen, amino, amino(C_{1-4})alkyl, cyano, nitro, hydroxyl, oxo (=O), $H_2NC(O)$, (C_{1-3})alkoxycarbonyl, (di)(C_{1-6})alkylaminocarbonyl, (C_{1-4})alkyl or (C_{1-3})alkoxy, wherein (C_{1-3})alkoxycarbonyl, (di)(C_{1-6})alkylaminocarbonyl, (C_{1-4})alkyl and (C_{1-3})alkoxy are optionally substituted with one or more halogen, amino or hydroxyl;

(iv) (C_{3-5})heterocycloalkylcarbonyl, optionally substituted with one or more groups selected from halogen, amino, amino(C_{1-4})alkyl, cyano, nitro, hydroxyl, oxo (=O), $H_2NC(O)$, (C_{1-3})alkoxycarbonyl, (di)(C_{1-6})alkylaminocarbonyl, (C_{1-4})alkyl or (C_{1-3})alkoxy, wherein (C_{1-3})alkoxycarbonyl, (di)(C_{1-6})alkylaminocarbonyl, (C_{1-4})alkyl

and (C_{1-3})alkoxy are optionally substituted with one or more halogen, amino or hydroxyl;

(v) (C_{3-5})heterocycloalkylamino, optionally substituted with one or more groups selected from halogen, amino, amino(C_{1-4})alkyl, cyano, nitro, hydroxyl, oxo (=O), $H_2NC(O)$, (C_{1-3})alkoxycarbonyl, (di)(C_{1-6})alkylaminocarbonyl, (C_{1-4})alkyl or (C_{1-3})alkoxy, wherein (C_{1-3})alkoxycarbonyl, (di)(C_{1-6})alkylaminocarbonyl, (C_{1-4})alkyl and (C_{1-3})alkoxy are optionally substituted with one or more halogen, amino or hydroxyl;

(vi) (C_{3-5})cycloalkylaminocarbonyl, optionally substituted with one or more groups selected from halogen, amino, amino(C_{1-4})alkyl, cyano, nitro, hydroxyl, oxo (=O), $H_2NC(O)$, (C_{1-3})alkoxycarbonyl, (di)(C_{1-6})alkylaminocarbonyl, (C_{1-4})alkyl or (C_{1-3})alkoxy, wherein (C_{1-3})alkoxycarbonyl, (di)(C_{1-6})alkylaminocarbonyl, (C_{1-4})alkyl and (C_{1-3})alkoxy are optionally substituted with one or more halogen, amino or hydroxyl;

(vii) (C_{3-5})cycloalkylcarbonylamino, optionally substituted with one or more groups selected from halogen, amino, amino(C_{1-4})alkyl, cyano, nitro, hydroxyl, oxo (=O), $H_2NC(O)$, (C_{1-3})alkoxycarbonyl, (di)(C_{1-6})alkylaminocarbonyl, (C_{1-4})alkyl or (C_{1-3})alkoxy, wherein (C_{1-3})alkoxycarbonyl, (di)(C_{1-6})alkylaminocarbonyl, (C_{1-4})alkyl and (C_{1-3})alkoxy are optionally substituted with one or more halogen, amino or hydroxyl;

(viii) (C_{3-5})cycloalkyl(C_{1-4})alkyl, optionally substituted with one or more groups selected from halogen, amino, amino(C_{1-4})alkyl, cyano, nitro, hydroxyl, oxo (=O), $H_2NC(O)$, (C_{1-3})alkoxycarbonyl, (di)(C_{1-6})alkylaminocarbonyl, (C_{1-4})alkyl or (C_{1-3})alkoxy, wherein (C_{1-3})alkoxycarbonyl, (di)(C_{1-6})alkylaminocarbonyl, (C_{1-4})alkyl and (C_{1-3})alkoxy are optionally substituted with one or more halogen, amino or hydroxyl;

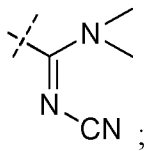
(ix) (C_{3-5})cycloalkylamino, optionally substituted with one or more groups selected from halogen, amino, amino(C_{1-4})alkyl, cyano, nitro, hydroxyl, oxo (=O), $H_2NC(O)$, (C_{1-3})alkoxycarbonyl, (di)(C_{1-6})alkylaminocarbonyl, (C_{1-4})alkyl or (C_{1-3})alkoxy, wherein (C_{1-3})alkoxycarbonyl, (di)(C_{1-6})alkylaminocarbonyl, (C_{1-4})alkyl and (C_{1-3})alkoxy are optionally substituted with one or more halogen, amino or hydroxyl;

(x) (C_{3-5})cycloalkylcarbonyl, optionally substituted with one or more groups selected from halogen, amino, amino(C_{1-4})alkyl, cyano, nitro, hydroxyl, oxo (=O), $H_2NC(O)$, (C_{1-3})alkoxycarbonyl, (di)(C_{1-6})alkylaminocarbonyl, (C_{1-4})alkyl or (C_{1-3})alkoxy, wherein (C_{1-3})alkoxycarbonyl, (di)(C_{1-6})alkylaminocarbonyl, (C_{1-4})alkyl and (C_{1-3})alkoxy are optionally substituted with one or more halogen, amino or hydroxyl;

(xi) (C_{2-9})heteroaryl(C_{1-4})alkyl, optionally substituted with one or more groups selected from halogen, amino, amino(C_{1-4})alkyl, cyano, nitro, hydroxyl, oxo (=O), $H_2NC(O)$, (C_{1-3})alkoxycarbonyl, (di)(C_{1-6})alkylaminocarbonyl, (C_{1-4})alkyl or (C_{1-3})alkoxy, wherein (C_{1-3})alkoxycarbonyl, (di)(C_{1-6})alkylaminocarbonyl, (C_{1-4})alkyl and (C_{1-3})alkoxy are optionally substituted with one or more halogen, amino or hydroxyl;

(xii) (C_{2-9})heteroarylcarbonyl, optionally substituted with one or more groups selected from halogen, amino, amino(C_{1-4})alkyl, cyano, nitro, hydroxyl, oxo (=O), $H_2NC(O)$, (C_{1-3})alkoxycarbonyl, (di)(C_{1-6})alkylaminocarbonyl, (C_{1-4})alkyl or (C_{1-3})alkoxy, wherein (C_{1-3})alkoxycarbonyl, (di)(C_{1-6})alkylaminocarbonyl, (C_{1-4})alkyl and (C_{1-3})alkoxy are optionally substituted with one or more halogen, amino or hydroxyl;

(xiii)



;

(xiv) (C_{2-4})alkynyl, optionally substituted with one or more (C_{1-4})alkyl, which (C_{1-4})alkyl may be substituted with hydroxyl or amino; or

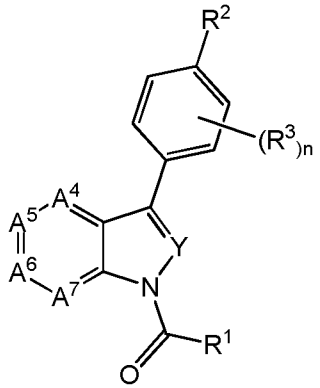
(xv) (C_{1-6})alkoxycarbonylamino,
(C_{1-6})alkylcarbonylamino,
(C_{1-6})alkylsulfonylamino(C_{0-4})alkyl,
(C_{1-6})alkylaminocarbonylamino,
(C_{1-6})alkyoxycarbonylamino(C_{0-4})alkyl,
Hydroxycarbonyl(C_{1-4})alkylamino,
Hydroxycarbonyl, or
(C_{1-6})alkylamino,

each optionally substituted with one or more (C_{1-4})alkyl, hydroxyl or amino;

R^8 is halogen, cyano, amino, nitro, hydroxy, oxo(=O), $H_2NC(O)$-, (C_{1-3})alkoxycarbonyl, (di)(C_{1-6})alkylaminocarbonyl, (C_{1-4})alkyl, (C_{3-7})cycloalkyl, (C_{3-5})heterocycloalkyl, (C_{1-4})alkenyl, (C_{3-6})cycloalkoxy or (C_{1-3})alkoxy, wherein (C_{1-3})alkoxycarbonyl, (di)(C_{1-6})alkylaminocarbonyl, (C_{1-4})alkyl and (C_{1-3})alkoxy are optionally substituted with one, two or three halogens; and

x is 0, 1, 2, 3, 4 or 5.

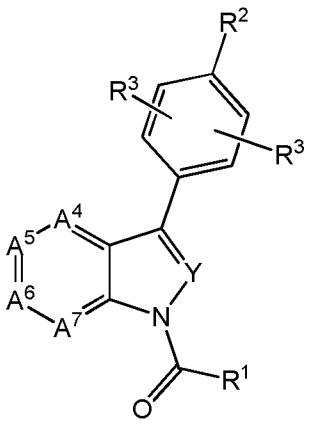
In a first embodiment of the compound having Formula I is a compound of having Formula Ia



Ia

and a pharmaceutically acceptable salt or solvate thereof.

In a second embodiment of the compound having Formula I is a compound of claim 1 having Formula Ib

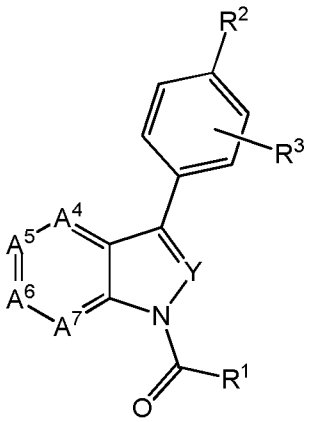


Ib

and a pharmaceutically acceptable salt or solvate thereof.

In a first subset of the invention is a compound wherein Y is N.

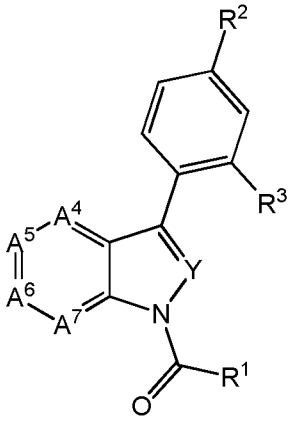
In a third embodiment of the compound having Formula I is a compound having Formula Ic



Ic

and a pharmaceutically acceptable salt or solvate thereof.

In a fourth embodiment of the compound having Formula I is a compound having Formula Id

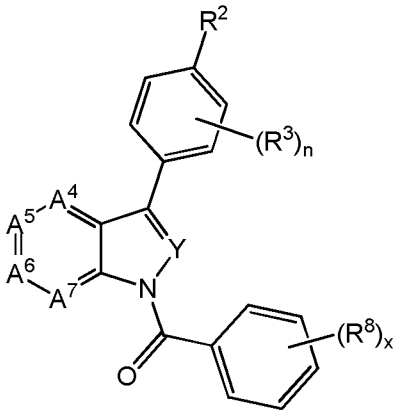


Id

and a pharmaceutically acceptable salt or solvate thereof.

In a first subset of the fourth embodiment is a compound wherein Y is N.

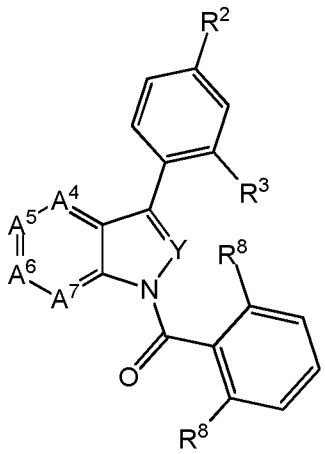
In a first subset of the first embodiment is a compound having Formula Ie



Ie

and a pharmaceutically acceptable salt or solvate thereof.

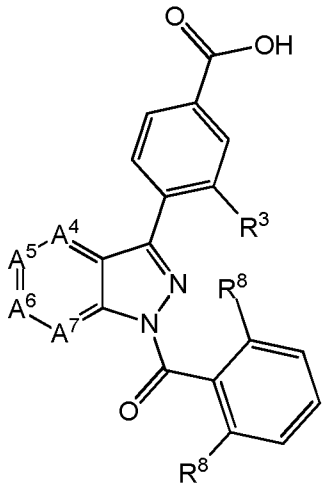
In a second subset is a compound having Formula If



If

and a pharmaceutically acceptable salt or solvate thereof.

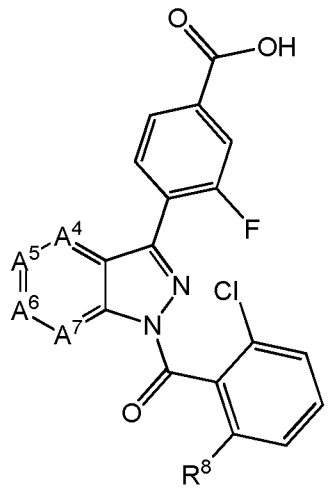
In a third subset is a compound having Formula Ig



Ig

and a pharmaceutically acceptable salt or solvate thereof.

In a fourth subset is a compound having Formula Ih



Ih

and a pharmaceutically acceptable salt or solvate thereof.

In a fifth subset of the first embodiment is a compound wherein A^4, A^5, A^6, A^7 are selected from the group consisting of: (i) CR^4, CR^5, CR^6, CR^7; (ii) N, CR^5, CR^6, CR^7; (iii) CR^4, N, CR^6, CR^7; (iv) CR^4, CR^5, N, CR^7; (v) CR^4, CR^5, CR^6, N; (vi) N, N, CR^6,CR^7; (vii) CR^4, N, N, CR^7; (viii) CR^4, CR^5, N, N; (ix) N, CR^5, N, CR^7; (x) CR^4, N, CR^6, N; and (xi) N, CR^5, CR^6, N.

In a sixth subset is a compound wherein A^4, A^5, A^6, A^7 are selected from the group consisting of: (i) CR^4, CR^5, CR^6, CR^7; (ii) N, CR^5, CR^6, CR^7; and (iii) CR^4, N, CR^6, CR^7.

In a seventh subset is a compound wherein A^4, A^5, A^6, A^7 is (i) CR^4, CR^5, CR^6, CR^7, or (ii) N, CR^5, CR^6, CR^7; and Y is N.

In an eighth subset is a compound wherein R^1 is

(i) (C_{3-7})cycloalkyl or (C_{3-5})heterocycloalkyl, both optionally substituted with one or more R^8;

(ii) (C_{2-9})heteroaryl(C_{0-4})alkyl, optionally substituted with one or more R^8; or

(iii) (C_{6-14})aryl(C_{0-4})alkyl, optionally substituted with one or more R^8.

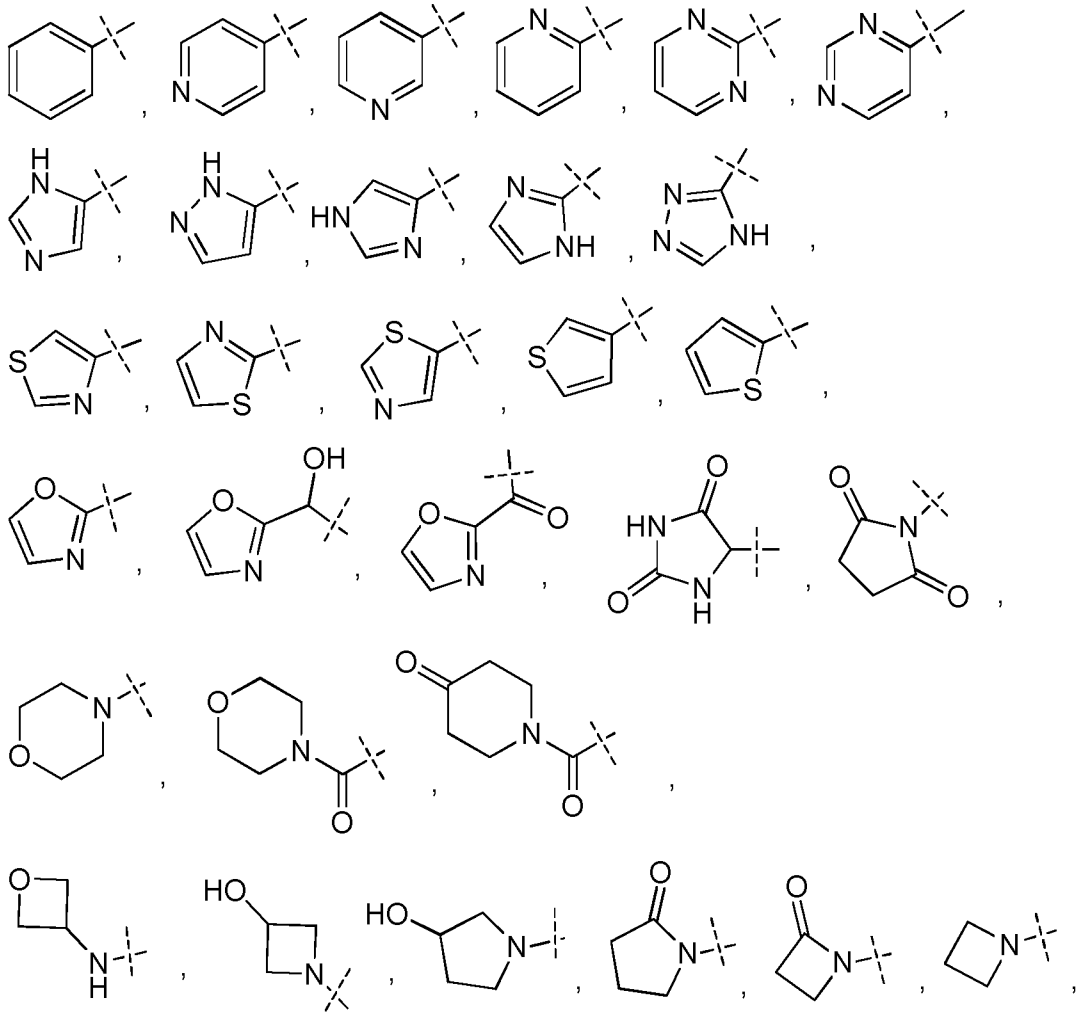
In a ninth subset is a compound wherein R^1 is (i) (C_{2-9})heteroaryl, or (ii) (C_{6-14})aryl, optionally substituted with one, two, three, four or five R^8.

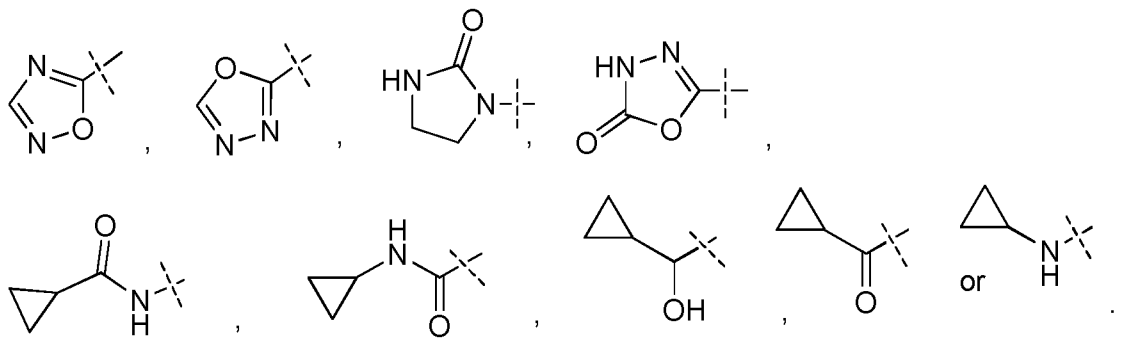
In a tenth subset is a compound wherein R^1 is (C_{6-14})aryl, optionally substituted with one or two R^8.

In an eleventh subset is a compound wherein R^1 is phenyl, optionally substituted with one or two R^8.

In a twelfth subset is a compound wherein R^2 is C(O)OH.

In a thirteenth subset is a compoundwherein R^6 is





A still further embodiment of the compounds of Formula I, Ia, Ib, Ic, Id, Ie, If, Ig and Ih, are compounds wherein one of R^4, R^5, R^6, and R^7 is other than hydrogen.

The invention also relates to those compounds wherein all specific definitions for A^1 through A^4, R^1 through R^8, R^a, Y, m, n and x and all substituent groups in the various aspects of the inventions defined here above occur in any combination within the definition of the compound of Formula I.

Non-limiting examples of the compounds of the present invention include:

(E)-4-(1-(2-chloro-6-(prop-1-enyl)benzoyl) -1H-pyrazolo[4,3-b]pyridin-3-yl)-3-fluorobenzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-4- formyl-1H-indazol-3-yl)benzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-1H- pyrazolo[4,3-b]pyridin-3-yl)-1H-indazole-7-carboxylic acid;

4-(1-(2-chloro-6-cyclopropoxybenzoyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)benzoic acid;

3-fluoro-4-(1-(2-phenylpropanoyl)-1H-indazol-3-yl)benzoic acid;

3-fluoro-4-[1-(methoxyacetyl)-1H-indazol-3-yl]benzoic acid;

3-fluoro-4-[1-(pyridin-3-ylcarbonyl)-1Hindazol-3-yl]benzoic acid;

3-fluoro-4-{1-[(2-oxopyrrolidin-1-yl)acetyl]-1Hindazol-3-yl}benzoic acid;

3-fluoro-4-[1-(naphthalen-1-ylcarbonyl)-1Hindazol-3-yl]benzoic acid;

3-fluoro-4-{1-[(1-methyl-1H-indol-2-yl)carbonyl]-1Hindazol-3-yl}benzoic acid;

4-{1-[(2-bromo-3-methylphenyl)carbonyl]-1H-indazol-3-yl}-3-fluorobenzoic acid;

4-[1-(2,3-dihydro-1H-inden-4-ylcarbonyl)-1Hindazol-3-yl]-3-fluorobenzoic acid;

4-(1-{[3-(tertbutoxycarbonyl)-3-azabicyclo[3.1.0]hex-6-yl]carbonyl}-1H-indazol-3-yl)-3-

fluorobenzoic acid;

4-[1-(2,3-dihydro-1-benzofuran-7-ylcarbonyl)-1Hindazol-3-yl]-3-fluorobenzoic acid;

4-[1-(1-benzofuran-7-ylcarbonyl)-1Hindazol-3-yl]-3-fluorobenzoic acid;

4-{1-[(2-bromo-3-chlorophenyl)carbonyl]-1H-indazol-3-yl}-3-fluorobenzoic acid;

3-fluoro-4-(1-(tetrahydrofuran-2-carbonyl)-1H-indazol-3-yl)benzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6- (morpholine-4-carbonyl)-1H-indazol-3-yl)benzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-((2S,6R)-2,6-dimethylmorpholine-4-carbonyl)-1H-indazol-3-yl)-3-fluorobenzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(4-oxopiperidine-1-carbonyl)-1H-indazol-3-yl)-3-fluorobenzoic acid;

2-acetamido-4-(1-(2-chloro-6-(trifluoromethyl) benzoyl)-1H-indazol -3-yl)benzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)-2-(methylsulfonamido)benzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl) benzoyl)-6- (3-hydroxyazetidin-1-yl)-1H-indazol-3-yl)benzoic acid;

4-(6-(azetidin-1-yl)-1-(2-chloro-6-(trifluoromethyl)benzoyl)-1H-indazol-3-yl)-3-fluorobenzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(cyclopropylamino)-1H-indazol-3-yl)-3-fluorobenzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(oxetan-3-ylamino)-1H-indazol-3-yl)-3-fluorobenzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(3-hydroxypyrrolidin-1-yl)-1H-indazol-3-yl)-3-fluorobenzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-morpholino-1H-indazol-3-yl)benzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6- (methoxycarbonylamino)-1H-indazol-3-yl)-3-fluorobenzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(N- methylacetamido)-1H-indazol-3-yl)-3-fluorobenzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(cyclopropanecarboxamido)-1H-indazol-3-yl)-3-fluorobenzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(methylsulfonamido)-1H-indazol-3-yl)-3-fluorobenzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(3-methylureido)-1H-indazol-3-yl)-3-fluorobenzoic acid;

4-(6-acetamido-1-(2-chloro-6-(trifluoromethyl)benzoyl)-1H-indazol-3-yl)-3-fluorobenzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(N-methylmethylsulfonamido)-1H-indazol-3-yl)-3-fluorobenzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(1,3-dimethylureido)-1H-indazol-3-yl)-3-fluorobenzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(2-oxo- imidazolidin-1-yl)-1H-indazol-3-yl)-3-fluorobenzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6- (2-oxoazetidin-1-yl)-1H-indazol-3-yl)-3-fluorobenzoic acid;

4-(6-(2-carboxyethylamino)-1-(2-chloro-6- (trifluoromethyl)benzoyl)-1H-indazol-3-yl)-3-fluorobenzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(3-methyl-2-oxoimidazolidin-1-yl)-1H-indazol-3-yl)-3-fluorobenzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(2-oxopyrrolidin-1-yl)-1H-indazol-3-yl)-3-fluorobenzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(mor pholine-4-carbonyl)-1H-indazol-3-yl)benzoic acid;

3-(4-carboxyphenyl)-1-(2-chloro-6-(trifluoromethyl) benzoyl)-1H-indazole-6-carboxylic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(cyclopropylcarbamoyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)-3-fluorobenzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(cyclopropyl(methyl)carbamoyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)-3-fluorobenzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6- (cyclo Propyl (hydroxy)methyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)-3-fluorobenzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(cyclop ropane-carbonyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)-3-fluorobenzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(hydroxy(oxazol-2-yl)methyl)-1H-pyrazolo[4,3-b]pyridine-3-yl)-3-fluorobenzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(oxazole-2-carbonyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)-3-fluorobenzoic acid;

sodium 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(5-methyloxazol-2-yl)-1H-indazol-3-yl)benzoate;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(5-methyloxazol-2-yl)-1H-indazol-3-yl)-3-fluorobenzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(3-hydroxyprop-1-ynyl)-1H-indazol-3-yl)benzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(3-hydroxybut-1-ynyl)-1H-indazol-3-yl)-3-fluorobenzoic acid;

4-(6-(3-aminoprop-1-ynyl)-1-(2-chloro-6-(trifluo romethyl)benzoyl)-1H-indazol-3-yl)-3-fluorobenzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl) -6-ethynyl-1H-indazol-3-yl)benzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(3-methyl-1,2,4-oxadiazol-5-yl)-1H-indazol-3-yl)-3-fluorobenzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(5-(hydroxymethyl)oxazol-2-yl)-1H-indazol-3-yl)-3-fluorobenzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(1-methyl-1H-imidazol-4-yl)-1H-indazol-3-yl)-3-fluorobenzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(oxazol-2-yl)-1H-indazol-3-yl)-3-fluorobenzoic acid;

4-(6-(5-bromooxazol-2-yl)-1-(2-chloro-6-(trifluoromethyl)benzoyl)-1H-indazol-3-yl)-3-fluorobenzoic acid;

(E)-4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(N'-cyano-N,N-dimethylcarbamimidoyl)-1H-indazol-3-yl)-3-fluorobenzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-1H-indazol-3-yl)-3-fluorobenzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(4H-1,2,4-triazol-3-yl)-1H-indazol-3-yl)-3-fluorobenzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-indazol-3-yl)-3-fluorobenzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(1-methyl-1H-imidazol-2-yl)-1H-indazol-3-yl)-3-fluorobenzoic acid;

4-(1-(2-chloro-6-trifluorobenzoyl)-6-(thiazol-2-yl)-1H-indazol-3-yl)benzoic acid;

4-[1-{[2-chloro-6-(trifluoromethyl)phenyl]carbonyl}-6-(1-methyl-1H-imidazol-5-yl)-1H-indazol-3-yl]benzoic acid;

4-[1-{[2-chloro-6-(trifluoromethyl)phenyl]carbonyl}-6-(5-methylthiophen-3-yl)-1H-indazol-3-yl]benzoic acid;

4-(1-{[2-chloro-6-(trifluoromethyl)phenyl]carbonyl}-6-pyrimidin-2-yl-1H-indazol-3-yl)benzoic acid;

4-(1-{[2-chloro-6-(trifluoromethyl)phenyl]carbonyl}-6-pyrimidin-4-yl-1H-indazol-3-yl)benzoic acid;

4-[1-{[2-chloro-6-(trifluoromethyl)phenyl]carbonyl}-6-(1-methyl-1H-imidazol-4-yl)-1H-indazol-3-yl]benzoic acid;

4-[1-{[2-chloro-6-(trifluoromethyl)phenyl]carbonyl}-6-(1,3-thiazol-4-yl)-1H-indazol-3-yl]benzoic acid;

4-(6-[4-(aminomethyl)pyridin-2-yl]-1-{[2-chloro-6-(trifluoromethyl)phenyl]carbonyl}-1H-indazol-3-yl)benzoic acid;

4-(1-{[2-chloro-6-(trifluoromethyl)phenyl]carbonyl}-6-pyridin-2-yl-1H-indazol-3-yl)benzoic acid;

4-[1-{[2-chloro-6-(trifluoromethyl)phenyl]carbonyl}-6-(1,3-thiazol-5-yl)-1H-indazol-3-yl]benzoic acid;

4-(1-(2-chloro-6-trifluorobenzoyl)-6-(thiazol-2-yl)-1H-indazol-3-yl)benzoic acid;

4-(1-{[2-chloro-6-(trifluoromethyl)phenyl]carbonyl}-6-pyridin-4-yl-1H-indazol-3-yl)benzoic acid;

4-[1-{[2-chloro-6-(trifluoromethyl)phenyl]carbonyl}-6-(4-cyanophenyl)-1H-indazol-3-yl]benzoic acid;

4-[1-{[2-chloro-6-(trifluoromethyl)phenyl]carbonyl}-6-(3-cyanophenyl)-1H-indazol-3-yl]benzoic acid;

4-[1-{[2-chloro-6-(trifluoromethyl)phenyl]carbonyl}-6-(2-cyanophenyl)-1H-indazol-3-yl]benzoic acid;

4-[1-{[2-chloro-6-(trifluoromethyl)phenyl]carbonyl}-6-(2-fluorophenyl)-1H-indazol-3-yl]benzoic acid;

4-[1-{[2-chloro-6-(trifluoromethyl)phenyl]carbonyl}-6-(3-fluorophenyl)-1H-indazol-3-yl]benzoic acid;

4-[1-{[2-chloro-6-(trifluoromethyl)phenyl]carbonyl}-6-(4-fluorophenyl)-1H-indazol-3-yl]benzoic acid;

4-[1-{[2-chloro-6-(trifluoromethyl)phenyl]carbonyl}-6-(1-methyl-1H-pyrazol-5-yl)-1H-indazol-3-yl]benzoic acid;

methyl 4-(1-(2-chloro-6-trifluorobenzoyl)-6-(4-hydroxyphenyl)-1H-indazol-3-yl)benzoate;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6- (methylsulfonamidomethyl)-1H-indazol-3-yl)benzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(2,5- dioxoimidazolidin-4-yl)-1H-indazol-3-yl)-3-fluorobenzoic acid;

4-(5-(tert-butoxycarbonylamino)-1-(2-chloro-6- (trifluoromethyl)benzoyl)-1H-pyrrolo[2,3-c]pyridin-3-yl)-3-fluorobenzoic acid;

4-(6-(tert-butoxycarbonylamino)-1-(2-chloro-6- (trifluoromethyl)benzoyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)-3-fluorobenzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(methylamino)-1H- pyrazolo[4,3-b]pyridin-3-yl)-3-fluorobenzoic acid;

4-(5-acetamido-1-(2-chloro-6-(trifluoromethyl)- benzoyl)-1H-pyrrolo[2,3-c]pyridin-3-yl)-3-fluorobenzoic acid; and

4-(1-(2- chloro-6-(trifluoromethyl)benzoyl)-5-(methylamino)-1H-pyrrolo[2,3-c]pyridin-3-yl)-3-fluorobenzoic acid.

The terms used herein have their ordinary meaning and the meaning of such terms is independent at each occurrence thereof. That notwithstanding, and except where stated otherwise, the following definitions apply throughout the specification and claims. Chemical names, common names, and chemical structures may be used interchangeably to describe the same structure. If a chemical compound is referred to using both a chemical structure and a chemical name, and an ambiguity exists between the structure and the name, the structure predominates. These definitions apply regardless of whether a term is used by itself or in combination with other terms, unless otherwise indicated. Hence, the definition of "alkyl"

applies to "alkyl" as well as the "alkyl" portions of "hydroxyalkyl," "fluoroalkyl," "alkoxy", etc.

As used herein, and throughout this disclosure, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

The term "alkyl," as used herein, refers to an aliphatic hydrocarbon group having one of its hydrogen atoms replaced with a bond having the specified number of carbon atoms. In different embodiments, an alkyl group contains, for example, from 1 to 6 carbon atoms (C_1-C_6 alkyl) or from 1 to 3 carbon atoms (C_1-C_3 alkyl). Non-limiting examples of alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, neopentyl, isopentyl, n-hexyl, isohexyl and neohexyl. In one embodiment, an alkyl group is linear. In another embodiment, an alkyl group is branched.

Unless specified otherwise, "alkyl" includes both branched- and straight-chain saturated aliphatic hydrocarbon groups, including all isomers, having the specified number of carbon atoms; for example, "$C_{1\text{-}6}$ alkyl" (or "C_1-C_6 alkyl") includes all of the hexyl alkyl and pentyl alkyl isomers as well as n-, iso-, sec- and t-butyl, n- and isopropyl, ethyl and methyl. "Alkylene" refers to both branched- and straight-chain saturated aliphatic hydrocarbon groups, including all isomers, having the specified number of carbons, and having two terminal end chain attachments; for example, the term "A-C_4alkylene-B" represents, for example, A-CH_2-CH_2-CH_2-CH_2-B, A-CH_2-CH_2-$CH(CH_3)$-CH_2-B, A-CH_2-$CH(CH_2CH_3)$-B, A-CH_2-$C(CH_3)(CH_3)$-B, and the like. "Alkoxy" represents a linear or branched alkyl group of indicated number of carbon atoms attached through an oxygen bridge; for example "C_1-C_6 alkoxy" includes -OCH_3, -OCH_2CH_3, -$OCH(CH_3)_2$, -$O(CH_2)_5CH_3$, and the like.

Unless otherwise specifically noted as only "unsubstituted" or only "substituted", alkyl groups are unsubstituted or substituted with 1 to 3 substituents on each carbon atom, with halo, C_1-C_{20} alkyl, CF_3, NH_2, $N(C_1$-C_6 alkyl$)_2$, NO_2, oxo, CN, N_3, -OH, -$O(C_1$-C_6 alkyl), C_3-C_{10} cycloalkyl, $(C_{3\text{-}7})$cycloalkyl, $(C_{3\text{-}5})$heterocycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, (C_0-C_6 alkyl) $S(O)_{0\text{-}2}$-, (C_0-C_6 alkyl)$S(O)_{0\text{-}2}$(C_0-C_6 alkyl)-, (C_0-C_6 alkyl)C(O)NH-, H_2N-C(NH)-, H_2N-C(O)(NH)-, -$O(C_1$-C_6 alkyl)CF_3, (C_0-C_6 alkyl)C(O)-, (C_0-C_6 alkyl)OC(O)-, (C_0-C_6 alkyl)$O(C_1$-C_6 alkyl)-, (C_0-C_6 alkyl)$C(O)_{1\text{-}2}$(C_0-C_6 alkyl)-, (C_0-C_6 alkyl)OC(O)NH-, -$NH(C_1$-C_6 alkyl)NHC(O)NH(C_1-C_6 alkyl), NHC(O)OC_1-C_6 alkyl, -$NH(C_1$-C_6 alkyl)$NHSO_2(C_1$-C_6 alkyl), -(C_0-C_6 alkyl)$NHSO_2(C_1$-C_6 alkyl), aryl, aralkyl, heterocycle, heterocyclylalkyl, halo-

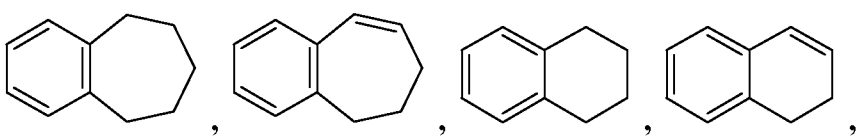
aryl, halo-aralkyl, halo-heterocycle, halo-heterocyclylalkyl, cyano-aryl, cyano-aralkyl, cyano-heterocycle and cyano-heterocyclylalkyl.

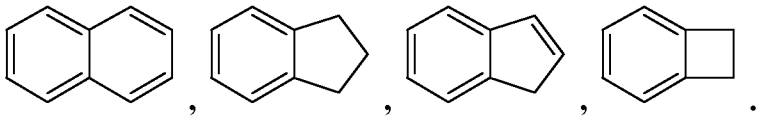
The term "alkenyl" means a straight or branched carbon chain having the specified number of carbon atoms with at least one carbon-carbon double bond. Examples of alkenyl include, but are not limited to, vinyl, allyl, isopropenyl, pentenyl, hexenyl, heptenyl, 1-propenyl, 2-butenyl, 2-methyl-2-butenyl, 2,4-hexadienyl, and the like.

The term "alkynyl" means a straight or branched carbon chain having the specified number of carbon atoms with at least one carbon-carbon triple bond. Examples of alkynyl include, but are not limited to ethynyl, propargyl, 1-propynyl, 2-butynyl, and the like.

The term “carbocycle” (and variations thereof such as “carbocyclic” or “carbocyclyl”) as used herein, unless otherwise indicated, refers to (i) a C_3 to C_8 monocyclic, saturated or unsaturated ring or (ii) a C_7 to C_{12} bicyclic saturated or unsaturated ring system. Each ring in (ii) is either attached via a bond to, or fused (including spirofused) to, the other ring, and each ring is saturated or unsaturated. The carbocycle may be attached to the rest of the molecule at any carbon atom which results in a stable compound.

Saturated carbocyclics form a subset of carbocycles in which the entire ring system (mono- or polycyclic) is saturated. Saturated monocyclic carbocyclic rings are also referred to as cycloalkyl rings, e.g., cyclopropyl, cyclobutyl, etc. The fused bicyclic carbocycles are a further subset of the carbocycles in which a C_7 to C_{10} bicyclic ring system in which each ring is saturated or unsaturated and two adjacent carbon atoms (or in the case of spirofused, one carbon atom) are shared by each of the rings in the ring system. A saturated bicyclic carbocycle is one in which both rings are saturated. An unsaturated bicyclic carbocycle is one in which one ring is unsaturated and the other is unsaturated or saturated. Unless otherwise noted, carbocycle is unsubstituted or substituted with C_{1-6} alkyl, C_{1-6} alkenyl, C_{1-6} alkynyl, aryl, halogen, NH_2 or OH. A subset of the fused bicyclic unsaturated carbocycles are those bicyclic carbocycles in which one ring is a benzene ring and the other ring is saturated or unsaturated, with attachment via any carbon atom that results in a stable compound. Representative examples of this subset include the following:



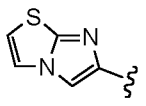
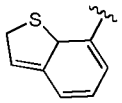


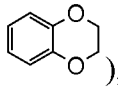
Aromatic carbocycles form another subset of the carbocycles. The term "aryl" refers to aromatic mono- and poly-carbocyclic ring systems in which the individual carbocyclic rings in the polyring systems are fused or attached to each other via a single bond. Suitable aryl groups include phenyl, naphthyl, and biphenyl.

The term “cycloalkyl” means a cyclic ring of an alkane having the specified total ring carbon atoms; for example cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl.

The term “heterocycle” (and variations thereof such as “heterocyclic” or “heterocyclyl”) broadly refers to (i) a stable 4- to 8-membered, saturated or unsaturated monocyclic ring, or (ii) a stable 7- to 12-membered bicyclic ring system, wherein each ring in (ii) is either attached via a bond to, or fused (including spirofused) to, the other ring, and each ring is saturated or unsaturated, and the monocyclic ring or bicyclic ring system contains one or more heteroatoms (e.g., from 1 to 6 heteroatoms, or from 1 to 4 heteroatoms) selected from N, O and S and a balance of carbon atoms (the monocyclic ring typically contains at least one carbon atom and the ring systems typically contain at least two carbon atoms); and wherein any one or more of the nitrogen and sulfur heteroatoms is optionally oxidized, and any one or more of the nitrogen heteroatoms is optionally quaternized. Unless otherwise specified, the heterocyclic ring may be attached at any heteroatom or carbon atom, provided that attachment results in the creation of a stable structure. Unless otherwise specified, when the heterocyclic ring has substituents, it is understood that the substituents may be attached to any atom in the ring, whether a heteroatom or a carbon atom, provided that a stable chemical structure results.

Saturated heterocyclics form a subset of the heterocycles; i.e., the term "saturated heterocyclic" generally refers to a heterocycle as defined above in which the entire ring system (whether mono- or poly-cyclic) is saturated. The term "saturated heterocyclic ring" refers to a 4- to 8-membered saturated monocyclic ring or a stable 7- to 12-membered bicyclic ring system which consists of carbon atoms and one or more heteroatoms selected from N, O and S. Representative examples include piperidinyl, piperazinyl, azepanyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, oxazolidinyl, isoxazolidinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, isothiazolidinyl, 1,4-dioxanyl, 1,4-thioxanyl, tetrahydropyranyl, tetrahydrofuryl (or tetrahydrofuranyl), tetrahydrothienyl, and tetrahydrothiopyranyl.

Heteroaromatics form another subset of the heterocycles; i.e., the term "heteroaromatic" (alternatively "heteroaryl") generally refers to a heterocycle as defined above in which the entire ring system (whether mono- or poly-cyclic) is an aromatic ring system. The term "heteroaromatic ring" refers a 5- or 6-membered monocyclic aromatic ring or a 7- to 12-membered bicyclic aromatic ring, and which consists of carbon atoms and one or more heteroatoms selected from N, O and S. In the case of substituted heteroaryl rings containing at least one nitrogen atom (e.g., pyridine), such substitutions can be those resulting in N-oxide formation. Representative examples of monocyclic heteroaromatic rings include pyridyl, pyrrolyl, pyrazinyl, pyrimidinyl, pyridazinyl, thienyl (or thiophenyl), thiazolyl, furanyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, and thiadiazolyl. Examples of bicyclic heteroaromatic rings include benzotriazolyl, indolyl, benzoxazolyl, benzofuranyl, benzothienyl, benzothiazolyl, benzimidazolyl, isoindolyl, indazolyl, quinoxalinyl, quinazolinyl, cinnolinyl, quinolinyl, isoquinolinyl, naphthyridinyl, pyrazolo[3,4-b]pyridine, imidazo[2,1-b](1,3)thiazole, (i.e., ), 6-(1-pyrrolyl)-3-pyridyl, 4-(1-pyrrolyl)phenyl, 4-(pyrid-3-yl)phenyl, 4-(pyrid-4-yl)phenyl, and benzothiophenyl (i.e. ).

Another subset of heterocycles is unsaturated heterocycles in which one or both rings are unsaturated (provided the entire ring system is not aromatic). Representative examples of unsaturated heterocycles include dihydrofuranyl, dihydrothienyl, dihydropyranyl, dihydroimidazolyl, indolinyl, isoindolinyl, chromanyl, isochromanyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, tetrahydronaphthyridinyl, 2,3-dihydrobenzofuranyl, 1,4-benzoxazinyl, 1,3-benzoxazolinyl, 2,3-dihydrobenzo-1,4-dioxinyl (i.e., ), and benzo-1,3-dioxolyl (i.e., ). In certain contexts herein,  is alternatively referred to as phenyl having as a substituent methylenedioxy attached to two adjacent carbon atoms. Also included are groups such as chromone and coumarin.

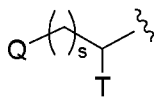
Unless otherwise specifically noted as only unsubstituted or only substituted, cycloalkyl, cycloalkenyl, heterocycloalkyl, aryl (including phenyl) and heteroaryl groups are unsubstituted or substituted (also referred to as "optionally substituted"). Unless the

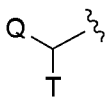
substituents are specifically provided, substituents for substituted or optionally substituted cycloalkyl, heterocycloalkyl, cycloalkenyl, aryl (including phenyl, and as an isolated substituent or as part of a substituent such as in aryloxy and aralkyl), heteroaryl (as an isolated substituent or as part of a substituent such as in heteroaryloxy and heteroaralkyl) are one to three groups independently selected from halogen (or halo), C_1-C_6 alkyl optionally substituted with one to five fluorine, NH_2, $N(C_1$-C_6 alkyl$)_2$, NO_2, oxo, CN, N_3, -OH, -O(C_1-C_6 alkyl) optionally substituted with one to five fluorine, C_3-C_{10} cycloalkyl, (C_{3-7})cycloalkyl, (C_{3-5})heterocycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, (C_0-C_6 alkyl)S(O)$_{0-2}$-, aryl-S(O)$_{0-2}$-, (C_0-C_6 alkyl)S(O)$_{0-2}$(C_0-C_6 alkylene)-, (C_0-C_6 alkyl)C(O)NH-, H_2N-C(NH)-, (C_0-C_6 alkyl)C(O)-, (C_0-C_6 alkyl)OC(O)-, (C_0-C_6alkyl)O(C_1-C_6 alkylene)-, (C_0-C_6 alkyl)C(O)$_{1-2}$(C_0-C_6 alkylene)-, (C_0-C_6 alkyl)$_2$NC(O)-, (C_0-C_6 alkyl)OC(O)NH-, aryl, aralkyl, heteroaryl, heteroaralkyl, halo-aryl, halo-aralkyl, halo-heteroaryl, halo-heteroaralkyl, cyano-aryl, cyano-aralkyl, cyano-heteroaryl and cyano-heteroaralkyl.

The term "halogen" (or “halo”) refers to fluorine, chlorine, bromine and iodine (alternatively referred to as fluoro (F), chloro (Cl), bromo (Br), and iodo (I)).

The term "haloalkyl" means alkyl having the specified number of carbon atoms in which from one to all of the hydrogen atoms have been replaced by a halogen atom.

The terms "aralkyl" and "heteroaralkyl" refer to an aryl/heteroaryl linked to the rest of the molecule via a C_1 to C_4 alkylene.

The term “C_0” as employed in expressions such as “C_{0-6} alkylene” means a direct covalent bond; or when employed in experessions such as "C_{0-6} alkyl" means hydrogen. Similarly, when an integer defining the presence of a certain number of atoms in a group is equal to zero, it means that the atoms adjacent thereto are connected directly by a bond; for example, in the structure 

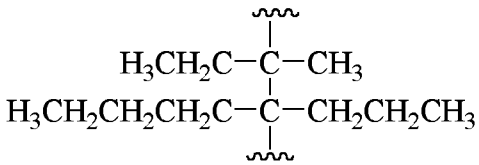
, wherein s is an integer equal to zero, 1 or 2, the structure is 

when s is zero; or it means that the indicated atom is absent; for example -S(O)$_0$- means -S-.

Unless expressly stated to the contrary, an “unsaturated” ring is a partially or fully unsaturated ring. For example, an “unsaturated monocyclic C_6 carbocycle” refers to cyclohexene, cyclohexadiene, and benzene.

Unless expressly stated to the contrary, all ranges cited herein are inclusive. For example, a heterocycle described as containing from "1 to 4 heteroatoms" means the heterocycle can contain 1, 2, 3 or 4 heteroatoms.

When any variable occurs more than one time in any constituent or in any formula depicting and describing compounds of the invention, its definition on each occurrence is independent of its definition at every other occurrence. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. For variable definitions containing terms having repeated terms, e.g., $(CRiRj)_r$, where r is the integer 2, Ri is a defined variable, and Rj is a defined variable, the value of Ri may differ in each instance in which it occurs, and the value of Rj may differ in each instance in which it occurs. For example, if Ri and Rj are independently selected from the group consisting of methyl, ethyl, propyl and butyl, then $(CRiRj)_2$ can be



The term (C_{1-6})alkyl as used hereinabove means a branched or unbranched alkyl group having 1-6 carbon atoms, for example methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, n-pentyl and n-hexyl. Preferred is (C_{1-4})alkyl.

The term (C_{1-5})alkyl means a branched or unbranched alkyl group having 1-5 carbon atoms, for example methyl, ethyl, propyl, isopropyl, butyl, tert-butyl and n-pentyl.

The term (C_{1-4})alkyl as used herein means a branched or unbranched alkyl group having 1-4 carbon atoms, being methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl.

The term (C_{1-3})alkoxy means an alkoxy group having 1-3 carbon atoms, the alkyl moiety being branched or unbranched.

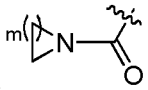
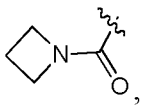
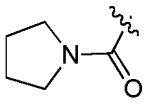
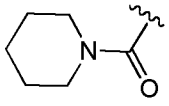
The term (C_{1-3})alkoxycarbonyl means an alkoxycarbonyl group having 1-3 carbon atoms in the alkoxy moiety, the alkoxy moiety having the same meaning as previously defined.

The term (di)(C_{1-6})alkylaminocarbonyl means an alkylaminocarbonyl group, the amino group of which is monosubstituted or disubstituted independently with an alkyl group which

contains 1-6 carbon atoms and which has the same meaning as previously defined. Preferred alkyl group is (C_{1-4})alkyl.

The term (C_{3-7})cycloalkyl means a cycloalkyl group having 3-7 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. 5-6 Carbon atoms are preferred.

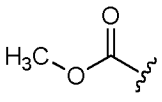
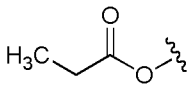
The term (C_{3-5})heterocycloalkyl means a heterocycloalkyl group having 3-5 carbon atoms, including 1-3 heteroatoms selected from N, O and/or S, which may be attached via a nitrogen if feasible, or a carbon atom. Preferred number of heteroatoms is one or two. Most preferred number is one. Preferred heteroatoms are N or O. Most preferred are piperazinyl, tetrahydropyranyl, morpholinyl and pyrrolidinyl.

A group having the formula  , means a heterocyclocarbonyl group such as  ,  , and  , each optionally substituted with one or more (C_{1-10})alkyl, halogen, amino, cyano, hydroxy, and (C_{1-3})alkoxy.

The term (C_{2-9})heteroaryl means an aromatic group having 2-9 carbon atoms and 1-3 heteroatoms selected from N, O and S, like imidazolyl, thiadiazolyl, pyridinyl, pyrimidinyl, thiophenyl or furyl, pyrazolyl, isoxazolyl or quinolyl. Preferred number of heteroatoms is one or two. Preferred heteroaryl groups are pyrazolyl, thiophenyl, isoxazolyl, pyridyl and quinolyl. The (C_{2-5})heteroaryl group may be attached via a carbon atom or a nitrogen, if feasible.

The term (C_{6-14})aryl means an aromatic hydrocarbon group having 6-14 carbon atoms, such as phenyl, naphthyl, tetrahydronaphthyl, indenyl, anthracyl, More preferred are (C_{6-10})aryl groups. The most preferred aromatic hydrocarbon group is phenyl.

As used herein, the term "X_a-X_b", shall have the same meaning as the term "X_{a-b}", wherein X is any atom and a and b are any integers. For example, "C_1-C_4" shall have the same meaning as "C_{1-4}". Additionally, when referring to a functional group generically, "A^x" shall have the same meaning, and be interchangeable with, "AX", wherein "A" is any atom and "x" or "X" are any integer. For example, "R^1" shall have the same meaning, and be interchangeable with, "R1".

In the above definitions with multifunctional groups, the attachment point is at the last group. For example, the term (C_{1-3})alkoxycarbonyl refers to, e.g.  , and the term (C1-4)alkylcarbonyloxy refers to, e.g.  .

The term “substituted” means that one or more hydrogens on the designated atom/atoms is/are replaced with a selection from the indicated group, provided that the designated atom’s normal valency under the existing circumstances is not exceeded, and that the substitution results in a stable compound. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. “Stable compound” or “stable structure” is defined as a compound or structure that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent. Accordingly, the term "one or more" when referring to a substituent and/or variable means that one or more hydrogens on the designated atom/atoms is/are replaced with a selection from the indicated group, provided that the designated atom’s normal valency under the existing circumstances is not exceeded, and that the substitution results in a stable compound.

The term “optionally substituted” means that a substitution with the specified groups, radicals or moieties, may or may not be made on the specified group.

When, in the definition of a substituent, is indicated that “all of the alkyl groups” of said substituent are optionally substituted, this also includes the alkyl moiety of an alkoxy group.

The use of the terms "salt", "solvate", “ester”, "prodrug" and the like, is intended to equally apply to the salt, solvate, ester and prodrug of enantiomers, stereoisomers, rotamers, tautomers, positional isomers, racemates or prodrugs of the inventive compounds.

The term "effective amount" as used herein, refers to an amount of the compound of Formula (I) and/or an additional therapeutic agent, or a composition thereof, that is effective in producing the desired therapeutic, ameliorative, inhibitory or preventative effect when administered to a subject suffering from an RORgammaT-mediated disease or disorder. In the combination therapies of the present invention, as effective amount can refer to each individual agent or to the combination as a whole, wherein the amounts of all agents administered are together effective, but wherein the component agent of the combination may not be present individually in an effective amount.

A "subject" is a human or non-human mammal. In one embodiment, a subject is a human. In another embodiment, a subject is a chimpanzee.

It should be noted that any carbon as well as heteroatom with unsatisfied valences in the text, schemes, examples and tables herein is assumed to have the sufficient number of hydrogen atom(s) to satisfy the valences.

The compounds of this invention include the prodrugs, hydrates or solvates of the compounds.

Optical Isomers - Diastereomers - Geometric Isomers – Tautomers

The compounds of Formula I may contain asymmetric or chiral centers, and, therefore, exist in different stereoisomeric forms. It is intended that all stereoisomeric forms of the compounds of Formula (I) as well as mixtures thereof, including racemic mixtures, form part of the present invention. In addition, the present invention embraces all geometric and positional isomers. For example, if a compound of Formula (I) incorporates a double bond or a fused ring, both the cis- and trans-forms, as well as mixtures, are embraced within the scope of the invention.

Compounds described herein may contain an asymmetric center and may thus exist as enantiomers. Where the compounds according to the invention possess two or more asymmetric centers, they may additionally exist as diastereomers. The present invention includes all such possible stereoisomers as substantially pure resolved enantiomers, racemic mixtures thereof, as well as mixtures of diastereomers. The above Formula I is shown without a definitive stereochemistry at certain positions. The present invention includes all stereoisomers of Formula I and pharmaceutically acceptable salts thereof. Diastereoisomeric pairs of enantiomers may be separated by, for example, fractional crystallization from a suitable solvent, and the pair of enantiomers thus obtained may be separated into individual stereoisomers by conventional means, for example by the use of an optically active acid or base as a resolving agent or on a chiral HPLC column. Further, any enantiomer or diastereomer of a compound of the general Formula I may be obtained by stereospecific synthesis using optically pure starting materials or reagents of known configuration.

When compounds described herein contain olefinic double bonds, unless specified otherwise, such double bonds are meant to include both E and Z geometric isomers.

Some of the compounds described herein may exist with different points of attachment of hydrogen, referred to as tautomers. For example, compounds including carbonyl -$CH_2C(O)$- groups (keto forms) may undergo tautomerism to form hydroxyl –CH=C(OH)- groups (enol forms). Both keto and enol forms, individually as well as mixtures thereof, are included within the scope of the present invention.

Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods well known to those skilled in the art, such as, for example, by chromatography and/or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (e.g. chiral auxiliary such as a chiral alcohol or Mosher's acid chloride), separating the diastereomers and converting (e.g. hydrolyzing) the individual diastereomers to the corresponding pure enantiomers. Also, some of the compounds of Formula (I) may be atropisomers (e.g. substituted biaryls) and are considered as part of this invention. Enantiomers can also be separated by use of chiral HPLC column.

It is also possible that the compounds of Formula I may exist in different tautomeric forms, and all such forms are embraced within the scope of the invention. Also, for example, all keto-enol and imine-enamine forms of the compounds are included in the invention.

All stereoisomers (for example, geometric isomers, optical isomers and the like) of the present compounds (including those of the salts, solvates, esters and prodrugs of the compounds as well as the salts, solvates and esters of the prodrugs), such as those which may exist due to asymmetric carbons on various substituents, including enantiomeric forms (which may exist even in the absence of asymmetric carbons), rotameric forms, atropisomers, and diastereomeric forms, are contemplated within the scope of this invention, as are positional isomers. Individual stereoisomers of the compounds of the invention may, for example, be substantially free of other isomers, or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers. The chiral centers of the present invention can have the S or R configuration as defined by the IUPAC 1974 Recommendations.

Salts

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids. When the compound of the present

invention is acidic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic bases, including inorganic bases and organic bases. Salts derived from such inorganic bases include aluminum, ammonium, calcium, copper (ic and ous), ferric, ferrous, lithium, magnesium, manganese (ic and ous), potassium, sodium, zinc and the like salts. Preferred are the ammonium, calcium, magnesium, potassium and sodium salts. Salts prepared from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines derived from both naturally occurring and synthetic sources. Pharmaceutically acceptable organic non-toxic bases from which salts can be formed include, for example, arginine, betaine, caffeine, choline, N,N'-dibenzyl-ethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, dicyclohexylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like.

When the compound of the present invention is basic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic inorganic and organic acids. Such acids include, for example, acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid and the like. Preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, and tartaric acids.

The compounds of Formula I can form salts which are also within the scope of this invention. Reference to a compound of Formula I herein is understood to include reference to salts thereof, unless otherwise indicated.

The term pharmaceutically acceptable salt represents those salts which are, within the scope of medical judgement, suitable for use in contact for the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. They may be obtained during the final isolation and purification of the compounds of the invention, or separately by reacting the free base function with a suitable mineral acid such as hydrochloric acid, phosphoric acid, or sulfuric acid, or with an organic acid such as for example ascorbic acid, citric acid, tartaric acid, lactic acid, maleic acid,

malonic acid, fumaric acid, glycolic acid, succinic acid, propionic acid, acetic acid, methanesulfonic acid, and the like. The acid function can be reacted with an organic or a mineral base, like sodium hydroxide, potassium hydroxide, calcium hydroxide, calcium carbonate, ammonium (e.g. diethylamine) or lithium hydroxide.

Solvates

The present invention includes within its scope solvates of compounds of Formula I.As used herein, the term "solvate" refers to a complex of variable stoichiometry formed by a solute (i.e., a compound of Formula I) or a pharmaceutically acceptable salt thereof and a solvent that does not interfere with the biological activity of the solute. Examples of solvents include, but are not limited to water, ethanol, and acetic acid. When the solvent is water, the solvate is known as hydrate; hydrate includes, but is not limited to, hemi-, mono, sesqui-, di- and trihydrates.

The compounds of the invention may form hydrates or solvates. It is known to those of skill in the art that charged compounds form hydrated species when lyophilized with water, or form solvated species when concentrated in a solution with an appropriate organic solvent. One or more compounds of the invention may exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like, and it is intended that the invention embrace both solvated and unsolvated forms. "Solvate" may also mean a physical association of a compound of this invention with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolatable solvates. Non-limiting examples of suitable solvates include ethanolates, methanolates, and the like. "Hydrate" is a solvate wherein the solvent molecule is H_2O.

Prodrugs

The present invention includes within its scope the use prodrugs of the compounds of this invention. In general, such prodrugs will be functional derivatives of the compounds of this invention which are readily convertible in vivo into the required compound. Thus, in the methods of treatment of the present invention, the term "administering" shall encompass the

treatment of the various conditions described with a compound of formula I or with a compound which may not be a compound of formula I, but which converts to a compound of formula I in vivo after administration to the patient. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs," ed. H. Bundgaard, Elsevier, 1985.

A discussion of prodrugs is provided in T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems (1987) 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, (1987) Edward B. Roche, ed., American Pharmaceutical Association and Pergamon Press. The term "prodrug" means a compound (e.g, a drug precursor) that is transformed in vivo to yield a compound of Formula I or a pharmaceutically acceptable salt, hydrate or solvate of the compound. The transformation may occur by various mechanisms (e.g. by metabolic or chemical processes), such as, for example, through hydrolysis in blood. A discussion of the use of prodrugs is provided by T. Higuchi and W. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987.

Isotopes

In the compounds of generic Formula I, the atoms may exhibit their natural isotopic abundances, or one or more of the atoms may be artificially enriched in a particular isotope having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number predominantly found in nature. The present invention is meant to include all suitable isotopic variations of the compounds of generic Formula I. For example, different isotopic forms of hydrogen (H) include protium (^{1}H) and deuterium (^{2}H). Protium is the predominant hydrogen isotope found in nature. Enriching for deuterium may afford certain therapeutic advantages, such as increasing in vivo half-life or reducing dosage requirements, or may provide a compound useful as a standard for characterization of biological samples. Isotopically-enriched compounds within generic Formula I can be prepared without undue experimentation by conventional techniques well known to those skilled in the art or by processes analogous to those described in the Schemes and Examples herein using appropriate isotopically-enriched reagents and/or intermediates.

Utilities

Compounds of the present invention alter the interaction of coregulator proteins with Retinoic Acid Receptor-related Orphan Receptor gamma t (RORgammaT) and thereby antagonize RORgammaT-mediated transcriptional activity, and as such are useful in the treatment of diseases and conditions in which inhibition of RORgammaT is desirable, such as autoimmune and inflammatory diseases and disorders.

Accordingly, another embodiment of the present invention provides a method for treating a disease or condition mediated by RORgammaT in a subject comprising administering to the subject an amount of a compound having Formula I, Ia, Ib, Ic, Id, Ie, If, Ig or Ih, or a pharmaceutically acceptable salt or solvate thereof, that is effective for treating the disease or condition mediated by RORgammaT in the subject.

The compounds according to the invention can be used in therapy.

A further aspect of the invention resides in the use of compounds according to the invention or a pharmaceutically acceptable salt thereof for the treatment of RORgammaT-mediated diseases or RORgammaT mediated conditions.

Another aspect of the invention resides in the use of compounds or a pharmaceutically acceptable salt thereof having the general formula I for the treatment of autoimmune diseases, in particular those diseases in which Th17 cells and non-Th17 cells, which express Th17 hallmark cytokines play a prominent role. These include, but are not limited to, the treatment of rheumatoid arthritis, psoriasis, inflammatory bowel disease, Crohn's disease, ankylosing spondylitis and multiple sclerosis.

In another aspect, compounds or a pharmaceutically acceptable salt thereof having the general formula I can be used for treatment of inflammatory diseases in which Th17 cells and/or non-Th17 cells, which express Th17 hallmark cytokines play a prominent role such as, but not limited to respiratory diseases, osteoarthritis and asthma. Also, compounds or a pharmaceutically acceptable salt thereof having the general formula I can be used for treatment of infectious diseases in which Th17 cells and/or non-Th17 cells, which express Th17 hallmark cytokines play a prominent role such as, but not limited to mucosal leishmaniasis.

Compounds or a pharmaceutically acceptable salt thereof having the general formula I can also be used for treatment of other diseases in which Th17 cells and/or non-Th17 cells, which express Th17 hallmark cytokines play a prominent role such as, but not limited to

Kawasaki disease and Hashimoto's thyroiditis.

In one aspect is the disease or condition is an autoimmune disease or inflammatory disease. The disease or condition includes, but is not limited to, multiple sclerosis, inflammatory bowel disease, Crohn's disease, ankylosing spondylitis, psoriasis, rheumatoid arthritis, asthma, osteoarthritis, Kawasaki disease, Hashimoto's thyroiditis or mucosal leishmaniasis.

In another aspect, the compounds according to the invention can be used in therapies to treat or prevent multiple sclerosis, inflammatory bowel disease, Crohn's disease, psoriasis, rheumatoid arthritis, asthma, osteoarthritis, Kawasaki disease, Hashimoto's thyroiditis and mucosal leishmaniasis.

In another aspect the compounds according to the invention can be used to treat or prevent psoriasis.

In yet another aspect the compounds according to the invention can be used to treat inflammatory bowel disease.

This aspect of the present invention further includes the use of a compound of Formula I, Ia, Ib, Ic, Id, Ie, If, Ig or Ih, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for the treatment of a disease or condition mediated by RORgammaT.

Route of Administration/Dosage

The compounds of this invention can be administered for the treatment or prevention of afflictions, diseases and illnesses according to the invention by any means that effects contact of the active ingredient compound with the site of action in the body of a warm-blooded animal. For example, administration can be oral, topical, including transdermal, ocular, buccal, intranasal, inhalation, intravaginal, rectal, intracisternal and parenteral. The term "parenteral" as used herein refers to modes of administration which include subcutaneous, intravenous, intramuscular, intraarticular injection or infusion, intrasternal and intraperitoneal. For the purpose of this disclosure, a warm-blooded animal is a member of the animal kingdom possessed of a homeostatic mechanism and includes mammals and birds.

The compounds can be administered by any conventional means available for use in conjunction with pharmaceuticals, either as individual therapeutic agents or in a combination of therapeutic agents. They can be administered alone, but are generally administered with a

pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

The dosage administered will be dependent on the age, health and weight of the recipient, the extent of disease, kind of concurrent treatment, if any, frequency of treatment and the nature of the effect desired. Usually, a daily dosage of active ingredient compound will be from about 1.0-2000 milligrams per day. Ordinarily, from 10 to 500 milligrams per day in one or more applications is effective to obtain desired results. These dosages are the effective amounts for the treatment and prevention of afflictions, diseases and illnesses described above, e.g., autoimmune and inflammatory diseases and disorders.

Compositions include e.g. those suitable for oral, sublingual, subcutaneous, intravenous, intramuscular, nasal, local, or rectal administration, and the like, all in unit dosage forms for administration.

For oral administration, the active ingredient may be presented as discrete units, such as tablets, capsules, powders, granulates, solutions, suspensions, and the like.

For parenteral administration, the pharmaceutical composition of the invention may be presented in unit-dose or multi-dose containers, e.g. injection liquids in predetermined amounts, for example in sealed vials and ampoules, and may also be stored in a freeze dried (lyophilized) condition requiring only the addition of sterile liquid carrier, e.g. water, prior to use.

Mixed with such pharmaceutically acceptable auxiliaries, e.g. as described in the standard reference, Gennaro, A.R. et al., Remington: *The Science and Practice of Pharmacy* (20th Edition., Lippincott Williams & Wilkins, 2000, see especially Part 5: Pharmaceutical Manufacturing), the active agent may be compressed into solid dosage units, such as pills, tablets, or be processed into capsules or suppositories. By means of pharmaceutically acceptable liquids the active agent can be applied as a fluid composition, e.g. as an injection preparation, in the form of a solution, suspension, emulsion, or as a spray, e.g. a nasal spray.

For making solid dosage units, the use of conventional additives such as fillers, colorants, polymeric binders and the like is contemplated. In general any pharmaceutically acceptable additive which does not interfere with the function of the active compounds can be used. Suitable carriers with which the active agent of the invention can be administered as solid compositions include lactose, starch, cellulose derivatives and the like, or mixtures thereof, used in suitable amounts. For parenteral administration, aqueous suspensions,

isotonic saline solutions and sterile injectable solutions may be used, containing pharmaceutically acceptable dispersing agents and/or wetting agents, such as propylene glycol or butylene glycol.

Pharmaceutical Compositions

Another aspect of the present invention provides pharmaceutical compositions comprising a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof and one or more pharmaceutically acceptable excipients. The term "excipient" and "carrier" may be used interchangeably. The term "composition", as in pharmaceutical composition, is intended to encompass a product comprising the active ingredient(s), and the inert ingredient(s) (pharmaceutically acceptable excipients) that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by admixing a compound of Formula I, additional active ingredient(s), and pharmaceutically acceptable excipients.

The pharmaceutical compositions of the present invention comprise a compound represented by Formula I (or pharmaceutically acceptable salts thereof) as an active ingredient, a pharmaceutically acceptable carrier and optionally other therapeutic ingredients or adjuvants. The compositions include compositions suitable for oral, rectal, topical, and parenteral (including subcutaneous, intramuscular, and intravenous) administration, although the most suitable route in any given case will depend on the particular host, and nature and severity of the conditions for which the active ingredient is being administered. The pharmaceutical compositions may be conveniently presented in unit dosage form and prepared by any of the methods well known in the art of pharmacy.

The active ingredient can be administered orally in solid dosage forms, such as capsules, tablets, troches, dragées, granules and powders, or in liquid dosage forms, such as elixirs, syrups, emulsions, dispersions, and suspensions. The active ingredient can also be administered parenterally, in sterile liquid dosage forms, such as dispersions, suspensions or solutions. Other dosages forms that can also be used to administer the active ingredient as an ointment, cream, drops, transdermal patch or powder for topical administration, as an

ophthalmic solution or suspension formation, i.e., eye drops, for ocular administration, as an aerosol spray or powder composition for inhalation or intranasal administration, or as a cream, ointment, spray or suppository for rectal or vaginal administration.

Gelatin capsules contain the active ingredient and powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract.

Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance.

In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene gycols are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, are suitable stabilizing agents. Also used are citric acid and its salts and sodium EDTA. In addition, parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl- or propylparaben, and chlorobutanol.

Suitable pharmaceutical carriers are described in *Remington's Pharmaceutical Sciences*, A. Osol, a standard reference text in this field.

For administration by inhalation, the compounds of the present invention may be conveniently delivered in the form of an aerosol spray presentation from pressurized packs or nebulisers. The compounds may also be delivered as powders which may be formulated and the powder composition may be inhaled with the aid of an insufflation powder inhaler device. The preferred delivery system for inhalation is a metered dose inhalation (MDI) aerosol, which may be formulated as a suspension or solution of a compound of Formula I in suitable propellants, such as fluorocarbons or hydrocarbons.

For ocular administration, an ophthalmic preparation may be formulated with an appropriate weight percent solution or suspension of the compounds of Formula I in an appropriate ophthalmic vehicle, such that the compound is maintained in contact with the

ocular surface for a sufficient time period to allow the compound to penetrate the corneal and internal regions of the eye.

Useful pharmaceutical dosage-forms for administration of the compounds of this invention include, but are not limited to, hard and soft gelatin capsules, tablets, parenteral injectables, and oral suspensions.

A large number of unit capsules are prepared by filling standard two-piece hard gelatin capsules each with 100 milligrams of powdered active ingredient, 150 milligrams of lactose, 50 milligrams of cellulose, and 6 milligrams magnesium stearate.

A mixture of active ingredient in a digestible oil such as soybean oil, cottonseed oil or olive oil is prepared and injected by means of a positive displacement pump into gelatin to form soft gelatin capsules containing 100 milligrams of the active ingredient. The capsules are washed and dried.

A large number of tablets are prepared by conventional procedures so that the dosage unit is 100 milligrams of active ingredient, 0.2 milligrams of colloidal silicon dioxide, 5 milligrams of magnesium stearate, 275 milligrams of microcrystalline cellulose, 11 milligrams of starch and 98.8 milligrams of lactose. Appropriate coatings may be applied to increase palatability or delay absorption.

A parenteral composition suitable for administration by injection is prepared by stirring 1.5% by weight of active ingredient in 10% by volume propylene glycol. The solution is made to volume with water for injection and sterilized.

An aqueous suspension is prepared for oral administration so that each 5 milliliters contain 100 milligrams of finely divided active ingredient, 100 milligrams of sodium carboxymethyl cellulose, 5 milligrams of sodium benzoate, 1.0 grams of sorbitol solution, U.S.P., and 0.025 milliliters of vanillin.

The same dosage forms can generally be used when the compounds of this invention are administered stepwise or in conjunction with another therapeutic agent. When drugs are administered in physical combination, the dosage form and administration route should be selected depending on the compatibility of the combined drugs. Thus the term coadministration is understood to include the administration of the two agents concomitantly or sequentially, or alternatively as a fixed dose combination of the two active components.

The present invention also relates to a pharmaceutical composition comprising compounds or pharmaceutically acceptable salts thereof having the general formula I in

admixture with pharmaceutically acceptable auxiliaries and optionally other therapeutic agents. The auxiliaries must be "acceptable" in the sense of being compatible with the other ingredients of the composition and not deleterious to the recipients thereof.

The invention further includes a pharmaceutical composition, as hereinbefore described, in combination with packaging material suitable for said composition, said packaging material including instructions for the use of the composition for the use as hereinbefore described.

The exact dose and regimen of administration of the active ingredient, or a pharmaceutical composition thereof, may vary with the particular compound, the route of administration, and the age and condition of the individual subject to whom the medicament is to be administered.

In general parenteral administration requires lower dosages than other methods of administration which are more dependent upon absorption. However, a dosage for humans preferably contains 0.0001-100 mg per kg body weight. The desired dose may be presented as one dose or as multiple subdoses administered at appropriate intervals throughout the day. The dosage as well as the regimen of administration may differ between a female and a male recipient.

Combination Therapy

Compounds of the present invention, and their salts and solvates, and physiologically functional derivatives thereof, may be employed alone or in combination with other therapeutic agents for the treatment of diseases and conditions associated with inappropriate IL-17 pathway activity. Combination therapies according to the present invention thus comprise the administration of at least one compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, or a physiologically functional derivative thereof, and the use of at least one other pharmaceutically active agent. The compound(s) of formula (I) and the other pharmaceutically active agent(s) may be administered together or separately and, when administered separately this may occur simultaneously or sequentially in any order. The amounts of the compound(s) of formula (I) and the other pharmaceutically active agent(s) and the relative timings of administration will be selected in order to achieve the desired combined therapeutic effect. For the treatment of the inflammatory and autoimmune diseases, rheumatoid arthritis, psoriasis, inflammatory bowel disease, ankylosing spondylitis, SLE,

uveitis, atopic dermatitis, COPD, asthma and allergic rhinitis a compound of formula (I) may be combined with one or more other active agents such as: (1) TNF-a inhibitors; (2) non-selective COX-I/COX-2 inhibitors; (3) COX-2 inhibitors; (4) other agents for treatment of inflammatory and autoimmune diseases including glucocorticoids, methotrexate, leflunomide, sulfasalazine, azathioprine, cyclosporin, tacrolimus, penicillamine, bucillamine, actarit, mizoribine, lobenzarit, ciclesonide, hydroxychloroquine, d-penicillamine, aurothiomalate, auranofin or parenteral or oral gold, cyclophosphamide, Lymphostat-B, BAFF/APRIL inhibitors and CTLA-4-Ig or mimetics thereof; (5) leukotriene biosynthesis inhibitor, 5-lipoxygenase (5-LO) inhibitor or 5-lipoxygenase activating protein (FLAP) antagonist; (6) LTD4 receptor antagonist; (7) PDE4 inhibitor; (8) antihistamine HI receptor antagonists; (9) al- and a2-adrenoceptor agonist; (10) anticholinergic agents; (1 1) β-adrenoceptor agonists; (12) insulin-like growth factor type I (IGF-1) mimetic; (13) glucocorticosteroids; (14) kinase inhibitors such as inhibitors of the Janus Kinases (JAK 1 and/or JAK2 and/or JAK 3 and/or TYK2), p38 MAPK and IKK2; (15) B-cell targeting biologies such as rituximab; (16) selective costimulation modulators such as abatacept; (17) interleukin inhibitors, such as IL-1 inhibitor anakinra, IL-6 inhibitor tocilizumab, and IL12/IL-23 inhibitor ustekinumab. It could also be combined with anti-IL17 antibodies to obtain additive/synergistic responses for the treatment of inflammatory and autoimmune diseases.

It will be clear to a person skilled in the art that, where appropriate, the other therapeutic ingredient(s) may be used in the form of salts, for example as alkali metal or amine salts or as acid addition salts, or prodrugs, or as esters, for example lower alkyl esters, or as solvates, for example hydrates, to optimise the activity and/or stability and/or physical characteristics, such as solubility, of the therapeutic ingredient. It will be clear also that, where appropriate, the therapeutic ingredients may be used in optically pure form.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical composition and thus pharmaceutical compositions comprising a combination as defined above together with a pharmaceutically acceptable diluent or carrier represent a further aspect of the invention. These combinations are of particular interest in respiratory diseases and are conveniently adapted for inhaled or intranasal delivery.

The individual compounds of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical compositions. Preferably, the individual compounds will be administered simultaneously in a combined

pharmaceutical composition. Appropriate doses of known therapeutic agents will be readily appreciated by those skilled in the art.

Accordingly, the pharmaceutical compositions of the present invention include those that also comprise at least one additional therapeutically active agent, in addition to the compound of Formula I, Ia, Ib, Ic, Id, Ie, If, Ig or Ih.

The invention further includes a compound of Formula I in combination with one or more other drug(s).

METHODS OF SYNTHESIS

Methods for preparing the compounds of this invention are illustrated in the following schemes and examples. Other synthetic protocols will be readily apparent to those skilled in the art. The examples illustrate the preparation of the compounds of Formula I and as such are not to be considered as limiting the invention set forth in the claims appended hereto. Unless otherwise indicated, all variables are as previously defined.

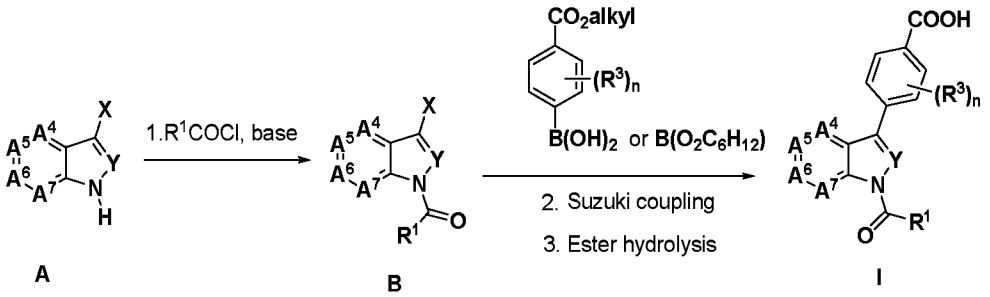
All the end products of the formula I were analyzed by NMR, LCMS. Intermediates were analyzed by NMR and/or TLC and/or LCMS. Most compounds were purified by reverse phase HPLC, MPLC on silica gel, recrystallization and/or swish (suspension in a solvent followed by filtration of the solid). The course of the reactions was followed by thin layer chromatography (TLC) and/or LCMS and/or NMR and reaction times are given for illustration only.

Abbreviations used herein are as follows: EtOAc: Ethyl acetate; PE: Petroleum ether; EA: Ethyl acetate; DCM: Dichloro methane; DMF: N,N-Dimethylformamide; Dppf: 1,1′-Bis(diphenylphosphino)ferrocene; AcOH: Acetic acid; DMAC: N,N –Dimethylacetamide; DMAP: N,N-dimethylpyridin-4-amine; TEA: Triethylamine; PYAOP: (7-Azabenzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphat e; $Pd(PPh_3)_4$:Tetrakis(Triphenylphosphine)Palladium(0); $Pd(dppf)Cl_2$: [1,1'-Bis(diphe nylphosphino) ferrocene]dichloropalladium (II); $Pd_2(dba)_3$: Tris(dibenzylideneace tone)dipalladium(0); BnBr: Benzyl bromide; Ac_2O: Acetic an hydride; LiHMDS: Lithium bis(trimethylsilyl)amide; $PhNTf_2$: N-Phenyl-bis(trifluoromethane sulfonimide); S-Phos: 2-

Dicyclohexylphosphino-2',6'-dimethoxybiphenyl; X-Phos: 2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl; CPME: Cyclopentyl methyl ether.

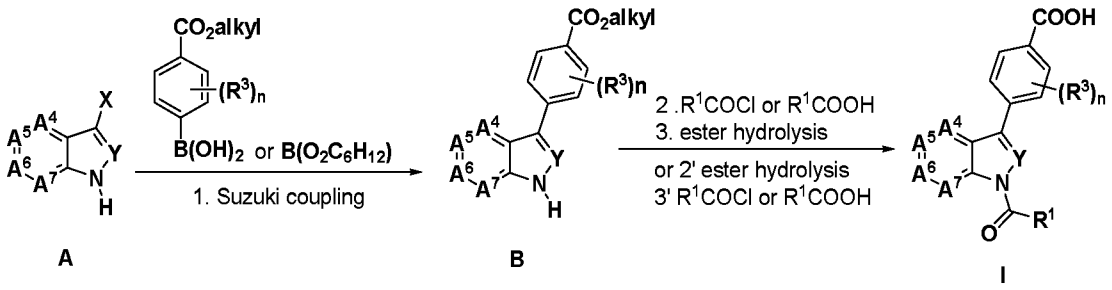
Scheme **1** illustrates a genera method toward the preparation of compounds of formula **I**. Starting from halide **A**, N-acylation with either carboxylic acids or corresponding acid chloride in the presence of base led to the formation of compound **B**. Subsequent Suzuki coupling with pinacol boronic ester or acid followd by ester hydrolysis afforded the final compound. In certain cases, ester hydrosis occurred under the Suzuki coupling condition and led to the formation of final product within one pot..

SCHEME 1



Alternatively the final compound **I** could also be prepared by switching the order of reaction sequence between acylation and Suzuki coupling (see Scheme **2**). Suzuki coupling first by reacting halide **A** with pinacol boronic ester or acid gave intermediate **B**. Subsequent acylation followed by hydrolysis furnished final product. In some cases where the amide was unstable under hydrolysis conditions, the ester moiety could be hydrolyzed first followed by reacting with acid or acid chloride to give the final product.

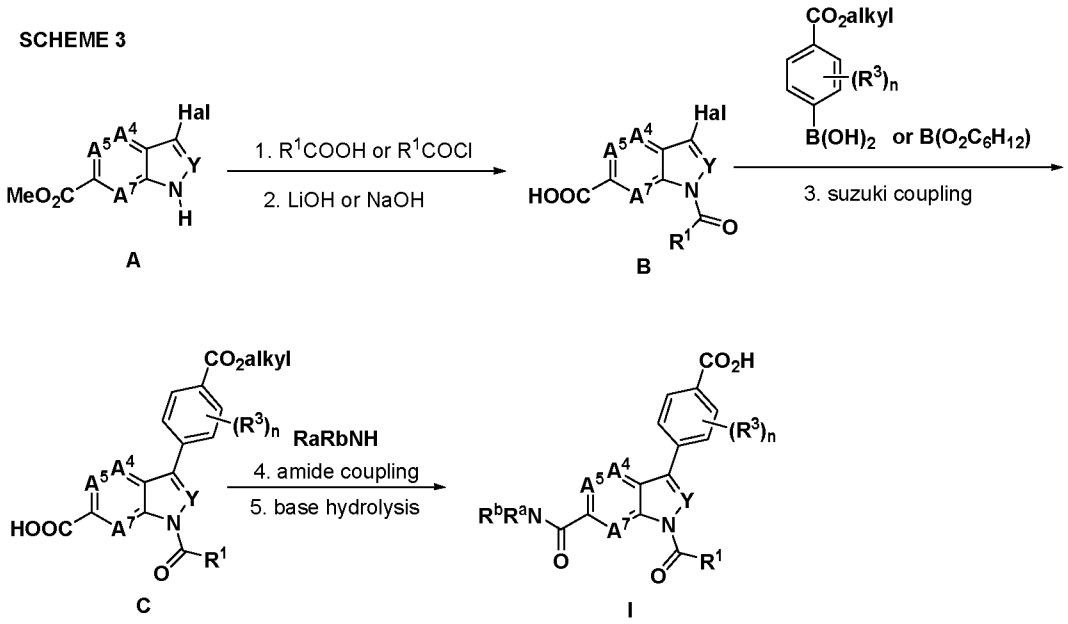
SCHEME 2



Scheme **3** illustrates a general method for the prepartion of compounds of formula **I** , which contain an amide moiety at A^6 position. Starting from halide **A**, acylation followed by ester

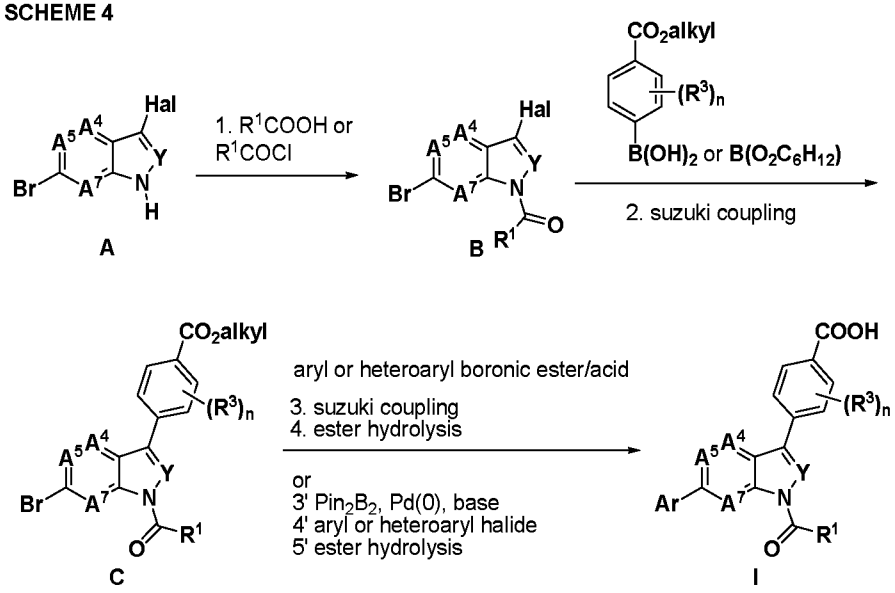
hydrolysis gave intermediate **B**. Subsequent Suzuki coupling afforded acid **C**. Standard amide coupling followed by hydrolysis led to the formation of the final product.

SCHEME 3



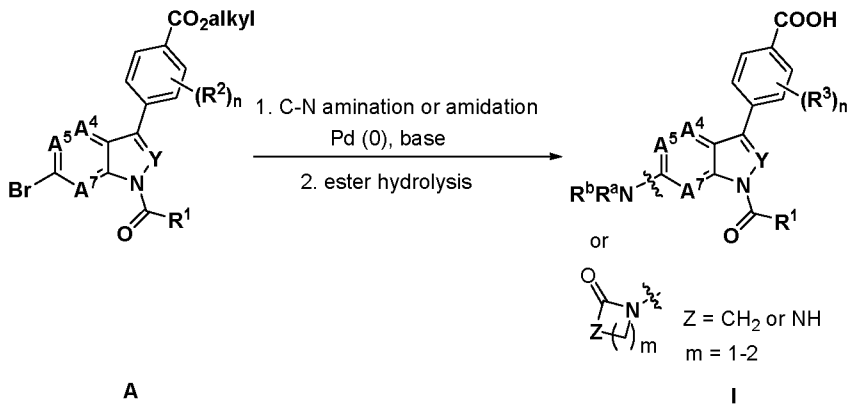
Scheme **4** illustrates a general method for compounds containing aryl or heteroaryl substituents at A^6 postion. Starting from halide **A**, acylation followed by suzuki compound furnished common intermediate **B**. Subsequent Suzuki coupling and ester hydrolysis gave the final product. Alternatively, Compound **B** could be converted into pinacol boronic ester or acid first, followed by subsequent Suzukin coupling with appropriate aryl or heteraryl halide and hydrolysis delivered the final product.

SCHEME 4



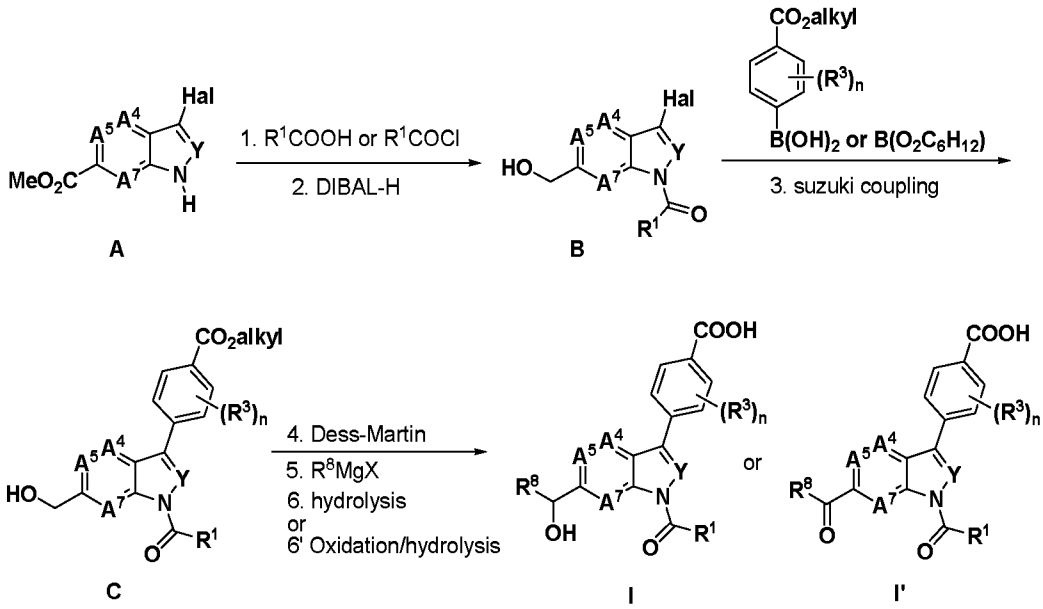
Scheme **5** illustrates a general method for the preparation of compounds containing amine or lactam moiety at A^6 position. Starting from common intermedaite **A** (see Scheme **4** for its preparation), Pd-catalzyed reaction with primary or secondary amines or latams followed by ester hydrolysis furnished the final product.

SCHEME 5



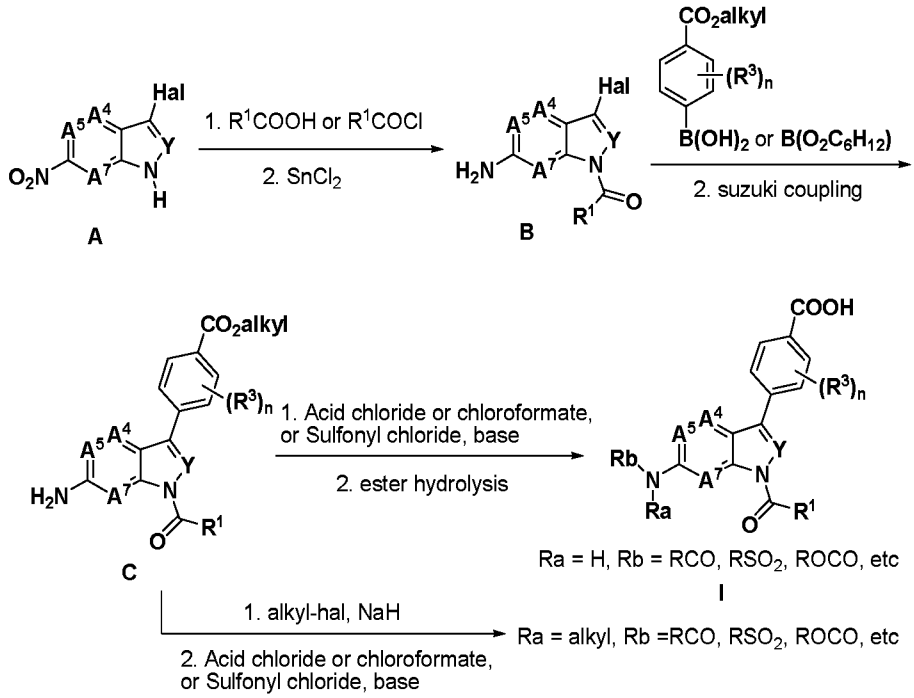
Scheme **6** illustrates a general method for the preparation of compounds which contain alcohol or ketone moiety at A^6 position. Starting with halide **A**, acylation followed by reduction of the ester moitey with reducing agent (such as DIBAL-H) afforded compound **B**. Suzuki coupling with boronic ester or acid gave compound **C**. Oxidation of the primary alcohol, followed by reacting with Grignard reagent and subsequent ester hydrolysis to give the final compound **I**. Alternatively, oxidation of the product from Grignard addition, followed by ester hydrolysis afford ketone derivative **I'**.

SCHEME 6



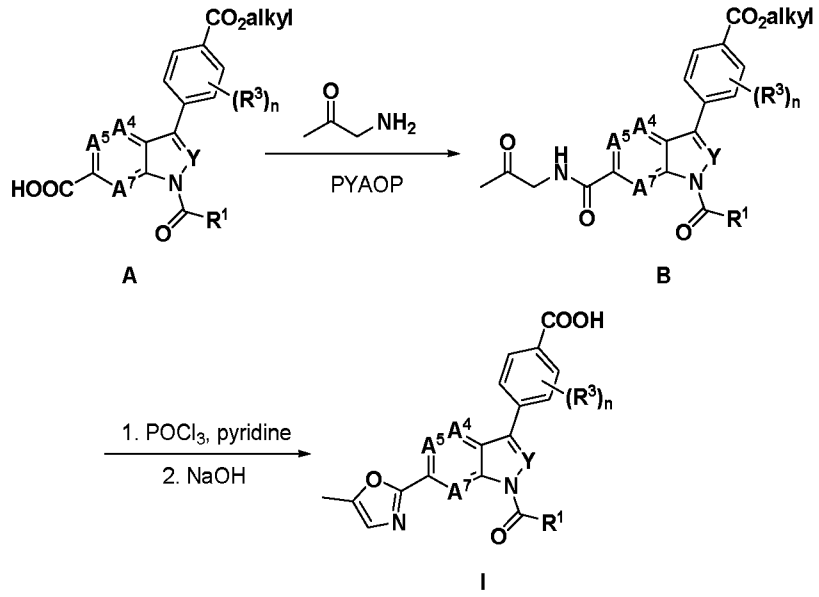
Scheme 7 illustrates a general method for the preparation of compounds, which contain amide, sulfonamides or carbamate of primary or secondary amines at A^6 position. Starting from compound **A**, acylation followed by reduction of NO_2 with reducing agent (such as $SnCl_2$) afforded compound **B**. Subsequent Suzuki coupling gave common intermedate **C**. Stardard amide, sulfonamide, or carbamate formation reactions followed by ester hydrolysis gave the final compounds **I**. Alternatively, Compound **C** could be alkylated first with halide in the presence of base to afford a new intermediate which contains a secondray amine. Subsequent standard formation of amides, sulfonamides and carbamates and hydrolysis furnish the final compounds.

SCHEME 7



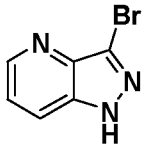
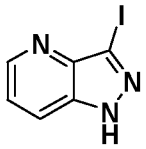
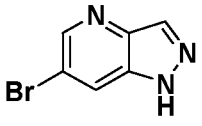
Scheme **8** illustrates a general strategy for the preparation of compounds, which contain heteroaryl substituetns at A^6 poistion, but couldn't access through Suzuki coupling as shown in Scheme **4**. Starting from carboxylic acid **A** (see scheme **4** for its synthesis), amide coupling afforded intermediate **B**. Subsequent cyclization by reacting with $POCl_3$ in the presence of pyridine, followed by ester hydrolysis led to the formation of final product **I**, which contains an oxazole substituent at A^6 position. The same stratetgy was also used for the synthesis of a number of other analogs contain a different heterocyles at ths position. Construction of those heterocyles can follow those well-known routes in the literature.

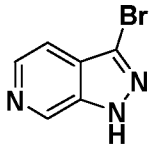
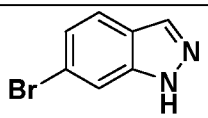
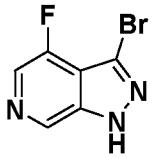
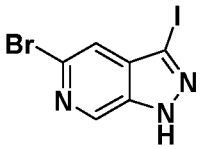
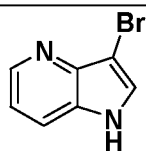
SCHEME 8



COMMERCIALLY AVAILABLE / PREVIOUSLY DESCRIBED MATERIALS

The following table lists commercial sources, and previously disclosed synthetic routes for chemical materials employed in the synthesis of intermediates, and examples of the instant invention. The list is not intended to be exhaustive, exclusive, or limiting in any way.

Structure	Source
	Aldrich
	Frontier
	Frontier
	Alfa

	Bellen
	Aldrich
	Labpartner
	Labpartner
	Labpartner
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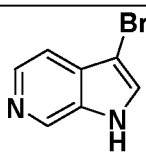
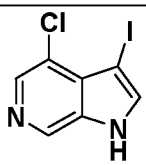
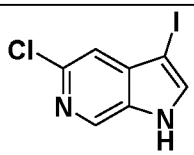
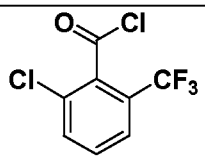
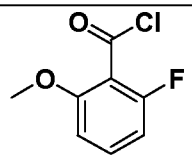
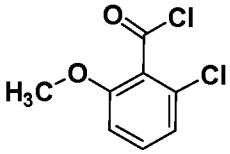
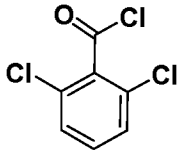
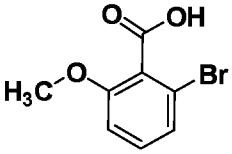
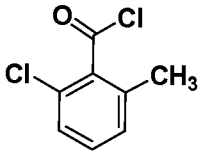
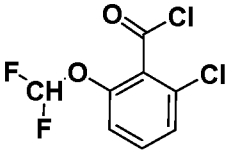
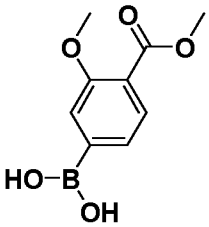
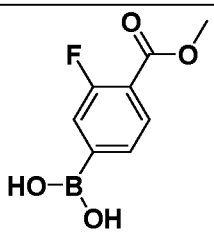
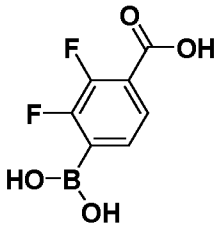
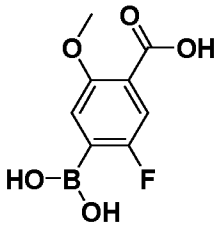
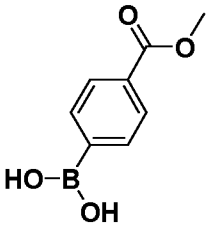
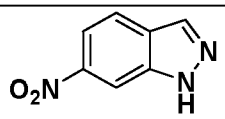
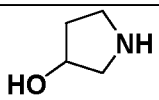
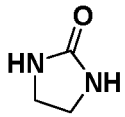
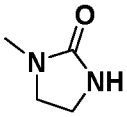
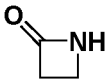
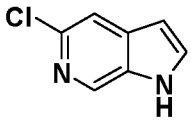
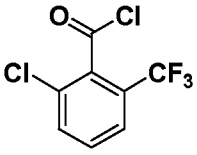
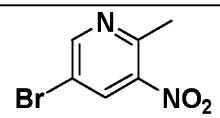
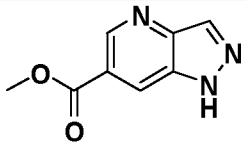
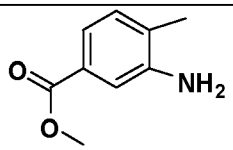
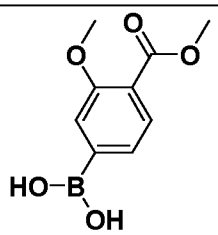
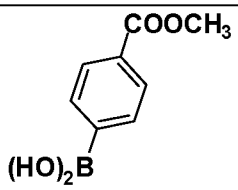
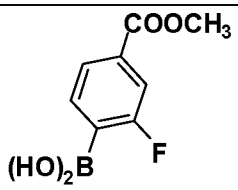
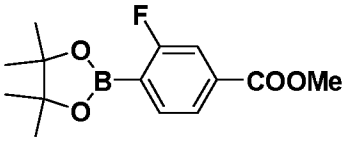
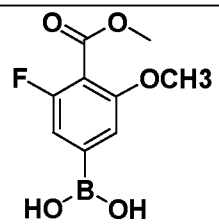
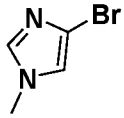
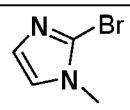
	Sinova
	Labpartner
	Labpartner
	Alfa

	Alfa
	Chemische Berichte, 1982, 115(3), 1089 -1102
	Alfa
	Alfa
	Alfa
	WO2007/144327 A2
	Combi-blocks
	Alfa

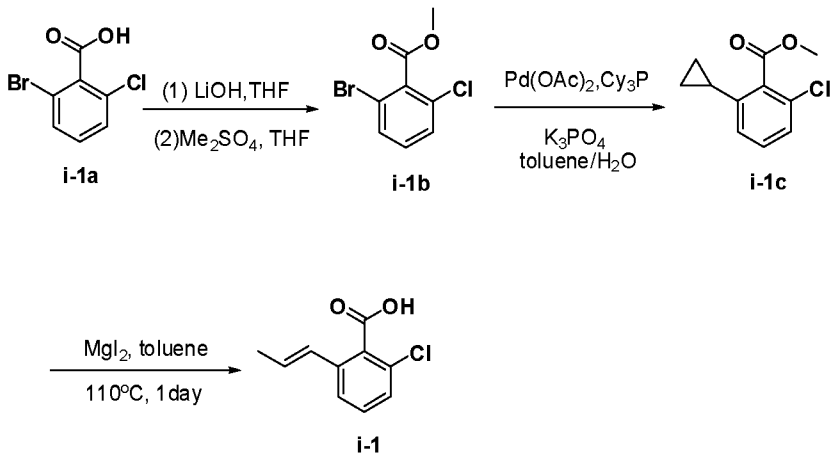
	Combi-blocks
	Anisyn
	Aldrich
	Acros
	Alfa Aesar
	ADAMAS
	Acros
	Aldrich
	Combi-blocks
	Alfa

	Labpartner
	Labpartner
	Labpartner
	Combi-blocks
	Combi-blocks
	Combi-blocks
	Combi-blocks
	Combi-blocks
	Aldrich
	Aldrich

INTERMEDIATES

Preparation of (E)-2-chloro-6-(prop-1-enyl)benzoic acid (i-1)

SCHEME i-1



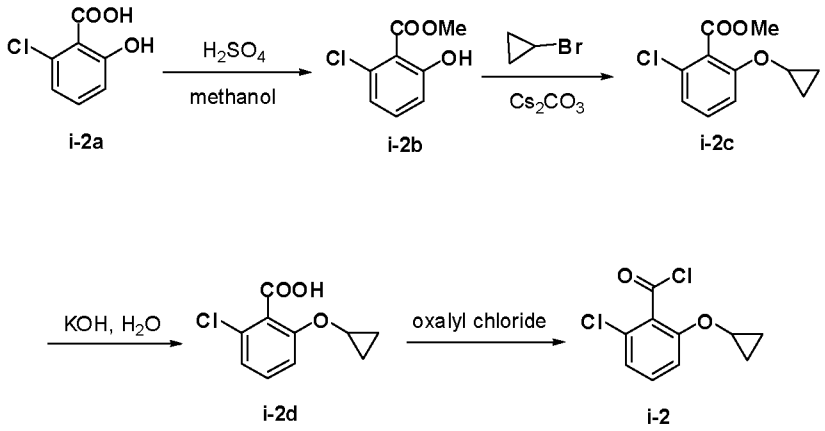
Step 1. Preparation of methyl 2-bromo-6-chlorobenzoate (i-1b). $LiOH.H_2O$ (180 mg, 4.24 mmol) was added to a solution of 2-bromo-6-chlorobenzoic acid (**i-1a**) (1.0 g, 4.24 mmol) in THF (30 ml). The mixture was stirred at 25 °C for 1h. Then the Me_2SO_4 (1.1 g, 8.48 mmol) was added to the reaction mixture. The mixture was warmed to 85 °C and stirred at 85 °C for 21 h. After cooled, $NH_3.H_2O$ was added dropwise to the mixture until pH=7-8. The solution was poured into water and THF was evaporated. The water layer was extracted with EA (60 ml). The organic layer was dried over Na_2SO_4 and concentrated to obtain 800 mg (75%) of the title compound. LCMS (ESI): calc'd for $C_8H_6BrClO_2$ $[M+H]^+$: 251, found: 251.

Step 2. Preparation of methyl 2-chloro-6-cyclopropylbenzoate (i-1c). Methyl 2-bromo-6-chlorobenzoate (**i-1b**) (0.8 g, 3.2 mmol), cyclopropylboronic acid (330 mg, 3.84 mmol), $Pd(OAc)_2$ (72 mg, 0.32 mmol), Cy_3P (180 mg, 0.64 mmol) and K_3PO_4 (2.0 g, 9.6 mmol) were mixed in toluene (12 ml) and H_2O (1.2 ml). The reaction mixture was stirred at 100 °C for overnight under N_2 atmosphere. After cooled, the mixture was poured into water (30 ml) and extracted with EA (50 ml). The organic layer was dried over Na_2SO_4 and concentrated to obtain a residue. The residue was purified by chromatography on silica gel (PE/EA=10:1) to

obtain 350 mg (52%) of the title compound. LCMS (ESI): calc'd for $C_{11}H_{11}ClO_2$ $[M+H]^+$: 211, found: 211.

Step 3. Preparation of (E)-2-chloro-6-(prop-1-enyl)benzoic acid (i-1). To a suspension of anhydrous MgI_2 (880 mg, 3.18 mmol) in toluene (15 ml) was added a solution of methyl 2-chloro-6-cyclopropylbenzoate (**i-1c**) (400 mg, 1.9 mmol) in toluene (5 ml). The mixture was refluxed under exclusion of moisture, cooled and poured into 10% aqueous $NaHCO_3$ (20 ml). The acid was isolated by acidification of the aqueous phase with 15% HCl followed by extraction with EA. The combined organic layers were washed with water, dried over Na_2SO_4 and concentrated to obtain the crude product. The crude product was purified by chromatography on silica gel (PE/EA=3:1) to obtain 200 mg (54%) of the title compound. LCMS (ESI): calc'd for $C_{10}H_9ClO_2$ $[M+H]^+$: 197, found: 197.

SCHEME i-2

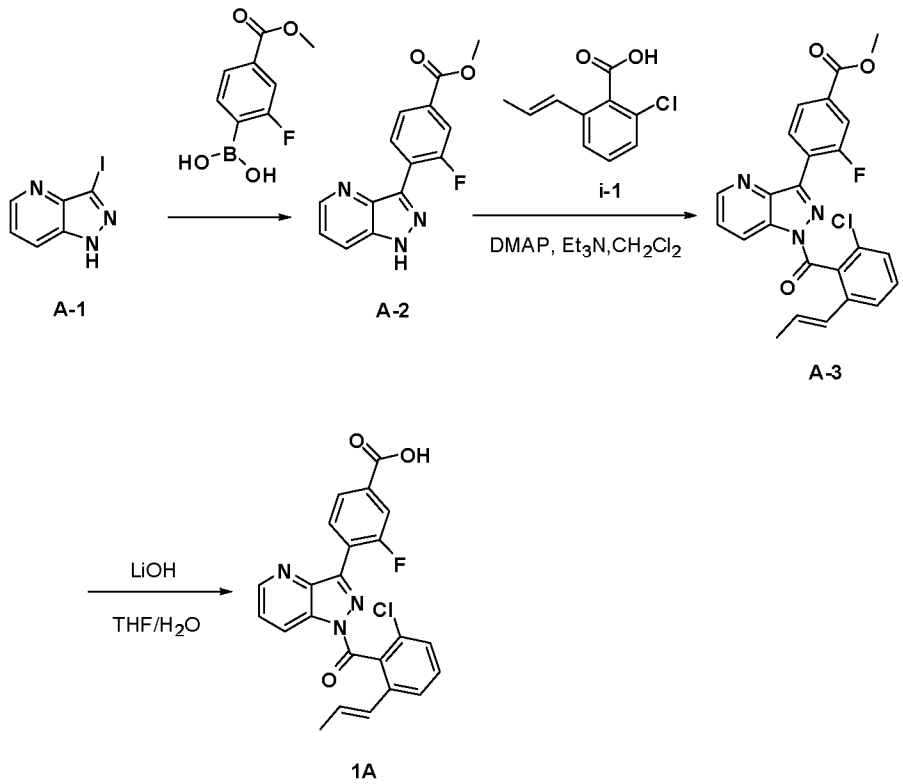


Preparation of methyl 2-chloro-6-hydroxybenzoate (i-2b). To the solution of 2-chloro-6-hydroxybenzoic acid (**i-2a**) (1.71 g, 10 mmol) in CH_3OH (100 ml) was added concentrated sulfuric acid (10 ml) drop wise. The mixture solution was protected by N_2 and stirred at 85 °C for 30 h. the solution was concentrated to be purified by chromatography column (EA:PE=1:4) to afford 1.5 g product (81%). LCMS (ESI) calc'd $[M+H]^+$: 186.59, found: 187.0.

Step 2. Preparation of methyl 2-chloro-6-cyclopropoxybenzoate (i-2c). The mixture of **i-2b** (186 mg, 1mmol), bromocyclopropane (1.2 g, 10.0 mmol), Cs_2CO_3 (414 mg, 3.0 mmol), DMAC (15 ml) was protected by N_2 and stirred at 150 °C for 24 h. Then the solution was filtered and concentrated to be purified by chromatography column (EA: PE =1:4) to afford 198 mg product (87%). LCMS (ESI) calc'd $[M+H]^+$: 226.66, found: 227.1.

Step 3. Preparation of methyl 2-chloro-6-cyclopropoxybenzoic acid (i-2d). To the solution of 2-chloro-6-cyclopropoxybenzoate (**i-2c**) (226mg, 1.0 mmol) in CH_3OH (10 ml) and H_2O (10 ml) was added KOH (200 mg). The mixture solution was stirred at 85 °C for 12 h, the solution was acidified by aqueous HCl (1M) 50 ml, exacted with EA (30ml×3), concentrated and purified by chromatography column (EA:PE=1:1) to afford 186 mg product (87%). LCMS (ESI) calc'd $[M+H]^+$: 212.63, found: 212.9.

Step 4. Preparation of 2-chloro-6-cyclopropoxybenzoyl chloride (i-2). To the solution of methyl 2-chloro-6-cyclopropoxybenzoic acid (**i-2d**) (212 mg, 1 mmol) and DMF (0.1 ml) dissolved in anhydrous DCM (10 ml) was added oxalyl chloride (190 mg, 1.5 mmol) drop wise. The mixture solution was protected by N_2 and stirred at r.t for 0.5 h. Then the solution was concentrated to afford 300 mg (crude) for the next step without further purification.



Step 1. Preparation of 4-bromo-3-hydroxy-2-nitrobenzoic acid (i-5b). To a suspension of 3-hydroxy-2-nitrobenzoic acid (**i-5a**) (2.0 g, 10.9 mmol) in acetic acid (4 mL) was added a solution of bromine (0.59 mL, 11.4 mmol) in acetic acid (3 mL) dropwise via a addition funnel over 0.5 h, then the reaction mixture was stirred in the dark at 60 °C. for 12 h. After cooled to room temperature, the reaction mixture was concentrated to give the desired product as a yellow solid (contained 30% of di-brominated products). The crude product was dissolved in THF (90 mL) and a solution of sodium hydrosulfite (11.2 g, 54.5 mmol) in water (50 mL) was added. The reaction mixture was stirred at 60 °C for 40 min. After the reaction mixture was cooled to room temperature, the aqueous layer was separated and extracted with ethyl acetate. The combined organics were dried with Na_2SO_4, filtered and concentrated. The crude material was purified by column chromatography (PE:EA =3:1) to afford the desired product (1.17 g, 46%) as a pale-brown solid. LCMS (ESI) calc'd [M+H]+: 261.9, found: 262.

Step 2. Preparation of methyl 4-bromo-3-hydroxy-2-nitrobenzoate (i-5c). To the solution of methyl 4-bromo-3-hydroxy-2-nitrobenzoic acid (**i-5b**) (1.1g, 4.2mmol) in MeOH (30 ml), 2ml of 98% sulfuric acid was added dropwise. The mixture solution was stirred at 90 °C for 16h. Cooled to RT, 200ml EA was added, washed with H_2O(20ml x 3) and brine (50ml),

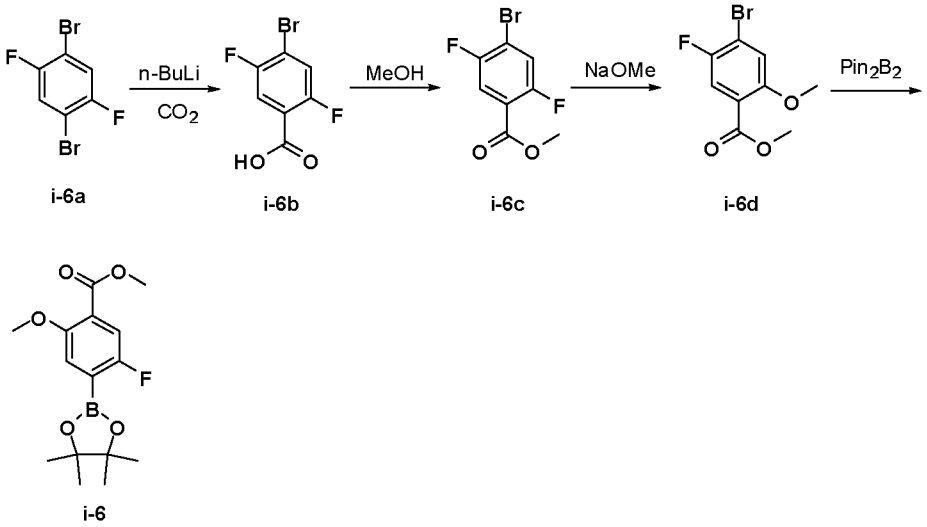
dried with Na_2SO_4, concentrated to afford 1.1 g product (yield: 95%). LCMS (ESI) calc'd [M+H]+: 274.9, found: 276.

Step 3. Preparation of methyl 2-amino-4-bromo-3-hydroxybenzoate (i-5d). To the solution of methyl 4-bromo-3-hydroxy-2-nitrobenzoate (**i-5c**) (1.1mg, 4 mmol) in HOAc(15ml) was added Fe(670mg, 12mmol) , the mixture was stirring for 1 h at 60 °C. Cooled to RT, 100ml EA was added, filtered and concentrated. Purified with chromatogram (PE:EA=5:1) to afford 960mg product (97%). LCMS (ESI) calc'd [M+H]+: 244.97, found: 246.

Step 4. Preparation of methyl 7-bromo-2-oxo-2,3-dihydrobenzo [d]oxazole -4-carboxylate (i-5e). Methyl 2-amino-4-bromo-3-hydroxybenzoate (**i-5d**) (960mg, 3.9 mmmol) in THF (5ml) was added CDI (956mg, 5.9mmmol) . The mixture was stirred at 80 °C for 3h. The solution was concentrated and purified with chromatogram (PE:EA=5:1) to afford 950 mg product (95%). LCMS (ESI) calc'd [M+H]+: 270.95, found: 272.

Step 5. Preparation of methyl 2-oxo-7-(4,4,5,5–tetramethyl-1,3,2-dioxaborolan -2-yl)-2,3-dihydrobenzo[d]oxazole-4-carboxylate (i-5). Methyl 7-bromo-2 -oxo-2,3-dihydrobenzo[d]oxazole-4-carboxylate (**i-5e**) (950mg, 3.5mmmol), Pin_2B_2(1.78g, 7 mmol), KOAc(1.37g, 14mmol) and (dppf)$PdCl_2$ (256mg, 0.35mmol) were mixed in dioxane(15ml) under N_2 protection. The mixture was stirred at 80 °C for 12h. The solution was concentrated and concentrated, purified with chromatogram (PE:EA=5:1) to afford 670 mg product (95%). LCMS (ESI) calc'd [M+H]+: 270.9, found: 272.

SCHEME i-6



Step 1. Preparation of 4-bromo-2,5-difluorobenzoic acid (i-6b). To the solution of 1,4-dibromo-2,5-difluorobenzene (**i-6a**) (27.0 g, 100 mmol) in THF(500 ml) was added n-BuLi (60 ml, 2M) dropwise at -78°C and stirred for 3 h which was protected by N_2 .Then the solution was poured to excess dry ice over 0.5 h. Added 300 ml water to the solution, washed with EA (100 ml×3). The aqueous solution was acidified with HCl (2M), extracted with EA (150 ml×3) and the organic layer was dried and concentrated. The crude material was purified by chromatography column (EA:PE = 1:10) to afford 18.24 g product (76%). LCMS (ESI) calc'd $[M+H]^+$: 237.00, found: 237.1.

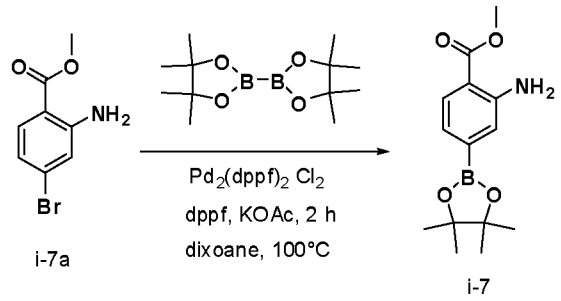
Step 2. Preparation of methyl 4-bromo-2,5-difluorobenzoate (i-6c). To the solution of 4-bromo-2,5-difluorobenzoic acid (**i-6b**) (18.24 g, 77.3 mmol) in CH_3OH (200 ml) was added Concentrated sulfuric acid (5 ml) drop wise. The mixture solution was protected by N_2 and stirred at 85 °C for 30 h. The solution was concentrated and purified by chromatography column (EA:PE=1:20) to afford 17.6 g product (91%). LCMS (ESI) calc'd $[M+H]^+$: 251.01, found: 250.9.

Step 3. Preparation of methyl 4-bromo-5-fluoro-2-methoxybenzoate (i-6d). To a solution of methyl 4-bromo-2,5-difluorobenzoate (**i-6c**) (17.6 g, 70.4 mmol) in anhydrous DMF (200 ml) was added CH_3ONa (4.56g, 84.48 mmol). The mixture solution was protected by N_2 and stirred at rt for 16 h.. The reaction was diluted with 500 ml EA and washed with water

(100ml×3). The organic layer was dried and conc- entrated to be purified by chromatography column (EA:PE=1:20) to afford 14.2 g product (77%). LCMS (ESI) calc'd $[M+H]^+$: 263.06, found: 263.01.

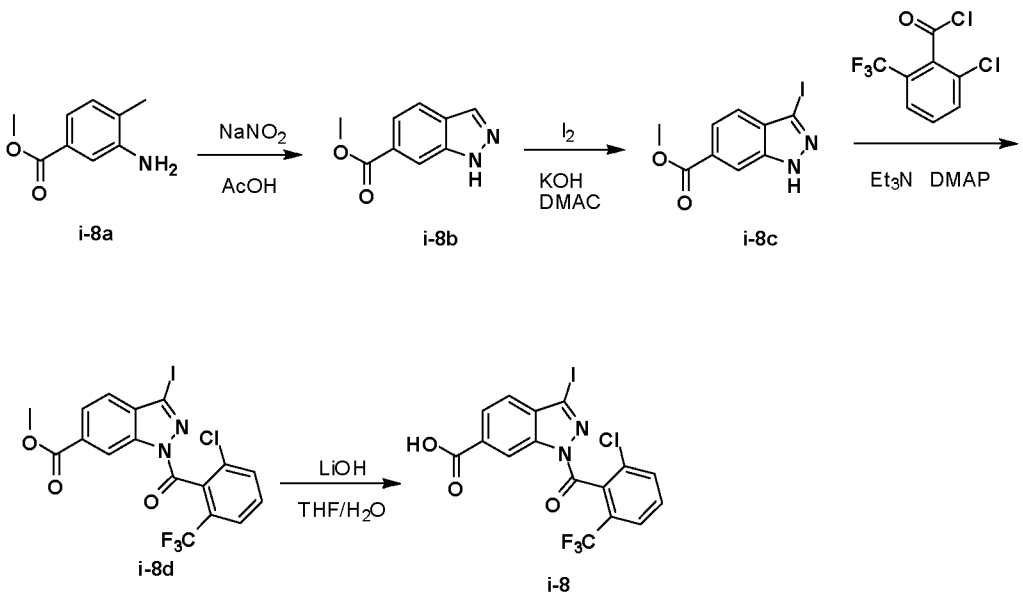
Step 4. Preparation of 2 methyl 5-fluoro-2-methoxy-4-(4,4,5,5-tetramethyl -1,3,2-dioxaborolan-2-yl)benzoate (i-6). The mixture of methyl 4-bromo-5-fluoro-2-methoxybenzoate (**i-6d**) (14.2 mg, 54.2mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (13.8 g, 54.2 mmol), $Pd(dppf)_2Cl_2$ (224mg, 0.2 mmol), Dioxane(150 ml) was degassed and protected by N_2 and stirred at 80 °C for 4 h. Then the solution was filtered and concentrated to be purified by chromatography column (EA:PE=1:4) to afford 10.6 g product (63%). LCMS (ESI) calc'd [M+H]+: 310.13, found: 310.2.

SCHEME i-7



Step 1. Preparation of methyl 2-amino-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborola- n-2-yl)benzoate (i-7). To a mixture of methyl 2-amino -4-bromobenzoate (**i-7a**) (1.15 g, 5 mmol), 4,4,4',4',5,5,5',5'–octamethyl -2,2'-bi(1,3,2-dioxaborolane) (1.27 g, 5 mmol), $Pd(dppf)Cl_2$ (204 mg, 0.25 mmol), dppf(138 mg, 0.25 mmol) and KOAc (1.47g, 15 mmol) was added dioxane (20 ml), and the mixture was heated at 100°C under argon for 2 h. The mixture was cooled down, diluted with CH_2Cl_2 (50 mL). The organic layer was separated, washed with brine, dried over Na_2SO_4, concentrated. The residue was purified by flash chromatography (Pentane/EtOAc 5/1) to give 1.5 g (89 %) of the title compound. ^{1}HNMR (500 MHz, CDCL3) δ7.84 (1H, d),7.12 (1H, s), 7.05(1H,d),5.68(2H, bs), 3.86(3H, s), 1.33(12H, s).

SCHEME i-8



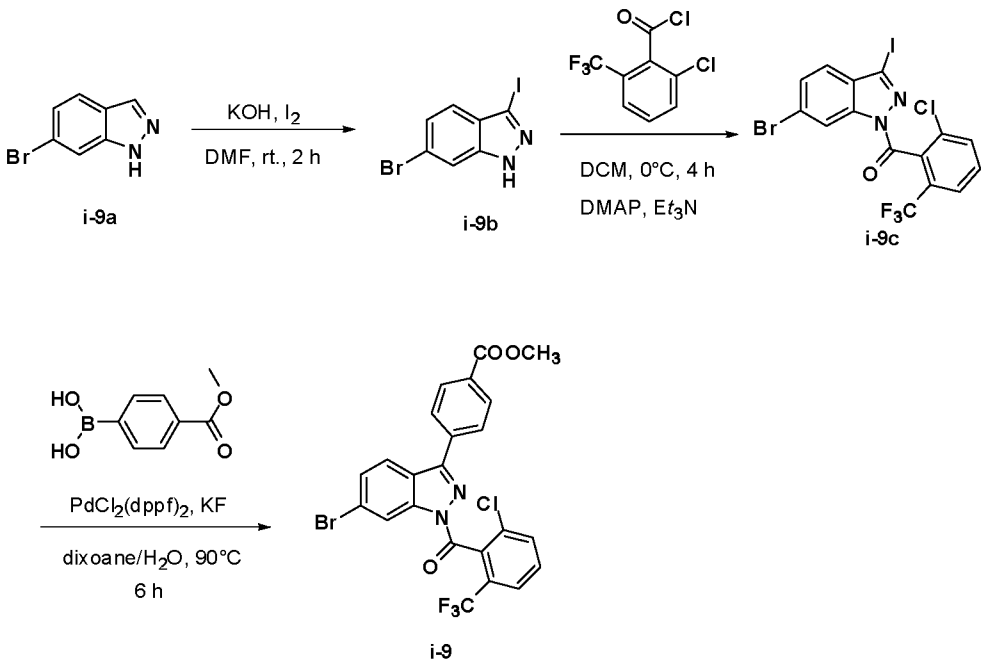
Step 1. Preparation of methyl 1H-indazole-6-carboxylate (i-8b). Methyl 3-amino-4-methylbenzoate (**i-8a**) (5.0 g, 30.2 mmol) was dissolved in AcOH (140 mL). Sodium nitrite (2.1 g, 30.2 mmol) in water (3.5 mL) was added dropwise to the solution of starting material under ice-cooling at room temperature. The icebath was removed and the mixture was stirred overnight. Half of the solvents were then evaporated, the mixture was diluted with water (80 mL) and extracted with EtOAc (3 x 30 mL). The collected organic phase was washed with water and brine (2 x 200 mL), dried and evaporated to afford **i-8b** (4.4 g, 83%). LCMS (ESI): calc'd for $C_9H_8N_2O_2$, $[M+H]^+$: 177, found: 177.

Step 2. Preparation of methyl 3-iodo-1H-indazole-6-carboxylate (i-8c). Methyl 1H-indazole-6-carboxylate (**i-8b**) (5.0 g, 28.3 mmol) was dissolved in anhydrous DMAC (50 mL). Iodine (14.4 g, 56.7 mmol) and potassium hydroxide (6.3 g, 113.5 mmol) were added in portions under ice-cooling at room temperature. The ice bath was removed and the mixture was stirred at room temperature for 1h. The reaction was monitored by TLC (25% MeOH in chloroform) then it was slowly quenched with Sat. $Na_2S_2O_3$ aqueous (100 mL), diluted with water (50 mL) and extracted with EtOAc (3 x 100 mL). The organic phase was evaporated and triturated with n-hexane. The precipitated material was filtered and dried to afford a brown solid **i-8c** (5.3 g, 62%). LCMS (ESI): calc'd for C9H7IN2O2, [M+H]+: 303, found: 303.

Step 3. Preparation of methyl 1-(2-chloro-6-(trifluoromethyl)benzoyl) -3-iodo- 1H-indazole-6-carboxylate (i-8d). To a 250 mL round-bottomed flask, was added Methyl 3-iodo-1H-indazole-6-carboxylate (**i-8c**) (11.7 g, 38.7 mmol), 2-chloro-6-(trifluoromethyl)benzoyl chloride (9.1 g, 38.7 mmol), DMAP (4.72 g, 38.7 mmol) and CH_2Cl_2 (30 mL). After stirring at r.t. for 3 minutes, TEA (11.2 mL, 77 mmol) was added slowly. The reaction mixture was stirred at r.t. for overnight. LC-MS showed no starting materials remained. Then the mixture was poured to 30 mL water, the lower (organic) and upper (aqueous) phases are separated. The aqueous phase is extracted twice with 20 mL CH_2Cl_2. The combined organic phases are washed successively with two 20 mL portions of water and 10 mL of brine. The reaction resulting organic phase is dried over anhydrous sodium sulfate, filtered and concentrated at reduced pressure to give a yellow solid. The residue was purified by column chromatography on 60 g of silica gel eluting with Petroleum ether /EtOAc from 50/1 to 10/1, to give a fawn solid **i-8d** (16.5 g, 84%). LCMS (ESI): calc'd for $C_{17}H_9ClF_3IN_2O_3$, [M+H]+: 509, found: 509.

Step 4. Preparation of 1-(2-chloro-6-(trifluoromethyl)benzoyl)-3-iodo-1H-indazo- le-6-carboxylic acid (i-8). A mixture of methyl 1-(2-chloro-6-(trifluoromethyl) benz- oyl)-3-iodo-1H-indazole-6-carboxylate (**i-8d**) (16.5g, 32.5 mmol) and LiOH (3.40g, 162.40 mmol) in 10 ml THF and 50 ml H_2O was stirred at RT overnight. The solvent was evaporated and the residue was dissolved in water. 5% HCl aqueous was added until pH~4-5. The precipitated solid was filtered, washed with water and n-hexane, dried to afford an off white solid **i-8** (16.0g, 83%). LCMS (ESI): calc'd for $C_{16}H_7ClF_3IN_2O_3$, , $[M+H]^+$: 495, found: 495.

SCHEME i-9



Step 1. Preparation of 6-bromo-3-iodo-1H-indazole (i-9b). To a flask was added 6-bromo-1H-indazole (**i-9a**) (1.96 g, 10 mmol), KOH (1.68 g, 30 mmol) and DMF (60 mL), followed by the addition of I_2 (5.08 g, 20 mmol) in portions. The reaction mixture was stirred at RT for 1 h. The mixture was diluted with H_2O, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 * 50 mL). The combined organics were washed with H_2O, brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatograph (PE/EA=10/1) to afford 2.84 g (88%) of the title compound. LCMS (ESI) calc'd for $C_7H_4BrIN_2$ $[M+H]^+$: 322.86, found: 323.

Step 2. Preparation of (6-bromo-3-iodo-1H-indazol-1-yl)(2-chloro-6-(trifluoromethyl)phenyl)methanone (i-9c). To a flask was added 6-bromo-3-iodo-1H-indazol e (**i-9b**) (3.22 g, 10 mmol), DMAP (1.22 g, 10 mmol), TEA (2.77 mL, 20 mmol) and DCM (50 mL), followed by the addition of 2-chloro-6-(trifluoromethyl) benzoyl chloride (2.61 g, 10 mmol) slowly. The reaction mixture was stirred at RT for 5 h. The mixture was diluted with H_2O, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL), The combined organics were washed with H_2O, brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatograph (PE/EA=10/1) to afford 4.9

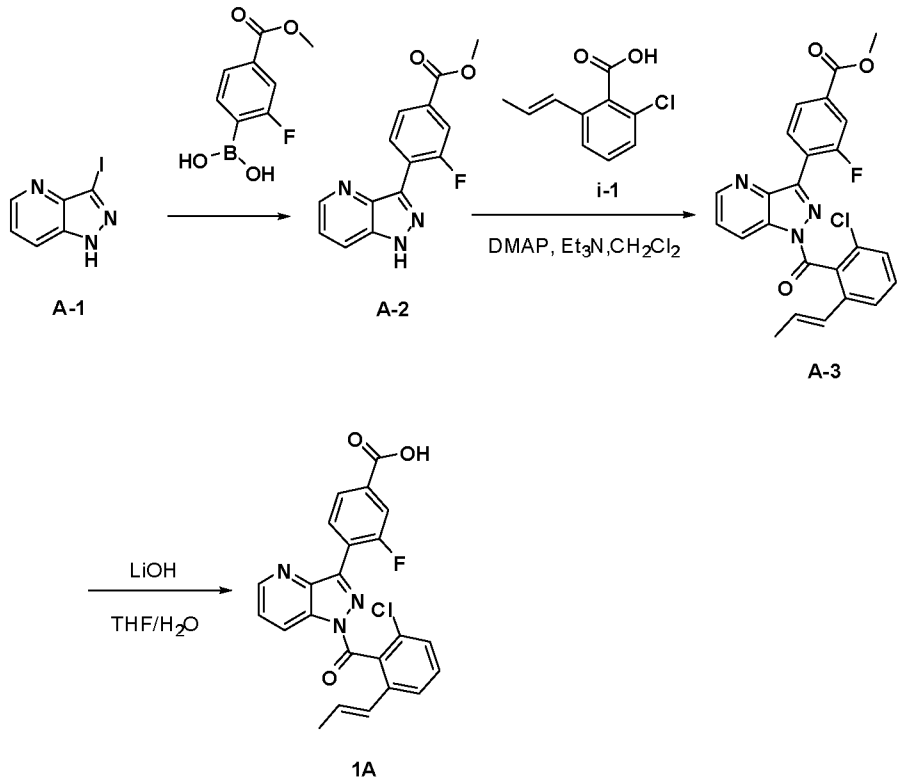
g (82 %) of the title compound. LCMS (ESI) calc'd for $C_{15}H_6BrClF_3IN_2O$ $[M+H]^+$: 528.83, found: 529.

Step 3. Preparation of methyl 4-(6-bromo-1-(2-chloro-6-(trifluoromethyl) benzo- yl)-1H-indazol-3-yl)benzoate (i-9). To a mixture of (6-bromo-3-iodo-1H-inda zol-1-yl)(2-chloro-6-(trifluoromethyl)phenyl)methanone (**i-9c**) (1.058 g, 2 mmol), 4-(methoxycarbonyl)phenylboronic acid (360 mg, 2 mmol), $PdCl_2(dppf)_2$ (82 mg, 0.1 mmol) and KF (290 mg, 5 mmol) was added dioxane (25 ml) and H_2O (0.5 ml), and the mixture was heated at 90 °C under argon for 6 h. The mixture was cooled down, diluted with CH_2Cl_2 (180 ml). The organic layer was separated, washed with brine, dried over Na_2SO_4, concentrated. The residue was purified by SiO_2 (PE/EA from10/1 to 20/1) to give 850 mg (81%) of the title compound. LCMS (ESI) calc'd for $C_{23}H_{13}BrClF_3N_2O_3$ $[M+H]^+$: 536.98, found: 537.

EXAMPLES

Example 1A: Preparation of (E)-4-(1-(2-chloro-6-(prop-1-enyl)benzoyl) -1H-pyrazolo[4,3-b]pyridin-3-yl)-3-fluorobenzoic acid (1A)

SCHEME A.



Step 1. Preparation of methyl 3-fluoro-4-(1H-pyrazolo [4, 3-b]pyridin-3-yl) benzoate(A-2). A mixture of 3-bromo-1H-pyrazolo[4,3-b]pyridine (A-1) (196.9 mg, 1 mol), 4-(methoxycarbonyl)phenylboronic acid (198 mg, 1 mol), Pd(PPh3)4 (115 mg, 0.1 mol) and K2CO3 (420 mg, 3mol) were suspended in 1,4-dioxane (5 ml) and H2O (1 ml). The reation mixture was heated at 110°C in a microwave reactor for 2h. The result mixture was diluted with H2O (30 ml) and the aqueous layer was extracted with ethyl acetate (30 ml × 2). The combined organic layers were washed with brine (30 ml ×1), dried over anhydrous Na2SO4 and concentrated to get the crude product A-2 as brown oil. LCMS (ESI) calc'd for C14H10FN3O2 [M+H] +: 272.08, found: 272.

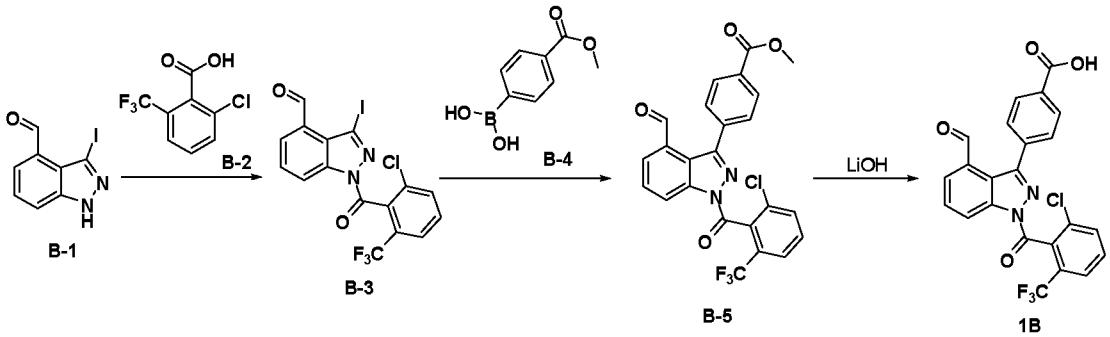
Step 2. Preparation of (E)-methyl 4-(1-(2-chloro-6-(prop-1-enyl)benzoyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)-3-fluorobenzoate (A-3). $(COCl)_2$ (907 mg, 7.14 mmol) was added dropwise to a solution of (E)-2-chloro-6-(prop-1-enyl)benzoic acid (**i-1**) (700 mg, 3.57 mmol) and 3 drops of DMF in DCM (20 ml).The resulted solution was stirred at room temperature for 30 min. Then the solution was added to a solution of methyl 3-fluoro-4-(1H-pyrazolo[4,3-b]pyridin-3-yl)benzoate (**A-2**) (968 mg, 3.57 mmol), Et_3N (720 mg, 7.14 mmol) and DMAP (436 mg, 3.57 mmol) in DCM (20 ml). The solution was stirred at room

temperature for 3h. Then the reaction mixture was poured into water and separated. The organic layer was dried over Na_2SO_4 and concentrated to obtain a crude product. The crude product was purified by on silica gel (PE/EA=6:1) to afford 133 mg of the title compound. LCMS (ESI) calc'd for $C_{24}H_{17}ClFN_3O_3$ $[M+H]^+$: 450, found: 450.

Step 3. Preparation of (E)-4-(1-(2-chloro-6-(prop-1-enyl)benzoyl)-1H –pyrazolo [4,3-b]pyridin-3-yl)-3-fluorobenzoic acid (1A). To a solution of (E)-methyl 4-(1-(2- chloro-6-(prop-1-enyl)benzoyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)-3-fluorobenzoate (**A-3**) (120 mg, 2.67 mmol) in THF (15mL) and H_2O (15mL) was added $LiOH.H_2O$ (112 mg, 2.67 mmol), and the mixture was stirred at 30 °C for 2h. The mixture was neutralized with 2N HCl to pH = 3-4. The mixture was extracted with EA (50 ml). The organic layer was dried over Na_2SO_4 and concentrated to obtain a crude product. The crude product was purified by pre-HPLC to afford 17 mg (15%) of the title compound as white solid. LCMS (ESI): calc'd for $C_{23}H_{15}ClFN_3O_3$ $[M+H]^+$: 436, found: 436; ^{1}HNMR (400 MHz, DMSO) δ 8.94 (2H, m), 8.26-8.23 (1H, t), 7.91-7.72 (4H, m), 7.57-7.48 (2H, m), 6.45-6.43 (1H, m), 6.34-6.30 (1H, d), 1.75-1.74 (3H, d).

EXAMPLE 1B: Preparation of 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-4- formyl-1H-indazol-3-yl)benzoic acid (1B)

SCHEME B.



Step 1. Preparation of 1-(2-chloro-6-(trifluoromethyl)benzoyl)-3-iodo-1H –indazole-4-carbaldehyde (B-3). The mixture of 2-chloro-6-(trifluoromethyl)benzoic acid (**B-2**) (0.46 g, 2.07 mol) and $(COCl)_2$ (0.32 mL, 3.76 mol) in DCM (10 mL) and DMF (5drops) was stirred at room temperature for 1h. The solvent was removed and the residue was dissolved in DCM (10 mL). To the mixture of 3-iodo-1H-indazole-4-carbaldehyde (**B-1**) (0.51 g, 1.88 mol), DMAP (23 mg,0.19 mol) and Et_3N (0.52 mL, 3.76 mol) in DCM (10 mL) was added the

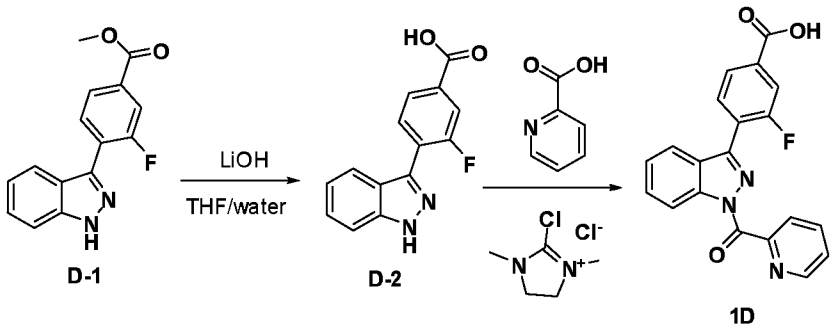
aboved DCM solution dropwise and the reaction mixture was stirred at room temperature overnight. The result solution was diluted with H_2O (50 mL) and the aqueous layer was extracted with DCM (30 mL×3). The combined organic layers were washed with brine (30 mL×1),dried over anhydrous Na_2SO_4 and concentrated. The residue was chromatographed on silica gel(PE:EA 8:1 to 4:1) to get the desired product **B-3** as a white solid. LCMS (ESI) calc'd for $C_{16}H_7ClF_3IN_2O_2$ $[M+H]^+$: 479, found: 479.

Step 2. Preparation of methyl 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-4- formyl-1H-indazol-3-yl)benzoate (B-5). A mixture of 1-(2-chloro-6- (trifluorom- ethyl)benzoyl)-3-iodo-1H-indazole-4-carbaldehyde (**B-3**) (0.5 g, 1.05 mol), 4-(meth- oxycarbonyl)phenylboronic acid (**B-4**) (0.28 g, 1.57 mol), $Pd(PPh_3)_4$ (0.13 g, 0.11 mol) and K_2CO_3 (0.43 g, 3.15 mol) were suspended in 1,4-dioxane (10 mL) and H_2O (2 mL). The reation mixture was heated at 100 °C in a microwave reactor for 1.5h. The result mixture was diluted with H_2O (50 mL) and the aqueous layer was extracted with ethyl acetate (50 mL × 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was chromatographed on silica gel (PE:EA = 4:1) to get the desired product **B-5** as a pale yellow solid. LCMS (ESI) calc'd for $C_{24}H_{14}ClF_3N_2O_4$ $[M+H]^+$:487, found: 487.

Step 3. Preparation of 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-4-formyl- 1H-indazol-3-yl)benzoic acid (1B). The mixture of methyl 4-(1-(2-chloro- 6-(trifluoromethyl)benzoyl)-4-formyl-1H-indazol-3-yl)benzoate (**B-5**) (40 mg, 0.08 mol) and LiOH (17 mg, 0.41 mol) in THF (4 mL) and H_2O (2 mL) was stirred at room temperature for 4h. The reaction mixture was diluted with H_2O (20 mL). 2M HCl solution was added to adjust the pH=3 and the aqueous layer was extracted with ethyl acetate (20 mL × 3). The combined organic layers were washed with brine (20 mL × 1), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified with Prep-HPLC to get the desired product **1B** as a white solid. LCMS (ESI): calc'd for $C_{23}H_{12}ClF_3N_2O_4$ $[M+H]^+$: 473, found: 473; ^{1}HNMR (400 MHz, DMSO) δ 10.07 (1H, s), 8.89 (1H, d, J=8.4Hz), 8.13 (1H, d, J=7.2Hz), 8.03-8.07 (4H, m), 7.99 (1H, d, J=8.0Hz), 7.83-7.87 (1H, m), 7.70 (2H, d, J=8.4Hz).

EXAMPLE 1D: Preparation of 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)-1H-indazole-7-carboxylic acid (1D)

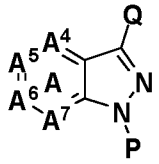
SCHEME D.

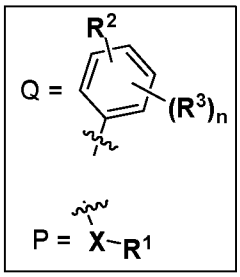


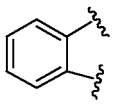
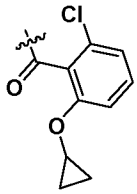
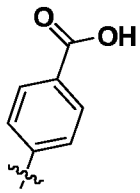
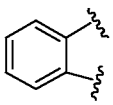
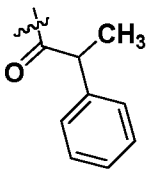
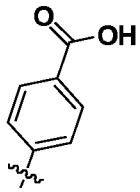
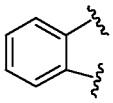
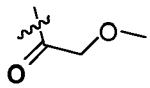
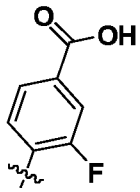
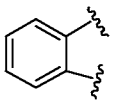
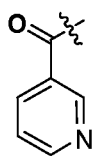
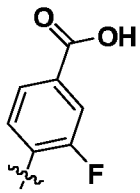
Step 1. Preparation of 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-1H-pyrazolo [4,3-b]pyridin-3-yl)-1H-indazole-7-carboxylic acid (1D). To a 1 dram vial was added methyl 3-fluoro-4-(1H-indazol-3-yl)benzoate (**D-1**) (30 mg, 0.111mmol), LiOH (1M, 0.333ml), methanol (0.25ml) and THF (0.5ml), The reaction mixtures were stirred at RT for 2 hours. The mixtures were then evaporated under reduced pressure. The remaining residues were then dissolved in DCM (0.5ml) and added to other 1 dram vials that contained picolinic acid (27 mg, 0.222mmol), 2-chloro-1,3-dimethylimidazolinium chloride (37.5 mg, 0.222 mmol), and DCM (1 ml) which was stirring at RT for 4 h. The combined mixtures were stirred overnight at RT and then evaporated under reduced pressure. The reactions were then diluted with 1.0 mL DMSO, filtered, and purified by mass-triggered reverse phase HPLC, eluting with a 1% ammonium hydroxide buffered water/acetonitrile gradient over a Waters X-Bridge C-18 column, to afford desired products. LCMS (ESI) calc´d for $C_{20}H_{12}FN_3O_3$ [M+H]+: 362.1, found: 362.1.

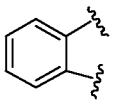
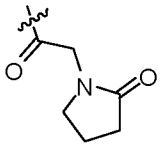
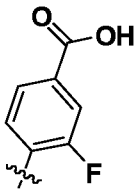
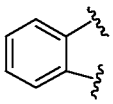
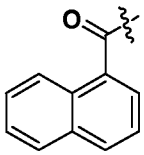
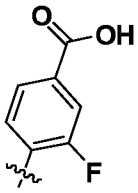
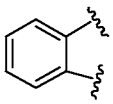
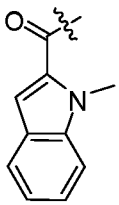
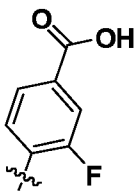
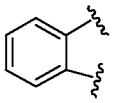
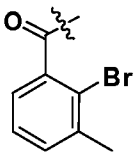
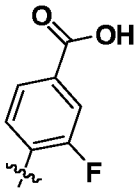
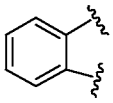
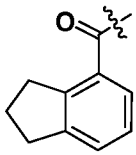
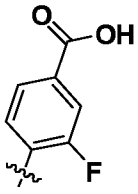
The following examples shown in **TABLE 1** were prepared following similar procedures described for **Examples A, B, C, D** in **Schemes A-D**, which can be achieved by those of ordinary skill in the art of organic synthesis.

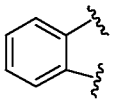
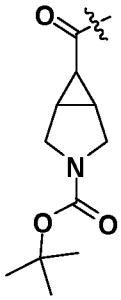
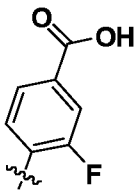
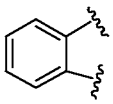
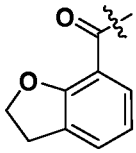
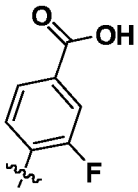
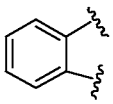
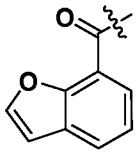
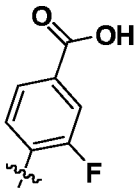
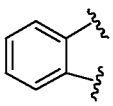
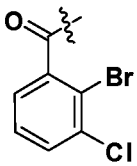
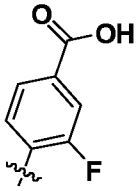
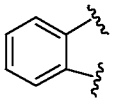
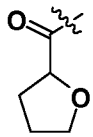
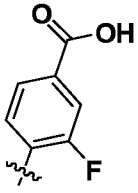
TABLE 1





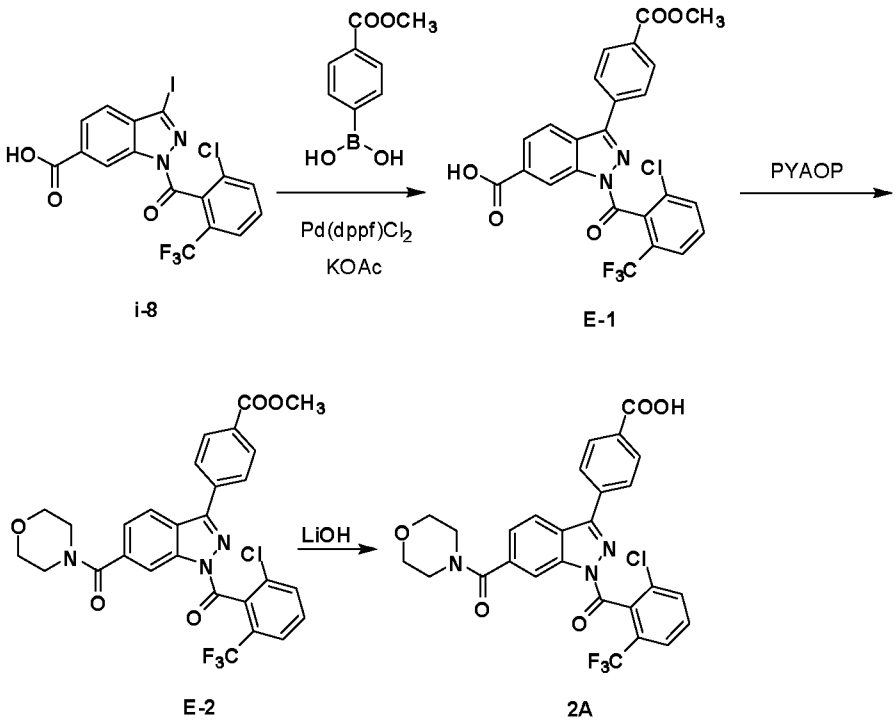
Ex.	Chemical Name	A ring	P	Q	LCMS $[M+H]^+$ Found
1H	4-(1-(2-chloro-6-cyclopropoxybenzoyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)benzoic acid				434
1I	3-fluoro-4-(1-(2-phenylpropanoyl)-1H-indazol-3-yl)benzoic acid				389
1J	3-fluoro-4-[1-(methoxyacetyl)-1H-indazol-3-yl]benzoic acid				329
1K	3-fluoro-4-[1-(pyridin-3-ylcarbonyl)-1Hindazol-3-yl]benzoic acid				362

1L	3-fluoro-4-{1-[(2-oxopyrrolidin-1-yl)acetyl]-1Hindazol-3-yl}benzoic acid				382
1M	3-fluoro-4-[1-(naphthalen-1-ylcarbonyl)-1Hindazol-3-yl]benzoic acid				411
1N	3-fluoro-4-{1-[(1-methyl-1H-indol-2-yl)carbonyl]-1Hindazol-3-yl}benzoic acid				414
1O	4-{1-[(2-bromo-3-methylphenyl)carbonyl]-1H-indazol-3-yl}-3-fluorobenzoic acid				454
1P	4-[1-(2,3-dihydro-1H-inden-4-ylcarbonyl)-1Hindazol-3-yl]-3-fluorobenzoic acid				401

1Q	4-(1-{[3-(tertbutoxycarbonyl)-3-azabicyclo[3.1.0]hex-6-yl]carbonyl}-1H-indazol-3-yl)-3-fluorobenzoic acid				465
1R	4-[1-(2,3-dihydro-1-benzofuran-7-ylcarbonyl)-1Hindazol-3-yl]-3-fluorobenzoic acid				403
1S	4-[1-(1-benzofuran-7-ylcarbonyl)-1Hindazol-3-yl]-3-fluorobenzoic acid				401
1T	4-{1-[(2-bromo-3-chlorophenyl)carbonyl]-1H-indazol-3-yl}-3-fluorobenzoic acid				474
1U	3-fluoro-4-(1-(tetrahydrofuran-2-carbonyl)-1H-indazol-3-yl)benzoic acid				355

EXAMPLE 2A: Preparation of 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(morpholine-4-carbonyl)-1H-indazol-3-yl)benzoic acid (2A)

SCHEME E



Step 1. Preparation of 1-(2-chloro-6-(trifluoromethyl)benzoyl)-3-(4-(methoxycarbonyl)phenyl)-1H-indazole-6-carboxylic acid (E-1). A mixture of **i-8** (300 mg, 0.61 mmol), 4-(methoxycarbonyl)phenylboronic acid (165 mg, 0.92 mmol), Pd(dppf) Cl_2 (50 mg, 0.061 mmol) and KOAc (181 mg, 1.83mmol) in 10 ml dioxane and 2 ml pure H_2O was heated to 95 ^{0}C for 2h with microwave. Then it was diluted with EtOAC (50 ml), washed with brine (50 ml × 2), dried over anhydrous Na_2SO_4, concentrated. Then it was purified by silica gel column (Petroleum ether/EtOAc = 20/1) to get white solid **E-1** (180 mg, 59%). LCMS (ESI): calc'd for $C_{24}H_{14}ClF_3N_2O_5$, $[M+H]^+$: 503.1, found: 503.1.

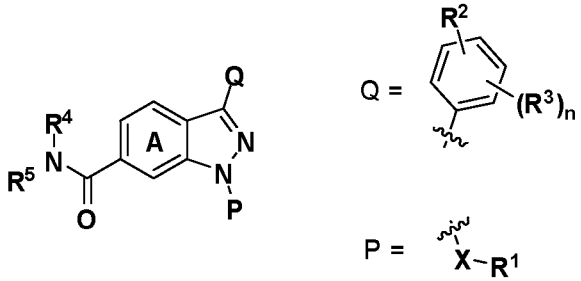
Step 2. Preparation of methyl 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl) -6-(morpholine-4-carbonyl)-1H-indazol-3-yl)benzoate (E-2). The compound **E-1** (180 mg, 0.36mmol) was dissolved in CH_2Cl_2 (15 mL). morpholine (37mg,0.43mmol), PYAOP (374

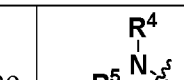
mg, 0.72mmol) was added and the mixture was stirred at room temperature for 2 mins. TEA (0.16mL, 1.08mmol) was added and the mixture was stirred at room temperature for 2h. Then it was diluted with EtOAC (20 ml), washed with brine (2 × 20 ml), dried over anhydrous Na_2SO_4, concentrated get white solid **E-2** (195 mg, 95%). LCMS (ESI): calc'd for $C_{28}H_{21}ClF_3N_3O_5$, $[M+H]^+$: 572, found: 572.

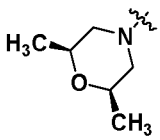
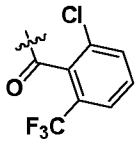
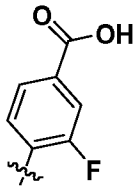
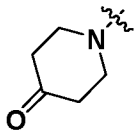
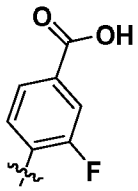
Step 3. Preparation of 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6- (morpholine-4-carbonyl)-1H-indazol-3-yl)benzoic acid (2A). A mixture of **E-2** (195mg, 0.34mmol) and $LiOH.H_2O$ (72mg, 1.7mmol) in 10 ml THF and 10 ml pure H_2O was stirred at RT for 2 hours. The solvent was evaporated and the residue was dissolved in water. HCl (5% sol in water) was added until pH=4-5. The precipitated solid was filtered, washed with water and n-hexane, dried to afford an off white solid **2A** (184mg, 97%). LCMS (ESI): calc'd for $C_{27}H_{19}ClF_3N_3O_5$, $[M+H]^+$: 558.1 found: 558.1. 1HNMR (400MHz, DMSO) δ 8.55(1H, s), 8.32-8.34(1H, d, J = 8 Hz), 8.05-8.11(3H, m), 8.01-8.03 (1H, d, J = 8 Hz), 7.95-7.97 (2H, d, J = 8Hz), 7.87-7.91 (1H, m), 7.69-7.71 (1H, d, J = 8 Hz), 3.52-3.72 (8H, m).

The following examples shown in **TABLE 2** were prepared following similar procedures described for **Examples E** in **Schemes E**, which can be achieved by those of ordinary skill in the art of organic synthesis.

TABLE 2

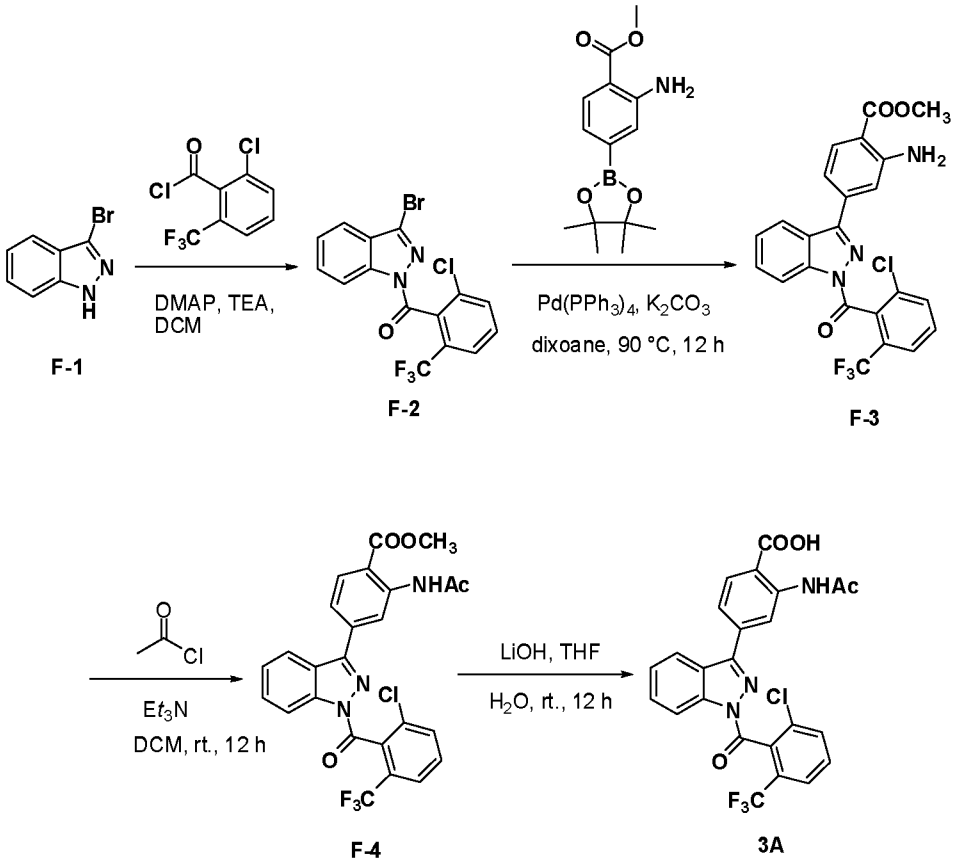


Ex.	Chemical Name		P	Q	LCMS $[M+H]^+$ Found

2B	4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-((2S,6R)-2,6-dimethylmorpholine-4-carbonyl)-1H-indazol-3-yl)-3-fluorobenzoic acid				604
2C	4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(4-oxopiperidine-1-carbonyl)-1H-indazol-3-yl)-3-fluorobenzoic acid				588

EXAMPLE 3A: Preparation of 2-acetamido-4-(1-(2-chloro-6-(trifluoromethyl) benzoyl)-1H-indazol -3-yl)benzoic acid (3A).

SCHEME F



Step 1. Preparation of (3-bromo-1H-indazol-1-yl)(2-chloro-6-(trifluoromethyl)phenyl)methanone. (F-2). To a solution of 3-bromo-1H-indazole (**F-1**) (200 mg, 1.02 mmol) in DCM (20 mL) was added DMAP (12.5 mg, 0.1 mmol), TEA (0.3 mL, 2 mmol), 2-chloro-6-(trifluoromethyl)benzoyl chloride (370 mg, 1.53 mmol) in DCM (5 mL) was added slowly, the reaction mixture was stirred at RT for 3 h, then diluted with EA (100 mL), washed with Sat. $NaHCO_3$ aqueous, water and brine, concentrated and purified with flash chromatograph (PE:EA=10:1) to give 400 mg (99%) of title compound as a yellow solid. LCMS (ESI) calc'd for $C_{15}H_7BrClF_3N_2O$ $[M+H]^+$, 402.9, found: 403, 405.

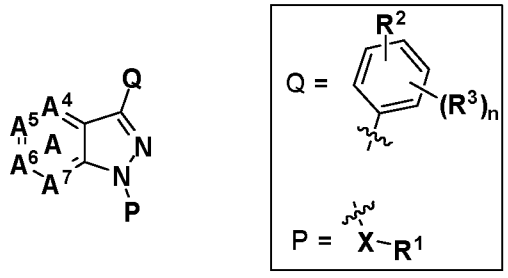
Step 2. Preparation of methyl 2-amino-4-(1-(2-chloro-6-(trifluoro methyl) benzoyl)-1H-indazol-3-yl)benzoate (F-3). To a mixture of **F-2** (110 mg, 0.4 mmol), methyl 2-amino-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate(168 mg, 0.4 mmol), $Pd(PPh_3)_4$(46 mg, 0.04 mmol) and K_2CO_3 (138 mg, 1 mmol) was added dioxane (15 ml) and H_2O (1 ml), and the mixture was heated at 90°C under argon for 6 h. The mixture was cooled down, diluted

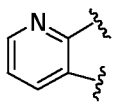
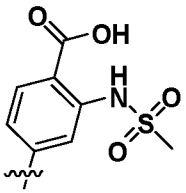
with CH_2Cl_2 (50 mL). The organic layer was separated, washed with brine, dried over Na_2SO_4, concentrated. The residue was purified by Prep-TLC (Pentane/EtOAc 10/1) to give 155 mg (71%) of the title compound. LCMS (ESI) calc'd for $C_{23}H_{15}ClF_3N_3O_3$ $[M+H]^+$, 474, found: 474.

Step 2. Preparation of methyl 2-acetamido-4-(1-(2-chloro-6-(trifluoromethyl) benzoyl)-1H-indazol-3-yl)benzoate (F-4). To a flask was added compound **F-3** (180mg, 0.38 mmol), acetyl chloride (36 mg, 0.46 mmol), and DCM (30 mL), followed by the addition of TEA (1.3 mL, 0.95 mmol) slowly. The reaction mixture was stirred at rt for 2 h. The mixture was diluted with H_2O, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (. The combined organics were washed with H_2O, brine, dried over Na_2SO_4, and concentrated. The residue was purified by Prep-TLC (Pentane/EtOAc, 10/1) to afford 210 g (97 %) of the title compound. LCMS (ESI) calc'd for $C_{25}H_{17}ClF_3N_3O_4$ $[M+H]^+$: 516, found: 516.

Step 3. Preparation of 2-acetamido-4-(1-(2-chloro-6-(trifluoromethyl) benzoyl) -1H-indazol -3-yl)benzoic acid (3A). To a stirred solution of compound **F-4** (210mg, 0.41 mmol) was added THF (8.0 mL), H_2O (2.0 mL) and $LiOH{\cdot}H_2O$ (172 mg, 4.1 mmol) and the solution was stirred at r.t. overnight. LCMS showed disappearance of staring material. The solution was adjusted to pH 4.0 using 1N HCl and poured into THF (30 mL), washed with Brine (20mL). The organic layer was dried over Na_2SO_4, the organic layer was evaporated and submitted for Prep-HPLC. 45 mg product was collected (23 %). LCMS (ESI) calc'd for $C_{24}H_{15}ClF_3N_3O_4$ $[M+H]^+$: 502, found: 502. ^{1}HNMR (500 MHz, DMSO) δ11.72 (1H,bs),9.09 (1H, s), 8.59(1H,d),8.23(1H, d), 8.06(3H,m), 7.88(2H, m),7.07(1H, *s*),7.49(1H, d),2.15(3H,s).

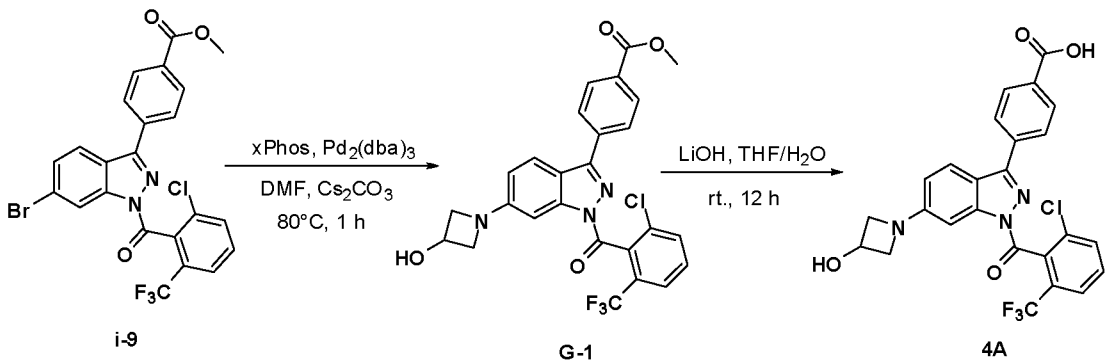
TABLE 3



Ex.	Chemical Name	A ring	P	Q	LCMS $[M+H]^+$ Found
3B	4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)-2-(methylsulfonamido)benzoic acid				539

Example 4A. Preparation of 4-(1-(2-chloro-6-(trifluoromethyl) benzoyl)-6- (3-hydroxyazetidin-1-yl)-1H-indazol-3-yl)benzoic acid (4A)

SCHEME G



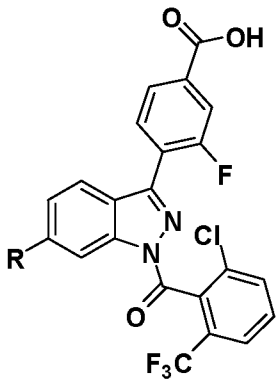
Step 1. Preparation of Methyl4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(3-hydroxyazetidin-1-yl)-1H-indazol-3-yl)benzoate (G-1). To a mixture of methyl-4-(6- bromo-1-(2-chloro-6-(trifluoromethyl)benzoyl)-1H-indazol-3-yl)benzoate (**i-9**) (108 mg, 0.2 mmol), azetidin-3-ol (26mg, 0.24 mmol), $Pd_2(dba)_3$ (16 mg, 0.02 mmol), Xphos (20 mg, 0.04 mmol) and Cs_2CO_3 (196 mg, 0.6 mmol) was added dioxane (10 ml), and the mixture was heated at 90°C under argon for 6 h. The mixture was cooled down, diluted with CH_2Cl_2 (100 ml). The organic layer was separated, washed with brine, dried over Na_2SO_4, concentrated. The residue

was purified by Prep-TLC (Pentane/EtOAc=10/1) to give 120 mg of the title compound (98%). LCMS (ESI) calc'd for $C_{26}H_{19}ClF_3N_3O_4$ $[M+H]^+$: 530.1 found: 530.

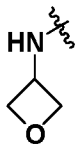
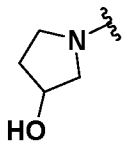
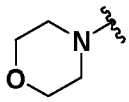
Step 2. Preparation of 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6- (3-hydroxyazetidin-1-yl)-1H-indazol-3-yl)benzoic acid (4A). To a stirred solution of Methyl 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(3-hydroxyazetidin-1-yl)-1H- indazol-3-yl)benzoate (**G-1**) (159mg, 0.3 mmol) was added THF (8.0 ml), H_2O (2.0 ml) and $LiOH{\cdot}H_2O$ (126 mg, 3 mmol) and the solution was stirred at r.t. overnight. LCMS showed disappearance of staring material. The solution was adjusted to pH 4.0 using 1N HCl and poured into THF (30 ml), washed with Brine (20mL). The organic layer was dried over Na_2SO_4, the organic layer was evaporated and submitted for Prep-HPLC (ACN/H_2O). 55 mg product was collected (68 %). LCMS (ESI) calc'd for $C_{25}H_{17}ClF_3N_3O_4$ $[M+H]^+$: 516.09, found: 516; ^{1}HNMR (500 MHz, DMSO) δ13.24 (1H,s),8.05 (3H, d), 8.03 (2H, d), 7.87(3H, t), 7.36(1H, s),6.73 (1H,d), 5.72 (1H, bs), 4.67 (1H, m), 4.30 (2H, d), 3.76 (2H, d).

The following examples shown in **TABLE 4** were prepared following similar procedures described for **Examples 4A** in **Scheme G**, which can be achieved by those of ordinary skill in the art of organic synthesis.

TABLE 4

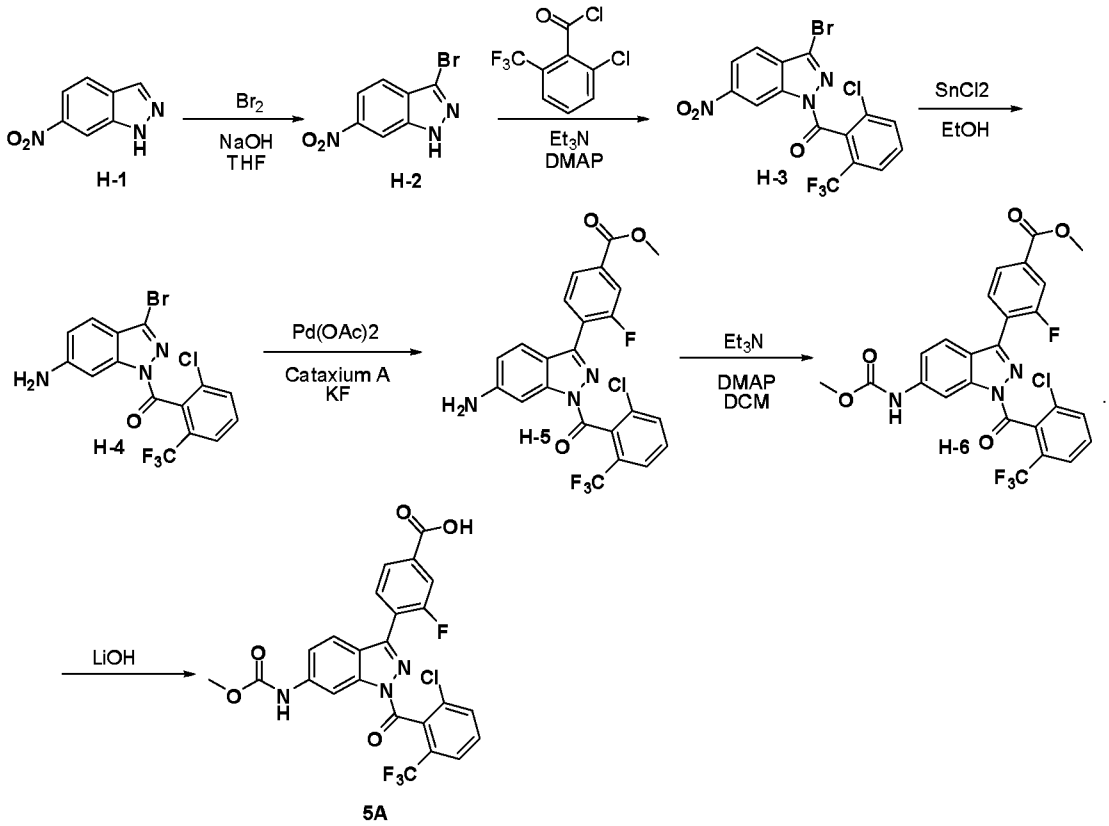


Example	Chemical Name	R	LCMS $[M+H]^+$ Found

4B	4-(6-(azetidin-1-yl)-1-(2-chloro-6-(trifluoromethyl)benzoyl)-1H-indazol-3-yl)-3-fluorobenzoic acid		518
4D	4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(cyclopropylamino)-1H-indazol-3-yl)-3-fluorobenzoic acid		518
4F	4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(oxetan-3-ylamino)-1H-indazol-3-yl)-3-fluorobenzoic acid		534
4G	4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(3-hydroxypyrrolidin-1-yl)-1H-indazol-3-yl)-3-fluorobenzoic acid		548
4H	4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-morpholino-1H-indazol-3-yl)benzoic acid		530

Example 5A. Preparation of 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(methoxycarbonylamino)-1H-indazol-3-yl)-3-fluorobenzoic acid (5A)

Scheme H.



Step 1. Preparation of 3-bromo-6-nitro-1H-indazole (H-2). A mixture of 6-nitro-1H-indazole (**H-1**) (5 g, 30 mmol) and NaOH (2 M, 20 ml) in 20 ml THF, Br_2 (9.5 g, 60 mmol) dissolved in NaOH (2 M, 100 ml) was added, the mixture was stirred at RT for 1 night. The solvent was evaporated, The precipitated solid was filtered, washed with water (30 ml) and n-hexane (50 ml), dried to afford an off white solid **H-2**. LCMS (ESI): calc'd for $C_7H_4BrN_3O_2$ $[M+H]^+$: 242 found: 242.

Step 2. Preparation of (3-bromo-6-nitro-1H-indazol-1-yl)(2-chloro-6-(trifluoro methyl)phenyl)methanone (H-3). To a 250 mL round-bottomed flask, was added 3-bromo-6-nitro-1H-indazole (**H-2**) (9.4 g, 38.7 mmol), (2-chloro-6-(trifluoromethyl) benzoyl chloride) (10.3g, 42.6mmol), DMAP (472 mg, 3.87 mmol) and CH_2Cl_2 (100mL), after stirring at RT for 3 minutes, TEA (11.2 mL, 77 mmol) was added slowly. The reaction mixture is stirred at RT for overnight. LC-MS showed no starting materials remained. Then the mixture was poured to 30 mL water, the lower (organic) and upper (aqueous) phases are separated. The aqueous phase is extracted twice with 50 ml CH_2Cl_2. The combined organic phases are washed successively with two 20 ml portions of water and 10 ml of brine. The

reaction resulting organic phase is dried over anhydrous sodium sulfate, filtered and concentrated at reduced pressure to give a yellow solid. The residue was purified by column chromatography (PE /EA from 50/1 to 10/1), to give a solid **H-3**. LCMS (ESI): calc'd for $C_{15}H_6BrClF_3N_3O_3$ $[M+H]^+$: 448, found: 448.

Step 3. Preparation of (6-amino-3-bromo-1H-indazol-1-yl)(2-chloro-6-(trifluoro methyl)phenyl)methanone (H-4). A mixture of (3-bromo-6-nitro-1H- indazol-1-yl) (2-chloro-6-(trifluoromethyl)phenyl)methanone (**H-3**) (10g, 20 mmol) and $SnCl_2$ (21 g, 10 mmol) in 100 ml EtOH , the mixture was stirred at 80 °C for 4 hours The solvent was evaporated with EtOAc(100 ml×3) and water (200 ml), The organic phase was collected and evaporated dried to afford an off white solid **H-4**. LCMS (ESI): calc'd for $C_{15}H_8BrClF_3N_3O$, $[M+H]^+$: 418 found:418.

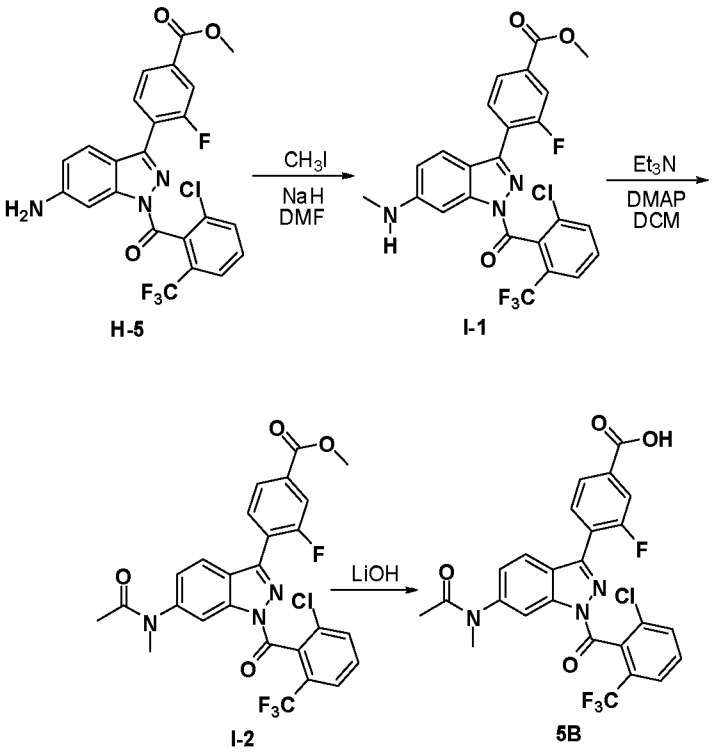
Step 4. Preparation of methyl 4-(6-amino-1-(2-chloro-6-(trifluoromethyl)ben- zoyl)-1H-indazol-3-yl)-3-fluorobenzoate (H-5). A 30ml Microwave vial were charged with (6-amino-3-bromo-1H-indazol-1-yl)(2-chloro-6-(trifluoromethyl) phen- yl)methanone (**H-4**) (2 g, 4.8 mmol), 2-fluoro-4-(methoxycarbonyl) phenylboronic acid (1g, 5.2 mmol), $Pd(OAc)_2$ (54 mg, 0.24 mmol), Catacxium A (86 mg, 0.24 mmol) and KF (835 mg, 14.4 mmol) dissolved in unhydrous THF (5 ml), A stir bar was added, the vial was sealed , the reaction was heated for 2 hours at a constant temperature of 80 °C, The mixture was filtered and the filtrate was collected , purified by column chromatography (DCM) to get the desired product **H-5**. LCMS (ESI): calc'd for $C_{23}H_{14}ClF_4N_3O_3$ $[M+H]^+$: 492 found: 492.

Step 5. Preparation of methyl 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6 - (methoxycarbonylamino)-1H-indazol-3-yl)-3-fluorobenzoate (H-6). Methyl 4-(6- amino-1-(2-chloro-6-(trifluoromethyl)benzoyl)-1H-indazol-3-yl)-3-fluorobenzoate (**H-5**)(186 mg, 0.38mmol), methyl carbonochloridate (40 mg, 0.43mmol), DMAP (5 mg, 0.04 mmol) and CH_2Cl_2 (100 mL), after stirring at RT for 3 minutes, TEA (0.1 mL, 0.77 mmol) was added slowly. The reaction mixture is stirred at RT overnight. The solvent was concentrated at reduced pressure to give a yellow solid **H-6**. LCMS (ESI): calc'd for $C_{25}H_{16}ClF_4N_3O_5$ $[M+H]^+$: 550, found: 550.

Step 6. Preparation of 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(methoxy-carbonylamino)-1H-indazol-3-yl)-3-fluorobenzoic acid (5A). A mixture of methyl 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(methoxycarbonylamino)-1H-indazol-3 -yl)-3-fluorobenzoate (**H-6**) (38 mg, 0.07 mmmol) and $LiOH.H_2O$ (16 mg, 0.37 mmmol) in 10 ml THF and 10 ml pure H_2O was stirred at RT for 2 hours. The solvent was evaporated and the residue was dissolved in water. HCl (5% sol in water) was added until pH =4-5. The precipitated solid was filtered, washed with water (10 ml) and n-hexane (10 ml), dried to afford an off white solid **5A**. LCMS (ESI): calc'd for $C_{24}H_{14}ClF_4N_3O_5$ $[M+H]^+$: 536 found: 536; 1HNMR (400 MHz, DMSO) δ 13.54 (1H, s), 10.32 (1H, s), 8.93 (1H, s), 7.97-8.03 (2H, m), 7.83-7.91 (4H, m), 7.70-7.75 (1H, m), 7.61-7.63 (1H, d, J= 8 Hz), 3.76 (3H, s).

Example 5B. Preparation of 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(N-methylacetamido)-1H-indazol-3-yl)-3-fluorobenzoic acid (5B)

Scheme I



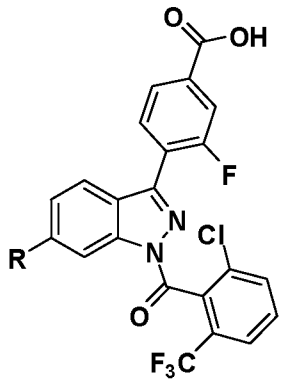
Step 1. Preparation of methyl 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(methylamino)-1H-indazol-3-yl)-3-fluorobenzoate (I-1). A mixture of Methyl 4-(6-ami- no-1-(2-chloro-6-(trifluoromethyl)benzoyl)-1H-indazol-3-yl)-3-fluorobenzoate (**H-5)** (344 mg, 0.7 mmmol) in 10 ml DMF under ice bath, CH_3I (0.07 ml, 0.14mmol) was added, and then the icebath was removed and stirred at RT for 5 hours. The solvent was extracted with EtOAc (30 ml) and water (3 × 20 ml), the organic phase was collected and the residue purified by column chromatography of silic gel eluting with (PE/DCM=2:1) to get the desired product **I-1**. LCMS (ESI) calc'd for $C_{24}H_{16}ClF_4N_3O_3$ $[M+H]^+$: 506, found: 506.

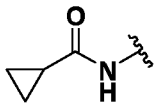
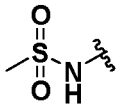
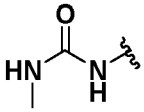
Step 2. Preparation of 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(N-methylacetamido)-1H-indazol-3-yl)-3-fluorobenzoate (I-2). Methyl 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(methylamino)-1H-indazol-3-yl)-3-fluorobenzoate (**I-1**) (19 2 mg, 0.38mmol), acetyl chloride (33 mg, 0.43mmol), DMAP (5 mg, 0.04 mmol) and CH_2Cl_2 (100mL), after stirring at RT for 3 minutes, TEA (0.1 ml, 0.77 mmol) was added slowly. The reaction mixture is stirred at RT for overnight. The solvent was concentrated at reduced pressure to give a yellow solid **I-3**. LCMS (ESI): calc'd for $C_{26}H_{18}ClF_4N_3O_4$ $[M+H]^+$: 548, found: 548.

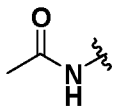
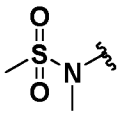
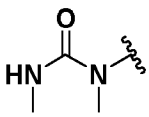
Step 3. Preparation of 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(N-methylacetamido)-1H-indazol-3-yl)-3-fluorobenzoic acid (5B). A mixture of 4-(1-(2- chloro-6-(trifluoromethyl)benzoyl)-6-(N-methylacetamido)-1H-indazol-3-yl)-3-fluorobenzoate (**I-2**) (38 mg, 0.07mmol) and $LiOH.H_2O$ (16mg, 0.37mmol) in 10 ml THF and 10 ml pure H_2O was stirred at RT for 2 hours. The solvent was evaporated and the residue was dissolved in water. HCl (5% in water) was added until pH = 4-5. The precipitated solid was filtered, washed with water (10 ml) and n-hexane (10 ml), dried to afford an off white solid **5B**. LCMS (ESI): calc'd for $C_{25}H_{16}ClF4N_3O_4[M+H]^+$: 534 found: 534; 1HNMR (400 MHz, DMSO) δ 8.46(1H, s), 7.98-8.05(3H, m), 7.87-7.93 (3H, s), 7.76 (1H, s), 7.61-7.63(1H, d, J= 8 Hz), 3.36 (3H, s), 2.01 (3H, s).

The following examples shown in **TABLE 5** were prepared following similar procedures described for **Examples # 5A, 5B** in **Schemes H, I**, which can be achieved by those of ordinary skill in the art of organic synthesis.

TABLE 5

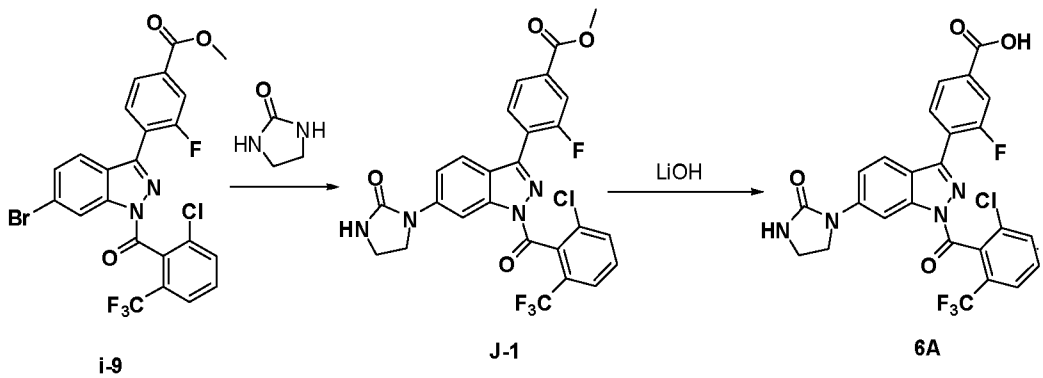


Example	Chemical Name	R	LCMS $[M+H]^+$ Found
5C	4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(cyclopropanecarboxamido)-1H-indazol-3-yl)-3-fluorobenzoic acid		546
5D	4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(methylsulfonamido)-1H-indazol-3-yl)-3-fluorobenzoic acid		556
5E	4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(3-methylureido)-1H-		535

	indazol-3-yl)-3-fluorobenzoic acid		
5F	4-(6-acetamido-1-(2-chloro-6-(trifluoromethyl)benzoyl)-1H-indazol-3-yl)-3-fluorobenzoic acid		520
5G	4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(N-methylmethylsulfonamido)-1H-indazol-3-yl)-3-fluorobenzoic acid		570
5H	4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(1,3-dimethylureido)-1H-indazol-3-yl)-3-fluorobenzoic acid		549

Example 6A. Preparation of 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(2-oxo-imidazolidin-1-yl)-1H-indazol-3-yl)-3-fluorobenzoic acid (6A)

Scheme J

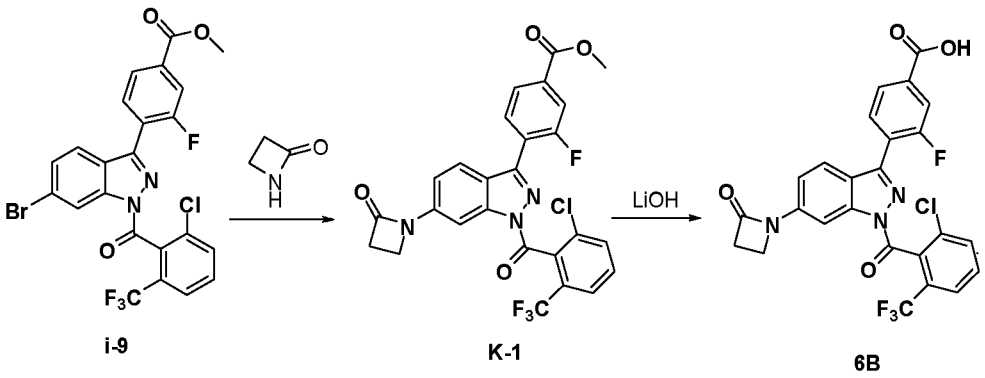


Step 1. Preparation of methyl-4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(2-oxoimidazolidin-1-yl)-1H-indazol-3-yl)-3-fluorobenzoate (J-1). To a microwave tube was added methyl-4-(6-bromo-1-(2-chloro-6-(trifluoromethyl) benzoyl)-1H-ind- azol-3-yl)-3-fluorobenzoate (**i-9**) (70mg, 0.14 mmol), dioxane (1.5ml), imidazolidin -2-one (17mg,0.21mmol), $Pd_2(dba)_3$ (6.3mg, 0.007mmol), xant-phos (11.7 mg, 0.021 mmol), Cs_2CO_3(86 mg,0.28 mmol). The solution was microwaved at 100°C for 2 hours and the organic layer was evaporated to use in next step without purificatiom. LCMS (ESI) calc'd for $C_{26}H_{17}ClF_4N_4O_4$ $[M+H]^+$: 561, found: 561.

Step 2. Preparation of 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(2-oxoimidazolidin-1-yl)-1H-indazol-3-yl)-3-fluorobenzoic acid (6A). To a stirred solution of methyl 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(2-oxoimidazolidin-1-yl)-1H- indazol-3-yl)-3-fluorobenzoate (**J-1**) in dioxane(1.5ml) from last step was added $LiOH{\cdot}H_2O$ (59mg, 1.4mmol) and H_2O (0.5 ml). The solution was stirred overnight and LCMS showed major product peak. The solution was adjusted to pH=3 using 1 N HCl. The upper organic layer was collected and the aqueous layer was extracted with THF (2x1mL). The combined organic layer was added 0.5mL MeOH and submitted for Prep-HPLC (H_2O/ACN) gave 10mg product, yield for two steps 26%. LCMS (ESI) calc'd for C25H15ClF4N4O4 $[M+H]^+$: 547, found: 547; ^{1}HNMR (400 MHz, DMSO) δ 13.44 (1H, s), 8.75 (1H, s), 8.01 (2H,m), 7.98-7.89 (5H, m), 7.71 (1H,d), 4.08-4.05(2H, d), 3.52-3.33 (2H, d).

Example 6B. Preparation of 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6- (2-oxoazetidin-1-yl)-1H-indazol-3-yl)-3-fluorobenzoic acid (6B)

Scheme K

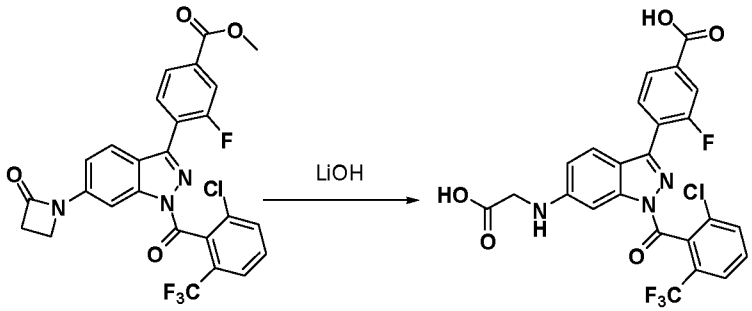


Step 1. Preparation of methyl 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(2-oxoazetidin-1-yl)-1H-indazol-3-yl)-3-fluorobenzoate (K-1). The mixture of methyl 4-(6-bromo-1-(2-chloro-6-(trifluoromethyl)benzoyl)-1H-indazol-3-yl)-3-fluorobenzo- ate (**i-9**) (554 mg,1.0 mmol), $Pd(dppf)_2Cl_2$ (79 mg,0.1 mmol), azetidin-2-one (114 mg, 2.0 mmol), TEA (20 ml) and DMF (20 ml) was purged with N_2 and stirred at 90°C overnight. LCMS showed the SM was consumed totally and the expected product appeared. The resulting solution was filtered and concentrated to purify by column chromatograph (PE/EA) to give 248 mg product as a white solid (45%). LCMS (ESI) calc'd for $C_{26}H_{16}ClF_4N_3O_4$ $[M+H]^+$: 545.87, found: 546.2.

Step 2. Preparation of 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(2-oxoazeti- din-1-yl)-1H-indazol-3-yl)-3-fluorobenzoic acid (6B). To the solution of methyl 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(2-oxoazetidin-1-yl)-1H-indazol-3-yl)- 3-fluorobenzoate (**K-1**) (53.1 mg, 0 .1mmol) in THF (30 ml) and water(10 ml) was added LiOH (240 mg, 10 mmol). The mixture solution was stirred at 0°C for 2 h. Added 100 ml HCl aqueous,exacted with EA (30ml×3), the organic layer was concentrated to be purified by chromatography column (EA:PE=1:1) to afford 27 mg product (51%). LCMS (ESI) calc'd for $C_{25}H_{14}ClF_4N_3O_4$ $[M+H]^+$: 531.84, found: 532.1; ^{1}HNMR (400 MHz, $CDCl_3$) δ:13.5(1H,w), 8.46(1H,s),7.98(6H,m), 7.72(1H,t), 7.61(1H,d), 3.85(2H, m), 3.21(2H, m).

Example 6C. Preparation of 4-(6-(2-carboxyethylamino)-1-(2-chloro-6-(trifluoromethyl)benzoyl)-1H-indazol-3-yl)-3-fluorobenzoic acid (6C)

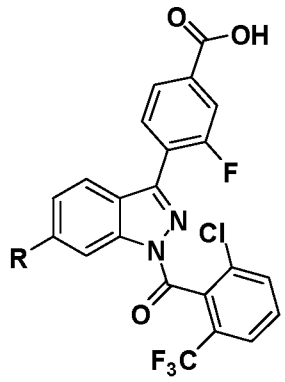
Scheme L

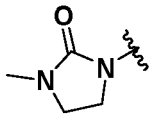
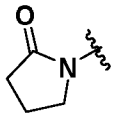


Step 1. Preparation of 4-(6-(2-carboxyethylamino)-1-(2-chloro-6-(trifluoromethyl)benzoyl)-1H-indazol-3-yl)-3-fluorobenzoic acid (6C). To the solution of methyl 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(2-oxoazetidin-1-yl)-1H-indazol-3-yl)-3-fluorobenzoate (**K-1**) (53.1 mg, 0.1mmol) in THF (30 ml) and water(10 ml) was added LiOH (240 mg, 10 mmol). The mixture solution was stirred at rt for 12 h. Added 100 ml HCl aqueous, exacted with EA (30ml×3), the organic layer was concentrated to be purified by chromatography column (EA:PE=1:1) to affor 39 mg product (yield:72%). LCMS (ESI) calc'd for $C_{24}H_{14}ClF_4N_3O_5$ $[M+H]^+$: 549.86, found: 550.1. ^{1}HNMR (400 MHz, $CDCl_3$) δ:13.1(2H,w), 7.9(5H,m), 7.66(1H,t), 7.541(2H,m),6.91(1H,m), 3.41(2H, m), 2.62(2H, m).

The following examples shown in **TABLE 6** were prepared following similar procedures described for **Examples #6A, 6B, 6C** in **Schemes J, K, L**, which can be achieved by those of ordinary skill in the art of organic synthesis.

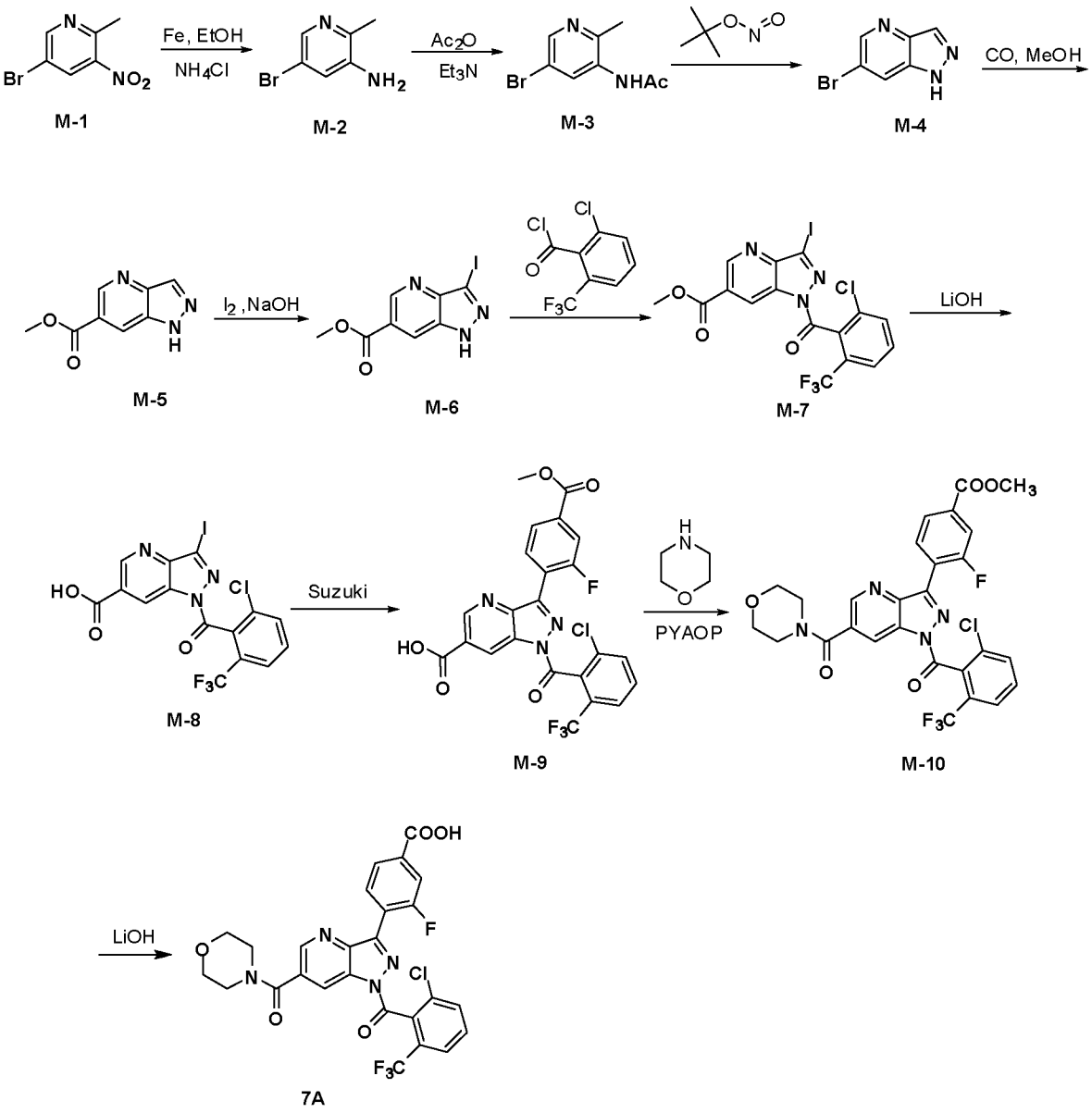
TABLE 6



Example	Chemical Name	R	LCMS $[M+H]^+$ Found
6D	4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(3-methyl-2-oxoimidazolidin-1-yl)-1H-indazol-3-yl)-3-fluorobenzoic acid		561
6E	4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(2-oxopyrrolidin-1-yl)-1H-indazol-3-yl)-3-fluorobenzoic acid		546

Example 7A. Preparation of 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(mor pholine-4-carbonyl)-1H-indazol-3-yl)benzoic acid (7A)

Scheme M



Step 1. Preparation of 5-bromo-2-methylpyridin-3-amine (M-2). To a solution of 5-bromo-2-methyl-3-nitropyridine (**1**) (15 g, 69.4 mmol) in EtOH (300 mL) and water (70 ml), was added iron powder (46.7 g, 833 mmol) and ammonium chloride (4.5 g, 83.4 mmol) successively at rt. The reaction mixture was heated to 90 °C for 40 min. The reaction was filtered hot and rinsed with EtOAc. The filtrate was washed with a saturated aqueous solution of sodium bicarbonate (200 mL), brine, dried over magnesium sulfate and solvent removed in vacuo to give the title compound as an orange solid, (11.7 g, 62.9 mmol, 90%). LCMS (ESI) calc'd for $C_6H_7BrN_2$ $[M+H]^+$: 187, found: 187, 188.

Step 2. Preparation of N-(5-bromo-2-methylpyridin-3-yl)acetamide (M-3). To a solution of 5-bromo-2-methylpyridin-3-amine (**M-2**) (10.7 g, 57.5 mmol) in dichloromethane (575 mL) was added acetic anhydride (12 mL, 126.5 mmol) at 0 °C, followed by triethylamine (22 mL, 158 mmol). The mixture was allowed to warm to ambient temperature and stirred for 18 hours at which point a further equivalent of acetic anhydride (6 mL, 63 mmol) was added. The mixture was stirred at ambient temperature for a further 18 hours. The reaction mixture was quenched with a saturated aqueous solution of sodium bicarbonate (500 mL) and the organic phase washed with saturated aqueous sodium chloride (500 mL), dried over magnesium sulfate and concentrated in vacuo to give a brown solid. This solid was triturated with 30% ethyl acetate in hexanes to yield the title compound as an off-white solid, (8.28 g, 36 mmol, 63%). ^{1}HNMR (400 MHz, CD_3OD): δ ppm 8.31 (s, lH), 8.18 (s, lH), 2.43 (s, 3H), 2.18 (s, 3H). LCMS (ESI) calc'd for $C_8H_9BrN_2O$ $[M+H]^+$: 228.99, found: 229, 230.

Step 3. Preparation of 6-bromo-1H-pyrazolo[4,3-b]pyridine (M-4). To a solution of N-(5-bromo-2-methylpyridin-3-yl)acetamide (**M-3**) (8.3 g, 36 mmol) in chloroform (550 mL) at ambient temperature was added potassium acetate (4.3 g, 43.6 mmol), acetic acid (2.5 mL, 43.6 mmol) and followed by acetic anhydride (6.9 mL, 72.6 mmol). The mixture was stirred at ambient temperature for 15 minutes before being heated to 40 °C. *Tert*-butyl nitrite (6.5 mL, 54 mmol) was then added dropwise. The reaction was then stirred at 60 °C for 48 hours. The reaction mixture was poured slowly into a saturated solution of sodium bicarbonate (500 mL) at 0 °C. The organic phase was retained and the aqueous phase extracted with dichloromethane (500 mL). The combined organics were then concentrated to a brown oil which was dissolved in methanol (500 mL). Aqueous sodium hydroxide (2 M, 500 mL) was added at 0 °C and the mixture stirred at ambient temperature for 1 hour before the methanol was removed in vacuo. The aqueous mixture was then extracted with ethyl acetate (3 × 500 mL). The combined organics dried over magnesium sulfate, and the solvent removed in vacuo to give the title compound as a light brown solid (5.5 g, 27.9 mmol, 77%). ^{1}HNMR (400, CD_3OD): δ ppm 8.55 (s, lH), 8.24 (s, lH), 8.21 (s, 1H). LCMS (ESI) calc'd for $C_6H_4BrN_3$ $[M+H]^+$: 197.96, found: 198, 199.

Step 4. Preparation of methyl 1H-pyrazolo[4,3-b]pyridine-6-carboxylate (M-5). To a solution of 6-bromo-1H-pyrazolo[4,3-b]pyridine (**M-4**) (0.5 g, 2.5 mmol) in methanol (15

ml) and acetonitrile (7 ml) was added Et_3N (2.2 ml, 5.6 mmol), Binap (0.17 g, 0.63 mmol) and palladium dichloride (0.17 g, 0.27 mmol). The mixture was placed under 20 bar of carbon monoxide, stirred at 100 ℃ for 18 h. The mixture was cooled, filtered and purified by Pre-TLC to give 310 mg white solid. (69 %). LCMS (ESI) calc'd for $[M+H]^+$: 178.1, found: 178.1.

Step 5. Preparation of methyl 3-iodo-1H-pyrazolo[4,3-b]pyridine-6-carboxyl- ate (M-6). To a solution of methyl 1H-pyrazolo[4,3-b]pyridine- 6-carboxylate (**M-5**) (316 mg, 1.8 mmol) in DMAC (30 ml) was added KOH (40 mg, 7.18 mmol). The vigorously stirred mixture was treated with iodine (550 mg, 2.15 mmol) and added portionwise over 5 minutes then stirred for 60 minutes. The reaction was quenched with 20 ml of 20% citric acid solution, followed by 16 ml of saturated $NaHSO_3$ solution, then adjusted to pH = 8 with solid $NaHCO_3$ and partitioned between ethyl acetate and water. The organic extract was dried and concentrated to a dark-red oil contain DMAC for next step directly. LCMS (ESI) calc'd for $[M+H]^+$: 304.1, found: 304.1.

Step 6. Preparation of methyl 1-(2-chloro-6-(trifluoromethyl)benzoyl)-3-iodo- 1H-pyrazolo[4,3-b]pyridine-6-carboxylate (M-7). To the solution of methyl 3-iodo -1H-pyrazolo[4,3-b]pyridine-6-carboxylate (**M-6**) (400 mg, 1.32 mmol), Et_3N (290 mg) and DMAP (32 mg, 0.26 mmol) dissolved in anhydrous DCM (10 ml) was added 2-chloro-6-(trifluoromethyl)benzoyl chloride (630 mg, 2.64 mmol) in anhydrous DCM (10 ml) drop wise. The mixture solution was protected by N_2 and stirred at rt for 20 h. Then the solution was concentrated to to afford 500 mg product (78 %). LCMS (ESI) calc'd $[M+H]^+$: 510.1, found: 510.1.

Step 7. Preparation of 1-(2-chloro-6-(trifluoromethyl)benzoyl)-3-iodo- 1H-pyrazolo[4,3-b]pyridine-6-carboxylic acid (M-8). To the solution of methyl 1-(2-chloro- -(trifluoromethyl)benzoyl)-3-iodo-1H-pyrazolo[4,3-b]pyridine-6-carboxylate **M-7**) (700 mg, 1.37 mmol) in THF (15 mL) and H_2O (5 mL) was added LiOH (242 mg, 10.9 mmol). The mixture solution was stirred at RT or 24 h. Added water (10 ml), acidified by HCl (2 M), extracted with EtOAc (20 ml × 3), combined the organic layer, dried, filtered and

concentrated, purified by Pre-HPLC to afford 670 mg (99%). LCMS (ESI) calc'd $[M+H]^+$: 496.1, found: 496.1.

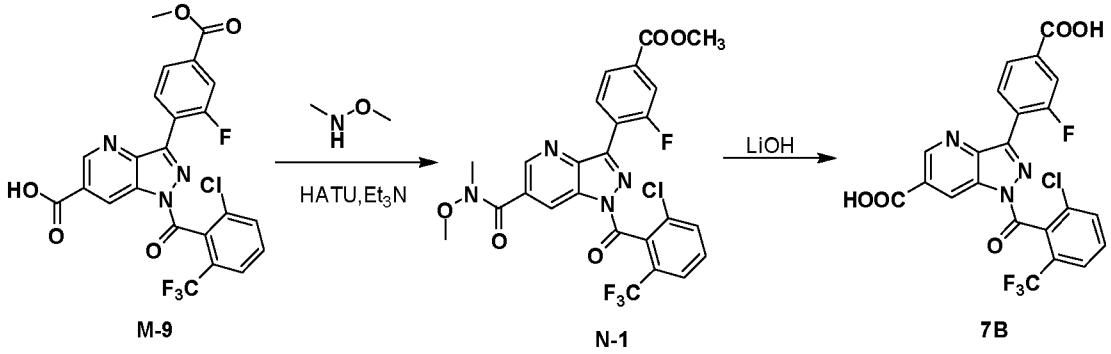
Step 8. Preparation of 1-(2-chloro-6-(trifluoromethyl)benzoyl)-3-(2-fluoro- 4-(methoxycarbonyl)phenyl)-1H-pyrazolo[4,3-b]pyridine-6-carboxylic acid (M-9). The mixture of 1-(2-chloro-6-(trifluoromethyl)benzoyl)-3-iodo-1H- pyrazolo[4,3-b] pyridine-6-carboxylic acid (**M-8**) (100 mg, 0.20 mmol), 2-fluoro-4-(methoxycarbonyl phenylboronic acid (100 mg, 0.5 mmol), $Pd(dppf)Cl_2$ (44 mg, 0.06 mmol), Na_2CO_3 (50 mg, 0.6 mmol) in dioxane (4 ml) and H_2O (0.5 mL) was stirred at 100°C in MW for 1 h. Then the solution was filtered and concentrated to be purified by Pre-HPLC to afford 60 mg product (58 %). LCMS (ESI) calc'd $[M+H]^+$: 522.0, found: 522.0.

Step 9. Preparation of methyl 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(morpholine-4-carbonyl)-1H-indazol-3-yl)benzoate (M-10).1-(2-Chloro-6-(trifluor- omethyl)benzoyl)-3-(2-fluoro-4-(methoxycarbonyl)phenyl)-1H-pyrazolo[4,3-b]pyrid- ine-6-carboxylic acid (**M-9**) (180 mg, 0.36 mmol) was dissolved in CH_2Cl_2 (15 mL). morpholine (37 mg,0.43 mmol), PYAOP (374 mg, 0.72 mmol) was added and the mixture was stirred at room temperature for 2 min. TEA (0.16 mL, 1.08 mmol) was added and the mixture was stirred at room temperature for 2 h. Then it was diluted with EtOAc (20 ml), washed with brine (20 ml × 2), dried with anhydrous Na_2SO_4, concentrated to get white solid 195 mg (95%). LCMS (ESI): calc'd for $C_{28}H_{21}ClF_3N_3O_5$, $[M+H]^+$: 572, found: 572.

Step 10. Preparation of 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(morphol- ine-4-carbonyl)-1H-indazol-3-yl)benzoic acid (7A). A mixture of methyl 4-(1-(2-ch- loro-6-(trifluoromethyl)benzoyl)-6-(morpholine-4-carbonyl)-1H-indazol-3-yl)benzoa- te (**M-10**) (195 mg, 0.34 mmol) and LiOH (72 mg, 1.7 mmol) in 10 ml THF and 10 ml H_2O was stirred at rt for 2 hour. The solvent was evaporated and the residue was dissolved in water. HCl (5% sol. in water) was added until pH 4-5. The precipitated solid was filtered, washed with water and n-hexane, dried to afford an off-white solid 184 mg (97%). LCMS (ESI): calc'd for $C_{27}H_{19}ClF_3N_3O_5$, $[M+H]^+$: 558.1 found: 558.1. 1HNMR (400MHz, DMSO) δ 8.55 (1H, s), 8.32-8.34 (1H, d, J = 8 Hz), 8.05-8.11 (3H, m), 8.01-8.03 (1H, d, J = 8 Hz), 7.95-7.97 (2H, d, J = 8Hz), 7.87-7.91 (1H, m), 7.69-7.71 (1H, d, J = 8 Hz), 3.52-3.72 (8H, m).

Example 7B: Preparation of 3-(4-carboxyphenyl)-1-(2-chloro-6-(trifluoromethyl) benzoyl)-1H-indazole-6-carboxylic acid (7B)

Scheme N

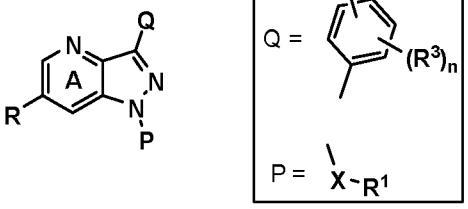


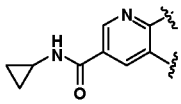
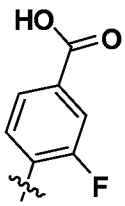
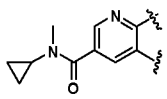
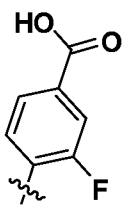
Step 1. Preparation of methyl 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(methoxy(methyl)carbamoyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)-3-fluorobenzoate (N-2).1-(2-Chloro-6-(trifluoromethyl)benzoyl)-3-(2-fluoro-4-(methoxycarbonyl)phenyl) -1H-pyrazolo[4,3-b]pyridine-6-carboxylic acid (**M-9**) (100 mg, 0.19 mmol) was dissolved in CH_2Cl_2 (10 mL), O,N-dimethylhydroxylamine (22 mg, 0.23 mmol), HATU (94 mg, 0.25 mmol) was added and the mixture was stirred at room temperature for 2 min. TEA (23 mg, 0.23 mmol) was added and the mixture was stirred at room temperature overnight. Then it was diluted with EtOAc (15 ml), washed with brine (15 ml×2), dried over anhydrous Na_2SO_4, concentrated to got crude solid **N-2** (80 mg). LCMS (ESI): calc'd for $C_{25}H_{17}ClF_4N_4O_5$, $[M+H]^+$: 564.7, found: 564.7.

Step 2. Preparation of 3-(4-carboxy-2-fluorophenyl)-1-(2-chloro-6-(trifluoromethyl)benzoyl)-1H-pyrazolo[4,3-b]pyridine-6-carboxylic acid (7B). A mixture of methyl 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(methoxy(methyl)carbamoyl)-1 H-pyrazolo[4,3-b]pyridin-3-yl)-3-fluorobenzoate (**N-1**) (80 mg, 0.14 mmol) and $LiOH•H_2O$ (30 mg, 0.7 mmol) in 5 ml THF and 5 ml H_2O was stirred at room temperature for 2 hours. The solvent was evaporated and the residue was dissolved in water. HCl (5% sol. in water) was added until pH 4-5. The product was extracted by EtOAc, concentrated to obtain crude solid. The product was purified by pre-HPLC to get **7B** (10 mg), yield 14.1%. Physical characterization data for **7B** is as follows: LCMS (ESI): calc'd for $C_{22}H_{10}ClF_4N_3O_5$, $[M+H]^+$: 508, found: 508.

^{1}HNMR (400 MHz, MeOD) δ 9.43-9.47 (2H, d, J=13.6Hz), 8.35-8.38 (1H, m), 7.99-8.02 (1H, d, J = 8 Hz), 7.89-7.93 (2H, m), 7.80-7.88 (2H, m).

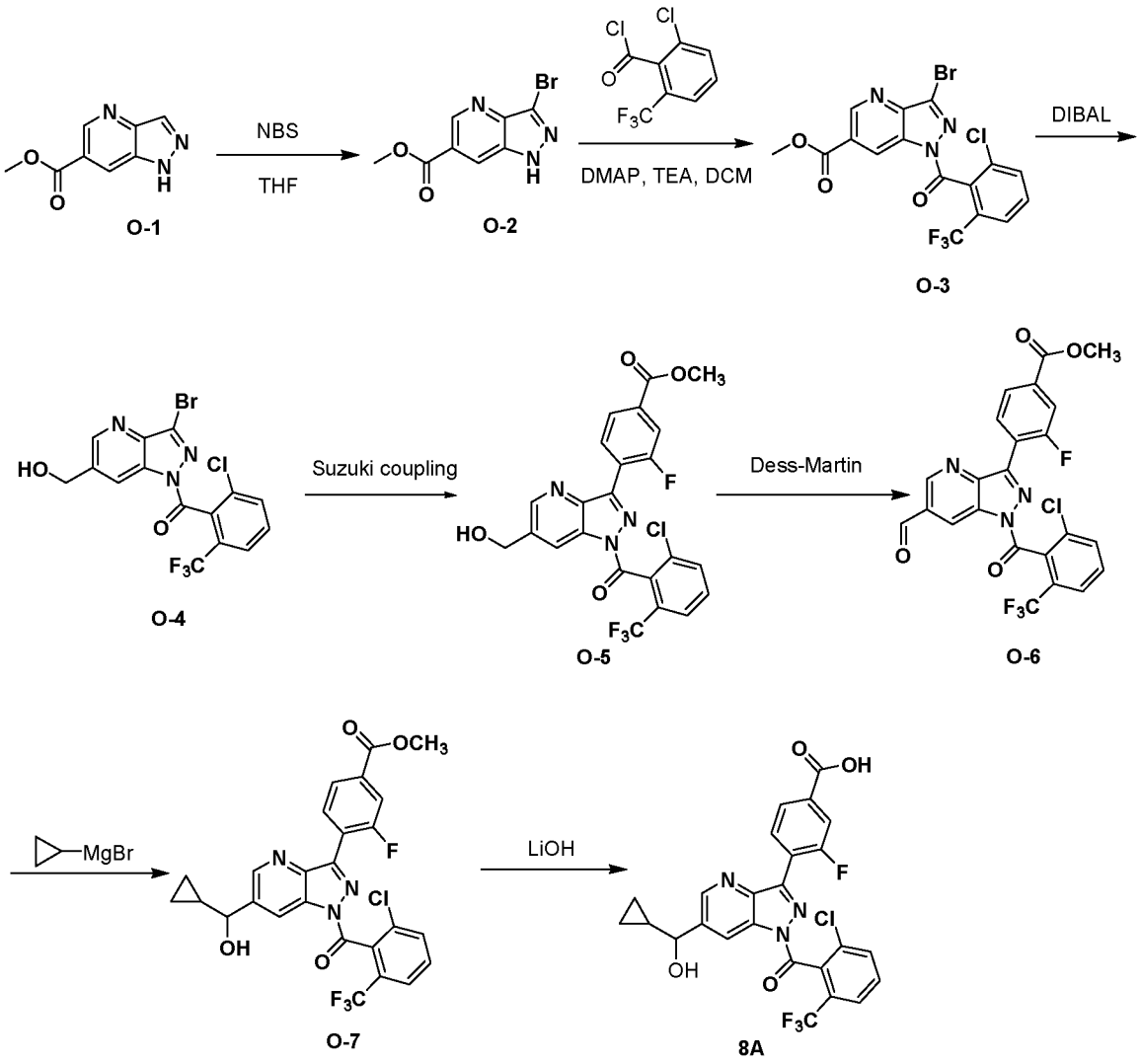
TABLE 7



Ex.	Chemical Name	A ring	P	Q	LCMS $[M+H]^+$ Found
7C	4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(cyclopropylcarbamoyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)-3-fluorobenzoic acid				547
7D	4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(cyclopropyl(methyl)carbamoyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)-3-fluorobenzoic acid				561

Example 8A: Preparation of 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6- (cyclo Propyl (hydroxy)methyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)-3-fluorobenzoic acid (8A)

SCHEME O



Step 1. Preparation of methyl 3-bromo-1H-pyrazolo[4,3-b]pyridine -6-carboxylate (O-2). To a solution of methyl 1H-pyrazolo[4,3-b]pyridine -6-carboxylate (**O-1**) (2 g, 11.3 mmol) in THF (50 mL) was added NBS (3 g, 16.9 mmoL), the reaction mixture was stirred overnight at rt, then methanol was added to quench the reaction, concentrated to give a crude product, triturated with EtOAc, filtered and collected the solid to give 2.5 g (87%) of title compound as a white solid. LCMS (ESI): calc'd for $C_8H_6BrN_3O_2$ $[M+H]^+$: 256, found: 256.

Step 2. Preparation of methyl 3-bromo-1-(2-chloro-6-(trifluoromethyl)benzoyl) -1H-pyrazolo[4,3-b]pyridine-6-carboxylate (O-3). To a solution of methyl 3-bromo

-1H-pyrazolo[4,3-b]pyridine-6-carboxylate (**O-2**) (2.5 g, 9.8 mmol) in DCM (100 mL) was added TEA (2 mL, 14.7 mmol), DMAP (240 mg, 2 mmol), then 2-chloro-6-(trifluoromethyl)benzoyl chloride (3.1 g, 12.7 mmol) in DCM (10 mL) was added dropwise, then the reaction was stirred for 3 h at rt, then diluted with EtOAc (200 mL), washed with sat. $NaHCO_3$ aqueous, water and brine, dried over Na_2SO_4, concentrated, purified by flash chromatograph (PE:EA=10:1) to give 4.3 g (95%) of title compound as a light yellow solid. LCMS (ESI): calc'd for $C_{16}H_8BrClF_3N_3O_3$ $[M+H]^+$: 462, found: 462.

Step 3. Preparation of (3-bromo-6-(hydroxymethyl)-1H-pyrazolo[4,3-b] pyridin-1-yl)(2-chloro-6-(trifluoromethyl)phenyl)methanone (O-4). To a solution of methyl 3-bromo-1-(2-chloro-6-(trifluoromethyl)benzoyl)-1H-pyrazolo[4,3-b] pyridine -6-carboxylate (**O-3**) (2 g, 4.3 mmol) in dried THF (50 mL) was added DIBAL (1M in THF, 13 mL) slowly at -40 °C, then the reaction mixture was warmed to rt and stirred for 3 h, the reaction mixture was cooled to 0 °C, 15% NaOH aqueous (5 ml), water (5 mL) was added slowly successively, and stirred for another 30 min, filtered and concentrated, purified with flash chromatograph (PE:EA=3:1) to give 1.4 g (75%) of title compound as a light yellow solid. LCMS (ESI): calc'd for $C_{16}H_8BrClF_3N_3O_3$ $[M+H]^+$: 434, found: 434.

Step 4. Preparation of methyl 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6- (hydroxymethyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)-3-fluorobenzoate (O-5). A mixture of (3-bromo-6-(hydroxymethyl)-1H-pyrazolo [4,3-b]pyridin-1-yl) (2-chloro-6- (trifluoromethyl)phenyl)methanone (**O-4**) (1.3 g, 3.0 mmol), 2-fluoro-4- (methoxycarbonyl) phenylboronic acid (1.2 g, 6.0 mmol), $Pd(dppf)Cl_2$ (367 mg, 0.45 mmol), and K_3PO_4 (1.9 g, 9.0 mmol) in 8 mL dioxane and water (7:1) was heated at 10 °C for 1 h with oil-bath. Then it was filtrated and washed with EtOAc, the organic phase was concentrated and the product was purified with column chromatography (PE:EA=3:1) to get yellow solid **O-5** (800 mg), yield 52.6%. Physical characterization data for **O-5** is as follows: LCMS (ESI): calc. $C_{23}H_{14}ClF_4N_3O_4$, 507.7; found: M+H=508.7.

Step 5. Preparation of methyl 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6- formyl-1H-pyrazolo[4,3-b]pyridin-3-yl)-3-fluorobenzoate (O-6). 4-(1-(2-Chloro-6-(trifluoromethyl)benzoyl)-6-(hydroxymethyl)-1H-pyrazolo[4,3-b]pyridine-3-yl)- 3-

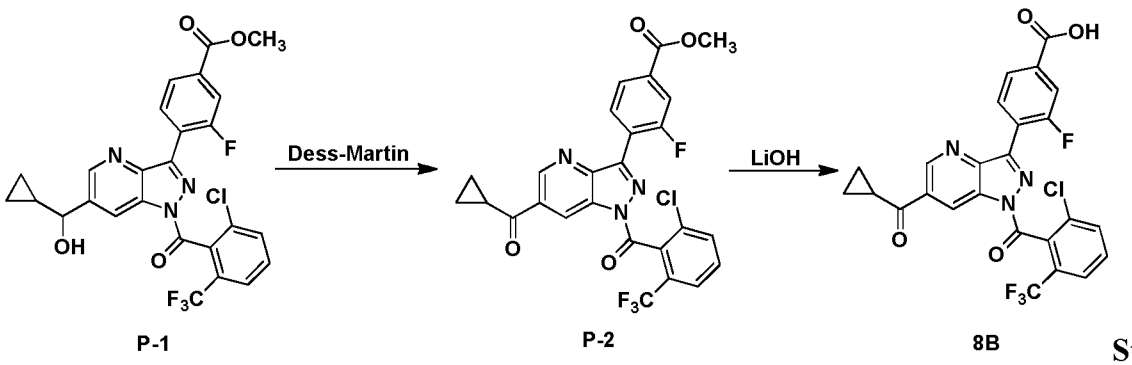
fluorobenzoate (**O-5**) (670 mg, 1.32 mmol) was dissolved in DCM (15 mL), Dess-Martin reagent (840 mg, 1.98 mmol) was added, then the mixture was stirred at room temperature for 2 h. The solvent was evaporated and the product was purified with column chromatography (PE:EA=3:1) to get solid **O-6** (580 mg), yield 87%. Physical characterization data for **O-6** is as follows: LCMS (ESI): calc. $C_{23}H_{12}ClF_4N_3O_4$, 505.7; found: M+H=506.7.

Step 6. Preparation of methyl 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(cyclopropyl(hydroxy)methyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)-3-fluorobenzoate (O-7). A 50 mL round-bottomed flask, is desgassed with nitrogen, cooled to -78 °C, cyclopropylmagnesium bromide (4 mL, 2.0 mmol) was added, then methyl 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-formyl-1H-pyrazolo[4,3-b]pyridine-3-yl)-3-fluorobenzoate (**0-6**) (80 mg, 0.16 mmol) in THF (3 mL, anhydrous) was added slowly. The mixture was stirred from -78 °C to rt for 4 h. Water was added, and the solvent was evaporated. The product was purified with Pre-HPLC to get white solid **O-7** (26 mg), yield 29.7%. Physical characterization data for **O-7** is as follows: LCMS (ESI): calc. $C_{26}H_{18}ClF_4N_3O_4$, 547.7; found: M+H=548.7.

Step 7. Preparation of 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(cyclopropyl (hydroxy)methyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)-3-fluorobenzoic acid (8A). A mixture of methyl 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(cyclopropyl (hydroxy)methyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)-3-fluorobenzoate (**O-7**) (26 mg, 0.05 mmol) and $LiOH•H_2O$ (10 mg, 0.24 mmol) in 2 ml THF and 2 ml H_2O was stirred at room temperature for 2 hours. The solvent was evaporated and the residue was dissolved in water. HCl (5% sol in water) was added until pH 4-5. The product was extracted by EtOAc, concentrated to obtain crude solid. The product was purified by pre-HPLC to get **O-8** (4 mg), yield 15.79%. Physical characterization data for **8A** is as follows: LCMS (ESI): calc. $C_{25}H_{16}ClF_4N_3O_4$, 533.7; found: M+H=533.7. ^{1}HNMR (400 MHz, MeOD) δ 8.97-9.00 (2H, d, J=12 Hz), 8.26-8.30 (1H, m), 7.98-8.00 (1H, d, J = 8Hz), 7.84-7.90 (3H, m), 7.77-7.81 (1H, m), 4.37-4.39 (1H, d, J = 8.4Hz), 1.29-1.33 (1H, m), 0.74-0.78 (1H, m), 0.67-0.72 (2H, m), 0.57-0.63 (1H, m).

Example 8B: Preparation of 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(cyclop ropane-carbonyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)-3-fluorobenzoic acid (8B)

SCHEME P

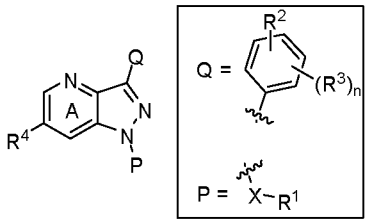


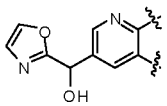
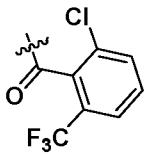
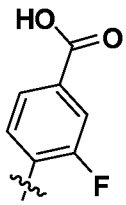
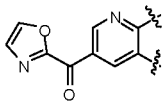
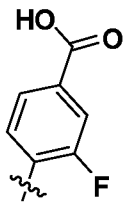
P-1 P-2 8B

Step 1. Preparation of methyl 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(cyclopropanecarbonyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)-3-fluorobenzoate (P-2). Methyl 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(cyclopropyl(hydroxy)methyl) -1H-pyrazolo[4,3-b]pyridin-3-yl)-3-fluorobenzoate (**P-1**) (25 mg, 0.05 mmol) was dissolved in DCM (5 mL), Dess-Martin reagent (29 mg, 0.069 mmol) was added, then the mixture was stirred at room temperature for 3 h. The solvent was evaporated and the product was purified with column chromatography (PE:EA=4:1) to get crude solid **P-2** (10 mg). Physical characterization data for **P-2** is as follows: LCMS (ESI): calc. $C_{26}H_{16}ClF_4N_3O_4$, 545.7; found: M+H=546.7.

Step 2. Preparation of 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6- (cyclopropan ecarbonyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)-3-fluorobenzoic acid (8B). A mixture of methyl 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(cyclopro panecarbonyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)-3-fluorobenzoate (**P-2**) (10 mg, 0.02 mmol) and LiOH•H_2O (8 mg, 0.18 mmol) in 2 mL THF and 2 mL H_2O was stirred at room temperature for 2 hours. The solvent was evaporated and the residue was dissolved in water. HCl (5% sol. in water) was added until pH 4-5. The product was extracted by EtOAc, concentrated to obtain crude solid. The product was purified by Pre-HPLC to get **3** (2 mg), yield 2.35%. Physical characterization data for **8B** is as follows: LCMS (ESI): calc. $C_{25}H_{14}ClF_4N_3O_4$, 531.7; found: M+H=531.7. ^{1}HNMR (400 MHz, DMSO) δ 9.553 (1H, s), 9.312 (1H, s), 8.377 (1H, s), 8.04-8.08 (1H, m), 7.96-8.01 (1H, m), 7.88-7.92 (1H, m), 7.01-7.84 (1H, d, J=10.4Hz), 3.16-3.18 (1H, m), 1.15-1.22 (4H, m).

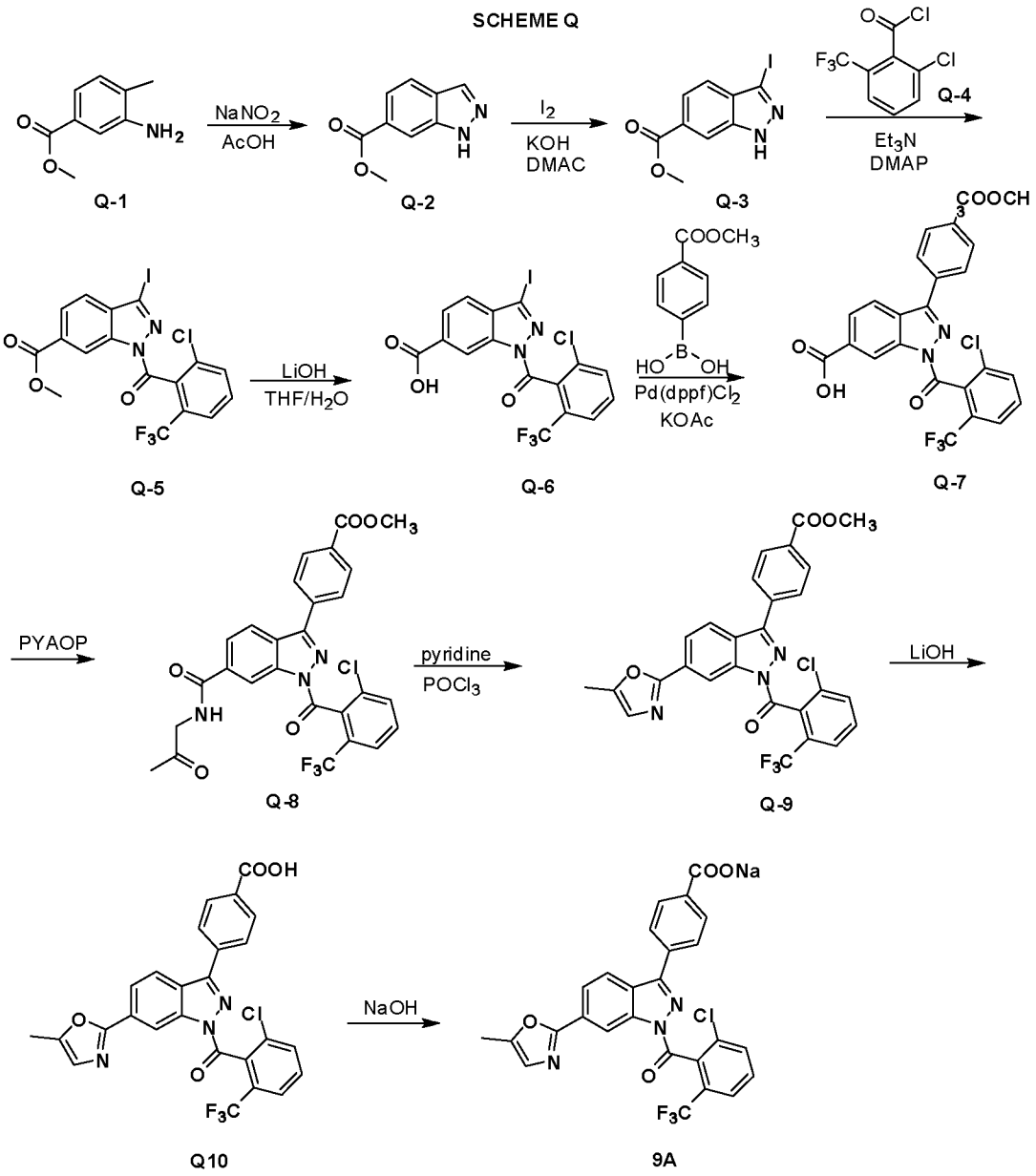
TABLE 8:



Ex.	Chemical Name	A ring	P	Q	LCMS $[M+H]^+$ Found
8C	4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(hydroxy(oxazol-2-yl)methyl)-1H-pyrazolo[4,3-b]pyridine-3-yl)-3-fluorobenzoic acid				561
8D	4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(oxazole-2-carbonyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)-3-fluorobenzoic acid				559

Example 9A: Preparation of sodium 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)

-6-(5-methyloxazol-2-yl)-1H-indazol-3-yl)benzoate (9A)



Step 1:

Preparation of methyl 1H-indazole-6-carboxylate (Q-2). Methyl 3-amino-4-methylbenzoate (**Q-1**) (5.0 g, 30.2 mmol) was dissolved in AcOH (140 mL). Sodium nitrite (2.1 g, 30.2 mmol) in water (3.5 mL) was added drop-wise to the solution of starting material under ice-cooling at room temperature. The ice-bath was removed and the mixture was stirred overnight. Half of the solvents were evaporated, the mixture was diluted with water (80 mL) and extracted with EtOAc (30 mL×3). The collected organic phase was washed with water and brine (200 mL×2), dried and evaporated to afford the crude product **Q-2** (4.4 g). LCMS (ESI): calc'd for $C_9H_8N_2O_2$, $[M+H]^+$: 177.1, found: 177.1.

Step 2: Preparation of methyl 3-iodo-1H-indazole-6-carboxylate (Q-3). Methyl 1H-indazole-6-carboxylate (**Q-2**) (5.0 g, 28.3 mmol) was dissolved in anhydrous DMAC (50 mL). Iodine (14.4 g, 56.7 mmol) and potassium hydroxide (6.3 g, 113.5 mmol) were added in portions under ice–cooling at room temperature. The ice-bath was removed and the mixture was stirred at room temperature for 1 h. The reaction was monitored by TLC (25% MeOH in chloroform) then it was slowly quenched with $Na_2S_2O_3$ (sat. sol. in water, 100 mL), diluted with water (50 mL) and extracted with EtOAC (100 mL×3). The organic phase was evaporated and triturated with n-hexane. The precipitated material was filtered and dried to afford a brown solid **Q-3** 5.3 g (62%). LCMS (ESI): calc'd for $C_9H_7IN_2O_2$, $[M+H]^+$: 302.9, found: 302.9.

Step 3: Preparation of methyl 1-(2-chloro-6-(trifluoromethyl)benzoyl) -3-iodo-1H -indazole-6-carboxylate (Q-5). To a 250 mL round-bottomed flask, was added compound methyl 3-iodo-1H-indazole-6-carboxylate (**Q-3**) (11.7 g, 38.7 mmol), 2-chloro-6-(trifluoromethyl)benzoyl chloride (**Q-4**) (10.3 g, 42.6 mmol), DMAP (4.72 g, 38.7 mmol) and CH_2Cl_2 (100 mL), after stirring at rt for 3 minutes, TEA (11.2 mL, 77 mmol) was added slowly. The reaction mixture is stirred at rt for overnight. LCMS showed no starting materials remained. Then the mixture was poured to 30 mL water, the lower (organic) and upper (aqueous) phases were separated. The aqueous phase is extracted twice with 20 mL CH_2Cl_2. The combined organic phases are washed successively with two 20 mL portions of water and 10 mL of brine. The resulting organic phase was dried over anhydrous sodium sulfate, filtered and concentrated at reduced pressure to give a yellow solid. The residue was purified by column chromatography on 60 g of silica gel eluting with PE /EA from 50/1 to 10/1, to give a fawn solid **Q-5** 16.5 g (84%). LCMS (ESI): calc'd for $C_{17}H_9ClF_3IN_2O_3$, $[M+H]^+$: 508.9, found: 508.9.

Step 4: Preparation of 1-(2-chloro-6-(trifluoromethyl)benzoyl)-3-iodo- 1H-Indaz ole-6-carboxylic acid (Q-6). A mixture of 1-(2-chloro-6-(trifluoromethyl) benzoyl)-3 -iodo-1H-indazole-6-carboxylate (**Q-5**) (16.5 g, 32.48 mmol) and LiOH (3.40 g, 162.40 mmol) in 10 mL THF and 50 mL pure H_2O was stirred at rt overnight. The solvent was evaporated and the residue was dissolved in water. HCl (5% sol. in water) was added until pH

4-5. The precipitated solid was filtered, washed with water and n-hexane, dried to afford an off white solid **Q-6** 16.0 g (83%). LCMS (ESI): calc'd for $C_{16}H_7ClF_3IN_2O_3$, $[M+H]^+$: 494.9, found: 494.9.

Step 5: Preparation of 1-(2-chloro-6-(trifluoromethyl)benzoyl)-3-(4- (methoxycar bonyl)phenyl)-1H-indazole-6-carboxylic acid (Q-7). A mixture of 1-(2-chloro-6-(trifluoromethyl)benzoyl)-3-iodo-1H-indazole-6-carboxylic acid (**Q-6**) (300 mg, 0.61 mmol), 4-(methoxycarbonyl) phenylboronic acid (165 mg, 0.92 mmol), $Pd(dppf)Cl_2$ (50 mg, 0.061 mmol) and KOAc (181 mg, 1.83 mmol) in 10 mL dioxane and 2 mL pure H_2O was heated to 95 °C for 2 h with microwave. Then it was diluted with EA (50 mL), washed with brine (50 mL×2), dried over anhydrous Na_2SO_4, concentrated. Then it was purified by silica gel column (Petroleum ether /EtOAc =20/1) to get white solid **Q-7** 180 mg (59%). LCMS (ESI): calc'd for $C_{24}H_{14}ClF_3N_2O_5$, $[M+H]^+$: 503.1, found: 503.1.

Step 6: Preparation of methyl 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl) -6-(2-oxopropylcarbamoyl)-1H-indazol-3-yl)benzoate (Q-8). 1-(2-Chloro-6- (trifluoro methyl)benzoyl)-3-(4-(methoxycarbonyl)phenyl)-1H-indazole-6-carboxylic acid (**Q-7**) (180 mg, 0.36 mmol) was dissolved in CH_2Cl_2 (15 mL). 1-aminopropan-2-one hydrochloride (47 mg, 0.43 mmol), PYAOP (374 mg, 0.72 mmol) was added and the mixture was stirred at room temperature for 2 mins. TEA (0.16 mL, 1.08 mmol) was added and the mixture was stirred at room temperature for 2 h. Then it was diluted with EtOAC (20 ml), washed with brine (20 ml×2), dried over anhydrous Na_2SO_4, concentrated to get crude product **Q-8** (191 mg), which was used to the next step without further purification. LCMS (ESI): calc'd for $C_{27}H_{19}ClF_3N_3O_5$, $[M+H]^+$: 558.1, found: 558.1.

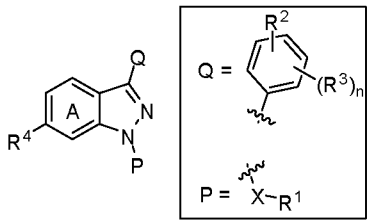
Step 7: Preparation of methyl 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl) -6-(5-methyloxazol-2-yl)-1H-indazol-3-yl)benzoate (Q-9). $POCl_3$ (3.5 mL) was added to a solution of methyl 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl) -6-(2-oxopropylcarba moyl)-1H-indazol-3-yl)benzoate (**Q-8**) (191 mg, 0.34 mmol) in pyridine (7 mL) at 25 °C. The resulted solution was then warmed to 70 °C and stirred for 6 hours. Upon completion, the reaction mixture was cooled to 25 °C, diluted with EtOAc (10 mL), poured into a cold (0 °C) solution of saturated aqueous $NaHCO_3$ (50 mL), and extracted with EtOAc (25 mL×3). The

combined organic layers were then washed with water (50 mL) and brine (50 mL), dried ($MgSO_4$), and concentrated to get a crude product **Q-9** (40 mg). LCMS (ESI): calc'd for $C_{27}H_{17}ClF_3N_3O_4$, $[M+H]^+$: 540.1, found: 540.1.

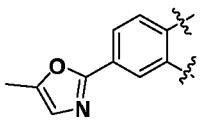
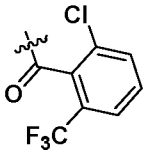
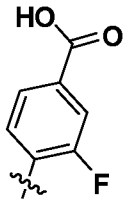
Step 8: Preparation of 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl) -6-(5-methylox azol-2-yl)-1H-indazol-3-yl)benzoic acid (Q-10). A mixture of methyl 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(5-methyloxazol-2-yl)-1H-indazol-3-yl)benzoate (**Q-9**) (40 mg, 0.07 mmol) and LiOH (16 mg, 0.37 mmol) in 10 mL THF and 10 mL pure H_2O was stirred at RT for 2 hours. The solvent was evaporated and the residue was dissolved in water. HCl (5% sol in water) was added until pH 4-5. The precipitated solid was filtered, washed with water and n-hexane, dried to afford an off white solid **Q-10** 36 mg (98%). LCMS (ESI): calc'd for $C_{26}H_{15}ClF_3N_3O_4$, $[M+H]^+$: 526 found: 526.

Step 9: Preparation of sodium 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl) -6-(5-methyloxazol-2-yl)-1H-indazol-3-yl)benzoate (9A). 4-(1-(2-Chloro-6- (trifluoro methyl)benzoyl)-6-(5-methyloxazol-2-yl)-1H-indazol-3-yl) benzoic acid (**Q-10**) (36 mg, 0.069 mmol) was added to pure H_2O (10 mL) to disperse equably with ultrasonic. Then 0.1 mol/L NaOH (0.7 mL, 0.07 mmol) was added to the solution at ice-bath. Then it was stirred at 0 °C for 30 mins. Then it was dried by Freeze dryer to get compound **9A** 38 mg (100%). LCMS (ESI): calc'd for $C_{26}H_{14}ClF_3N_3NaO_4$, $[M+H]^+$: 548, found: 548. ^{1}HNMR (400 MHz, DMSO) δ 9.04 (1H, s), 8.37-8.39 (1H, d, J = 8 Hz), 8.18-8.20 (1H, d, J = 8 Hz), 8.06-8.08 (1H, d, J = 8 Hz), 8.00-8.02 (3H, d, J = 8.8 Hz), 7.87-7.91 (1H, m), 7.78-7.80 (2H, d, J = 8 Hz), 7.16 (1H,s),2.48 (3H, s).

TABLE 9:

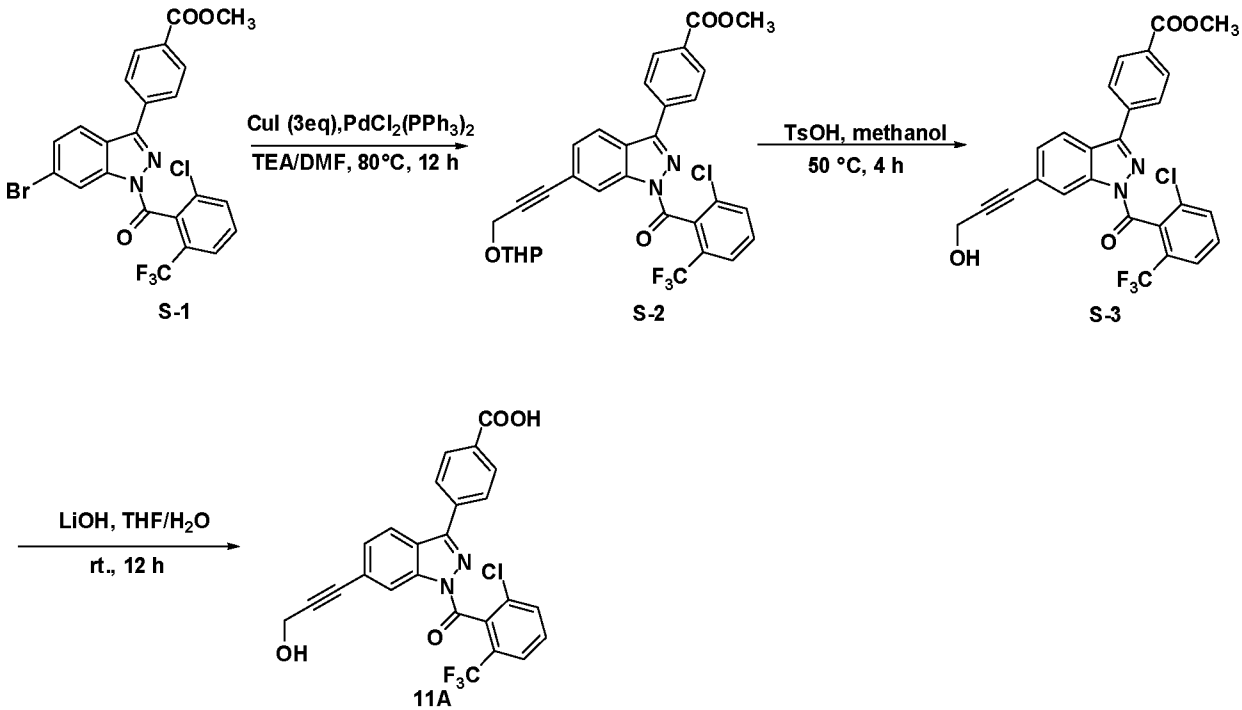


Ex.	Chemical Name	A ring	P	Q	LCMS $[M+H]^+$

					Found
9B	4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(5-methyloxazol-2-yl)-1H-indazol-3-yl)-3-fluorobenzoic acid				544

Example 11A: Preparation of 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(3-hydroxyprop-1-ynyl)-1H-indazol-3-yl)benzoic acid (11A)

SCHEME S



Step 1. Preparation of methyl 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl) -6-(3-(tetrahydro-2H-pyran-2-yloxy)prop-1-ynyl)-1H-indazol-3-yl)benzoate (S-2). To a solution of methyl 4-(6-bromo-1-(2-chloro-6-(trifluoromethyl) benzoyl)-1H-ind

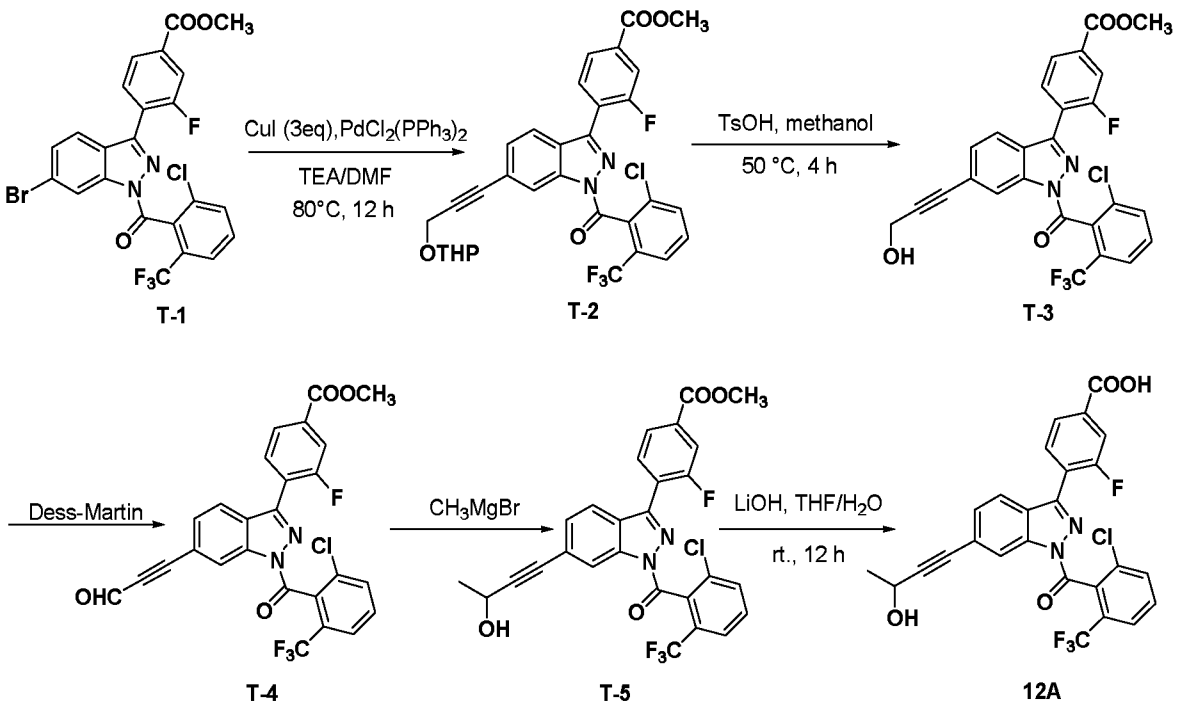
azol-3-yl)benzoate (**S-1**) (53.5 mg, 0.1 mmol) in DMF (5 mL) and TEA (10 mL) was added 2-(prop-2-ynyloxy)-tetrahydro-2H-pyran (16.8 mg, 0.12 mmol), copper(I) iodide (10 mg, 0.01 mmol) and $PdCl_2(PPh_3)_2$ (10 mg, 0.01 mmol) under Argon . The mixture was stirred under Argon for 2 hours at 80 °C. The mixture was diluted with H_2O. The aqueous layer was extracted with CH_2Cl_2 (3×50 mL). The combined organics were washed with H_2O, brine, dried over Na_2SO_4, and concentrated. The residue was purified by Prep-TLC (Pentane/EtOAc, 5/1) to afford 48 mg (58%) of the title compound. LCMS (ESI) calc'd for $C_{31}H_{24}ClF_3N_2O_5$ $[M+H]^+$: 597.1, found: 597.1.

Step 2. Preparation of methyl 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6- (3-hydroxyprop -1-ynyl)- 1H-indazol-3-yl)benzoate (S-3). To a solution of methyl 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(3-(tetrahydro-2H-pyran-2-yloxy)prop- 1-ynyl)-1H-indazol-3-yl)benzoate (**S-2**) (200 mg, 0.34 mmol) in MeOH (10 mL) was added TsOH (12 mg, 0.07 mmol) at 0 °C . The mixture was stirred for 12 hours at rt. The mixture was diluted with H_2O, The aqueous layer was extracted with CH_2Cl_2 (3×80 mL). The combined organics were washed with H_2O, brine, dried over Na_2SO_4, and concentrated. The residue was purified by Prep-TLC (Pentane/EtOAc, 3/1) to afford 110 mg (64%) of the title compound. LCMS (ESI) calc'd for $C_{26}H_{16}ClF_3N_2O_4$ $[M+H]^+$: 513.1, found: 513.1.

Step 3. Preparation of 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6- (3-hydroxy prop-1-ynyl)-1H-indazol-3-yl)benzoic acid (11A). To a stirred solution of methyl 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(3-hydroxyprop-1-ynyl)-1H-indazol-3-yl)benzoate (**S-3**) (300 mg, 0.5 mmol) was added THF (8.0 mL), H_2O (2.0 mL) and $LiOH{\cdot}H_2O$ (108 mg, 2.5 mmol) and the solution was stirred at r.t. overnight. LCMS showed disappearance of staring material. The solution was adjusted to pH 4.0 using 1N HCl and poured into THF (30 mL), washed with brine (20 mL). The organic layer was dried over Na_2SO_4, the organic layer was evaporated and submitted for Prep-HPLC. 100 mg product was collected. Yield: 32%. LCMS (ESI) calc'd for $C_{25}H_{14}ClF_3N_2O_4$ $[M+H]^+$: 499.1, found: 499.1. ^{1}HNMR (400 MHz, DMSO) δ 8.544 (1H, s), 8.28 (1H, d), 8.10 (8H, m), 7.70 (1H, d), 4.41 (1H, s).

Example 12A: Preparation of 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(3-hydroxybut-1-ynyl)-1H-indazol-3-yl)-3-fluorobenzoic acid (12A)

SCHEME T



Step 1. Preparation of methyl 4-(1-(2-chloro-6-(trifluoromethyl) benzoyl)-6-(3-(tetrahydro-2H-pyran-2-yloxy)prop-1-ynyl)-1H-indazol-3-yl)-3-fluorobenzoate (T-2). To a solution of methyl 4-(6-bromo- 1-(2-chloro-6-(trifluoromethyl)benzoyl)-1H-indazol-3-yl)-3-fluorobenzoate (**T-1**) (200 mg, 0.36 mmol) in DMF (10 mL) and TEA (20 mL) was added 2-(prop-2-ynyloxy)-tetrahydro-2H-pyran (60 mg, 0.43 mmol), copper(I) iodide (6.8 mg, 0.036 mmol) and $PdCl_2(PPh_3)_2$ (25 mg, 0.036 mmol) under Argon . The mixture was stirred under Argon for 2 hours at 80 °C. The mixture was diluted with H_2O, The aqueous layer was extracted with CH_2Cl_2 (3×50 mL). The combined organics were washed with H_2O, brine, dried over Na_2SO_4, and concentrated. The residue was purified by Prep-TLC (Pentane/EtOAc, 5/1) to afford 111 mg (51%) of the title compound. LCMS (ESI) calc'd for $C_{31}H_{23}ClF_4N_2O_5$ $[M+H]^+$: 615, found: 615.

Step 2. Preparation of methyl 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6- (3-hydroxyprop-1-ynyl)-1H-indazol-3-yl)-3-fluorobenzoate (T-3) To a solution of methyl 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(3-(tetrahydro-2H-pyran-2-ylox y)prop-1-ynyl)-1H-indazol-3-yl)-3-fluorobenzoate (**T-2**) (111 mg, 0.18 mmol) in MeOH/H_2O (20/2 mL) was added TsOH (15 mg, 0.09 mmol) at 0 °C . The mixture was stirred for 12 hours at rt. The mixture was diluted with H_2O, The aqueous layer was extracted with CH_2Cl_2

(3×80 mL). The combined organics were washed with H_2O, brine, dried over Na_2SO_4, and concentrated. The residue was purified by Prep-TLC (Pentane/EtOAc, 3/1) to afford filtered and concentrated to give 45 mg (47%) of the title compound. LCMS (ESI) calc'd for $C_{26}H_{15}ClF_4N_2O_4$ $[M+H]^+$: 531, found: 531.

Step 3. Preparation of methyl 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl) -6-(3-oxoprop-1-ynyl)-1H- indazol-3-yl)-3-fluorobenzoate (T-4) To a solution of methyl4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(3-hydroxyprop-1-ynyl)-1H-indazol-3-yl)-3-fluorobenzoate (**T-3**) (45 mg, 0.085 mmol) in DCM (20 mL) was added Dess-Martim reagent (108 mg, 0.25 mmol) at 0 °C. The mixture was stirred for 12 hours at rt. The mixture was diluted with H_2O and extracted with CH_2Cl_2 (3×80 mL). The combined organics were washed with H_2O, brine, dried over Na_2SO_4, and concentrated. The residue was purified by Prep-TLC (Pentane/EtOAc, 3/1) to afford 40 mg (88%) of the title compound. LCMS (ESI) calc'd for $C_{26}H_{13}ClF_4N_2O_4$ $[M+H]^+$: 529.1, found: 529.1.

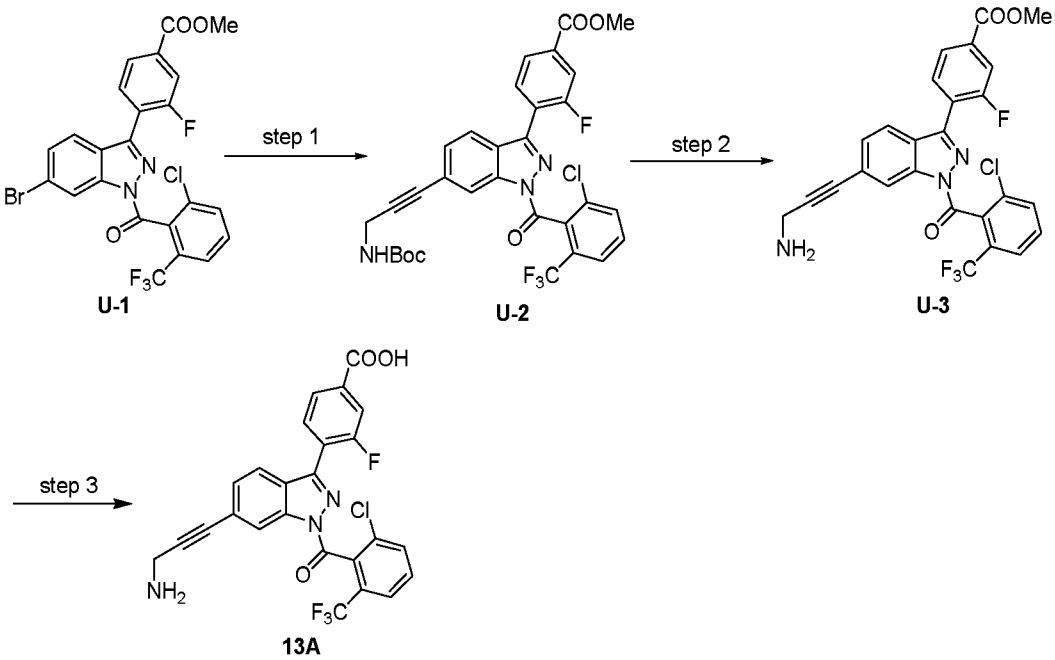
Step 4. Preparation of methyl 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl) -6-(3-hydroxybut-1-ynyl)-1H -indazol-3-yl)-3-fluorobenzoate (T-5) To a solution of methyl 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(3-oxoprop-1-ynyl) -1H- indazol-3-yl)-3-fluorobenzoate (**T-4**) (40 mg, 0.076 mmol) in dry THF (5 mL) was added MeMgBr (0.18 mL, 0.53 mmol, 3 M in ether) at -60 °C. The mixture was stirred for 2 hours at rt, the mixture was quenched with saturated NH_4Cl, The aqueous layer was extracted with EtOAc (3×80 mL), the combined organics were washed with H_2O, brine, dried over Na_2SO_4, and concentrated. The residue was purified by Prep-TLC (Pentane/EtOAc, 3/1) to afford 41 mg (85%) of the title compound. LCMS (ESI) calc'd for $C_{27}H_{17}ClF_4N_2O_4$ $[M+H]^+$: 545.1, found: 545.1.

Step 5. Preparation of methyl 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl) -6-(3-hydroxybut-1-ynyl)-1H -indazol-3-yl)-3-fluorobenzoate (12A). To a stirred solution of methyl 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl-6-(3-hydroxybut -1-ynyl)-1H -indazol-3-yl)-3-fluorobenzoate (**T-5**) (41 mg, 0.075 mmol) was added THF (8.0 mL), H_2O (2.0 mL) and $LiOH{\cdot}H_2O$ (32 mg, 0.75 mmol) and the solution was stirred at r.t. overnight. LCMS showed disappearance of staring material. The solution was adjusted to pH 4.0 using 1N HCl and poured into THF (30 mL), washed with brine (20 mL). The organic layer was dried over

Na_2SO_4, the organic layer was evaporated and submitted for Prep-HPLC to give 5 mg of product (yield 12%). LCMS (ESI) calc'd for $C_{26}H_{15}ClF_4N_2O_4$ $[M+H]^+$: 531, found: 531. ^{1}HNMR (400 MHz, DMSO) δ 13.5 (1H, bs), 8.526 (1H, s), 7.95 (6H, m), 7.76 (1H, t), 7.63 (1H, t),5.61 (1H,d) , 4.57 (1H, t),1.449-1.464 (3H, d).

Example 13A: Preparation of 4-(6-(3-aminoprop-1-ynyl)-1-(2-chloro-6-(trifluoromethyl)benzoyl)-1H-indazol-3-yl)-3-fluorobenzoic acid (13A)

SCHEME U



Step 1. Preparation of methyl 4-(6-(3-(tert-butoxycarbonylamino)prop-1- ynyl)-1 -(2-chloro-6-(trifluoromethyl)benzoyl)-1H-indazol-3-yl)-3-fluorobenzoate (U-2). The mixture of methyl 4-(6-bromo-1-(2-chloro-6-(trifluoromethyl)benzoyl) -1H-indazol-3-yl)-3-fluorobenzoate (**U-1**) (554 mg,1.0 mmol), $Pd(PPh_3)_2Cl_2$ (105 mg,0.1 mmol), CuI (60 mg, 0.15 mmol), Et_3N (20 mL) and DMF (20 mL) was purged with N_2 and stirred at 80 °C overnight. LCMS showed the starting material was consumed totally and formation of the desired product. The resulting solution was filtered and concentrated to purify by column chromatography to give 432 mg of product as a white solid (68.7%). LCMS (ESI) calc'd for $[M+H]^+$: 629.99, found: 630.1.

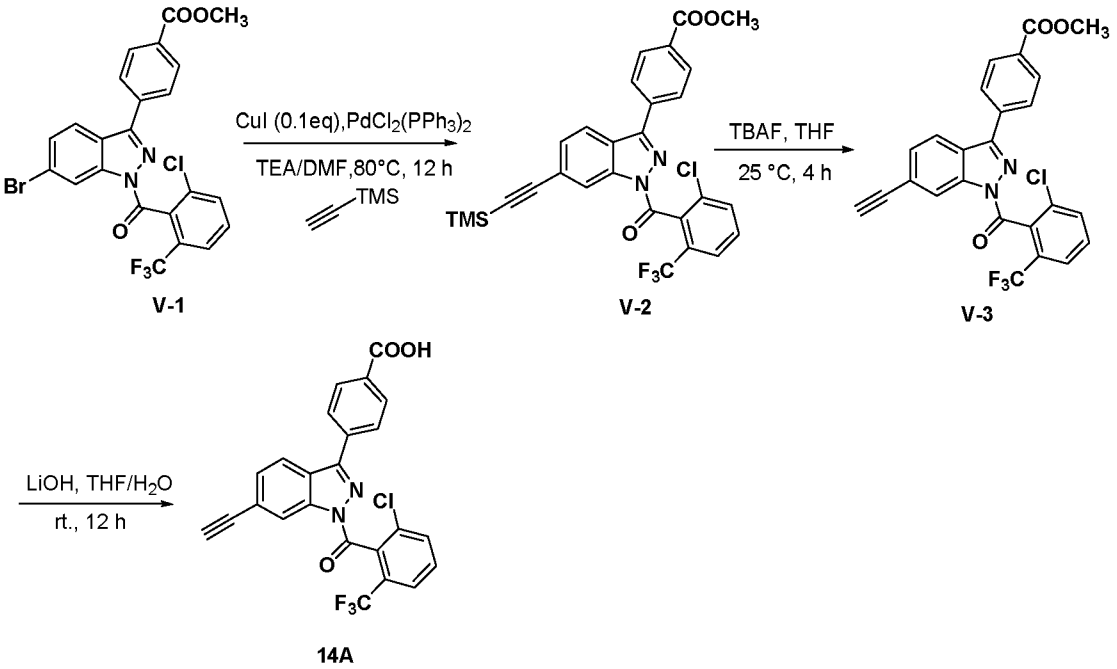
Step 2. Preparation of methyl 4-(6-(3-aminoprop-1-ynyl)-1-(2-chloro-6- (trifluoro

methyl)benzoyl)-1H-indazol-3-yl)-3-fluorobenzoate (U-3): To the solution of methyl 4-(6-(3-(tert-butoxycarbonylamino)prop-1-ynyl)-1-(2-chloro-6- (trifluorometh yl)benzoyl)-1H-indazol-3-yl)-3-fluorobenzoate **(U-2)** (629 mg, 1.0 mmol) in THF (30 mL) and water (10 mL) was added TFA (970 mg, 10 mmol). The mixture solution was stirred at rt for 10 h. The mixture was diluted with H_2O and exacted with EtOAc (30 mL×3). The combined organic layer was concentrated and purified by chromatography column (EA:PE=1:1) to afford 461 mg of product (yield: 87.5%). LCMS (ESI) calc'd $[M+H]^+$: 529.87, found: 530.1.

Step 3. Preparation of 4-(6-(3-aminoprop-1-ynyl)-1-(2-chloro-6-(trifluo romethyl) benzoyl)-1H-indazol-3-yl)-3-fluorobenzoic acid (13A): To the solution of methyl 4-(6-(3-aminoprop-1-ynyl)-1-(2-chloro-6-(trifluoromethyl)benzoyl) -1H-indazol-3-yl) -3-fluorobenzoate (**U-3**) (529 mg, 1.0 mmol) in THF (30 mL) and water (10 mL) was added LiOH (240 mg, 10 mmol). The mixture solution was stirred at rt for 10 h. The mixture was acidified with 2N HCl and exacted with EtOAc (30 mL×3). The combiend organic layer was purified by flash chromatography (EA:PE=1:1) to afford 431 mg of final product (yield: 84%). LCMS (ESI) calc'd $[M+H]^+$: 515.84, found: 516.1. ^{1}HNMR (400 MHz, $CDCl_3$) δ: 8.63 (1H, s), 8.41(2H, w), 8.02 (3H, m), 7.89 (3H, m), 7.76 (1H, t), 7.68 (1H, s), 4.12 (1H, s).

Example 14A: Preparation of 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl) -6-ethy nyl-1H-indazol-3-yl)benzoic acid (14A)

SCHEME V



Step 1.

Preparation of methyl 4-(1-(2-chloro-6-(trifluoromethyl) benzoyl)-6-((tri methylsilyl)ethynyl)-1H-indazol-3-yl)benzoate (V-2). To a solution of methyl 4-(6-bromo-1-(2-chloro-6-(trifluoromethyl)benzoyl)-1H-indazol-3-yl)benzoate (**V-1**) (108 mg, 0.2 mmol) in DMF (10 mL) and TEA (20 mL) was added ethynyltrimethylsilane (24 mg, 0.24 mmol), copper(I) iodide (4 mg, 0.02 mmol) and $PdCl_2(PPh_3)_2$ (14 mg, 0.02 mmol) under argon. The mixture was stirred under argon for 2 hours at 80 °C. The mixture was diluted with H_2O. The aqueous layer was extracted with CH_2Cl_2 (3×50 mL). The combined organics were washed with H_2O, brine, dried over Na_2SO_4, and concentrated. The residue was purified by Prep-TLC (Pentane/EtOAc, 5/1) to afford 90 mg (87%) of the title compound. LCMS (ESI) calc'd for $C_{28}H_{22}ClF_3N_2O_3Si$ $[M+H]^+$: 555.1, found: 555.1.

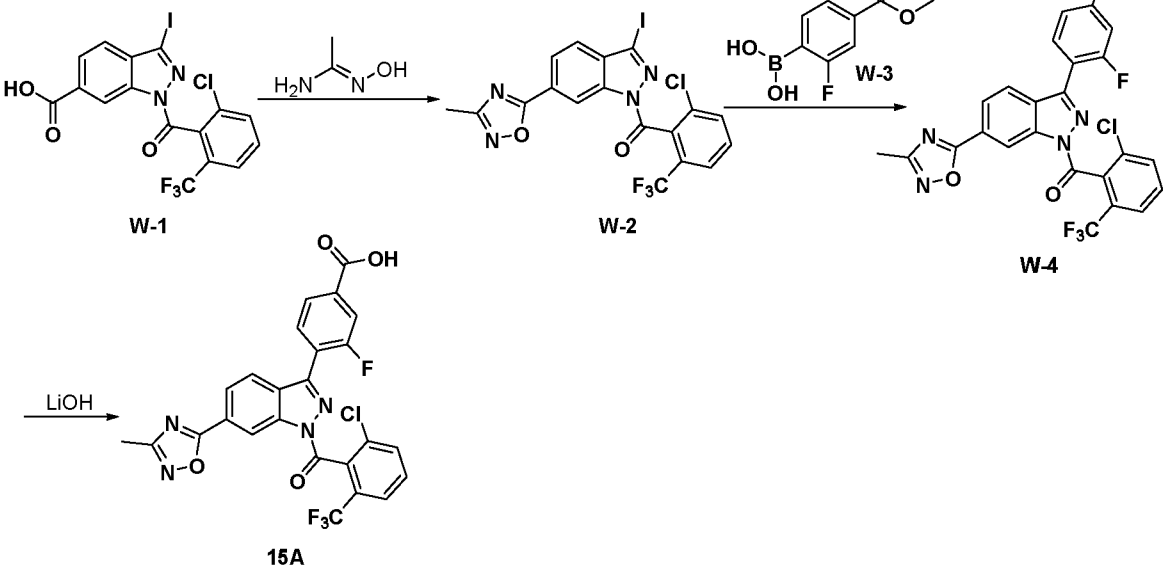
Step 2. Preparation of methyl 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl) -6-ethy nyl-1H-indazol-3-yl)benzoate (V-3). To a solution of methyl 4-(1-(2-chloro-6-(triflu oromethyl)benzoyl)-6-((trimethylsilyl)ethynyl)-1H-indazol-3-yl)benzoate (**V-2**) (50 mg, 0.09 mmol) in THF (10 mL) at 0 °C was added TBAF (23 mg, 0.09 mmol). The mixture was stirred for 12 hours at rt. The mixture was diluted with H_2O. The aqueous layer was extracted with CH_2Cl_2 (3×80 mL). The combined organics were washed with H_2O, brine, dried over Na_2SO_4, and concentrated. The residue was purified by Prep-TLC (Pentane/EtOAc, 5/1) to

afford 35 mg (92%) of the title compound. LCMS (ESI) calc'd for $C_{25}H_{14}ClF_3N_2O_3$ [M+H]+: 483, found: 483.

Step 3. Preparation of 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-ethynyl-1H-indazol-3-yl)benzoic acid (14A). To a stirred solution of methyl 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-ethynyl-1H-indazol-3-yl)benzoate (**V-3)** (170 mg, 0.35 mmol) was added THF (8.0 mL), H_2O (2.0 mL) and $LiOH·H_2O$ (74 mg, 1.76 mmol) and the solution was stirred at r.t. overnight. The solution was acidified with 1N HCl to pH = ~ 4.0, and diluted with THF (30 mL). The organic layer was separated and washed with brine (20 mL). The organic layer was dried over Na_2SO_4, concentrated, and purified by Prep-HPLC to afford 43 mg of final product (yield: 26%). LCMS (ESI) calc'd for $C_{25}H_{14}ClF_3N_2O_3$ [M+H]+: 483.1, found: 483.1. ^{1}HNMR (500 MHz, DMSO) δ 13.36 (1H, bs), 8.56 (1H, s), 8.30 (1H, d),8.10 (4H, d), 8.05 (3H, m), 7.76 (1H, d), 4.59 (1H, s).

Example 15A: Preparation of 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(3-methyl-1,2,4-oxadiazol-5-yl)-1H-indazol-3-yl)-3-fluorobenzoic acid (15A)

SCHEME W



Step 1. Preparation of (2-chloro-6-(trifluoromethyl)phenyl)(3-iodo-6- (3-methyl-1,2,4-oxadiazol-5-yl)-1H-indazol-1-yl)methanone (W-2). The mixture of 1-(2-chloro-6-(trifluoromethyl)benzoyl)-3-iodo-1H-indazole-6-carboxylic acid (**W-1**) (0.2 g, 0.4 mmol), N'-hydroxyacetimidamide (59 mg, 0.8 mmol), HATU (0.3 g, 0.8 mmol) and DIPEA (0.13 mL,

0.80 mmol) in DCM (20 mL) was stirred at rt for overnight. The reaction mixture was washed with 1M HCl solution, saturated $NaHCO_3$ solution, and brine respectively, dried over anhydrous Na_2SO_4 and concentrated. The residue was dissolved in 1,4-dioxane (20 mL) and heated at 100 °C for overnight. The solvent was removed under reduced pressure and the residue was diluted with H_2O (50 mL) and the aqueous layer was extracted with ethyl acetate (50 mL×3). The combined organic layers were washed with brine (50 mL×1), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified with Prep-TLC (PE:EA=5:2) to get the desired product **2** as a white solid (85 mg, 40%). LCMS (ESI) calc'd for $C_{18}H_9ClF_3IN_4O_2$ $[M+H]^+$: 533, found: 533.

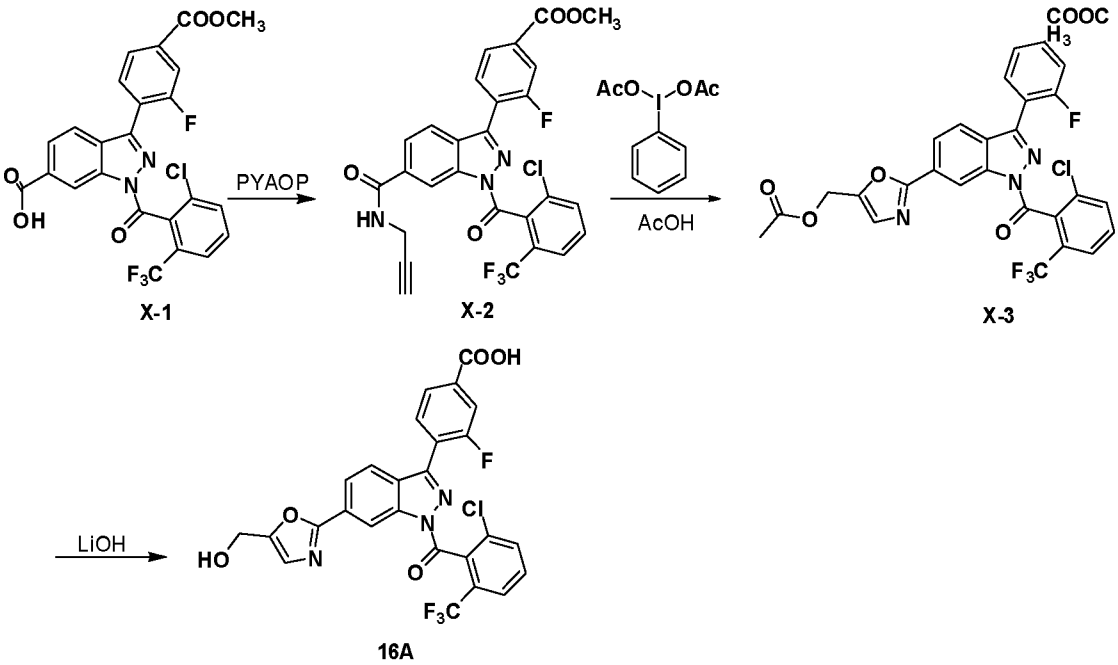
Step 2. Preparation of methyl 4-(1-(2-chloro-6-(trifluoromethyl) benzoyl) -6-(3-methyl-1,2,4-oxadiazol-5-yl)-1H-indazol-3-yl)-3-fluorobenzoate (W-4). A mixture of (2-chloro-6-(trifluoromethyl)phenyl)(3-iodo-6-(3-methyl-1,2,4-oxa diazol-5-yl)-1H -indazol-1-yl)methanone (**W-2**) (100 mg, 0.19 mol), **W-3** (56 mg, 0.29 mol), $Pd(OAc)_2$ (4 mg, 0.019 mol), s-phos (8 mg, 0.019 mol) and K_3PO_4 (121 mg, 0.57 mol) were suspended in 1,4-dioxane (5 mL) and H_2O (1 mL). The reation mixture was heated at 100 °C in a microwave reactor for 2 h. The result mixture was diluted with H_2O (50 mL) and the aqueous layer was extracted with ethyl acetate (50 mL×3). The combined organic layers were washed with brine (50 mL×1), dried over anhydrous Na_2SO_4 and concentrated to get the desired product **W-4** as a yellow solid (65 mg, 45%). LCMS (ESI) calc'd for $C_{26}H_{15}ClF_4N_4O_4$ $[M+H]^+$: 559, found: 559.

Step 3. Preparation of 4-(1-(2-chloro-6-(trifluoromethyl) benzoyl)-6-(3-methyl -1,2,4-oxadiazol-5-yl)-1H-indazol-3-yl)-3-fluorobenzoic acid (15A). A mixture of methyl 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(3-methyl -1,2,4-oxadiazol-5-yl) -1H-indazol-3-yl)-3-fluorobenzoate (**W-4**) (150 mg, 0.27 mmol) and LiOH (57 mg, 1.35 mmol) in THF (4 mL) and H_2O (2 mL) was stirred at room temperature for 4 h.The reaction mixture was diluted with H_2O (20 mL), and acidified with 2N HCl solution to pH=~3. The mixture was extracted with ethyl acetate (20 mL×3). The combined organic layers were washed with brine (20 mL×1), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified with Prep-HPLC to get the desired product **15A** as a white solid (130 mg, 90%). LCMS (ESI): calc'd for $C_{25}H_{13}ClF_4N_4O_4$ $[M+H]^+$: 545, found: 545; ^{1}HNMR (400 MHz, MeOD) δ 8.36 (1H, s), 8.34

(1H, d, J=8.4 Hz), 8.17 (1H, d, J=8.4Hz), 7.97-7.99 (2H, m), 7.89-7.94 (2H, m), 7.81 (1H, d, J = 8.4 Hz), 7.73-7.78 (1H, m), 2.54 (3H, s).

Example 16A: Preparation 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(5-(hydroxymethyl)oxazol-2-yl)-1H-indazol-3-yl)-3-fluorobenzoic acid (16A)

SCHEME X



Step 1: Preparation of methyl 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(prop-2-ynylcarbamoyl)-1H-indazol-3-yl)-3-fluorobenzoate (X-2). 1-(2-Chloro -6-trifluoromethyl)benzoyl)-3-(2-fluoro-4-(methoxycarbonyl)phenyl)-1H-indazole-6-carboxylic acid (**X-1**) (100 mg, 0.2 mmol) was dissolved in CH_2Cl_2 (15 mL), followed by the additon of prop-2-yn-1-amine (13 mg, 0.24 mmol) and PYAOP (208 mg, 0.4 mmol). The mixture was stirred at room temperature for 2 mins, followed by the addition of TEA (0.16 mL, 1.08 mmol). The mixture was stirred at room temperature for 2 h, diluted with EtOAC (20 mL), washed with brine (20 mL×2), dried over anhydrous Na_2SO_4, concentrated to give 85 mg of crude product, which was used to the next step without further purification. LCMS (ESI): calc'd for $C_{27}H_{16}ClF_4N_3O_4$, $[M+H]^+$: 557.1, found: 557.1.

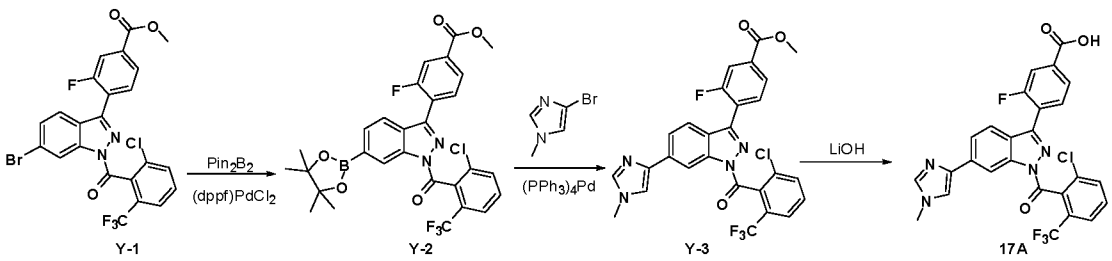
Step 2: Preparation of methyl 4-(6-(5-(acetoxymethyl)oxazol-2-yl)-1-(2-chloro-6-(trifluoromethyl)benzoyl)-1H-indazol-3-yl)-3-fluorobenzoate (X-3). Methyl-(1-(2-

chloro-6-(trifluoromethyl)benzoyl)-6-(prop-2-ynylcarbamoyl)-1H-indazol-3-yl)-3-fluorobenzoate **(X-2)** (85 mg, 0.15 mmol) was dissolved in AcOH (15 mL), followed by the addition of (diacetoxyiodo) benzene (73 mg, 0.23 mmol). The mixture was stirred at 90 °C for 12 hours. Then it was diluted with EtOAC (20 mL), washed with brine (20 mL×2), dried over anhydrous Na_2SO_4, concentrated to get the crude product **X-3** (60 mg), which was used to the next step without further purification. LCMS (ESI): calc'd for $C_{30}H_{19}ClF_4N_2O_6$, $[M+H]^+$: 614.1, found: 614.1.

Step 3: Preparation of 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(5-(hydroxyl methyl)oxazol-2-yl)-1H-indazol-3-yl)-3-fluorobenzoic acid (16A). A mixture of methyl 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(prop-2-ynyl carbamoyl)-1H-ind azol-3-yl)-3-fluorobenzoate (**X-3**) (25 mg, 0.04 mmol) and $LiOH{\cdot}H_2O$ (10 mg, 0.25 mmol) in 10 mL THF and 10 mL pure H_2O was stirred at RT for 2 hours. The solvent was evaporated and the residue was dissolved in water. HCl (5% sol. in water) was added until pH 4-5. The precipitated solid was filtered, washed with water and n-hexane, dried to afford an off white solid **16A** (15 mg, 80%). LCMS (ESI): calc'd for $C_{27}H_{15}ClF_4N_2O_5$, $[M+H]^+$: 558.1 found: 558.1. ^{1}HNMR (400 MHz, DMSO) δ 9.09 (1H, s), 8.22-8.24 (1H, d, J = 8 Hz), 8. 11-8.13 (1H, d, J = 8 Hz), 8.05-8.07 (1H, d, J = 8 Hz), 8.00-8.02(1H, d, J = 8 Hz), 7. 88-7.95 (3H, m), 7.77-7.81 (1H, m), 7.35 (1H, s), 4.63 (2H, s).

Example 17A: Preparation of 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(1-methyl-1H-imidazol-4-yl)-1H-indazol-3-yl)-3-fluorobenzoic acid (17A)

SCHEME Y



Step 1. Preparation of methyl 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazol-3-yl)-3-fluorobenzoate (Y-2). To the solution of methyl 4-(6-bromo-1-(2-chloro-6-(trifluoromethyl)benzoyl)-1H-ind azol-3-yl)-3-fluorobenzoate (**Y-1**) (161 mg, 0.29 mmol) in dioxane (5 mL) was added Pin_2B_2 (151 mg, 0.58 mmol), KOAc (115 mg, 1.16 mmol) and $(dppf)PdCl_2$ (21 mg, 0.029 mmol)

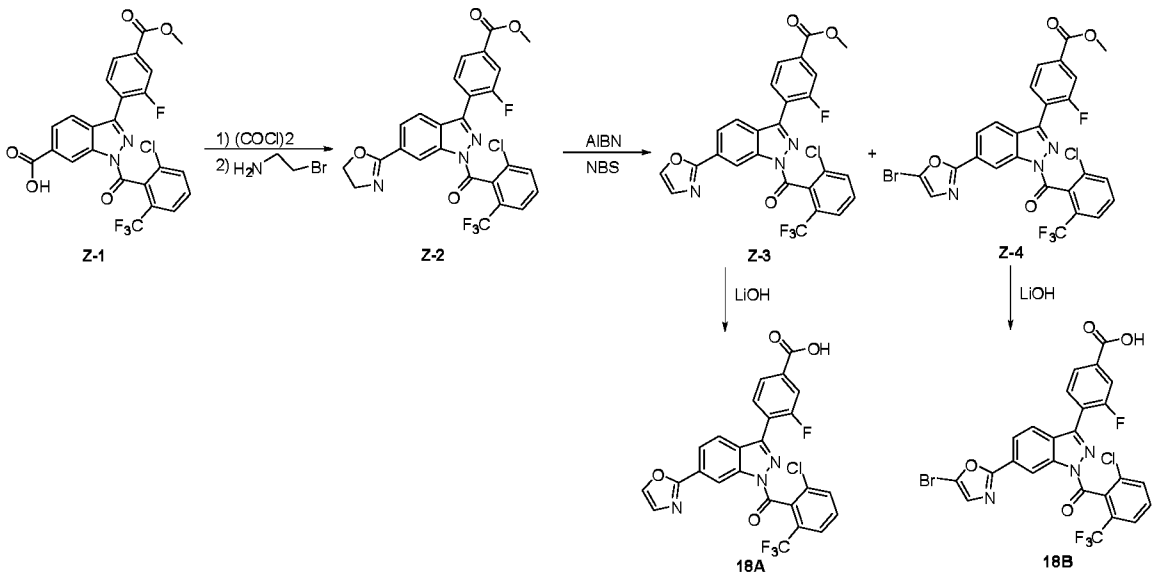
under N_2 protection. The mixture was heated at 90 °C for 6 h. Then the mixture was cooled down and diluted with EtOAc (100 mL), washed with H_2O (20 mL×3), and brine (20 mL), dried and concentrated. The residue was purified with chromatography (PE:EA=6:1) to afford 125 mg of final product (yield: 71%). LCMS (ESI) calc'd $[M+H]^+$: 602.0, found:602.1.

Step 2. Preparation of methyl 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(1-methyl-1H-imidazol-4-yl)-1H-indazol-3-yl)-3-fluorobenzoate (Y-3). To the solution of methyl 4-(6-bromo-1-(2-chloro-6-(trifluoromethyl)benzoyl) -1H-indazol-3-yl)-3-fluorobenzoate (**Y-2**) (50 mg, 0.083 mmol) in dioxane (5 mL) was added 4-bromo-1-methyl-1H-imidazole (20 mg, 0.1 mmol) , K_2CO_3 (30 mg, 0.2 mmol) and $(PPh_3)_4Pd$ (10 mg, 0.0083 mmol) under N_2 protection. The mixture was protected by N_2 and stirred at 85 °C for 16 h. The solution was cooled down, concentrated, and purified by Prep-HPLC (ACN:H_2O) to afford 5 mg of product (yield: 7.2 %). LCMS (ESI) calc'd $[M+H]^+$: 557, found: 557.

Step 3. Preparation of 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(1-methyl-1H-imidazol-4-yl)-1H-indazol-3-yl)-3-fluorobenzoic acid (17A). To the solution of methyl 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl) -6-(1-methyl-1H-imidazol-4-yl)-1H-indazol-3-yl)-3-fluorobenzoate (**Y-3**) (5 mg, 0.009 mmol) in THF (2 mL) and H_2O (0.5 mL) was added LiOH (1 mg, 0.045 mmol). The mixture solution was stirred at rt for 16 h, acidified by HCl (2N), extracted with EtOAc (10 mL×3). The organic layer was dried and concentrated to be purified by Prep-HPLC (ACN:H_2O) to afford 5 mg of final product (yield: 100%). LCMS (ESI) calc'd $[M+H]^+$: 543, found: 543.

Example 18A: Preparation of 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(oxazol-2-yl)-1H-indazol-3-yl)-3-fluorobenzoic acid (18A)

SCHEME Z



Step 1. Preparation of methyl 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(4,5-dihydrooxazol-2-yl)-1H-indazol-3-yl)-3-fluorobenzoate (Z-2). A mixture of 1-(2-chloro-6-(trifluoromethyl)benzoyl)-3-(2-fluoro-4-(methoxycarbonyl)phenyl)-1H-indazole-6-carboxylic acid (**Z-1**) (286 mg, 0.55 mmol) and $(COCl)_2$ (0.14 mL, 1.65 mmol) in DCM (5 mL) and DMF (2 drops) was stirred at room temperature for 1 h. The solvent was removed and the residue was dissolved in anhydrous toluene (5 mL). The resulting solution was added to a mixture of 2-bromoethanamine (86 mg, 0.7 mmol) and Et_3N (167 mg, 1.65 mmol) in anhydrous toluene (5 mL). The reaction mixture was stirred at 85 °C for 3 hours. The solvent was evaporated and the residue was purified by flash chromatography (PE:DCM=1:10) to give the desired product **Z-2**. LCMS (ESI) calc'd for $C_{26}H_{16}ClF_4N_3O_4$ $[M+H]^+$: 546, found: 546.

Step 2. Preparation of methyl 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(oxazol-2-yl)-1H-indazol-3-yl)-3-fluorobenzoate (Z-3). The mixture of methyl 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(4,5-dihydrooxazol-2-yl)-1H-indazol-3-yl)-3-fluorobenzoate (**Z-2**) (300 mg, 0.55 mmol), AIBN (9 mg, 0.055 mmol) and NBS (587 mg, 3.3 mmol) in CCl_4 (15 mL) under argon, the reaction mixture was refluxed for 12 hours. The solvent was evaporated and the residue was purified by column chromatography on silica gel eluting with (PE:DCM=1:4) to get the desired product **Z-3** (200 mg, 66%). LCMS (ESI) calc'd for $C_{26}H_{14}ClF_4N_3O_4$ $[M+H]^+$: 544, found: 544.

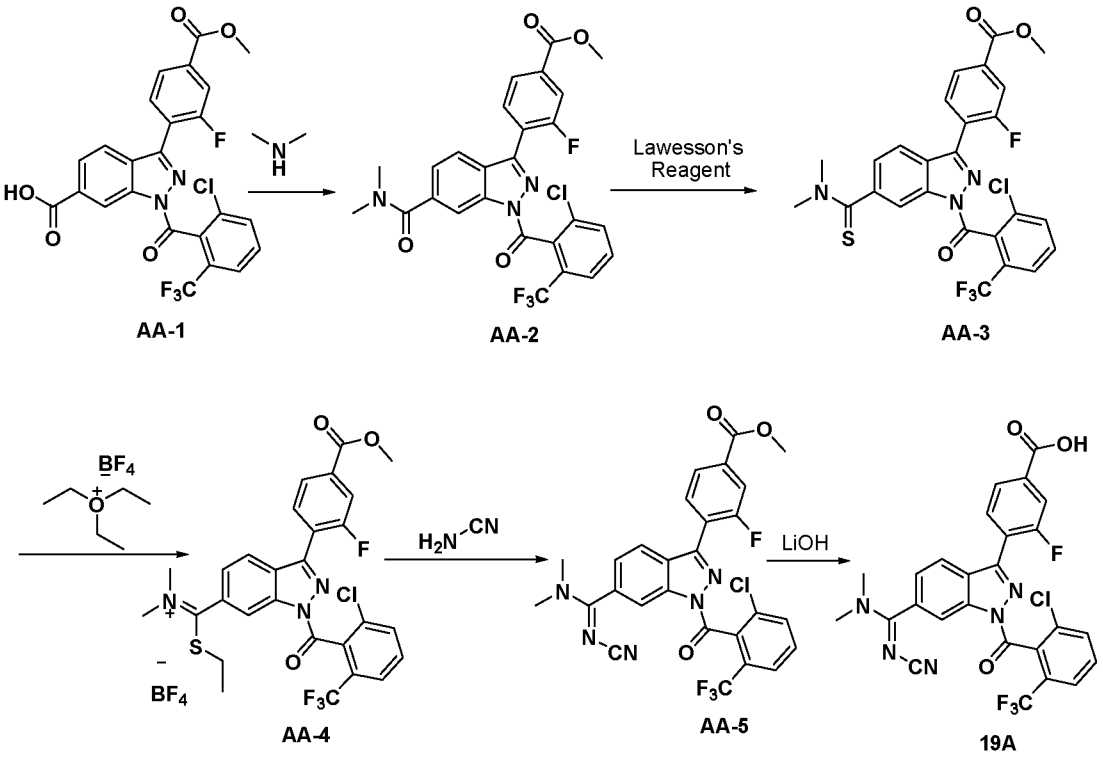
Step 3. Preparation of methyl 4-(6-(5-bromooxazol-2-yl)-1-(2-chloro-6-(trifluor omethyl)benzoyl)-1H-indazol-3-yl)-3-fluorobenzoate (Z-4). The same to the preparation of compound **Z-3** to get the desired product **Z-4**. LCMS (ESI) calc'd for $C_{26}H_{13}BrClF_4N_3O$ [M+H]+: 622, found: 622.

Step 4. Preparation of 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl) -6-(oxazol-2-yl)-1H-indazol-3-yl)-3-fluorobenzoic acid (18A). A mixture of methyl 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(oxazol-2-yl)-1H-indazol-3-yl)-3-fluorobenzoate (**Z-3**) (38 mg, 0.07 mmmol) and $LiOH·H_2O$ (16 mg, 0.37 mmol) in 10 mL THF and 10 mL pure H_2O was stirred at RT for 2 hours. The solvent was evaporated and the residue was dissolved in water. HCl (5% sol. in water) was added until pH = 4-5. The precipitated solid was filtered, washed with water (10 mL) and n-hexane (10 mL), dried to afford an off white solid **18A** (32 mg, 93%). LCMS (ESI): calc'd for $C_{25}H_{12}ClF_4N_3O_4$, $[M+H]^+$: 530 found: 530; ^{1}HNMR (400 MHz, DMSO) δ 13.57 (1H, s), 9.12 (1H, s), 8.40 (1H, s), 8.24-8.26 (1H, d, J= 8 Hz), 8.12-8.14 (1H, d, J= 8 Hz), 8.00-8.07 (2H, m), 7.88-7.95 (3H,m), 7.78-7.81 (1H, m) , 7.55 (1H, s).

Step 5. Preparation of 4-(6-(5-bromooxazol-2-yl)-1-(2-chloro-6-(trifluorometh yl)benzoyl)-1H-indazol-3-yl)-3-fluorobenzoic acid (18B). The same to the preparation of compound **18A** to get the desired product **18B**. LCMS (ESI): calc'd for $C_{25}H_{11}BrClF_4N_3O_4$, [M+H]+: 608 found: 608; ^{1}HNMR (400 MHz, DMSO) δ 13.57 (1H, s), 9.05 (1H, s), 8.19-8.21 (1H, d, J= 8 Hz), 8.12-8.14 (1H, d, J= 8 Hz), 8.05-8.06 (1H, d, J= 4 Hz), 8.00-8.02 (1H, d, J= 8 Hz), 7.93-7.95 (1H, d, J= 8 Hz), 7.86-7.88 (2H, m), 7.77-7.80 (1H, m), 7.61 (1H, s).

Example 19A: Preparation of (E)-4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(N'-cyano-N,N-dimethylcarbamimidoyl)-1H-indazol-3-yl)-3-fluorobenzoic acid (19A)

SCHEME AA



Step 1. Preparation of methyl 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(dimethylcarbamoyl)-1H-indazol-3-yl)-3-fluorobenzoate (AA-2). The mixture of 1-(2-chloro-6-(trifluoromethyl)benzoyl)-3-(2-fluoro-4-(methoxycarbonyl)phenyl)-1H-indazole-6-carboxylic acid (**AA-1**) (250 mg, 0.48 mmol), dimethylamine (2.0 M solution in THF, 0.36 mL, 0.72 mmol), HATU (220 mg, 0.58 mmol) and Et_3N (0.13 mL, 0.96 mmol) in DCM (10 mL) was stirred at room temperature for 1 h. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel (PE:EA 1:1) to get the desired product as a white solid (200 mg, 86%). LCMS (ESI) calc'd for $C_{26}H_{18}ClF_4N_3O_4$ $[M+H]^+$: 548, found: 548.

Step 2. Preparation of methyl 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(dimethylcarbamothioyl)-1H-indazol-3-yl)-3-fluorobenzoate (AA-3). The mixture of methyl4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(dimethylcarbamoyl)-1H-indazol-3-yl)-3-fluorobenzoate (**AA-2**) (240 mg, 0.44 mmol) and Lawesson Reagent (360 mg, 0.88 mmol) in toluene (10 mL) was stirred at 100 °C for 4 h. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel (PE:EA 5:1) to get the

desired product as a yellow solid (180 mg, 70%). LCMS (ESI) calc'd for $C_{26}H_{18}ClF_4N_3O_3S$ $[M+H]^+$: 564, found: 564.

Step 3. Preparation of tetrafluoroborate of methyl 4-(1-(2-chloro-6-(trifluoro methyl) benzoyl) -6-((dimethylamino)(ethylthio)methyl)-1H-indazol-3-yl)-3-fl uorobenzoate (AA-4). The mixture of methyl 4-(1-(2-chloro-6-(trifluor omethyl)benzoyl)-6-(dimethylcarbamothioyl)-1H-indazol-3-yl)-3-fluorobenzoate **(AA-3)** (145 mg, 0.26 mmol) and triethyloxonium tetrafluoroborate (1.0 M solution in DCM, 0.31 mL, 0.31 mmol) in DCE (6 mL) was stirred at 85 °C for overnight. The solvent was removed under reduced pressure to get the crude product as a yellow solid. The crude product was used in the next step without further purification. LCMS (ESI) calc'd for $C_{28}H_{23}BClF_8N_3O_3S$ $[M+H]^+$: 592, found: 592.

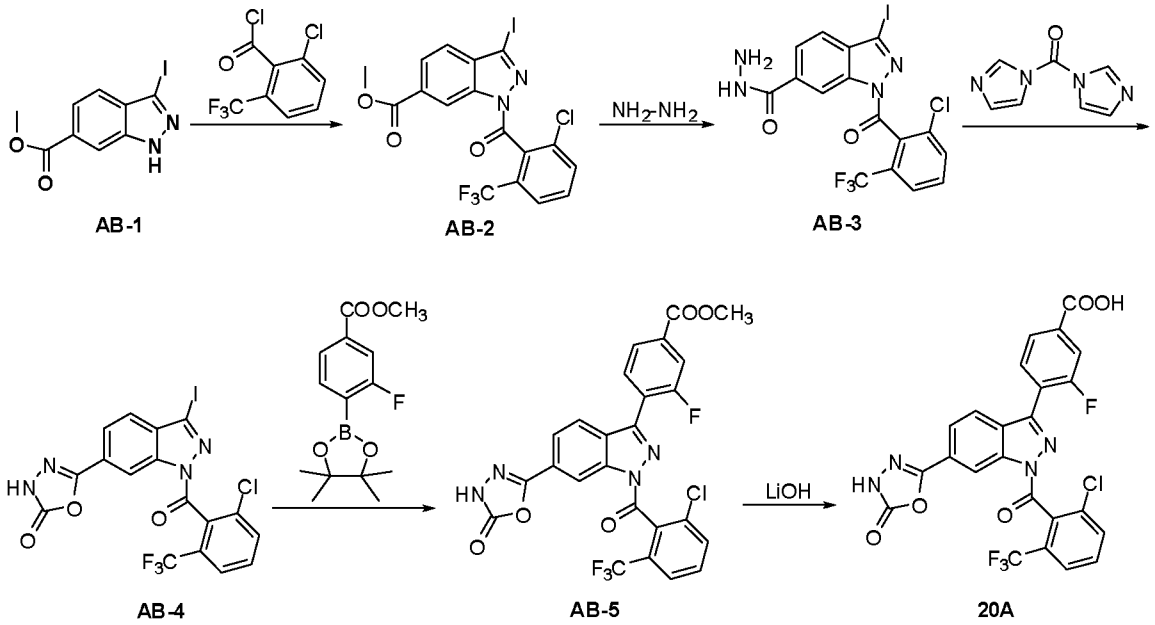
Step 4. Preparation of (E)-methyl 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6 -(N'-cyano-N,N-dimethylcarbamimidoyl)-1H-indazol-3-yl)-3-fluorobenzoate (AA-5). The mixture of methyl 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-((dimeth ylamino)(ethylthio)methyl)-1H-indazol-3-yl)-3-fluorobenzoate (**AA-4**) (150 mg, 0.26 mmol), cyanamide (37 mg, 0.88 mmol) and Et_3N (44 mg, 0.44 mmol) in MeOH (5 mL) was stirred at room temperature for 2 h. The result solution was diluted with water (30 mL) and the aqueous layer was extracted with EtOAc (20 mL×3). The combined organic layers were washed with 1N HCl solution (20 mL×1) then brine (20 mL×1), dried over anhydrous Na_2SO_4 and concentrated to get the desired crude product **AA-5** (160 mg) as a yellow solid. LCMS (ESI) calc'd for $C_{27}H_{18}ClF_4N_5O_3$ $[M+H]^+$: 572, found: 572.

Step 5. Preparation of (E)-4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(N'-cya no-N,N-dimethylcarbamimidoyl)-1H-indazol-3-yl)-3-fluorobenzoic acid (19A). The mixture of (E)-methyl 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(N'-cyano-N, N-dimethylcarbamimidoyl)-1H-indazol-3-yl)-3-fluorobenzoate (**AA-5**) (100 mg, 0.18 mmol) and LiOH (30 mg, 0.72 mmol) in THF (4 mL) and H_2O (2 mL) was stirred at room temperature for 3 h. The reaction mixture was diluted with H_2O (20 mL). 2 M HCl solution was added to adjust the pH=3 and the aqueous layer was extracted with ethyl acetate (20 mL×3). The combined organic layers were washed with brine (20 mL×1), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified with Prep-HPLC (acetonitrile-

water system) to get the desired product **6** as a white solid (50 mg, 50%). LCMS (ESI) calc'd for $C_{26}H_{16}ClF_4N_5O_3$ $[M+H]^+$: 558, found: 558; ^{1}HNMR (400 MHz, MeOD) δ 8.68 (1H, s), 8.15-8.18 (1H, m), 7.93-7.98 (2H, m), 7.87-7.91 (2H, m), 7.77-7.81 (1H, m), 7.72-7.76 (1H, m), 7.61 (1H, d, J=8.4Hz), 3.37 (3H, s), 3.09 (3H, s).

Example 20A: Preparation of 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-1H-indazol-3-yl)-3-fluorobenzoic acid (20A)

SCHEME AB



Step 1. Preparation of methyl 1-(2-chloro-6-(trifluoromethyl)benzoyl)-3-iodo-1H-indazole-6-carboxylate (AB-2). To a stirred solution of methyl 3-iodo-1H-indazole-6-carboxylate (**AB-1**) (2 g, 6.62 mmol) in anhydrous DCM (60 mL) at rt was added 2-chloro-6-(trifluoromethyl)benzoyl chloride (2.4 g, 9.93 mmol), DMAP (161 mg, 1.32 mmol), Et_3N (1.47 mg, 14.57 mmol). The solution was stirred at rt overnight. The solution was diluted with EtOAc (50 mL), filtered through celite and washed with DCM (40 mL). The combined organic layer was washed with H_2O (20 mL), brine (20 mL) and dried over anhydrous Na_2SO_4. The solution was evaporated with silica gel and loaded on a column. SGC (DCM) afforded 3.25 g product. Yield 98.5%. LCMS (ESI) calc'd for $C_{17}H_9ClF_3IN_2O_3$ $[M+H]^+$: 509, found: 509.

Step 2. Preparation of 1-(2-chloro-6-(trifluoromethyl)benzoyl)-3-iodo-1H-indaz

ole-6-carbohydrazide (AB-3). To a stirred solution of methyl1-(2-chloro-6-(trifluoro methyl)benzoyl)-3-iodo-1H-indazole-6-carboxylate (**AB-2**) (1000 mg, 1.97 mmol) in ethanol (40 mL) was added $NH_2NH_2{\cdot}H_2O$ (0. 31 ml, 9.83 mmol). The solution was stirred at reflux temperature overnight. LCMS showed complete transformation to the product. The solution was diluted with H_2O (100 mL), extracted with EtOAc (3×60 mL). The combined organic layer was washed with H_2O (2×20 mL), brine (30 mL) and dried over anhydrous Na_2SO_4. The solution was evaporated with silica gel and loaded on a column. Prep-TLC (DCM) afforded 176 mg product. Yield 18%. LCMS (ESI) calc'd for $C_{16}H_9ClF_3IN_4O_2$ $[M+H]^+$: 509, found: 509.

Step 3. Preparation of 5-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-3-iodo-1H-inda zol-6-yl)-1,3,4-oxadiazol-2(3H)-one (AB-4). To a stirred solution of 1-(2-chloro-6-(tr ifluoromethyl)benzoyl)-3-iodo-1H-indazole-6-carbohydrazide (**AB-3**) (100 mg, 0.196 mmol) in THF (2 mL) was added CDI (48 mg, 0.294 mmol) and Et_3N (30 mg, 0.294 mmol). The solution was stirred at rt overnight. The solution was diluted with H_2O (30 mL), extracted with EtOAc (2×30 mL) and organic layer was washed with H_2O (30 mL) and brine (30 mL) and dried over anhydrous Na_2SO_4. The organic layer was evaporated with silica gel and loaded on a silica gel column. SGC (PE/EA: 2/1) gave 60 mg product, yield 57%. LCMS (ESI) calc'd for $C_{17}H_7ClF_3IN_4O_3$ $[M+H]^+$: 535, found: 535.

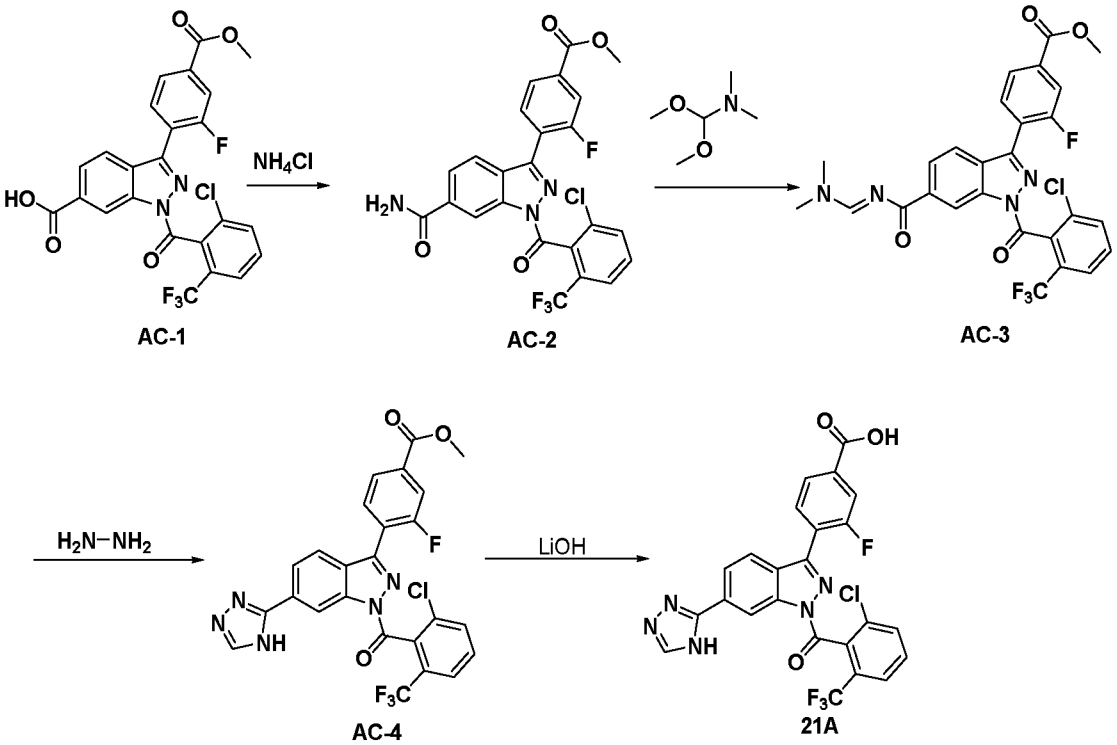
Step 4. Preparation of methyl 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(5-oxo -4,5-dihydro-1,3,4-oxadiazol-2-yl)-1H-indazol-3-yl)-3-fluorobenzoate (AB-5). To a microwave tube was added 5-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-3-iodo-1H-indazol-6-yl)-1,3,4-oxadiazol-2(3H)-one (**AB-4**) (60 mg, 0.11 mmol), methyl 3-fluoro -4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (44 mg, 0.22 mmol), $Pd(OAc)_2$ (trimer) (1.23 mg, 0.01 mmol), s-Phos (4.4 mg, 0.01mmol), K_3PO_4 (80 mg, 0.33 mmol), THF(1.5 mL), H_2O (0.3 mL). The solution was microwaved under Argon at 110 °C for 2 hours. LCMS showed major product peak. The upper solution was filtered and submitted for next step without further purification. LCMS (ESI) calc'd for $C_{25}H_{13}ClF_4N_4O_5$$[M+H]^+$: 560, found: 560.

Step 5. Preparation of 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(5-oxo-4,5-di

hydro-1,3,4-oxadiazol-2-yl)-1H-indazol-3-yl)-3-fluorobenzoic acid (20A). To a stirred solution of methyl4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(5-oxo-4,5-di hydro-1,3,4-oxadiazol-2-yl)-1H-indazol-3-yl)-3-fluorobenzoate (**AB-5**) (as generated in step 4) was added $LiOH{\cdot}H_2O$ (10 mg, 0.4 mmol) and H_2O (0.1 mL). The solution was stirred overnight and LCMS showed major product peak. The solution was adjusted to PH 3.0 using 1 N HCl. The upper organic layer was collected and the aqueous layer was extracted with THF (3×1 mL). The combined organic layer was added 0.5 mL MeOH and submitted for Prep-HPLC. Prep-HPLC (H_2O/ACN, 0.05% TFA) gave 15 mg product, yield for two steps 25%. LCMS (ESI) calc'd for $C_{24}H_{11}ClF_4N_4O_5$ $[M+H]^+$: 547, found: 547. ^{1}HNMR (400 MHz, DMSO) δ 13.60 (1H, s), 13.00 (1H, s), 8.87 (1H, s), 8.15-8.07 (1H, m), 8.06-8.03(3H, m), 8.02-8.00(3H, m), 7.79-7.76 (1H, m).

Example 21A: Preparation of 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(4H-1,2,4-triazol-3-yl)-1H-indazol-3-yl)-3-fluorobenzoic acid (21A)

SCHEME AC



Step 1. Preparation of methyl 4-(6-carbamoyl-1-(2-chloro-6-(trifluoromethyl)ben zoyl)-1H-indazol-3-yl)-3-fluorobenzoate (AC-2). The mixture of 1-(2-chloro-6-(trifluoromethyl)benzoyl)-3-(2-fluoro-4-(methoxycarbonyl)phenyl)-1H-indazole-6-carboxylic

acid (**AC-1**) (95 mg, 0.18 mmol), ammonium chloride (14.3 mg, 0.27 mmol), HATU (82 mg, 0.22 mmol) and Et_3N (76 uL, 0.54 mmol) in DCM (5 mL) was stirred at room temperature for 1 h. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel (PE:EA 1:1) to get the desired product as a white solid (60 mg, 68%). LCMS (ESI) calc'd for $C_{24}H_{14}ClF_4N_3O_4$ $[M+H]^+$: 520, found: 520.

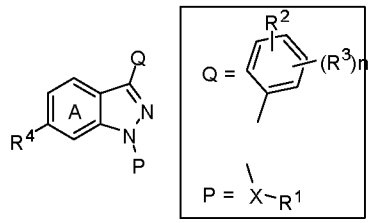
Step 2. Preparation of (E)-methyl 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-((dimethylamino)methylenecarbamoyl)-1H-indazol-3-yl)-3-fluorobenzoate (AC-3). The mixture of methyl 4-(6-carbamoyl-1-(2-chloro-6-(trifluoromethyl)benzoyl)-1H-indazol-3-yl)-3-fluorobenzoate (**AC-2**) (80 mg, 0.15 mmol) and dimethoxy-N,N-dimethylmethanamine (92 mg, 0.75 mmol) in EtOAc (5 mL) was stirred at 60 °C for overnight. The solvent was removed under reduced pressure to get the crude product as a white solid. The crude product was used in the next step without further purification. LCMS (ESI) calc'd for $C_{27}H_{19}ClF_4N_4O_4$ $[M+H]^+$: 575, found: 575.

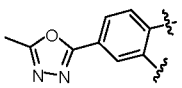
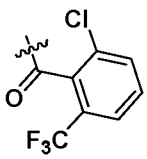
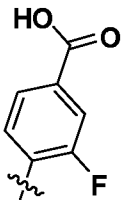
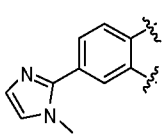
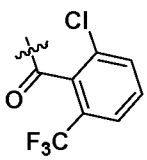
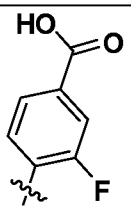
Step 3. Preparation of methyl 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(4H-1,2,4-triazol-3-yl)-1H-indazol-3-yl)-3-fluorobenzoate (AC-4). The mixture of (E)-methyl 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-((dimethylamino)methylene carbamoyl)-1H-indazol-3-yl)-3-fluorobenzoate (**AC-3**) (100 mg, 0.17 mmol) and hydrazine (27 mg, 0.85 mmol) in AcOH (5 mL) was stirred at room temperature for 2 h. The result solution was diluted with water (30 mL). $NaHCO_3$ solid was added to adjust the pH=8 and the aqueous layer was extracted with EtOAc (20 mL ×3). The combined organic layers were washed with brine (20 mL ×1), dried over anhydrous Na_2SO_4 and concentrated to get the desired product as a white solid (50 mg, 50%). LCMS (ESI) calc'd for $C_{25}H_{14}ClF_4N_5O_3$ $[M+H]^+$: 544, found: 544.

Step 4. Preparation of 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(4H-1,2,4-triazol-3-yl)-1H-indazol-3-yl)-3-fluorobenzoic acid (21A). The mixture of methyl 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(4H-1,2,4-triazol-3-yl)-1H-indazol-3-yl)-3-fluorobenzoate (**AC-4**) (100 mg, 0.18 mmol) and LiOH (38 mg, 0.90 mmol) in THF (4 mL) and H_2O (2 mL) was stirred at 30 °C for 1h. The reaction mixture was diluted with H_2O (20 mL). 2M HCl solution was added to adjust the pH=3 and the aqueous layer was extracted

with ethyl acetate (20 mL ×3). The combined organic layers were washed with brine (20 mL×1), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified with Prep-HPLC (acetonitrile-water system) to get the desired product **21A** as a white solid (95 mg, 96%). LCMS (ESI) calc'd for $C_{24}H_{12}ClF_4N_5O_3$ $[M+H]^+$: 530, found: 530. ^{1}HNMR (400 MHz, MeOD) δ 9.32 (1H, s), 8.56 (1H, s), 8.30 (1H, d, J=8.4Hz), 8.02-8.05 (1H, m), 7.92-7.97 (2H, m), 7.86-7.90 (2H, m), 7.72-7.80 (2H, m).

TABLE 10:

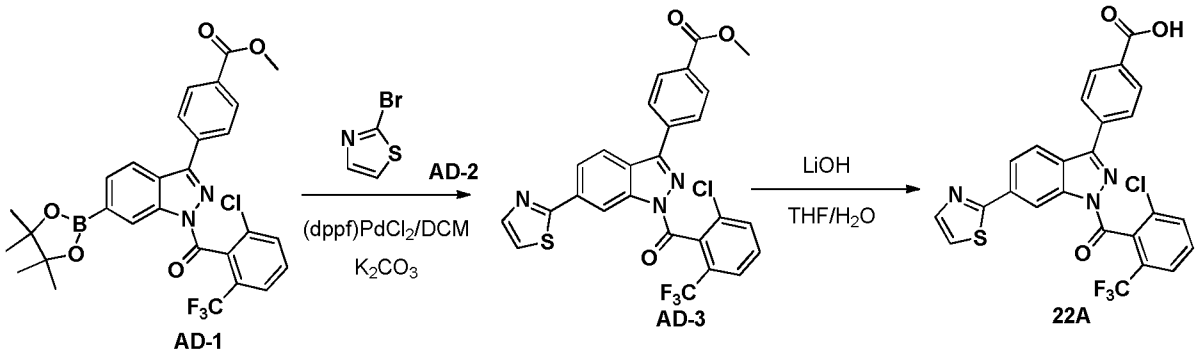


Example	Chemical Name	A ring	P	Q	LCMS $[M+H]^+$ Found
21B	4-(1-(2-chloro-6-(trifluoromethyl) benzoyl)-6-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-indazol-3-yl)-3-fluorobenzoic acid				545
21C	4-(1-(2-chloro-6-(trifluoromethyl) benzoyl)-6-(1-methyl-1H-				543

	imidazol-2-yl)-1H-indazol-3-yl)-3-fluorobenzoic acid				

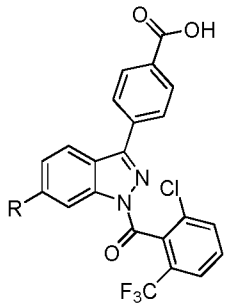
Example 22A: Preparation of 4-(1-(2-chloro-6-trifluorobenzoyl)-6-(thiazol-2-yl)-1H -indazol-3-yl)benzoic acid (22A)

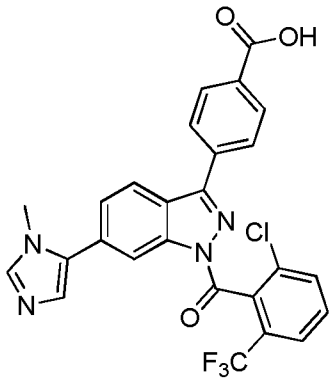
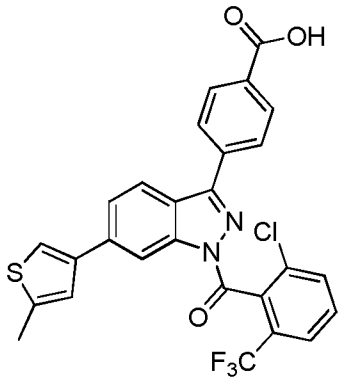
SCHEME AD

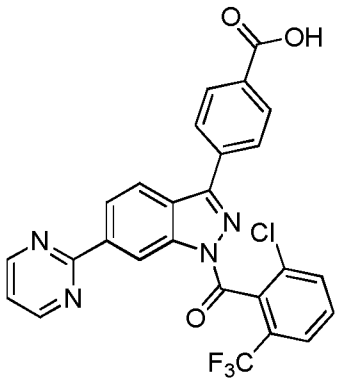
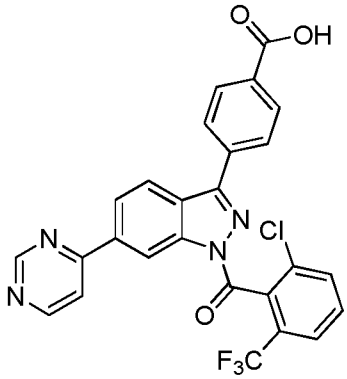
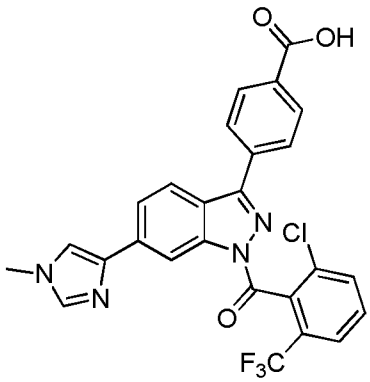
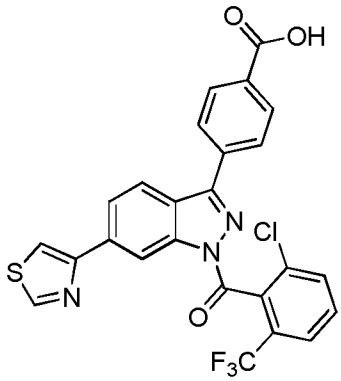


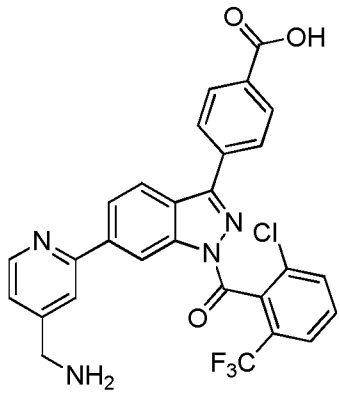
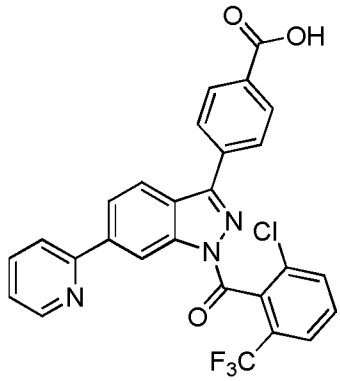
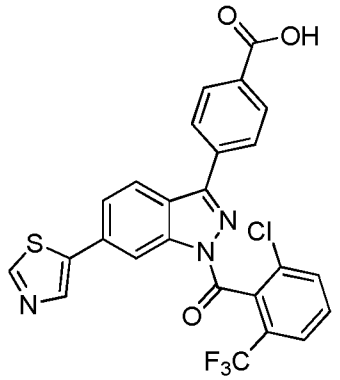
Step: Preparation of 4-(1-(2-chloro-6-trifluorobenzoyl)-6-(thiazol-2-yl)-1H-indazol -3-yl)benzoic acid (22A). To a 1 dram vial was added methyl 4-(1-(2-chloro-6-trifluorobenzoyl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazol-3-yl)benzoate (**AD-1**) (20 mg, 0.034 mmol), 2-bromothiazole (**AD-2**) (0.051 mmol), potassium carbonate (0.093 mL, 2M), dichloro 1-1'-bis(diphenylphosphino)ferrocine palladium (II) dichloromethane adduct (5.59 mg, 6.84 umol), and 1,4-dioxane (1 mL). The vessel was flushed with Argon and stirred overnight at 90 °C. The reactions were concentrated under reduced pressure. The remaining residue was dissolved in a 1:1 DCM/Methanol solution (1 mL) and SiliaBond DMT Resin (78 mg, 0.045 mmol) was then added. The mixture was stirred overnight at room temperature. The mixture was then filtered and concentrated under reduced pressure. Lithium hydroxide (1M, 0.186 mL), methanol (0.25 mL), and THF (0.5 mL) was then added and the reaction was stirred overnight at RT. The reactions were concentrated under reduced pressure. The reaction was then diluted with 1.0 mL DMSO, filtered, and purified by mass-triggered reverse phase HPLC, eluting with a 1% trifluoroacetic acid buffered water/acetonitrile gradient over a Waters X-Bridge C-18 column, to afford desired product (5 mg, 18% over two steps). LCMS (ESI) calc'd for $C_{24}H_{13}ClFN_3O_3S$ $[M+H]^+$: 478, found: 478.

TABLE 11:



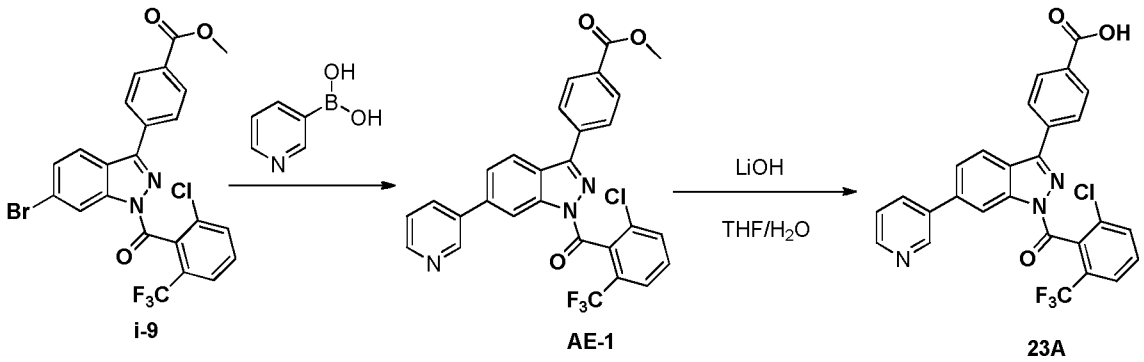
Ex.	Chemical Name	Structure	LCMS $[M+H]^+$ Calc'd/Found
22B	4-[1-{[2-chloro-6-(trifluoromethyl)phenyl]carbonyl}-6-(1-methyl-1H-imidazol-5-yl)-1H-indazol-3-yl]benzoic acid		475/475
22C	4-[1-{[2-chloro-6-(trifluoromethyl)phenyl]carbonyl}-6-(5-methylthiophen-3-yl)-1H-indazol-3-yl]benzoic acid		491/491

22D	4-(1-{[2-chloro-6-(trifluoromethyl)phenyl]carbonyl}-6-pyrimidin-2-yl-1H-indazol-3-yl)benzoic acid		473/473
22E	4-(1-{[2-chloro-6-(trifluoromethyl)phenyl]carbonyl}-6-pyrimidin-4-yl-1H-indazol-3-yl)benzoic acid		473/473
22F	4-[1-{[2-chloro-6-(trifluoromethyl)phenyl]carbonyl}-6-(1-methyl-1H-imidazol-4-yl)-1H-indazol-3-yl]benzoic acid		475/475
22G	4-[1-{[2-chloro-6-(trifluoromethyl)phenyl]carbonyl}-6-(1,3-thiazol-4-yl)-1H-indazol-3-yl]benzoic acid		478/478

22H	4-(6-[4-(aminomethyl)pyridin-2-yl]-1-{[2-chloro-6-(trifluoromethyl)phenyl]carbonyl}-1H-indazol-3-yl)benzoic acid		501/501
22I	4-(1-{[2-chloro-6-(trifluoromethyl)phenyl]carbonyl}-6-pyridin-2-yl-1H-indazol-3-yl)benzoic acid		472/472
22J	4-[1-{[2-chloro-6-(trifluoromethyl)phenyl]carbonyl}-6-(1,3-thiazol-5-yl)-1H-indazol-3-yl]benzoic acid		478/478

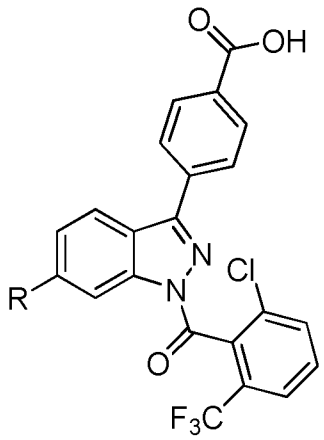
Example 23A: Preparation of 4-(1-(2-chloro-6-trifluorobenzoyl)-6-(thiazol-2-yl)-1H-indazol-3-yl)benzoic acid (23A)

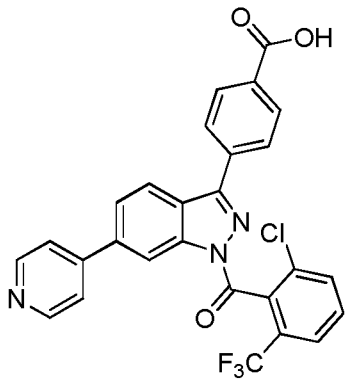
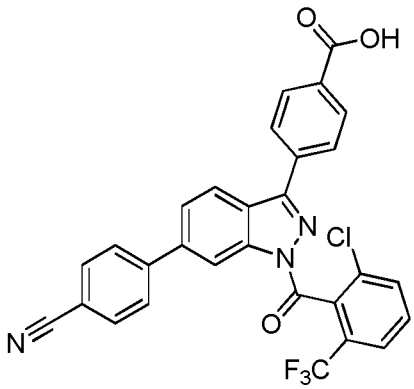
Scheme AE

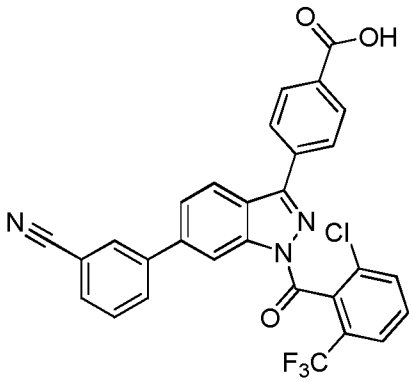
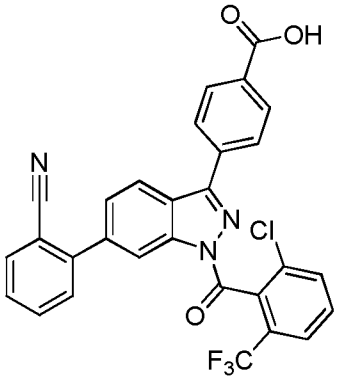
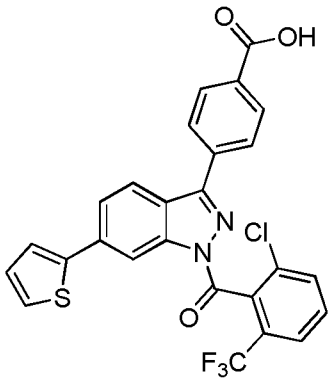
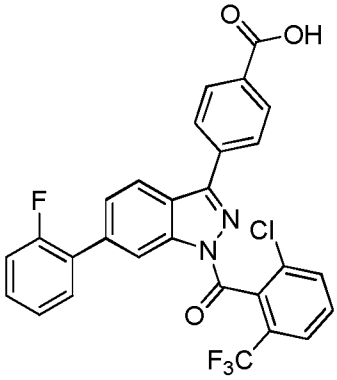


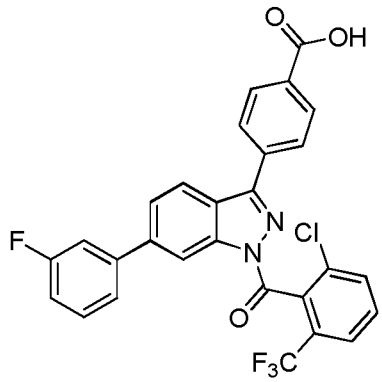
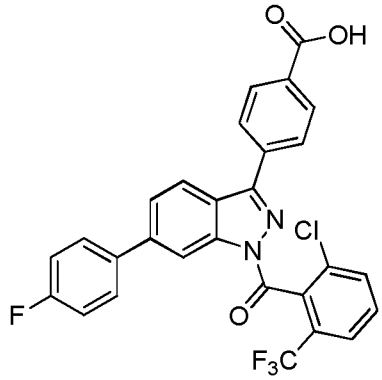
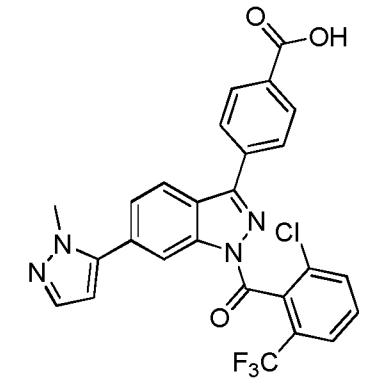
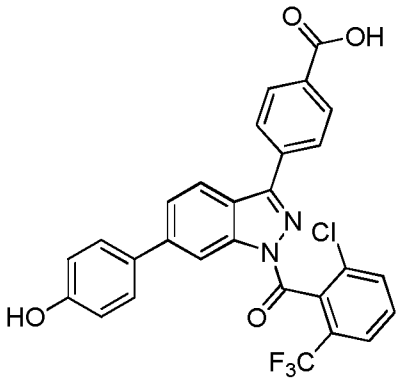
Step 1: Preparation of 4-(1-(2-chloro-6-trifluorobenzoyl)-6-(pyridin-3-yl)-1H- indazol-3-yl)benzoic acid (23A). To a 1 dram vial was added methyl 4-(6-bromo-1-(2-chloro-6-trifluorobenzoyl)-1H-indazol-3-yl)benzoate (i-9) (20 mg, 0.037 mmol), pyridin-3-ylboronic acid (6.9 mg, 0.056 mmol), potassium carbonate (2 M, 0.093 mL, 0.186 mmol), dichloro 1-1'-bis(diphenylphosphino)ferrocine palladium(II) dichloromethane adduct (6.07 mg, 7.44 umol), and 1,4-dioxane (1 mL). The vessel was flushed with Argon and stirred overnight at 90°C. The reactions were concentrated under reduced pressure. The remaining residue was dissolved in a 1:1 DCM/Methanol solution (1 mL) and SiliaBond DMT Resin (78 mg, 0.045 mmol) was then added. The mixture was stirred overnight at room temperature. The mixture was then filtered and concentrated under reduced pressure. Lithium hydroxide (1M, 0.186 mL), methanol (0.25 mL) and THF (0.5 mL) was then added and the reaction was stirred overnight at RT. The reactions were concentrated under reduced pressure. The reaction was then diluted with 1.0 mL DMSO, filtered, and purified by mass-triggered reverse phase HPLC, eluting with a 1% trifluoroacetic acid buffered water/acetonitrile gradient over a Waters X-Bridge C-18 column, to afford desired product. LCMS (ESI) calc'd for $C_{26}H_{15}ClFN_3O_3$ $[M+H]^+$: 472, found: 472. 1H ^{1}H NMR δ (ppm)(DMSO-d_6): 7.66 (1 H, t, J = 6.33 Hz), 7.85 (1 H, t, J = 8.15 Hz), 7.99-7.98 (6 H, m), 8.08 (2 H, d, J = 8.17 Hz), 8.37 (2 H, d, J = 8.35 Hz), 8.71 (1 H, d, J = 4.84 Hz), 8.78 (1 H, s), 9.09 (1 H, s).

TABLE 5:



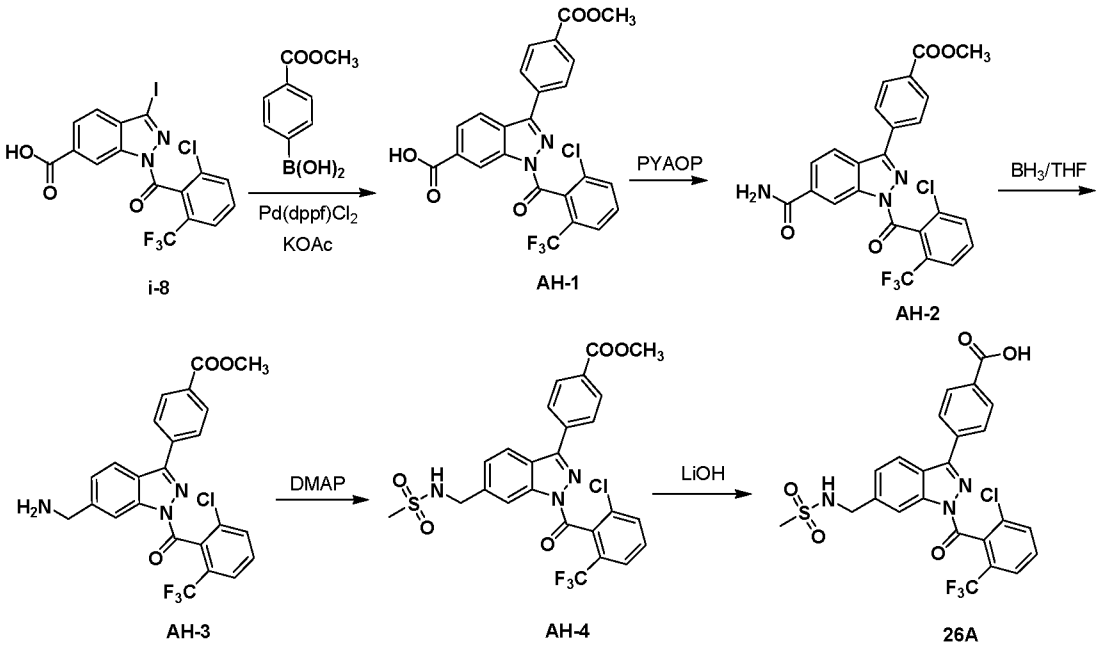
Ex.	Chemical Name	Structure	LCMS $[M+H]^+$ Calc'd/Found
23B	4-(1-{[2-chloro-6-(trifluoromethyl)phenyl]carbonyl}-6-pyridin-4-yl-1H-indazol-3-yl)benzoic acid		472/472
23C	4-[1-{[2-chloro-6-(trifluoromethyl)phenyl]carbonyl}-6-(4-cyanophenyl)-1H-indazol-3-yl]benzoic acid		496/496

23D	4-[1-{[2-chloro-6-(trifluoromethyl)phenyl]carbonyl}-6-(3-cyanophenyl)-1H-indazol-3-yl]benzoic acid		496/496
23E	4-[1-{[2-chloro-6-(trifluoromethyl)phenyl]carbonyl}-6-(2-cyanophenyl)-1H-indazol-3-yl]benzoic acid		496/496
23F	4-(1-{[2-chloro-6-(trifluoromethyl)phenyl]carbonyl}-6-thiophen-2-yl-1H-indazol-3-yl)benzoic acid		477/477
23G	4-[1-{[2-chloro-6-(trifluoromethyl)phenyl]carbonyl}-6-(2-fluorophenyl)-1H-indazol-3-yl]benzoic acid		489/489

23H	4-[1-{[2-chloro-6-(trifluoromethyl)phenyl]carbonyl}-6-(3-fluorophenyl)-1H-indazol-3-yl]benzoic acid		489/489
23I	4-[1-{[2-chloro-6-(trifluoromethyl)phenyl]carbonyl}-6-(4-fluorophenyl)-1H-indazol-3-yl]benzoic acid		489/489
23J	4-[1-{[2-chloro-6-(trifluoromethyl)phenyl]carbonyl}-6-(1-methyl-1H-pyrazol-5-yl)-1H-indazol-3-yl]benzoic acid		475/475
23K	methyl 4-(1-(2-chloro-6-trifluorobenzoyl)-6-(4-hydroxyphenyl)-1H-indazol-3-yl) benzoate		487/487

Example 26A: Preparation of 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(methylsulfonamidomethyl)-1H-indazol-3-yl)benzoic acid (26A)

Scheme AH



Step 1. Preparation of 1-(2-chloro-6-(trifluoromethyl)benzoyl)-3-(4-(methoxycarbonyl)phenyl)-1H-indazole-6-carboxylic acid (AH-1). A mixture of **i-8** (300 mg, 0.61 mmol), 4-(methoxycarbonyl)phenylboronic acid (165 mg, 0.92 mmol), $Pd(dppf)Cl_2$ (50 mg, 0.061 mmol) and KOAc (181 mg, 1.83 mmol) in 10 mL dioxane and 2 mL pure H_2O was heated to 95 ^0C for 2h with microwave. Then it was diluted with EtOAC (50 mL), washed with brine (50 mL x 2), dried over anhydrous Na_2SO_4, concentrated. Then it was purified by silica gel column (PE/EtOAc=20/1) to get white solid 180 mg (59%). LCMS (ESI): calc'd for $C_{24}H_{14}ClF_3N_2O_5$, $[M+H]^+$: 503.1, found: 503.1

Step 2. Preparation of methyl 4-(6-carbamoyl-1-(2-chloro-6-(trifluoromethyl)- benzoyl)-1H-indazol-3-yl)benzoate (AH-2). The compound **AH-1** (100 mg, 0.2 mmol) was dissolved in CH_2Cl_2 (15 mL). NH_4Cl (13 mg, 0.24 mmol), PYAOP (208 mg, 0.4 mmol) was added and the mixture was stirred at room temperature for 2 min. TEA (0.16 mL, 1.08 mmol) was added and the mixture was stirred at room temperature for 2h. Then it was diluted with EtOAC (20 mL), washed with brine (20 mL x 2), dried over anhydrous Na_2SO_4, concentrated get white solid **AH-2** 90 mg (90%). LCMS (ESI): calc'd for $C_{24}H_{15}ClF_3N_3O_4$, $[M+H]^+$: 502, found: 502.

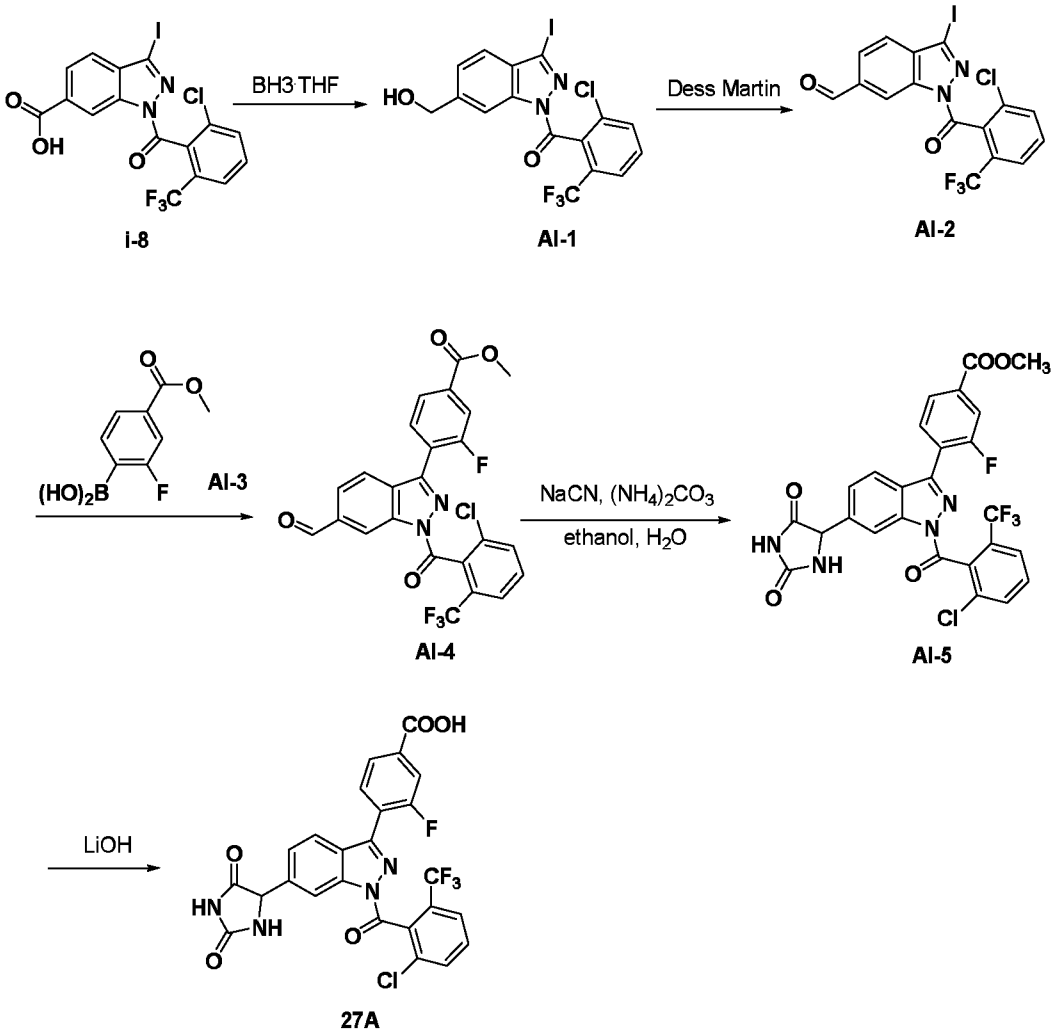
Step 3. Preparation of methyl 4-(6-(aminomethyl)-1-(2-chloro-6-(trifluoromethyl) benzoyl)-1H-indazol-3-yl)benzoate (AH-3). The compound **AH-2** (90 mg, 0.18 mmol) was dissolved in anhydrous THF (20 mL) under argon, BH_3.THF (0.9 mL, 0.9 mmol) was added and the mixture was refluxed for 12 h. MeOH was added to quench the excess BH_3. The mixture was evaporated and then got white solid 75 mg. LCMS (ESI): calc'd for $C_{24}H_{17}ClF_3N_3O_3$, $[M+H]^+$: 488.1, found: 488.1.

Step 4. Preparation of methyl 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(methylsulfonamidomethyl)-1H-indazol-3-yl)benzoate (AH-4). To a 50 mL round-bottomed flask was added compound **AH-3** (100 mg, 0.2 mmol), methanesulfonyl chloride (23 mg, 0.2 mmol) and CH_2Cl_2 (10 mL), after stirring at rt for 3 min, TEA (0.1 mL, 0.6 mmol) was added slowly. The reaction mixture was stirred at rt overnight. Then the mixture was poured to 30 mL water, the lower (organic) and upper (aqueous) phases were separated. The aqueous phase was extracted CH_2Cl_2 (20 mL x 2). The combined organic phases were washed successively with water (20 mL x 2) and 10 mL of brine. The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated at reduced pressure to give solid 22 mg. LCMS (ESI): calc'd for $C_{25}H_{19}ClF_3N_3O_5S$ $[M+H]^+$: 566.1, found: 566.1.

Step 5. Preparation of 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(methyl-sulfonamidomethyl)-1H-indazol-3-yl)benzoic acid (26A). A mixture of methyl 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(methylsulfonamidomethyl)-1H-indazol-3-yl)benzoate (**AH-4**) (22 mg, 0.04 mmol) and LiOH.H_2O (8 mg, 0.19mmol) in 10 mL THF and 10 mL pure H_2O was stirred at rt for 2h. The solvent was evaporated and the residue was dissolved in water. HCl (5% sol in water) was added until pH 4-5. The precipitated solid was filtered, washed with water and n-hexane, dried to afford an off-white solid 15 mg (80%). LCMS (ESI): calc'd for $C_{24}H_{17}ClF_3N_3O_5S$, $[M+H]^+$: 552.1 found: 552.1; ^{1}HNMR (400MHz, DMSO-d_6) δ 8.59 (s, 1H), 8.23-8.25 (d,1H, J =8Hz), 8.09-8.11 (d, 2H, J=8Hz), 8.04-8.06 (d, 1H, J=8Hz), 7.99-8.01 (d, 1H, J=8Hz), 7.94-7.96 (d, 2H, J=8Hz), 7.86-7.90 (m, 2H), 7.64-7.66 (d, 1H, J=8Hz), 4.46-4.48 (d, 2H, J=8Hz), 2.99 (s, 3H).

Example 27A: Preparation of 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(2,5-dioxoimidazolidin-4-yl)-1H-indazol-3-yl)-3-fluorobenzoic acid (27A)

Scheme AI



Step 1. Preparation of (2-chloro-6-(trifluoromethyl)phenyl)(6-(hydroxymethyl)- 3-iodo-1H-indazol-1-yl)methanone (AI-1). To a stirred solution of 1-(2-chloro-6-(trifluoromethyl)benzoyl)-3-iodo-1H-indazole-6-carboxylic acid (**i-8**) (2.00 g, 4.0 mmol) in THF (60 mL) was added BH_3·THF (20 mL, 20 mmol). The solution was refluxed overnight. The solution was evaporated and the solid weighted 2.5 g. It proceeded to next step without further purification. LCMS (ESI) calc'd for $C_{16}H_9ClF_3IN_2O_2$ $[M+H]^+$: 480.7, found: 480.9.

Step 2. Preparation of 1-(2-chloro-6-(trifluoromethyl)benzoyl)-3-iodo-1H- indazole-6-carbaldehyde (AI-2). To a stirred solution of (2-chloro-6- (trifluoromethyl)phenyl)(6-

(hydroxymethyl)-3-iodo-1H-indazol-1-yl)methanone (**AI- 1**) (2.5 g, 0.52 mmol) in DCM (160 mL) was added Des Martin Periodinane (3.7 g, 0.78 mmol). The solution was stirred for 1h. The mixture was filtered, the filtrate was washed with H_2O (100 mL) and brine (100 mL) and dried over Na_2SO_4. The solvent was then evaporated and purified with column chromatography (EtOAc/Hexanes=1/10) to give 1.2 g product. Yield for two steps 60%. LCMS (ESI) calc'd for $C_{16}H_7ClF_3IN_2O_2$ $[M+H]^+$: 478.7, found: 479.0.

Step 3. Preparation of methyl 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)- 6-formyl-1H-indazol-3-yl)-3-fluorobenzoate (AI-4). To a microwave tube was added 1-(2-chloro-6-(trifluoromethyl)benzoyl)-3-iodo-1H-indazole-6-carbaldehyde (**AI-2**) (400 mg, 0.83 mmol), 2-fluoro-4-(methoxycarbonyl)phenylboronic acid (**AI-3**) (320 mg, 1.66 mmol), $Pd(OAc)_2$ trimer (28 mg, 0.125 mmol), K_3PO_4(600 mg, 2.5 mmol), s-Phos (100 mg, 0.25 mmol), THF (8 mL), H_2O (2 mL). The mixture was microwaved at 110°C for 2 hours and the compound was submitted for Prep-HPLC. 178 mg product was obtained with a yield of 40%. LCMS (ESI) calc'd for $C_{24}H_{13}ClF_4N_2O_4$ $[M+H]^+$: 505, found: 505.

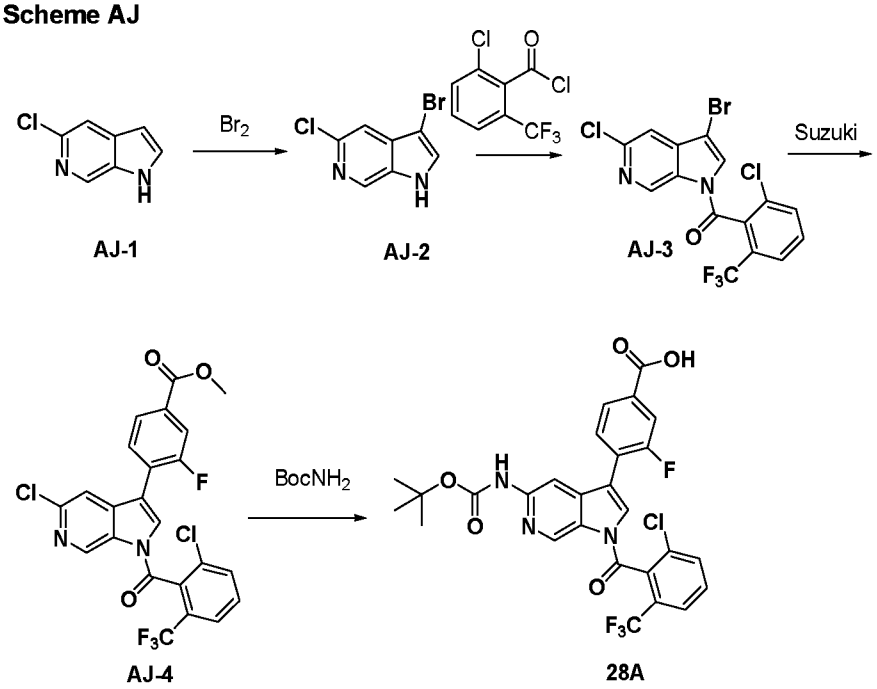
Step 4. Preparation of methyl 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6- (2,5-dioxoimidazolidin-4-yl)-1H-indazol-3-yl)-3-fluorobenzoate (AI-5). To a microwave tube was added methyl 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6- formyl-1H-indazol-3-yl)-3-fluorobenzoate (**AI-4**) (100 mg, 0.20 mmol), NaCN (19.6 mg, 0.40 mmol), $(NH_4)_2CO_3$ (76.8 mg, 0.8 mmol), ethanol (0.8 mL) and H_2O (0.8 mL). The mixture was microwaved under Argon at 110°C for 2 hours. The mixture was filtered and submitted for next step without further purification. LCMS (ESI) calc'd for $C_{26}H_{15}ClF_4N_4O_5$ $[M+H]^+$: 575, found: 575.

Step 5. Preparation of 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(2,5-dioxoimidazolidin-4-yl)-1H-indazol-3-yl)-3-fluorobenzoic acid (27A). To a stirred above solution of methyl 4-(1-(2- chloro-6-(trifluoromethyl)benzoyl)-6-(2,5- dioxoimidazolidin-4-yl)-1H-indazol-3-yl)-3-fluorobenzoate (**AI-5**) was added $LiOH{\cdot}H_2O$ (60 mg, 1.5 mmol) and H_2O (0.1 mL). The solution was stirred overnight. The solution was adjusted to PH 3.0 using 1 N HCl. The reaction mixture was extracted with THF (1 mL x 3). The combined organic layer was added 0.5 mL MeOH and submitted for Prep-HPLC. Prep-HPLC (H_2O/ACN, 0.05% TFA) gave 5 mg product, yield for two steps 4.5%. LCMS (ESI) calc'd for

$C_{25}H_{13}ClF_4N_4O_5$ [M+H]$^+$: 561, found: 561; ^{1}HNMR (400MHz, DMSO-d_6) δ 13.60 (s, 1H), 10.99 (s, 1H), 8.68 (s, 1H), 8.66 (s, 1H), 8.56-7.98 (m, 3H), 7.93-7.88 (m, 3H), 7.84-7.75 (d, 1H),7.73-7.60 (d, 1H).

Example 28A: Preparation of 4-(5-(tert-butoxycarbonylamino)-1-(2-chloro-6-(trifluoromethyl)benzoyl)-1H-pyrrolo[2,3-c]pyridin-3-yl)-3-fluorobenzoic acid (28A).

Scheme AJ



Step 1. 3-bromo-5-chloro-1H-pyrrolo[2,3-c]pyridine (AJ-2). To a stirred solution of 5-chloro-1H-pyrrolo[2,3-c]pyridine (**AJ-1**) (2.0 g, 13.3 mmol) in anhydrous DMF (80 mL) at r.t.was added Br_2 (0.68 mL, 13.3 mmol) dropwise. The solution was stirred at r.t for one hour. The solution was quenched with 10% $Na_2S_2O_3$ solution (100 mL) and diluted with H_2O (400 mL). The aqueous layer was extracted with EtOAc (100 mL x 4) and combined organic layer was washed with H_2O (50 mL x 3) and brine (50 mL x 3) and dried over anhydrous Na_2SO_4. The solution was evaporated and dried over vacuo and 2.9 g product (95%) was collected. LCMS (ESI) calc'd for $C_7H_4BrClN_2$ [M+H]$^+$: 231, found: 231.

Step 2. (3-bromo-5-chloro-1H-pyrrolo[2,3-c]pyridin-1-yl)(2-chloro-6-(trifluoromethyl)phenyl)methanone (AJ-3). To a stirred solution of 3-bromo-5-chloro- 1H-

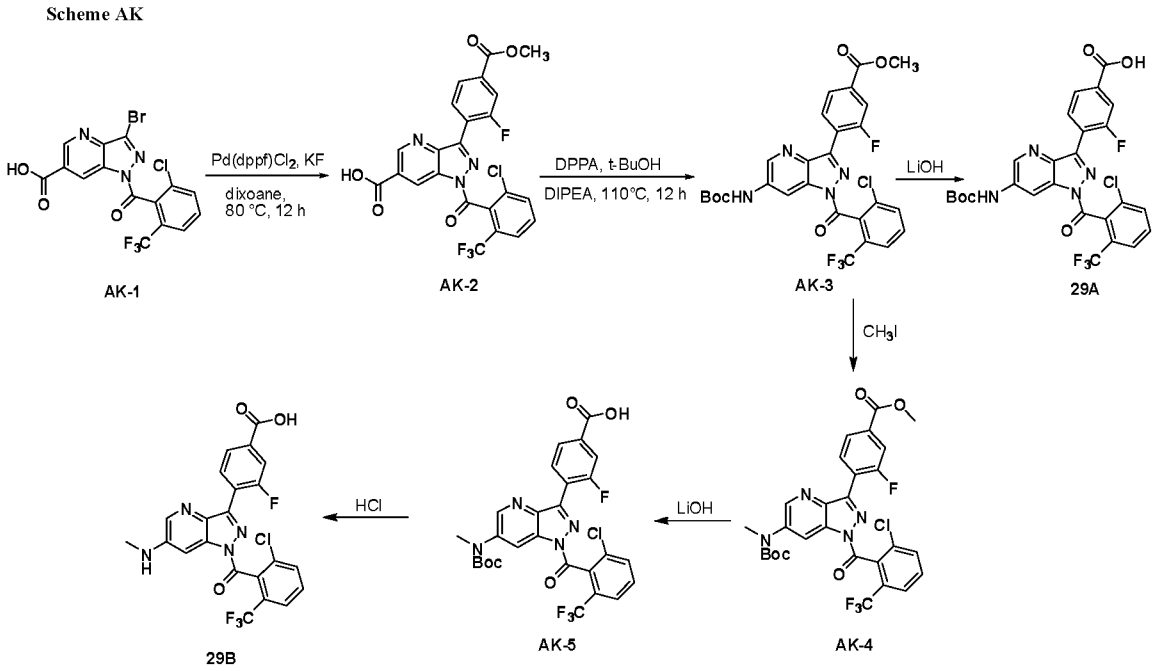
pyrrolo[2,3-c]pyridine (**AJ-2**) (2.9 g, 12.6 mmol) in anhydrous DMF (100 mL) was added 2-chloro-6-(trifluoromethyl)benzoyl chloride (4.6 g, 18.9 mmol) and NaH (60%) (1 g, 25.2 mmol). The solution was stirred at r.t for 2 hours. The solution was quenched with H_2O (400 mL). The suspension was extracted with EtOAc (150 mL x 3). The combined organic layer was washed with H_2O (100 mL x 2) and brine (100 mL x 2) and dried over anhydrous Na_2SO_4. The solution was evaporated and dried over vacuo and 5.7 g product was obtained. LCMS (ESI) calc'd for $C_{15}H_6BrCl_2F_3N_2O$ $[M+H]^+$: 437, found: 437.

Step 3. methyl 4-(5-chloro-1-(2-chloro-6-(trifluoromethyl)benzoyl)-1H-pyrrolo [2,3-c]pyridin-3-yl)-3-fluorobenzoate (AJ-4). To a microwave tube was added (3- bromo-5-chloro-1H-pyrrolo[2,3-c]pyridin-1-yl)(2-chloro-6-(trifluoromethyl)phenyl)-methanone (**AJ-3**) (650 mg, 1.5 mmol), 2-fluoro-4-(methoxycarbonyl)phenylboronic acid (450 mg, 2.25 mmol), $Pd(dppf)Cl_2$ (73 mg, 0.10 mmol), KOAc (300 mg, 3.0 mmol) and dioxane (12 mL). The mixture was microwaved at 110 °C for three hours and filtered through celite. The solvent was evaporated, the cude product was purified with columm chromatography (DCM/Hexanes: 1/1) to give 450 mg product (yield 60%). LCMS (ESI) calc'd for $C_{23}H_{12}Cl_2F_4N_2O_3$ $[M+H]^+$: 511, found: 511.

Step 4. 4-(5-(tert-butoxycarbonylamino)-1-(2-chloro-6-(trifluoromethyl)benzoyl)- 1H-pyrrolo[2,3-c]pyridin-3-yl)-3-fluorobenzoic acid (28A). To a microwave tube was added 4-(5-chloro-1-(2-chloro-6-(trifluoromethyl)benzoyl)-1H-pyrrolo[2,3-c] pyridin-3-yl)-3-fluorobenzoic acid (**AJ-4**) (50 mg, 0.1mmol), $BocNH_2$ (35 mg, 0.3mmol), NaOH (20 mg, 0.5 mmol), $Pd(OAc)_2$ (4 mg, 0.02 mmol), xant-Phos(20 mg, 0.04 mmol), dioxane (1 mL) and H_2O (0.05 mL). The mixture was microwaved at 90 °C for 1 hr. After filtration and evaporation, the crude product was submitted for prep-HPLC purification, which gave 5 mg title product (yield 17%). LCMS (ESI) calc'd for $C_{27}H_{20}ClF_4N_3O_5$ $[M+H]^+$: 578, found: 578; ^{1}HNMR (400MHz, DMSO-d_6) δ 13.40 (bs, 1H), 10.00 (s, 1H), 9.37(s, 1H), 8.02~8.09 (m, 3H), 7.88~7.93 (m, 3H), 7.81~7.84 (d, 1H), 7.70~7.74 (m, 1H), 1.48 (s, 9H).

Example 29A: Preparation of 4-(6-(tert-butoxycarbonylamino)-1-(2-chloro-6-(trifluoromethyl)benzoyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)-3-fluorobenzoic acid (29A)

and 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(methylamino)-1H- pyrazolo[4,3-b]pyridin-3-yl)-3-fluorobenzoic acid (29B)



Step 1. Preparation of 1-(2-chloro-6-(trifluoromethyl)benzoyl)-3-(2-fluoro-4-(methoxycarbonyl)phenyl) -1H-pyrazolo[4,3-b]pyridine-6-carboxylic acid (AK-2). To a mixture of 3-bromo-1-(2-chloro-6-(trifluoromethyl)benzoyl)-1H-pyrazolo[4,3-b] pyridine-6-carboxylic acid (**AK-1**) (224 mg, 0.5 mmol), boric acid (128 mg, 0.60 mmol), $PdCl_2(dppf)_2$ (48 mg, 0.05 mmol) and KF (90 mg, 1.5 mmol) was added dioxane (25 mL) and H_2O (0.5 mL), and the mixture was heated at 90 °C under argon for 16 h. The mixture was cooled down, diluted with CH_2Cl_2 (80 mL). The organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by Prep-TLC (EtOAc) to afford 220 mg (85 %) of the title compound as a white solid. LCMS (ESI) calc'd for $C_{23}H_{12}ClF_4N_3O_5$ $[M+H]^+$: 522.1, found: 522.1.

Step 2. Preparation of methyl 4-(6-(tert-butoxycarbonylamino)-1-(2-chloro-6-(trifluoromethyl)benzoyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)-3-fluorobenzoate (AK-3). To a mixture of 1-(2-chloro-6-(trifluoromethyl)benzoyl)-3-(2-fluoro-4-(methoxycarbonyl)phenyl)-1H-pyrazolo[4,3-b]pyridine-6-carboxylic acid **(AK-2)** (50 mg, 0.1 mmol), DPPA (41 mg, 0.15 mmol), DIPEA (38 mg, 0.3 mmol) and t-BuOH (10 mL) was heated at 90 °C under argon for 16h. The mixture was cooled down, diluted with CH_2Cl_2 (80

mL). The organic layer was separated, washed with brine, dried over Na_2SO_4, concentrated. The residue was purified by Prep-TLC (EtOAc) to afford 38 mg (64 %) of the title compound as a white solid. LCMS (ESI) calc'd for C27H21ClF4N4O5 $[M+H]^+$: 593.1 , found: 593.1.

Step 3. Preparation of 4-(6-(tert-butoxycarbonylamino)-1-(2-chloro-6-(trifluoromethyl)benzoyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)-3-fluorobenzoic acid (29A). To a stirred solution of methyl 4-(6-(tert-butoxycarbonylamino)-1-(2-chloro- 6-(trifluoromethyl)benzoyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)-3-fluorobenzoate (**AK-3**) (80 mg, 0.14 mmol) was added THF (5.0 mL), H_2O (1.0 mL) and $LiOH{\cdot}H_2O$ (57 mg, 1.4 mmol) and the solution was stirred at r.t. overnight. The solution was adjusted to PH 4.0 using 1N HCl and poured into THF (30 mL) and washed with brine (20 mL). The organic layer was dried over Na_2SO_4, the solvent was evaporated and submitted for Prep-HPLC to get 60 mg title product with a yield of 73%. LCMS (ESI) calc'd for $C_{26}H_{19}ClF_4N_4O_5$ $[M+H]^+$: 579.1, found: 579.1; ^{1}HNMR (500MHz, DMSO-d_6) δ 13.75 (bs, 1H),10.35 (s, 1H), 9.25 (s, 1H), 8.81-8.81 (d, 1H), 8.34 (t, 1H), 7.98 (m, 5H), 1.55 (s, 9H).

Step 4. Preparation of methyl 4-(6-(tert-butoxycarbonyl(methyl)amino)-1-(2- chloro-6-(trifluoromethyl)benzoyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)-3-fluorobenzoate (AK-4). To a solution of methyl 4-(6-(tert-butoxycarbonylamino)-1-(2-chloro-6-(trifluoromethyl)benzoyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)-3-fluorobenzoate (**AK-3**) (300 mg, 0.5 mmol) in DMF (10 mL) was added NaH (81 mg, 2 mmol, 60 %) portions over 5 min then stirred at 0 °C for 1 h. And then CH_3I (108 mg, 0.76 mmol) in THF (1 mL) was dropwise by syring, the reaction mixture was stirred at 0°C for 12 h, quenched with ice-water, and the aqueous layer was extracted with CH_2Cl_2 (50 mL x 3). The combined organics were washed with H_2O, brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (Pentane/EtOAc=10/1) to afford 280 mg (91 %) of the title compound. LCMS (ESI) calc'd for $C_{28}H_{23}ClF_4N_4O_5$ $[M+H]^+$: 607, found: 607.

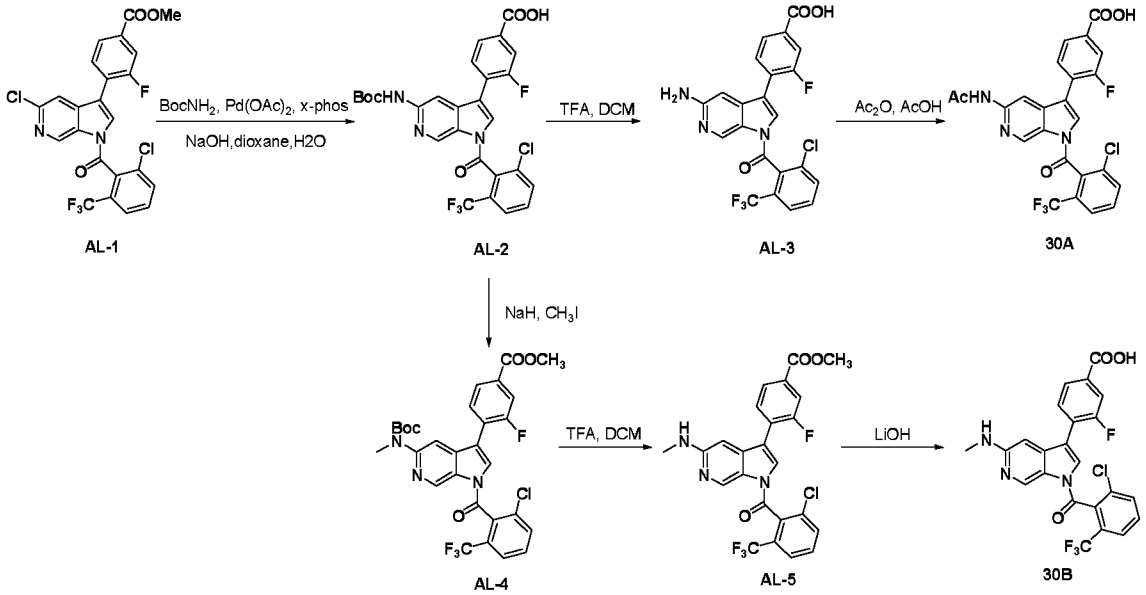
Step 5. Preparation of 4-(6-(tert-butoxycarbonyl(methyl)amino)-1-(2-chloro-6-(trifluoromethyl)benzoyl)- 1H-pyrazolo[4,3-b]pyridin-3-yl)-3-fluorobenzoic acid (AK-5). To a stirred solution of methyl 4-(6-(tert-butoxycarbonyl(methyl)amino)-1- (2-chloro-6-(trifluoromethyl)benzoyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)-3-fluorobenzoate (**AK-4**) (85 mg,

0.14 mmol) was added THF (5.0 mL), H_2O (1.0 mL) and $LiOH{\cdot}H_2O$ (57 mg, 1.4 mmol) and the solution was stirred at r.t. overnight. The solution was adjusted to pH 4.0 using 1N HCl and poured into THF (30 mL), washed with brine (20 mL). The organic layer was dried over Na_2SO_4, the organic solvent was evaporated and submitted for prep-HPLC. 61 mg product was collected. Yield: 71%. LCMS (ESI) calc'd for $C_{27}H_{21}ClF_4N_4O_5$ $[M+H]^+$: 593.1, found: 593.1.

Step 6. Preparation of 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(methyl- amino)-1H-pyrazolo [4,3-b]pyridin-3-yl)-3-fluorobenzoic acid (28B). To a stirred solution of 4-(6-(tert-butoxycarbonyl(methyl)amino)-1-(2-chloro-6-(trifluoromethyl) benzoyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)-3-fluorobenzoic acid (**AK-5**) (100 mg, 0.17 mmol) was added THF (5.0 mL), and 6 N HCl (4 mL) and the solution was stirred at room temperature for 4 h. The solution was adjusted to pH 4.0 using 2N NaOH and poured into THF (30 mL), washed with brine (20 mL). The organic layer was dried over Na_2SO_4, the organic solvent was evaporated and submitted for prep-HPLC. 20 mg product was collected. Yield: 25%. LCMS (ESI) calc'd for $C_{22}H_{13}ClF_4N_4O_3$ $[M+H]^+$: 493.1, found: 493.1; ^{1}HNMR (500MHz, DMSO-d_6) δ 13.74 (bs, 1H), 8.328 (s, 1H), 8.268 (t, 1H), 8.01 (d, 1H), 7.94 (d, 1H), 7.89 (m, 1H), 7.84 (d, 1H), 7.74 (m, 1H), 7.19 (d, 1H), 2.87 (d, 1H).

Example 30A: Preparation of 4-(5-acetamido-1-(2-chloro-6-(trifluoromethyl)- benzoyl)-1H-pyrrolo[2,3-c]pyridin-3-yl)-3-fluorobenzoic acid (30A) and 4-(1-(2- chloro-6-(trifluoromethyl)benzoyl)-5-(methylamino)-1H-pyrrolo[2,3-c]pyridin-3-yl)-3-fluorobenzoic acid (30B)

Scheme AL



Step 1. 4-(5-(tert-butoxycarbonylamino)-1-(2-chloro-6-(trifluoromethyl)benzoyl) -1H-pyrrolo[2,3-c]pyridin-3-yl)-3-fluorobenzoic acid (AL-2). To a stirred solution of methyl 4-(5-chloro-1-(2-chloro-6-(trifluoromethyl)benzoyl)-1H-pyrrolo[2,3-c] pyridin-3-yl)-3-fluorobenzoate (**AL-1**) (550 mg, 1.1 mmol) in dioxane (14 mL) and water (0.5 mL) was added $BocNH_2$ (389 mg, 3.3 mmol), $Pd(OAc)_2$ (50 mg, 0.22 mmol), xant-phos (256 mg, 0.44 mmol) and NaOH (222 mg, 5.5 mmol). The mixture was stirred under Ar at 90 °C for 1 h in the microwave reactor. The mixture was filtered and evaporated, MeOH (5 mL) was added. The resultant solution was submitted for Prep-HPLC under 0.01% TFA, 300 mg solid was obtained, yield: 47%. LCMS (ESI) calc'd for $C_{27}H_{20}ClF_4N_3O_5$ $[M+H]^+$: 578, found: 578.

Step 2. 4-(5-amino-1-(2-chloro-6-(trifluoromethyl)benzoyl)-1H-pyrrolo[2,3-c] pyridin-3-yl)-3-fluorobenzoic acid (AL-3). To a stirred solution of 4-(5-(tert-butoxy carbonylamino)-1-(2-chloro-6-(trifluoromethyl)benzoyl)-1H-pyrrolo[2,3-c]pyridin-3-yl)-3-fluorobenzoic acid (**AL-2**) (40 mg, 0.07 mmol) in DCM (0.5 mL) and TFA (0.5 mL) was stirred under Ar at rt for 5 h. The mixture was evaporated, the crude product was used to the next step directly. LCMS (ESI) calc'd for $C_{22}H_{12}ClF_4N_3O_3$ $[M+H]^+$: 478, found: 478.

Step 3. 4-(5-acetamido-1-(2-chloro-6-(trifluoromethyl)benzoyl)-1H-pyrrolo[2,3-c] pyridin-3-yl)-3-fluorobenzoic acid (30A). To a stirred solution of 4-(5-amino-1-(2- chloro-6-(trifluoromethyl)benzoyl)-1H-pyrrolo[2,3-c]pyridin-3-yl)-3-fluorobenzoic acid (**AL-3**) (30

mg, 0.06 mmol) in Ac_2O (1 mL) was added AcOH (0.2 mL) was stirred under Ar at 100 °C for 1 h. Evaporated the solvent, then added H_2O (1 mL), mixture was stirred at rt for 2 h. The mixture was purified by prep-HPLC under 0.01% TFA twice to give 10 mg product (yield: 24.5%). LCMS (ESI) calc'd for $C_{24}H_{14}ClF_4N_3O_4$ $[M+H]^+$: 520, found: 520; ^{1}HNMR (400MHz, DMSO-d_6) δ 13.37 (bs, 1H), 10.78 (s, 1H), 9.43 (s, 1H), 8.43 (s, 1H), 8.04 (dd, 2H), 7.93~7.87 (m, 3H), 7.81 (d, 1H), 7.71 (t, 1H), 2.12 (s, 3H).

Step 4. Methyl 4-(5-(tert-butoxycarbonyl(methyl)amino)-1-(2-chloro-6-(trifluoromethyl)benzoyl)-1H-pyrrolo[2,3-c]pyridin-3-yl)-3-fluorobenzoate (AL-4). To a stirred solution of 4-(5-acetamido-1-(2-chloro-6-(trifluoromethyl)benzoyl)-1H- pyrrolo[2,3-c]pyridin-3-yl)-3-fluorobenzoic acid (**AL-2**) (100 mg, 0.17 mmol) in anhydrous DMF (5 mL) at r.t. was added NaH (42 mg, 60%, 1 mmol) and then MeI (98 mg, 0.69 mmol). The solution was stirred at r.t for 3 hours. Ethyl Acetate (200 mL) was added and the solution was washed with brine (70 mL x 2). The solution was evaporated and 120 mg crude product was got and it was used in the next step without further purification. LCMS (ESI) calc'd for $C_{29}H_{24}ClF_4N_3O_5$ $[M+H]^+$: 606, found: 606.

Step 5. Methyl 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-5-(methylamino)-1H -pyrrolo[2,3-c]pyridin-3-yl)-3-fluorobenzoate (AL-5). To a stirred solution of methyl 4-(5-(tert-butoxycarbonyl(methyl)amino)-1-(2-chloro-6-(trifluoromethyl)- benzoyl)-1H-pyrrolo[2,3-c]pyridin-3-yl)-3-fluorobenzoate (**AL-4**) (120 mg, as generated from step 4) in DCM (4 mL) was added TFA (2 mL) under N_2. The solution was stirred at r.t. for 3 hours and evaporated. 70 mg crude product was collected. It was used for next step without further purification. LCMS (ESI) calc'd for $C_{24}H_{16}ClF_4N_3O_3$ $[M+H]^+$: 506, found: 506.

Step 6. 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-5-(methylamino)-1H–pyrrolo [2,3-c]pyridin-3-yl)-3-fluorobenzoic acid (30B). To a stirred solution of methyl 4- (1-(2-chloro-6-(trifluoromethyl)benzoyl)-5-(methylamino)-1H-pyrrolo[2,3-c]pyridin-3-yl)-3-fluorobenzoate (**AL-5**) (71mg, as generated from step 5) in THF (2 mL) was added H_2O (2 mL) and $LiOH{\cdot}H_2O$ (58 mg, 1.4 mmol). The solution was stirred at r.t for overnight and adjusted to PH~2 using 1N HCl. The upper layer was evaporated and submitted for Prep-

HPLC (CH_3CN/H_2O), which gave 52 mg product. Yield for three steps 60%. LCMS (ESI) calc'd for $C_{23}H_{14}ClF_4N_3O_3$ $[M+H]^+$: 492, found: 492.

Biological Assays

The compounds of the invention inhibit RORgammaT activity. Activation of RORgammaT activity can be measured using e.g. biochemical TR-FRET assay. In such an assay, interaction of cofactor-derived peptides with human RORgammaT-Ligand Binding Domain (LBD) can be measured. The TR-FRET technique is a sensitive biochemical proximity assay that will give information concerning the interaction of a ligand with the LBD, in the presence of cofactor derived peptides (Zhou et al., Methods 25:54-61, 2001).

To identify novel antagonists of RORgammaT, an assay was developed which employs the interaction of RORgammaT with its co-activator peptide SRC1_2. This peptide mimics the recruitment of co-activators to RORgammaT through its interaction with the LXXLL (eg NR box) motifs (Xie et al., J. Immunol. 175: 3800-09, 2005; Kurebayashi et al., Biochem. Biophys. Res. Commun. 315: 919-27, 2004; Jin et al., Mol. Endocrinology 24:923-29, 2010). The RORγ-Ligand Binding Domain TR-FRET Assay was run according to the following protocol.

HIS-tagged RORγ-LBD protein was expressed in SF9 cells using a baculovirus expression system. The RORγ-LBD protein was purified by glutathione sepharose chromatography. Separately, SF9 cells not expressing any recombinant protein were lysed and the lysate was added to the purified RORγ-LBD at 0.25 µl lysate (from 10,000 SF9 cells)/nM purified protein. The mixture was then diluted in assay buffer (50 mM Tris pH 7.0, 50 mM KCl, 1 mM EDTA, 0.1 mM DTT) to obtain RORγ-LBD final concentration of 3 nM in 384-well assay plate.

Compounds to be tested were injected to the assay plate using Acoustic Droplet Ejection technology by Echo 550 liquid handler (Labcyte, CA).

A stock of biotinylated-LXXLL peptide from coactivator SRC1 (Biotin-CPSSHSSLTERHKILHRLLQEGSPS) was prepared in assay buffer and added to each well (100 nM final concentration). A solution of Europium tagged anti-HIS antibody (1.25 nM final concentration) and APC conjugated streptavidin (8 nM final concentration) were also added to each well.

The final assay mixture was incubated for overnight at 4°C, and the fluorescence signal was measured on an Envision plate reader: (Excitation filter = 340 nm; APC emission = 665 nm; Europium emission = 615 nm; dichroic mirror = D400/D630; delay time = 100 μs, integration time = 200 μs).IC50 values for test compounds were calculated from the quotient of the fluorescence signal at 665 nm divided by the fluorescence signal at 615 nm.

BIOLOGICAL DATA

The following table tabulates the biological data disclosed for the instant invention.

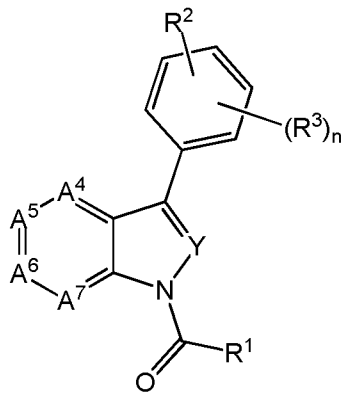
Examples	Fret IC_{50} (nM)
1A	52
1B	49
1D	>10000
1H	39
1I	4324
1J	5569
1K	>10000
1L	>10000
1M	335
1N	>10000
1O	54
1P	58
1Q	>10000
1R	969
1S	1477
1T	159
1U	>10000
2A	16
2B	15
2C	4
3A	1466
3B	1653
4A	500
4B	1326

4D	130
4F	23
4G	1060
4H	4321
5A	255
5B	153
5C	314
5D	493
5E	64
5F	48
5G	1502
5H	491
6A	85
6B	25
6C	22
6D	1511
6E	224
7A	69
7B	317
7C	87
7D	14
8A	143
8B	283
8C	218
8D	57
9A	63
9B	14
11A	48
12A	105
13A	20
14A	137
15A	241
16A	21
17A	12
18A	24
18B	26

19A	888
20A	120
21A	5
21B	17
21C	15
22A	754
22B	5606
22C	>10000
22D	155
22E	1441
22F	39
22G	356
22H	37
22I	274
22J	6391
23A	>10000
23B	>10000
23C	>10000
23D	>10000
23E	>10000
23F	>10000
23G	>10000
23H	>10000
23I	>10000
23J	>10000
23K	>10000
26A	876
27A	53
28A	182
29A	191
29B	13
30A	6
30B	209

CLAIMS

1. A compound according to Formula I



I

or a pharmaceutically acceptable salt or solvate thereof wherein,

Y is CH, CR^a, or N;

n = 0, 1, 2, 3 or 4;

A^4 is CR^4 or N,

A^5 is CR^5 or N,

A^6 is CR^6 or N,

A^7 is CR^7 or N,

with the proviso that no more than one or two of A^4-A^7 can be N;

R^a is (C_{1-4})alkyl or (C_{3-7})cycloalkyl;

R^1 is

(i) (C_{3-12})carbocyclyl(C_{0-4})alkyl;

(ii) a 4- to 12-membered heterocyclyl(C_{0-4})alkyl, or

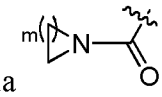
(iii) (C_{1-4})alkoxy,

each optionally substituted with one, two, three, four or five R^8;

R^2 is hydroxycarbonyl, hydroxycarbonyl(C_{1-10})alkyl, (C_{1-10})alkylsulfoxyaminocarbonyl, or carbamoyl;

R^3 is hydrogen, halogen, cyano, nitro, hydroxy, (C_{1-4})alkylcarbonyloxy, (C_{1-4})

alkylsulfonylamino, (C_{1-4}) alkylcarbonylamino, (C_{0-4}) alkylamino, (C_{1-4})alkyl, or (C_{1-4})alkoxy, wherein (C_{1-4})alkyl and (C_{1-4})alkoxy are optionally substituted with one or more halogen;

R^4-R^7 independently are hydrogen, halogen, amino, cyano, hydroxy, (C_{1-3})alkoxy, (C_{1-4})alkyl, (C_{0-10})alkylaminocarbonyl, (C_{0-6})alkyoxycarbonylamino, (di)(C_{1-6})alkylaminocarbonyl, (C_{1-6})alkylcarbonylamino, (C_{1-4})alkylamino, amino(C_{1-4})alkyl or formaldehyde, wherein (C_{1-3})alkoxy, (C_{1-4})alkyl, (C_{0-10})alkyl)aminocarbonyl, (di)(C_{1-6})alkylaminocarbonyl, (C_{1-4})alkylamino and amino(C_{1-4})alkyl are optionally substituted with one or more halogen, hydroxyl or (C_{1-3})alkoxy; or a group having the formula  , optionally substituted with one or more of the following: (C_{1-10})alkyl, halogen, amino, cyano, hydroxy, (C_{1-3})alkoxy, and wherein m is 1, 2, 3, or 4;

R^6 is, additionally,

(i) (C_{3-7})cycloalkyl or (C_{3-5})heterocycloalkyl, both optionally substituted with one or more groups selected from halogen, amino, amino(C_{1-4})alkyl, cyano, nitro, hydroxyl, oxo (=O), $H_2NC(O)$, (C_{1-3})alkoxycarbonyl, (di)(C_{1-6})alkylaminocarbonyl, (C_{1-4})alkyl or (C_{1-3})alkoxy, wherein (C_{1-3})alkoxycarbonyl, (di)(C_{1-6})alkylaminocarbonyl, (C_{1-4})alkyl and (C_{1-3})alkoxy are optionally substituted with one or more halogen, amino or hydroxyl;

(ii) (C_{2-9})heteroaryl, optionally substituted with one or more groups selected from halogen, amino, amino(C_{1-4})alkyl, cyano, nitro, hydroxyl, oxo (=O), $H_2NC(O)$, (C_{1-3})alkoxycarbonyl, (di)(C_{1-6})alkylaminocarbonyl, (C_{1-4})alkyl or (C_{1-3})alkoxy, wherein (C_{1-3})alkoxycarbonyl, (di)(C_{1-6})alkylaminocarbonyl, (C_{1-4})alkyl and (C_{1-3})alkoxy are optionally substituted with one or more halogen, amino or hydroxyl;

(iii) (C_{6-14})aryl, optionally substituted with one or more groups selected from halogen, amino, amino(C_{1-4})alkyl, cyano, nitro, hydroxyl, oxo (=O), $H_2NC(O)$, (C_{1-3})alkoxycarbonyl, (di)(C_{1-6})alkylaminocarbonyl, (C_{1-4})alkyl or (C_{1-3})alkoxy, wherein (C_{1-3})alkoxycarbonyl, (di)(C_{1-6})alkylaminocarbonyl, (C_{1-4})alkyl and (C_{1-3})alkoxy are optionally substituted with one or more halogen, amino or hydroxyl;

(iv) (C_{3-5})heterocycloalkylcarbonyl, optionally substituted with one or more groups selected from halogen, amino, amino(C_{1-4})alkyl, cyano, nitro, hydroxyl, oxo (=O), $H_2NC(O)$, (C_{1-3})alkoxycarbonyl, (di)(C_{1-6})alkylaminocarbonyl, (C_{1-4})alkyl or (C_{1-}

$_3$)alkoxy, wherein (C_{1-3})alkoxycarbonyl, (di)(C_{1-6})alkylaminocarbonyl, (C_{1-4})alkyl and (C_{1-3})alkoxy are optionally substituted with one or more halogen, amino or hydroxyl;

(v) (C_{3-5})heterocycloalkylamino, optionally substituted with one or more groups selected from halogen, amino, amino(C_{1-4})alkyl, cyano, nitro, hydroxyl, oxo (=O), $H_2NC(O)$, (C_{1-3})alkoxycarbonyl, (di)(C_{1-6})alkylaminocarbonyl, (C_{1-4})alkyl or (C_{1-3})alkoxy, wherein (C_{1-3})alkoxycarbonyl, (di)(C_{1-6})alkylaminocarbonyl, (C_{1-4})alkyl and (C_{1-3})alkoxy are optionally substituted with one or more halogen, amino or hydroxyl;

(vi) (C_{3-5})cycloalkylaminocarbonyl, optionally substituted with one or more groups selected from halogen, amino, amino(C_{1-4})alkyl, cyano, nitro, hydroxyl, oxo (=O), $H_2NC(O)$, (C_{1-3})alkoxycarbonyl, (di)(C_{1-6})alkylaminocarbonyl, (C_{1-4})alkyl or (C_{1-3})alkoxy, wherein (C_{1-3})alkoxycarbonyl, (di)(C_{1-6})alkylaminocarbonyl, (C_{1-4})alkyl and (C_{1-3})alkoxy are optionally substituted with one or more halogen, amino or hydroxyl;

(vii) (C_{3-5})cycloalkylcarbonylamino, optionally substituted with one or more groups selected from halogen, amino, amino(C_{1-4})alkyl, cyano, nitro, hydroxyl, oxo (=O), $H_2NC(O)$, (C_{1-3})alkoxycarbonyl, (di)(C_{1-6})alkylaminocarbonyl, (C_{1-4})alkyl or (C_{1-3})alkoxy, wherein (C_{1-3})alkoxycarbonyl, (di)(C_{1-6})alkylaminocarbonyl, (C_{1-4})alkyl and (C_{1-3})alkoxy are optionally substituted with one or more halogen, amino or hydroxyl;

(viii) (C_{3-5})cycloalkyl(C_{1-4})alkyl, optionally substituted with one or more groups selected from halogen, amino, amino(C_{1-4})alkyl, cyano, nitro, hydroxyl, oxo (=O), $H_2NC(O)$, (C_{1-3})alkoxycarbonyl, (di)(C_{1-6})alkylaminocarbonyl, (C_{1-4})alkyl or (C_{1-3})alkoxy, wherein (C_{1-3})alkoxycarbonyl, (di)(C_{1-6})alkylaminocarbonyl, (C_{1-4})alkyl and (C_{1-3})alkoxy are optionally substituted with one or more halogen, amino or hydroxyl;

(ix) (C_{3-5})cycloalkylamino, optionally substituted with one or more groups selected from halogen, amino, amino(C_{1-4})alkyl, cyano, nitro, hydroxyl, oxo (=O), $H_2NC(O)$, (C_{1-3})alkoxycarbonyl, (di)(C_{1-6})alkylaminocarbonyl, (C_{1-4})alkyl or (C_{1-3})alkoxy, wherein (C_{1-3})alkoxycarbonyl, (di)(C_{1-6})alkylaminocarbonyl, (C_{1-4})alkyl

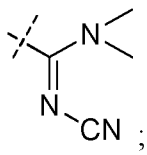
and (C_{1-3})alkoxy are optionally substituted with one or more halogen, amino or hydroxyl;

(x) (C_{3-5})cycloalkylcarbonyl, optionally substituted with one or more groups selected from halogen, amino, amino(C_{1-4})alkyl, cyano, nitro, hydroxyl, oxo (=O), $H_2NC(O)$, (C_{1-3})alkoxycarbonyl, (di)(C_{1-6})alkylaminocarbonyl, (C_{1-4})alkyl or (C_{1-3})alkoxy, wherein (C_{1-3})alkoxycarbonyl, (di)(C_{1-6})alkylaminocarbonyl, (C_{1-4})alkyl and (C_{1-3})alkoxy are optionally substituted with one or more halogen, amino or hydroxyl;

(xi) (C_{2-9})heteroaryl(C_{1-4})alkyl, optionally substituted with one or more groups selected from halogen, amino, amino(C_{1-4})alkyl, cyano, nitro, hydroxyl, oxo (=O), $H_2NC(O)$, (C_{1-3})alkoxycarbonyl, (di)(C_{1-6})alkylaminocarbonyl, (C_{1-4})alkyl or (C_{1-3})alkoxy, wherein (C_{1-3})alkoxycarbonyl, (di)(C_{1-6})alkylaminocarbonyl, (C_{1-4})alkyl and (C_{1-3})alkoxy are optionally substituted with one or more halogen, amino or hydroxyl;

(xii) (C_{2-9})heteroarylcarbonyl, optionally substituted with one or more groups selected from halogen, amino, amino(C_{1-4})alkyl, cyano, nitro, hydroxyl, oxo (=O), $H_2NC(O)$, (C_{1-3})alkoxycarbonyl, (di)(C_{1-6})alkylaminocarbonyl, (C_{1-4})alkyl or (C_{1-3})alkoxy, wherein (C_{1-3})alkoxycarbonyl, (di)(C_{1-6})alkylaminocarbonyl, (C_{1-4})alkyl and (C_{1-3})alkoxy are optionally substituted with one or more halogen, amino or hydroxyl;

(xiii)



;

(xiv) (C_{2-4})alkynyl, optionally substituted with one or more (C_{1-4})alkyl, which (C_{1-4})alkyl may be substituted with hydroxyl or amino; or

(xv) (C_{1-6})alkoxycarbonylamino,
(C_{1-6})alkylcarbonylamino,
(C_{1-6})alkylsulfonylamino(C_{0-4})alkyl,
(C_{1-6})alkylaminocarbonylamino,
(C_{1-6})alkyoxycarbonylamino(C_{0-4})alkyl,
Hydroxycarbonyl(C_{1-4})alkylamino,

Hydroxycarbonyl, or

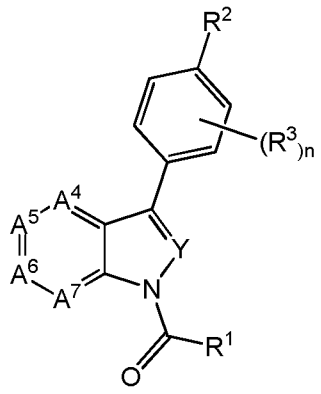
(C_{1-6})alkylamino,

each optionally substituted with one or more (C_{1-4})alkyl, hydroxyl or amino;

R^8 is halogen, cyano, amino, nitro, hydroxy, oxo(=O), $H_2NC(O)$-, (C_{1-3})alkoxycarbonyl, (di)(C_{1-6})alkylaminocarbonyl, (C_{1-4})alkyl, (C_{3-7})cycloalkyl, (C_{3-5})heterocycloalkyl, (C_{1-4})alkenyl, (C_{3-6})cycloalkoxy or (C_{1-3})alkoxy, wherein (C_{1-3})alkoxycarbonyl, (di)(C_{1-6})alkylaminocarbonyl, (C_{1-4})alkyl and (C_{1-3})alkoxy are optionally substituted with one, two or three halogens; and

x is 0, 1, 2, 3, 4 or 5.

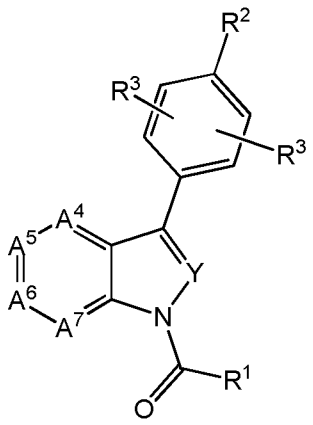
2. The compound of claim 1 having Formula Ia



Ia

and a pharmaceutically acceptable salt or solvate thereof.

3. The compound of claim 1 having Formula Ib

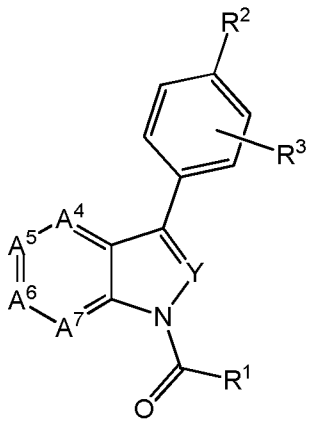


Ib

and a pharmaceutically acceptable salt or solvate thereof.

4. The compound of claim 3, wherein Y is N.

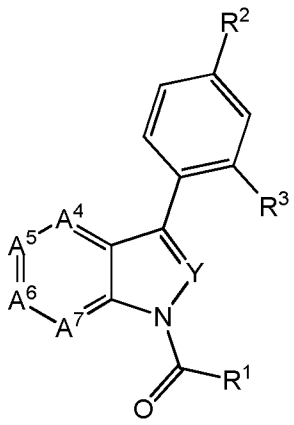
5. The compound of claim 3 having Formula Ic



Ic

and a pharmaceutically acceptable salt or solvate thereof.

6. The compound of claim 5 having Formula Id

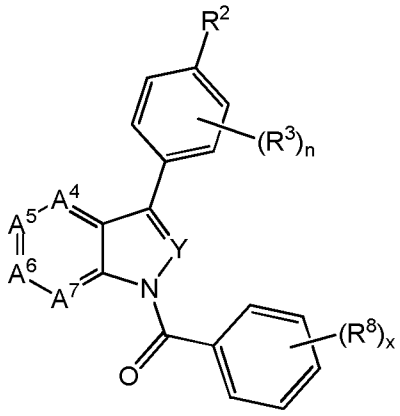


Id

and a pharmaceutically acceptable salt or solvate thereof.

7. The compound of claim 6, wherein Y is N.

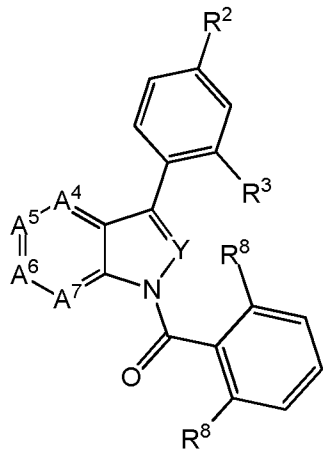
8. The compound of claim 2 having Formula Ie



Ie

and a pharmaceutically acceptable salt or solvate thereof.

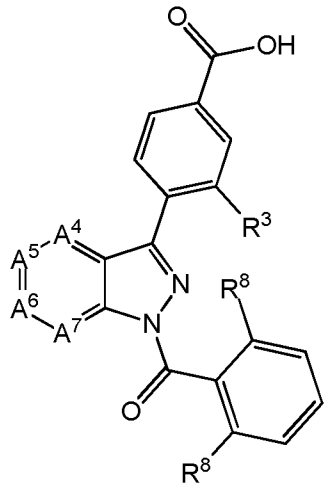
9. The compound of claim 8 having Formula If



If

and a pharmaceutically acceptable salt or solvate thereof.

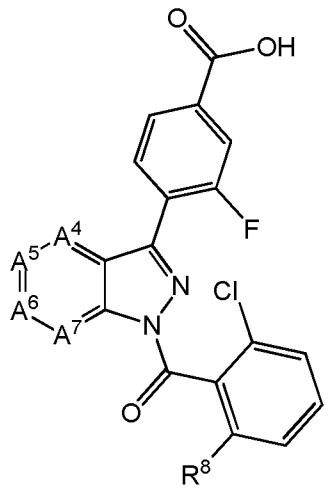
10. The compound of claim 9 having Formula Ig



Ig

and a pharmaceutically acceptable salt or solvate thereof.

11. The compound of claim 10 having Formula Ih



Ih

and a pharmaceutically acceptable salt or solvate thereof.

12. The compound of claim 1, wherein A^4, A^5, A^6, A^7 are selected from the group consisting of: (i) CR^4, CR^5, CR^6, CR^7; (ii) N, CR^5, CR^6, CR^7; and (iii) CR^4, N, CR^6, CR^7.

13. The compound of claim 12, wherein A^4, A^5, A^6, A^7 is (i) CR^4, CR^5, CR^6, CR^7, or (ii) N, CR^5, CR^6, CR^7; and Y is N.

14. The compound of claim 1, wherein R^1 is
(i) (C_{3-7})cycloalkyl or (C_{3-5})heterocycloalkyl, both optionally substituted with one or more R^8;
(ii) (C_{2-9})heteroaryl(C_{0-4})alkyl, optionally substituted with one or more R^8; or
(iii) (C_{6-14})aryl(C_{0-4})alkyl, optionally substituted with one or more R^8.

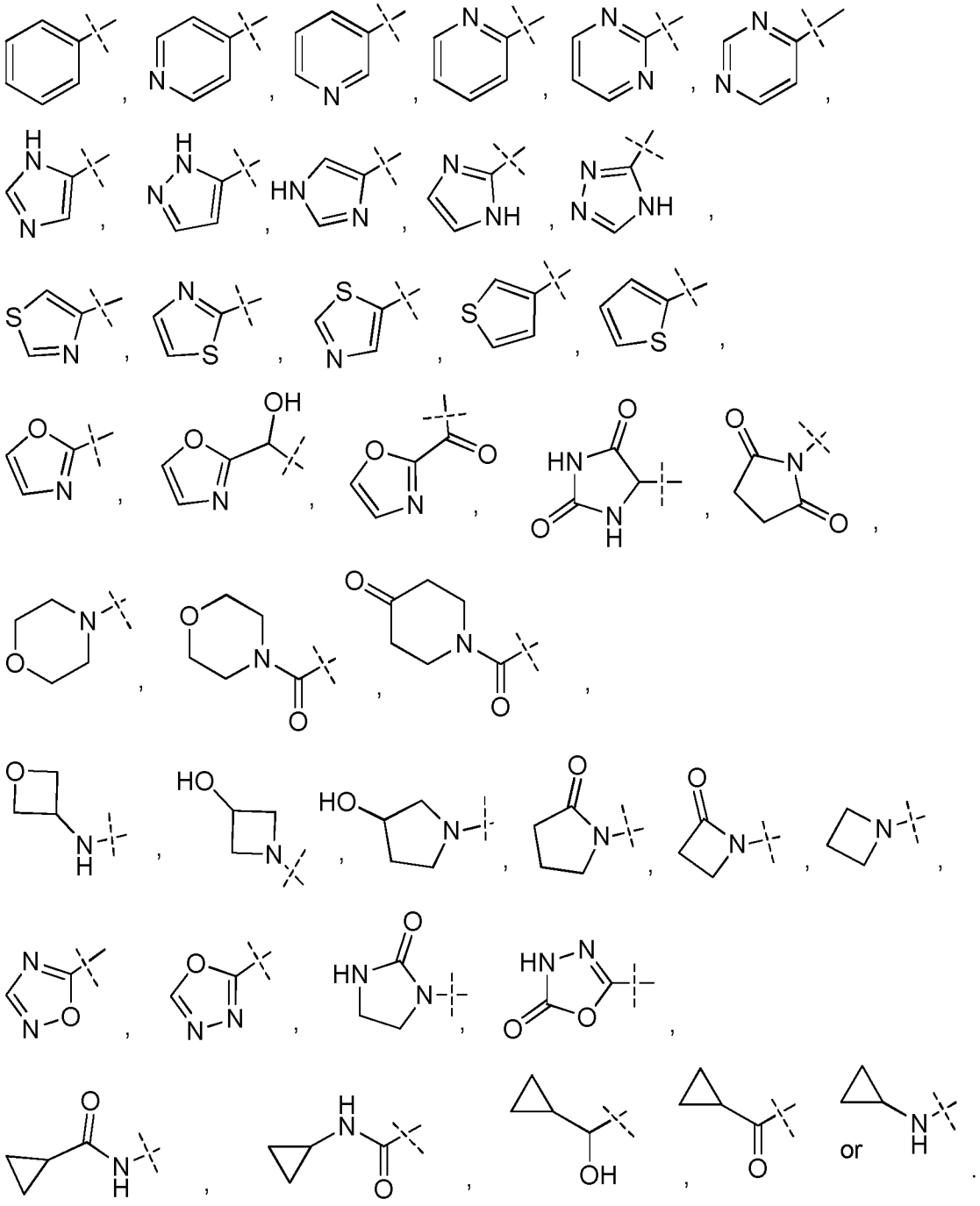
15. The compound of claim 14, wherein R^1 is (i) (C_{2-9})heteroaryl, or (ii) (C_{6-14})aryl, optionally substituted with one, two, three, four or five R^8.

16. The compound of claim 15, wherein R^1 is (C_{6-14})aryl, optionally substituted with one or two R^8.

17. The compound of claim 16, wherein R^1 is phenyl, optionally substituted with one or two R^8.

18. The compound of claim 17, wherein R^2 is C(O)OH.

19. The compound of claim 1, wherein R^6 is



20. A compound according to claim 1 selected from:

(E)-4-(1-(2-chloro-6-(prop-1-enyl)benzoyl) -1H-pyrazolo[4,3-b]pyridin-3-yl)-3-fluorobenzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-4- formyl-1H-indazol-3-yl)benzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-1H- pyrazolo[4,3-b]pyridin-3-yl)-1H-indazole-7-carboxylic acid;

4-(1-(2-chloro-6-cyclopropoxybenzoyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)benzoic acid;

3-fluoro-4-(1-(2-phenylpropanoyl)-1H-indazol-3-yl)benzoic acid;

3-fluoro-4-[1-(methoxyacetyl)-1H-indazol-3-yl]benzoic acid;

3-fluoro-4-[1-(pyridin-3-ylcarbonyl)-1Hindazol-3-yl]benzoic acid;

3-fluoro-4-{1-[(2-oxopyrrolidin-1-yl)acetyl]-1Hindazol-3-yl}benzoic acid;

3-fluoro-4-[1-(naphthalen-1-ylcarbonyl)-1Hindazol-3-yl]benzoic acid;

3-fluoro-4-{1-[(1-methyl-1H-indol-2-yl)carbonyl]-1Hindazol-3-yl}benzoic acid;

4-{1-[(2-bromo-3-methylphenyl)carbonyl]-1H-indazol-3-yl}-3-fluorobenzoic acid;

4-[1-(2,3-dihydro-1H-inden-4-ylcarbonyl)-1Hindazol-3-yl]-3-fluorobenzoic acid;

4-(1-{[3-(tertbutoxycarbonyl)-3-azabicyclo[3.1.0]hex-6-yl]carbonyl}-1H-indazol-3-yl)-3-fluorobenzoic acid;

4-[1-(2,3-dihydro-1-benzofuran-7-ylcarbonyl)-1Hindazol-3-yl]-3-fluorobenzoic acid;

4-[1-(1-benzofuran-7-ylcarbonyl)-1Hindazol-3-yl]-3-fluorobenzoic acid;

4-{1-[(2-bromo-3-chlorophenyl)carbonyl]-1H-indazol-3-yl}-3-fluorobenzoic acid;

3-fluoro-4-(1-(tetrahydrofuran-2-carbonyl)-1H-indazol-3-yl)benzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6- (morpholine-4-carbonyl)-1H-indazol-3-yl)benzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-((2S,6R)-2,6-dimethylmorpholine-4-carbonyl)-1H-indazol-3-yl)-3-fluorobenzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(4-oxopiperidine-1-carbonyl)-1H-indazol-3-yl)-3-fluorobenzoic acid;

2-acetamido-4-(1-(2-chloro-6-(trifluoromethyl) benzoyl)-1H-indazol -3-yl)benzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)-2-(methylsulfonamido)benzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl) benzoyl)-6- (3-hydroxyazetidin-1-yl)-1H-indazol-3-yl)benzoic acid;

4-(6-(azetidin-1-yl)-1-(2-chloro-6-(trifluoromethyl)benzoyl)-1H-indazol-3-yl)-3-fluorobenzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(cyclopropylamino)-1H-indazol-3-yl)-3-fluorobenzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(oxetan-3-ylamino)-1H-indazol-3-yl)-3-fluorobenzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(3-hydroxypyrrolidin-1-yl)-1H-indazol-3-yl)-3-fluorobenzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-morpholino-1H-indazol-3-yl)benzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6- (methoxycarbonylamino)-1H-indazol-3-yl)-3-fluorobenzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(N- methylacetamido)-1H-indazol-3-yl)-3-fluorobenzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(cyclopropanecarboxamido)-1H-indazol-3-yl)-3-fluorobenzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(methylsulfonamido)-1H-indazol-3-yl)-3-fluorobenzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(3-methylureido)-1H-indazol-3-yl)-3-fluorobenzoic acid;

4-(6-acetamido-1-(2-chloro-6-(trifluoromethyl)benzoyl)-1H-indazol-3-yl)-3-fluorobenzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(N-methylmethylsulfonamido)-1H-indazol-3-yl)-3-fluorobenzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(1,3-dimethylureido)-1H-indazol-3-yl)-3-fluorobenzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(2-oxo- imidazolidin-1-yl)-1H-indazol-3-yl)-3-fluorobenzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6- (2-oxoazetidin-1-yl)-1H-indazol-3-yl)-3-fluorobenzoic acid;

4-(6-(2-carboxyethylamino)-1-(2-chloro-6- (trifluoromethyl)benzoyl)-1H-indazol-3-yl)-3-fluorobenzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(3-methyl-2-oxoimidazolidin-1-yl)-1H-indazol-3-yl)-3-fluorobenzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(2-oxopyrrolidin-1-yl)-1H-indazol-3-yl)-3-fluorobenzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(mor pholine-4-carbonyl)-1H-indazol-3-yl)benzoic acid;

3-(4-carboxyphenyl)-1-(2-chloro-6-(trifluoromethyl) benzoyl)-1H-indazole-6-carboxylic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(cyclopropylcarbamoyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)-3-fluorobenzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(cyclopropyl(methyl)carbamoyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)-3-fluorobenzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6- (cyclo Propyl (hydroxy)methyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)-3-fluorobenzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(cyclop ropane-carbonyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)-3-fluorobenzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(hydroxy(oxazol-2-yl)methyl)-1H-pyrazolo[4,3-b]pyridine-3-yl)-3-fluorobenzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(oxazole-2-carbonyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)-3-fluorobenzoic acid;

sodium 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(5-methyloxazol-2-yl)-1H-indazol-3-yl)benzoate;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(5-methyloxazol-2-yl)-1H-indazol-3-yl)-3-fluorobenzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(3-hydroxyprop-1-ynyl)-1H-indazol-3-yl)benzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(3-hydroxybut-1-ynyl)-1H-indazol-3-yl)-3-fluorobenzoic acid;

4-(6-(3-aminoprop-1-ynyl)-1-(2-chloro-6-(trifluo romethyl)benzoyl)-1H-indazol-3-yl)-3-fluorobenzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl) -6-ethynyl-1H-indazol-3-yl)benzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(3-methyl-1,2,4-oxadiazol-5-yl)-1H-indazol-3-yl)-3-fluorobenzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(5-(hydroxymethyl)oxazol-2-yl)-1H-indazol-3-yl)-3-fluorobenzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(1-methyl-1H-imidazol-4-yl)-1H-indazol-3-yl)-3-fluorobenzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(oxazol-2-yl)-1H-indazol-3-yl)-3-fluorobenzoic acid;

4-(6-(5-bromooxazol-2-yl)-1-(2-chloro-6-(trifluoromethyl)benzoyl)-1H-indazol-3-yl)-3-fluorobenzoic acid;

(E)-4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(N'-cyano-N,N-dimethylcarbamimidoyl)-1H-indazol-3-yl)-3-fluorobenzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-1H-indazol-3-yl)-3-fluorobenzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(4H-1,2,4-triazol-3-yl)-1H-indazol-3-yl)-3-fluorobenzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(5-methyl-1,3,4-oxadiazol-2-yl)-1H-indazol-3-yl)-3-fluorobenzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(1-methyl-1H-imidazol-2-yl)-1H-indazol-3-yl)-3-fluorobenzoic acid;

4-(1-(2-chloro-6-trifluorobenzoyl)-6-(thiazol-2-yl)-1H-indazol-3-yl)benzoic acid;

4-[1-{[2-chloro-6-(trifluoromethyl)phenyl]carbonyl}-6-(1-methyl-1H-imidazol-5-yl)-1H-indazol-3-yl]benzoic acid;

4-[1-{[2-chloro-6-(trifluoromethyl)phenyl]carbonyl}-6-(5-methylthiophen-3-yl)-1H-indazol-3-yl]benzoic acid;

4-(1-{[2-chloro-6-(trifluoromethyl)phenyl]carbonyl}-6-pyrimidin-2-yl-1H-indazol-3-yl)benzoic acid;

4-(1-{[2-chloro-6-(trifluoromethyl)phenyl]carbonyl}-6-pyrimidin-4-yl-1H-indazol-3-yl)benzoic acid;

4-[1-{[2-chloro-6-(trifluoromethyl)phenyl]carbonyl}-6-(1-methyl-1H-imidazol-4-yl)-1H-indazol-3-yl]benzoic acid;

4-[1-{[2-chloro-6-(trifluoromethyl)phenyl]carbonyl}-6-(1,3-thiazol-4-yl)-1H-indazol-3-yl]benzoic acid;

4-(6-[4-(aminomethyl)pyridin-2-yl]-1-{[2-chloro-6-(trifluoromethyl)phenyl]carbonyl}-1H-indazol-3-yl)benzoic acid;

4-(1-{[2-chloro-6-(trifluoromethyl)phenyl]carbonyl}-6-pyridin-2-yl-1H-indazol-3-yl)benzoic acid;

4-[1-{[2-chloro-6-(trifluoromethyl)phenyl]carbonyl}-6-(1,3-thiazol-5-yl)-1H-indazol-3-yl]benzoic acid;

4-(1-(2-chloro-6-trifluorobenzoyl)-6-(thiazol-2-yl)-1H-indazol-3-yl)benzoic acid;

4-(1-{[2-chloro-6-(trifluoromethyl)phenyl]carbonyl}-6-pyridin-4-yl-1H-indazol-3-yl)benzoic acid;

4-[1-{[2-chloro-6-(trifluoromethyl)phenyl]carbonyl}-6-(4-cyanophenyl)-1H-indazol-3-yl]benzoic acid;

4-[1-{[2-chloro-6-(trifluoromethyl)phenyl]carbonyl}-6-(3-cyanophenyl)-1H-indazol-3-yl]benzoic acid;

4-[1-{[2-chloro-6-(trifluoromethyl)phenyl]carbonyl}-6-(2-cyanophenyl)-1H-indazol-3-yl]benzoic acid;

4-[1-{[2-chloro-6-(trifluoromethyl)phenyl]carbonyl}-6-(2-fluorophenyl)-1H-indazol-3-yl]benzoic acid;

4-[1-{[2-chloro-6-(trifluoromethyl)phenyl]carbonyl}-6-(3-fluorophenyl)-1H-indazol-3-yl]benzoic acid;

4-[1-{[2-chloro-6-(trifluoromethyl)phenyl]carbonyl}-6-(4-fluorophenyl)-1H-indazol-3-yl]benzoic acid;

4-[1-{[2-chloro-6-(trifluoromethyl)phenyl]carbonyl}-6-(1-methyl-1H-pyrazol-5-yl)-1H-indazol-3-yl]benzoic acid;

methyl 4-(1-(2-chloro-6-trifluorobenzoyl)-6-(4-hydroxyphenyl)-1H-indazol-3-yl)benzoate;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6- (methylsulfonamidomethyl)-1H-indazol-3-yl)benzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(2,5- dioxoimidazolidin-4-yl)-1H-indazol-3-yl)-3-fluorobenzoic acid;

4-(5-(tert-butoxycarbonylamino)-1-(2-chloro-6- (trifluoromethyl)benzoyl)-1H-pyrrolo[2,3-c]pyridin-3-yl)-3-fluorobenzoic acid;

4-(6-(tert-butoxycarbonylamino)-1-(2-chloro-6-(trifluoromethyl)benzoyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)-3-fluorobenzoic acid;

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(methylamino)-1H-pyrazolo[4,3-b]pyridin-3-yl)-3-fluorobenzoic acid;

4-(5-acetamido-1-(2-chloro-6-(trifluoromethyl)-benzoyl)-1H-pyrrolo[2,3-c]pyridin-3-yl)-3-fluorobenzoic acid; and

4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-5-(methylamino)-1H-pyrrolo[2,3-c]pyridin-3-yl)-3-fluorobenzoic acid.

21. A pharmaceutical composition comprising a compound of claim 1 or a pharmaceutically acceptable salt or solvate thereof and one or more pharmaceutically acceptable excipients.

22. The pharmaceutical composition of claim 21, which further comprises at least one additional therapeutically active agent.

23. Use of a compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for the treatment of a disease or condition mediated by Retinoic acid receptor-related Orphan Receptor gamma t (RORgammaT).

24. A method for treating a disease or condition mediated by RORgammaT in a subject comprising administering to the subject an amount of a compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, that is effective for treating the disease or condition mediated by RORgammaT in the subject.

25. The method of claim 24, wherein the disease or condition is an autoimmune disease or inflammatory disease.

26. The method of claim 25, wherein the disease or condition is multiple sclerosis, inflammatory bowel disease, Crohn's disease, ankylosing spondylitis, psoriasis, rheumatoid arthritis, asthma, osteoarthritis, Kawasaki disease, Hashimoto's thyroiditis or mucosal leishmaniasis.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2012/080131

A. CLASSIFICATION OF SUBJECT MATTER

See extra sheet

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: C07D231/-; C07D403/-; C07D471/-; A61K31/-

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, CNPAT, EPODOC, CNKI, CA, ISI Web of Knowledge: ROR, gamma,gammat, retinoic acid, retinoid, orphan, receptor?, inhibitor?, antagonist?, +benzoic w acid, Structure search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WANG Yongjun et al, Identification of SR1078, a synthetic agonist for the orphan nuclear receptors ROR α and RORγ, ACS CHEMICAL BIOLOGY, 2010, Vol. 5,No. 11, 1029-1034	1-26
A	WO 2006063167 A1 (SMITHKLINE BEECHAM CORP. et al.), 15 Jun. 2006 (15.06.2006), claim 1, abstract	1-26
A	EP 0429257 A2 (GLAXO GROUP LTD.), 29 May 1991 (29.05.1991), abstract	1-26
A	EP 2181710 A1 (PHENEX PHARM. AG), 05 May 2010 (05.05.2010), claims 1-12	1-26
E	WO 2012/106995 A1 (MERCK SHARP & DOHME CORP. et al.), 16 Aug. 2012 (16.08.2012), claims 1-20	1-19, 21-26

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim (S) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 Apr. 2013 (15.04.2013)	**16 May 2013 (16.05.2013)**
Name and mailing address of the ISA/CN The State Intellectual Property Office, the P.R.China 6 Xitucheng Rd., Jimen Bridge, Haidian District, Beijing, China 100088 Facsimile No. 86-10-62019451	Authorized officer ZHANG, Hengjun Telephone No. (86-10)82246670

Form PCT/ISA /210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2012/080131

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 24-26
because they relate to subject matter not required to be searched by this Authority, namely:
These claims relate to methods for treating diseases (PCT R39.1(iv)), but the search has been carried out and based on the use of the compound in manufacture of medicaments for treating corresponding diseases.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2012/080131

Patent Documents referred in the Report	Publication Date	Patent Family	Publication Date
WO 2006063167 A1	15.06.2006	EP 1828180 A1	05.09.2007
		JP 2008523085A	03.07.2008
		US 2009233955A1	17.09.2009
		JP4954086B2	13.06.2012
		US2012238588A1	20.09.2012
EP0429257A2	29.05.1991	AU6666990A	23.05.1991
		NO904987A	21.05.1991
		CA2030177A	18.05.1991
		FI905672A	18.05.1991
		PT95899A	13.09.1991
		ZA9009216A	30.10.1991
		JP3271288A	03.12.1991
		EP0429257A3	29.01.1992
		AU638510B	01.07.1993
EP2181710A1	05.05.2010	WO2010049144A2	06.05.2010
		WO2010049144A3	08.07.2010
		EP2349277A2	03.08.2011
		US2011263046A1	27.10.2011
		JP2012506998A	22.03.2012
WO 2012/106995 A1	16.08.2012	EP 2487159 A1	15.08.2012

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2012/080131

A (Continuation). **CLASSIFICATION OF SUBJECT MATTER**

C07D231/56 (2006.1) i

C07D403/10 (2006.1) i

C07D403/12 (2006.1) i

C07D471/04 (2006.1) i

A61K31/416 (2006.1) i

A61K31/41 (2006.1) i

A61K31/422 (2006.1) i

A61K31/437 (2006.1) i

A61P43/00 (2006.1) i

A61P37/00 (2006.1) i

A61P29/00 (2006.1) i