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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
26 January 2023 (26.01.2023)

WIPO | PCT

(10) International Publication Number
WO 2023/004280 A1

(51) International Patent Classification:
A61K 31/415 (2006.01) *C07D 231/02* (2006.01)
A61K 31/4155 (2006.01) *C07D 231/10* (2006.01)
A61P 25/16 (2006.01)

(21) International Application Number:
PCT/US2022/073830

(22) International Filing Date:
18 July 2022 (18.07.2022)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
63/223,337 19 July 2021 (19.07.2021) US

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

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

Published:
— *with international search report (Art. 21(3))*

(54) Title: SELECTIVE PYRAZOLE LRRK2 INHIBITORS AND METHODS FOR USE THEREOF

(57) Abstract: Compounds and methods are provided for the treatment of leucine-rich repeat kinase-2 (LRRK2)-related diseases associated with increased LRRK2 kinase activity, including but not limited to neurodegeneration, inflammatory bowel disease, and some cancers. Treatment is provided by administering an effective dose of a pyrazole LRRK2 inhibitor. In some embodiments the disease is a form of cancer related to germline or somatic variants in LRRK2.

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SELECTIVE PYRAZOLE LRRK2 INHIBITORS AND METHODS FOR USE THEREOF

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional Patent Application No. 63/223,337 filed July 19, 2021, which application is incorporated herein by reference in its entirety.

BACKGROUND

[0002] Parkinson's disease (PD) is a prevalent, progressive neurodegenerative disorder that most commonly occurs sporadically, through a conspiracy of aging with genetic and environmental risk factors, but also is inherited from dominant or recessive mutations. Although there are effective symptomatic therapies for PD, there is yet no treatment that targets the underlying cause(s) of any sporadic or inherited form of PD. Thus, the vision of precision medicine for PD remains distant.

[0003] Autosomal dominant, missense mutations in the Leucine Rich Repeat protein Kinase 2 (*LRRK2*) gene are the most common genetic predisposition to PD. *LRRK2* mutations account for approximately 1-5% of PD, and are inherited as an autosomal dominant trait with incomplete penetrance. The most common *LRRK2* mutation leads to a serine substitution of Gly2019 in subdomain VII of the kinase domain, which increases kinase activity 2-4 fold. Other less common pathogenic mutations in the ROC/COR domain (R1441G/C/H, Y1699C, and N1437H) have disrupted GTPase activity and increased kinase activity. In addition to increasing the risk for PD, genetic variants in *LRRK2* also have been shown to modulate the risk for inflammatory bowel disease, leprosy, and some forms of cancer.

[0004] Increased LRRK2 kinase activity is hypothesized to cause PD in those who inherit G2019S *LRRK2*, as well as other less common *LRRK2* mutations, and to contribute to the pathogenesis of sporadic PD in people with and without *LRRK2* mutations. As a test of this hypothesis, several groups have created varyingly selective LRRK2 inhibitors that block kinase activity in both wild-type and mutant forms of the enzyme. Unfortunately, these relatively non-G2019S selective LRRK2 inhibitors have been accompanied by concerning untoward effects in lung and kidney, calling into question their suitability for long-term treatment of older individuals. Therefore, more recent efforts have focused on creating highly selective kinase inhibitors of specific mutant forms of LRRK2.

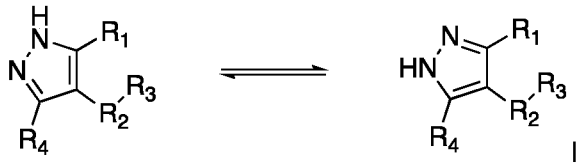
SUMMARY

[0005] Compounds and methods are provided for the treatment of leucine-rich repeat kinase-2 (LRRK2)-related diseases associated with increased LRRK2 kinase activity, including but not limited to neurodegeneration, inflammatory bowel disease, and some cancers. Treatment is provided by administering an effective dose of a pyrazole LRRK2 inhibitor. In some embodiments the disease is Parkinson's disease (PD), which may be familial or sporadic, e.g., associated with

mutations or idiopathic. In some embodiments the PD is familial and associated with LRRK2 G2019S mutation. In some embodiments the disease is an inflammatory disease, including for example inflammatory bowel disease, Crohn's disease, etc. In some embodiments the disease is a form of cancer related to germline or somatic variants in *LRRK2*.

[0006] In some embodiments the pyrazole LRRK2 inhibitor selectively inhibits mutated forms of human LRRK2, relative to the wild-type protein, e.g. the inhibitor has an activity against mutated forms that is greater than about 2X, greater than about 5X, greater than about 10X, greater than about 20X, greater than about 50X, greater than about 100X the level of activity relative to the wild-type human LRRK2 protein. In some embodiments the mutated form of human LRRK2 comprises an amino acid modification at residue G2019, including without limitation amino acid substitutions and deletions such as G2019S. In some embodiments the mutated form of human LRRK2 comprises an amino acid modification at one or more of residues G2019, I2020, and R1441, Y1699, N1437, including without limitation the mutations G2019S, I2020T, R1441C, R1441H, and R1141G. The most common LRRK2 mutation leads to a serine substitution of Gly2019 (G2019S or GS-LRRK2) in the kinase domain, which increases kinase activity 2-4 fold. Other pathogenic mutations in the ROC/COR domain (R1441G/C/H, Y1699C, and N1437H) disrupt LRRK2 GTPase activity and increase kinase activity.

[0007] In one embodiment, the present invention includes pyrazole compounds of formula (I), or derivatives or prodrugs thereof.



I

where

R_1 = H, F, Cl, Br, I Me, alkyl, OMe, O-alkyl, OCF_3, CF_3, CH_2F, CHF_2.

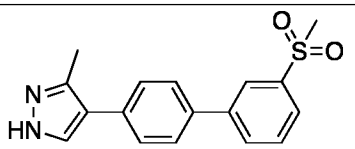
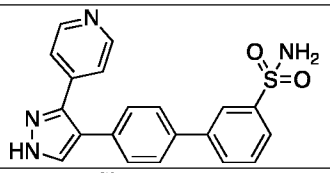
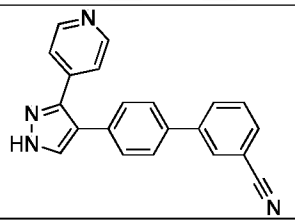
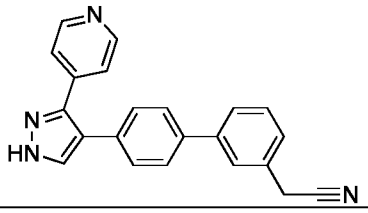
R_2, R_3 and R_4 can be an aryl or alkyl composed of a single ring (e.g., phenyl), or two or more condensed rings, such as 2 to 3 condensed rings (e.g., naphthyl), or two or more aromatic rings, such as 2 to 3 aromatic rings, which are linked by a single bond (e.g., biphenylyl), or a substituted aryl, that is mono-, di-, or tri-substituted with heterocycloalkyl, aryl, substituted aryl, heteroaryl, nitro, cyano (also referred to herein as nitrile), azido, halo, –OR, -SR, $-SF_5$, -CHO, –COR, –C(O)OR, $-C(O)-NR_2$, –OC(O)R, $-OC(O)NR_2$, -OC(O)OR, $--P(O)(OR)_2$, $-OP(O)(OR)_2$, –NR2, $-N+R_3$ (wherein a counterion may be present), $–CONR_2$, –NRCOR, -NHC(O)OR, $-NHC(O)NR_2$, $-NHC(NH)NR_2$, SO_3^-, $-SO_2OR$, $-OSO_2R$, $-SO_2NR_2$, or $-NRSO_2R$, where each R is, independently, hydrogen, lower alkyl, R′-substituted lower alkyl, aryl, R′-substituted aryl, heteroaryl, heteroaryl(alkyl), R′-substituted aryl(alkyl), or aryl(alkyl) and each R′ is, independently, hydroxy, halo, alkyloxy, cyano, thio, SF5, nitro, alkyl, halo- alkyl, or amino. Substituted alkyls which are substituted with one to three of the substituents selected from the

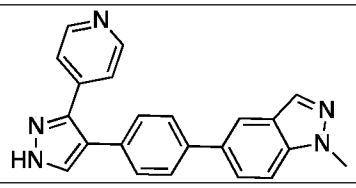
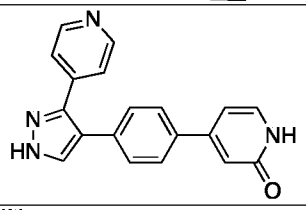
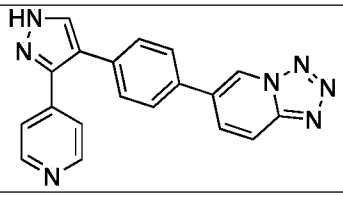
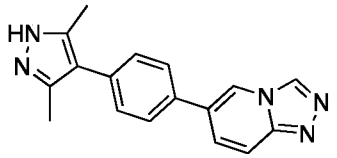
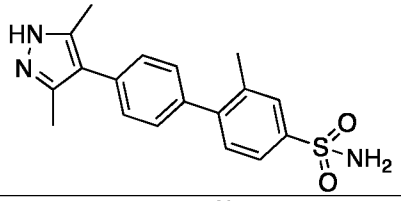
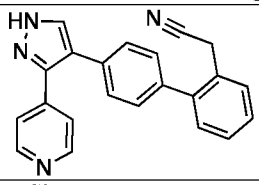
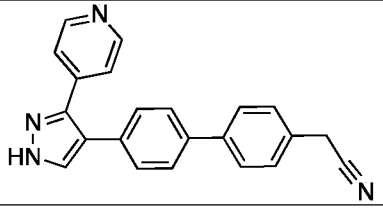
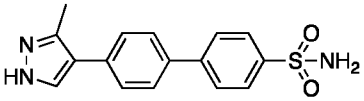
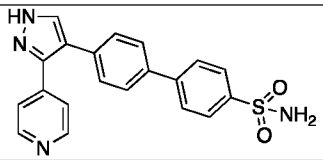
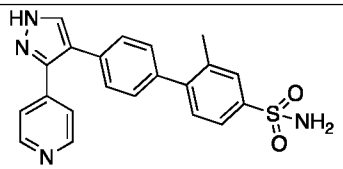
group consisting of alkynyl, cyano, halo, alkyloxy, thio, nitro, amino, or hydroxy are particularly of interest.

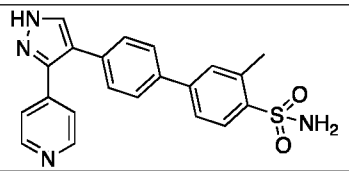
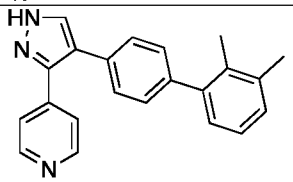
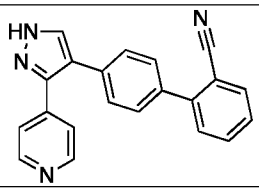
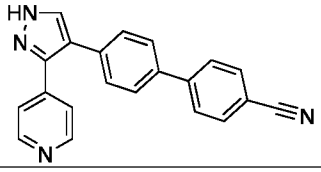
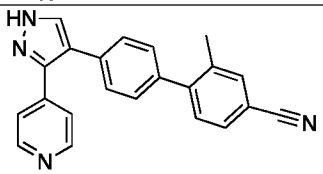
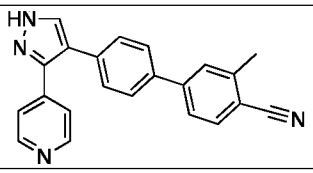
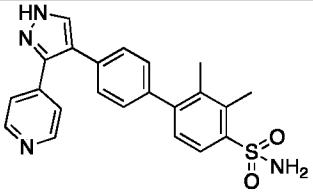
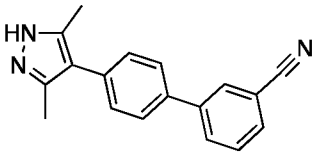
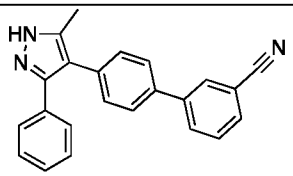
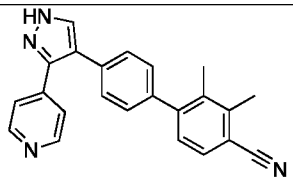
R_4 can be heterocycloalkyl, aryl, substituted aryl, heteroaryl, nitro, cyano (also referred to herein as nitrile), azido, halo, –OR, -SR, -SF_5, -CHO, –COR, –C(O)OR, -C(O)-NR_2, –OC(O)R, -OC(O)NR_2, -OC(O)OR, --P(O)$(OR)_2$, -OP(O)$(OR)_2$, –NR_2, -N^+R_3 (wherein a counterion may be present), –$CONR_2$, –NRCOR, -NHC(O)OR, -NHC(O)NR_2, -NHC(NH)NR_2, SO_3^-, -SO_2OR, -OSO_2R, -SO_2NR_2, or -$NRSO_2$R, where each R is, independently, hydrogen, lower alkyl, R′-substituted lower alkyl, aryl, R′-substituted aryl, heteroaryl, heteroaryl(alkyl), R′-substituted aryl(alkyl), or aryl(alkyl) and each R′ is, independently, hydroxy, halo, alkyloxy, cyano, thio, SF5, nitro, alkyl, halo- alkyl, or amino. Substituted alkyls which are substituted with one to three of the substituents selected from the group consisting of alkynyl, cyano, halo, alkyloxy, thio, nitro, amino, or hydroxy.

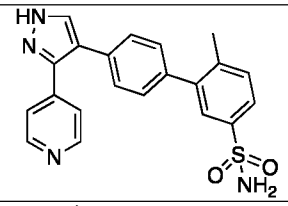
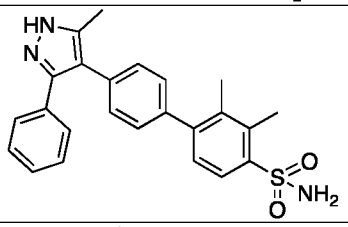
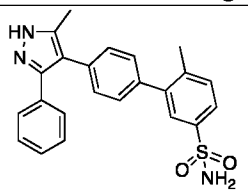
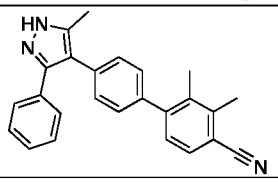
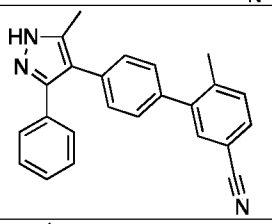
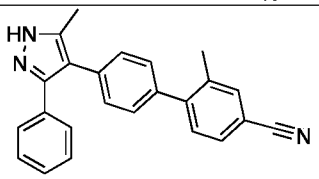
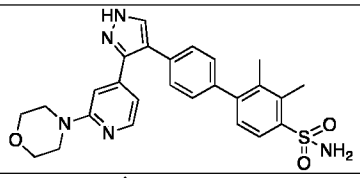
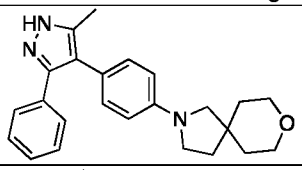
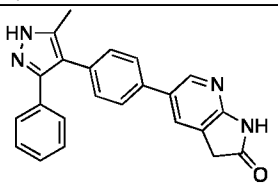
[0008] In some embodiments, a pyrazole LRRK2 inhibitor has a structure as shown below in Table 1, or derivatives or prodrugs thereof. In some embodiments, a pyrazole LRRK2 inhibitor is a selective inhibitor of a mutated form of human LRRK2 protein.

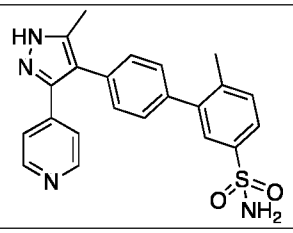
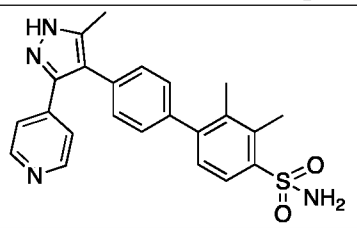
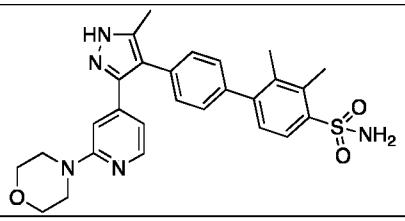
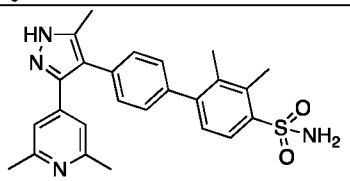
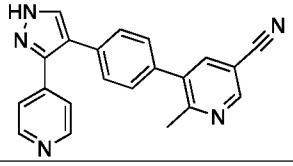
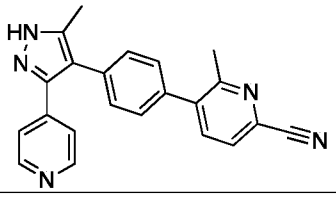
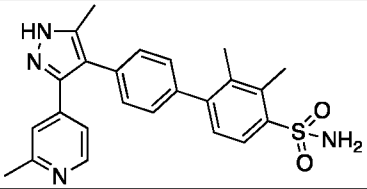
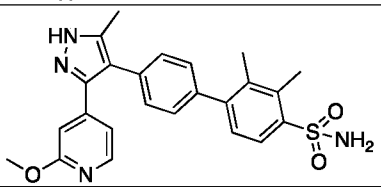
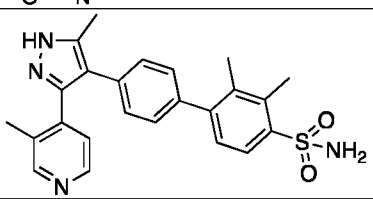
Table 1

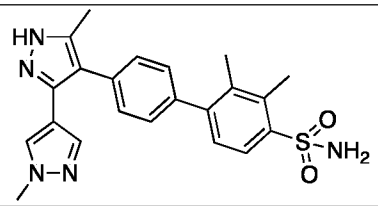
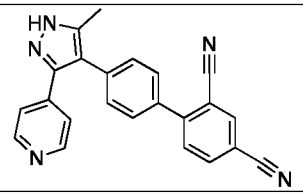
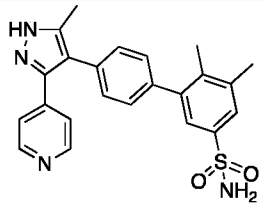
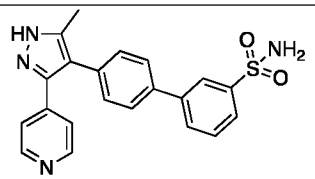
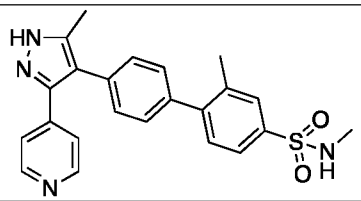
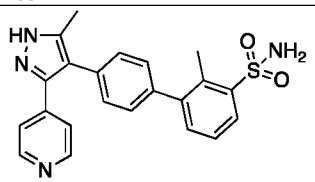
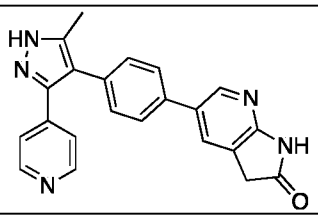
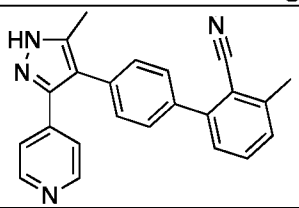
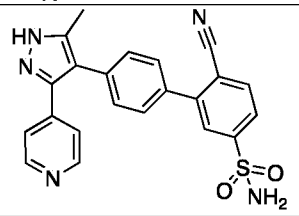
Compound ID	STRUCTURE	STRUCTURE_NAME
1		3-methyl-4-[4-(3-methylsulfonylphenyl)phenyl]-1H-pyrazole
2		3-[4-[3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide
3		3-[4-[3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzonitrile
4		2-[3-[4-[3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]phenyl]acetonitrile

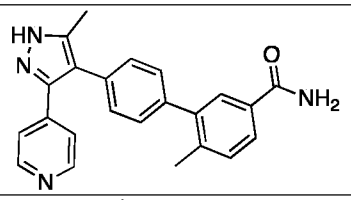
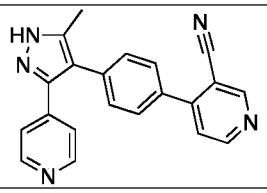
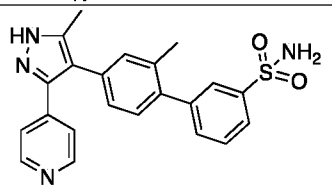
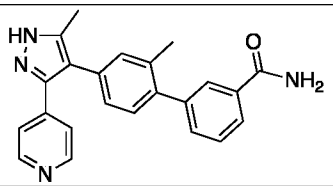
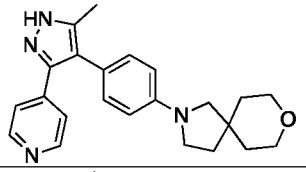
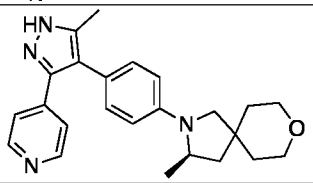
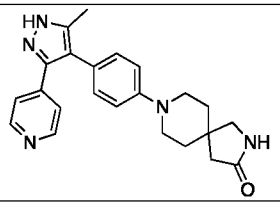
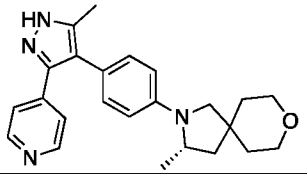
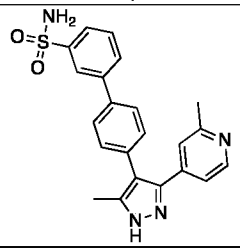
5		1-methyl-5-[4-[3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]indazole
6		4-[4-[3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-1H-pyridin-2-one
7		6-[4-[3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]tetrazolo[1,5-a]pyridine
8		6-[4-(3,5-dimethyl-1H-pyrazol-4-yl)phenyl]-[1,2,4]triazolo[4,3-a]pyridine
9		4-[4-(3,5-dimethyl-1H-pyrazol-4-yl)phenyl]-3-methyl-benzenesulfonamide
10		2-[2-[4-[3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]phenyl]acetonitrile
11		2-[4-[4-[3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]phenyl]acetonitrile
12		4-[4-(3-methyl-1H-pyrazol-4-yl)phenyl]benzenesulfonamide
13		4-[4-[3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide
14		3-methyl-4-[4-[3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide

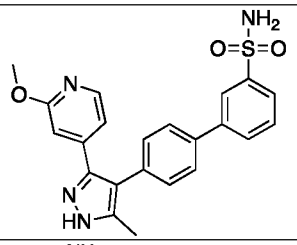
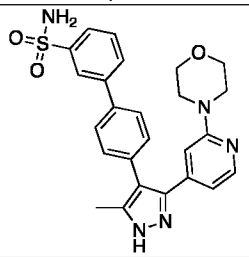
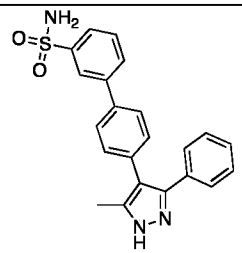
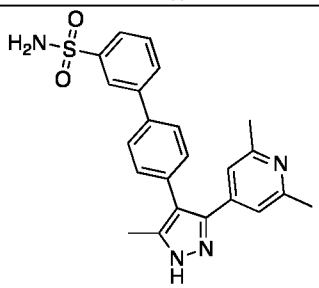
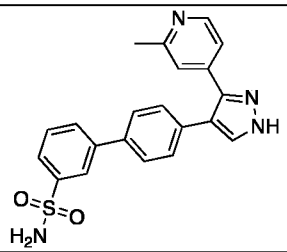
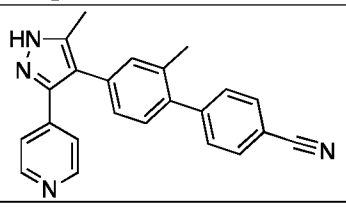
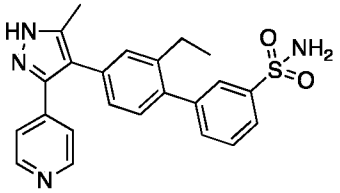
15		2-methyl-4-[4-[3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide
16		4-[4-[4-(2,3-dimethylphenyl)phenyl]-1H-pyrazol-3-yl]pyridine
17		2-[4-[3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzonitrile
18		4-[4-[3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzonitrile
19		3-methyl-4-[4-[3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzonitrile
20		2-methyl-4-[4-[3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzonitrile
21		2,3-dimethyl-4-[4-[3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide
22		3-[4-(3,5-dimethyl-1H-pyrazol-4-yl)phenyl]benzonitrile
23		3-[4-(5-methyl-3-phenyl-1H-pyrazol-4-yl)phenyl]benzonitrile
24		2,3-dimethyl-4-[4-[3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzonitrile

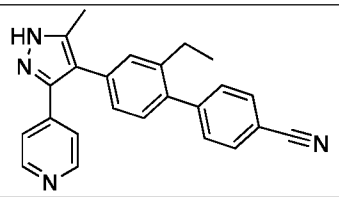
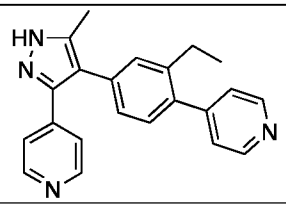
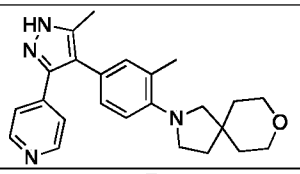
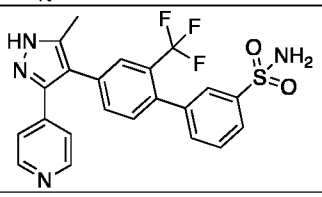
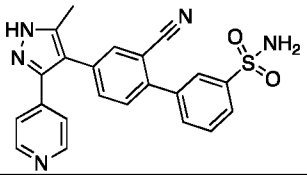
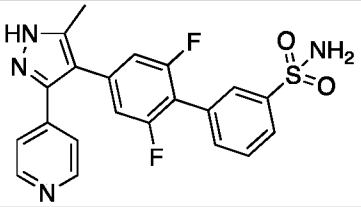
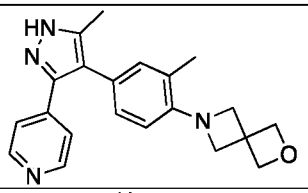
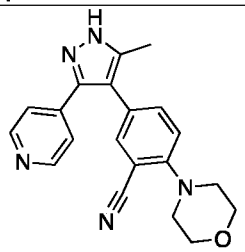
25		4-methyl-3-[4-[3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide
26		2,3-dimethyl-4-[4-(5-methyl-3-phenyl-1H-pyrazol-4-yl)phenyl]benzenesulfonamide
27		4-methyl-3-[4-(5-methyl-3-phenyl-1H-pyrazol-4-yl)phenyl]benzenesulfonamide
28		2,3-dimethyl-4-[4-(5-methyl-3-phenyl-1H-pyrazol-4-yl)phenyl]benzonitrile
29		4-methyl-3-[4-(5-methyl-3-phenyl-1H-pyrazol-4-yl)phenyl]benzonitrile
30		3-methyl-4-[4-(5-methyl-3-phenyl-1H-pyrazol-4-yl)phenyl]benzonitrile
31		2,3-dimethyl-4-[4-[3-(2-morpholino-4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide
32		2-[4-(5-methyl-3-phenyl-1H-pyrazol-4-yl)phenyl]-8-oxa-2-azaspiro[4.5]decane
33		5-[4-(5-methyl-3-phenyl-1H-pyrazol-4-yl)phenyl]-1,3-dihydropyrrolo[2,3-b]pyridin-2-one

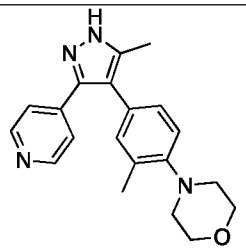
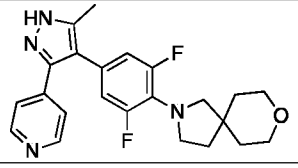
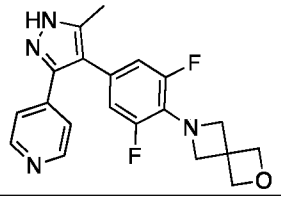
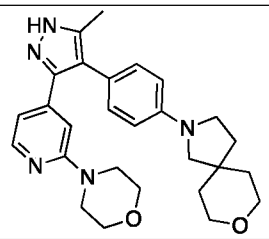
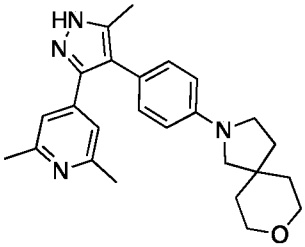
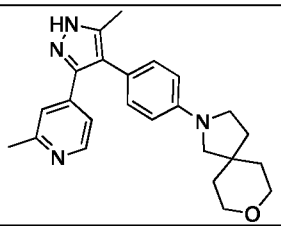
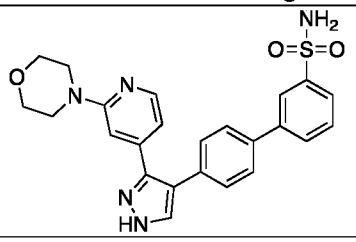
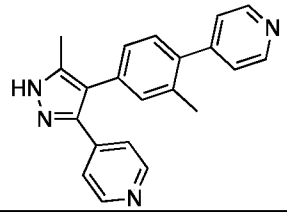
34		4-methyl-3-[4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide
35		2,3-dimethyl-4-[4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide
36		2,3-dimethyl-4-[4-[5-methyl-3-(2-morpholino-4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide
37		4-[4-[3-(2,6-dimethyl-4-pyridyl)-5-methyl-1H-pyrazol-4-yl]phenyl]-2,3-dimethyl-benzenesulfonamide
38		6-methyl-5-[4-[3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]pyridine-3-carbonitrile
39		6-methyl-5-[4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]pyridine-2-carbonitrile
40		2,3-dimethyl-4-[4-[5-methyl-3-(2-methyl-4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide
41		4-[4-[3-(2-methoxy-4-pyridyl)-5-methyl-1H-pyrazol-4-yl]phenyl]-2,3-dimethyl-benzenesulfonamide
42		2,3-dimethyl-4-[4-[5-methyl-3-(3-methyl-4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide

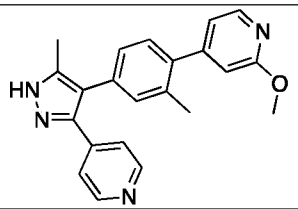
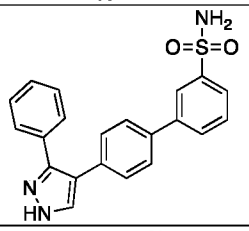
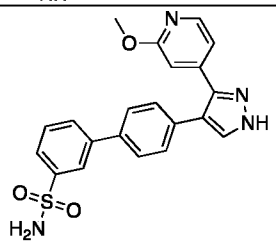
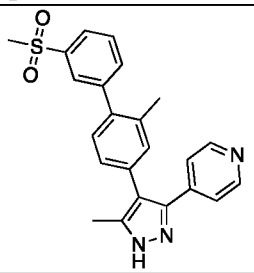
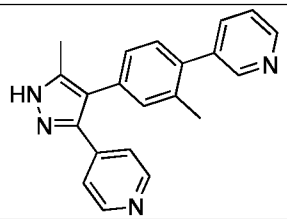
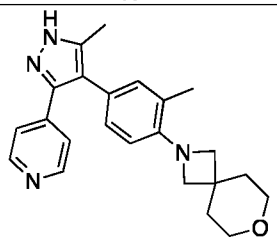
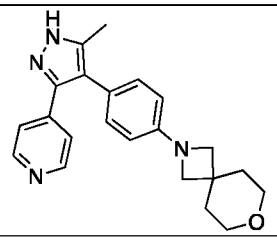
43		2,3-dimethyl-4-[4-[5-methyl-3-(1-methylpyrazol-4-yl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide
44		4-[4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzene-1,3-dicarbonitrile
45		3,4-dimethyl-5-[4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide
46		3-[4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide
47		N,3-dimethyl-4-[4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide
48		2-methyl-3-[4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide
49		5-[4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-1,3-dihydropyrrolo[2,3-b]pyridin-2-one
50		2-methyl-6-[4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzonitrile
51		4-cyano-3-[4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide

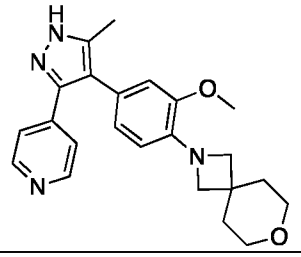
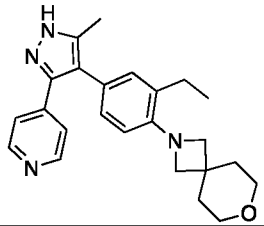
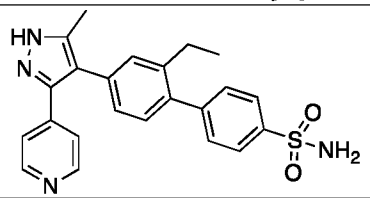
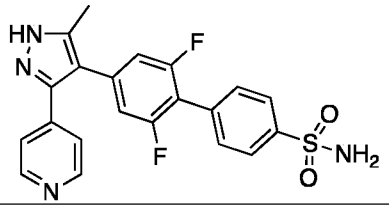
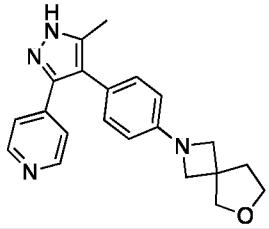
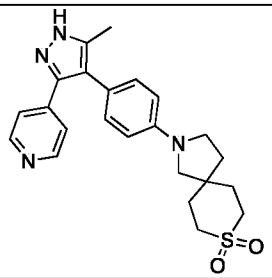
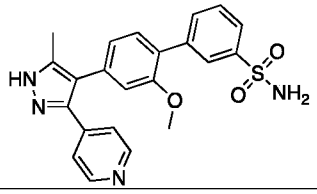
52		4-methyl-3-[4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzamide
53		4-[4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]pyridine-3-carbonitrile
54		3-[2-methyl-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide
55		3-[2-methyl-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzamide
56		2-[4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-8-oxa-2-azaspiro[4.5]decane
57		rac-(3R)-3-methyl-2-[4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-8-oxa-2-azaspiro[4.5]decane
58		8-[4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-2,8-diazaspiro[4.5]decan-3-one
59		rac-(3S)-3-methyl-2-[4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-8-oxa-2-azaspiro[4.5]decane
60		3-[4-[5-methyl-3-(2-methyl-4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide

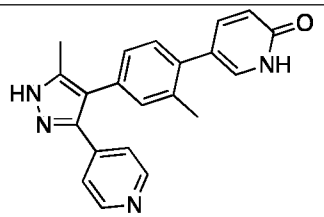
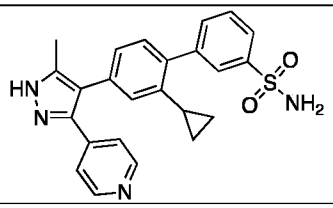
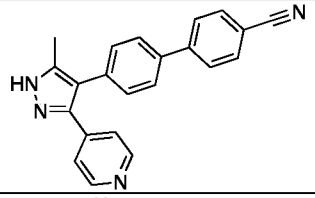
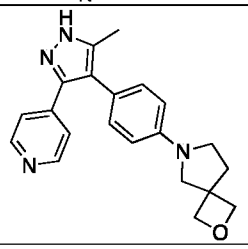
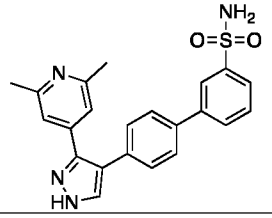
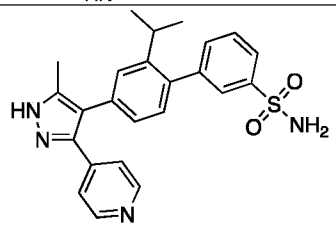
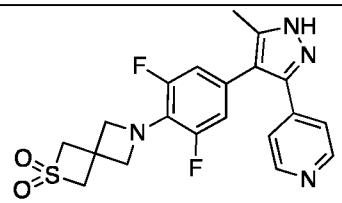
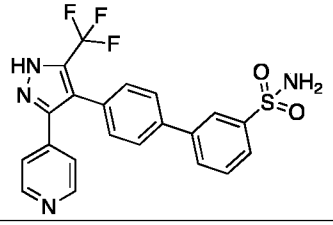
61		3-[4-[3-(2-methoxy-4-pyridyl)-5-methyl-1H-pyrazol-4-yl]phenyl]benzenesulfonamide
62		3-[4-[5-methyl-3-(2-morpholino-4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide
63		3-[4-(5-methyl-3-phenyl-1H-pyrazol-4-yl)phenyl]benzenesulfonamide
64		3-[4-[3-(2,6-dimethyl-4-pyridyl)-5-methyl-1H-pyrazol-4-yl]phenyl]benzenesulfonamide
65		3-[4-[3-(2-methyl-4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide
66		4-[2-methyl-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzonitrile
67		3-[2-ethyl-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide

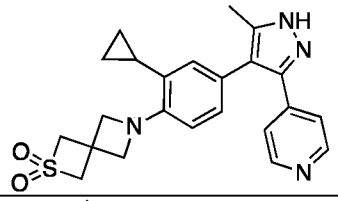
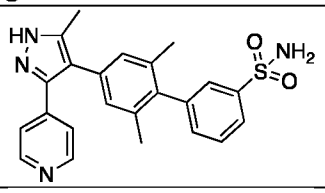
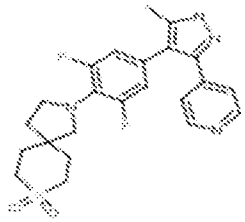
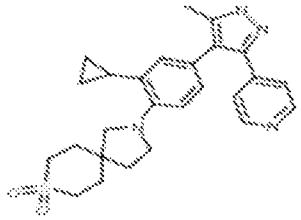
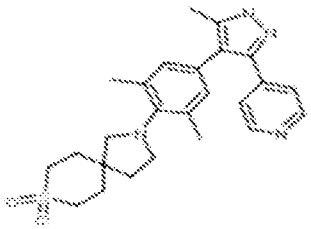
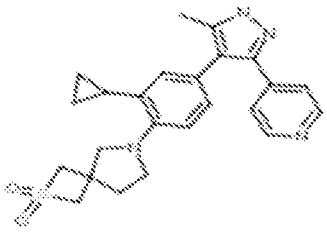
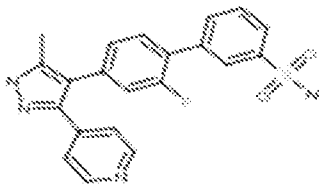
68		4-[2-ethyl-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzonitrile
69		4-[2-ethyl-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]pyridine
70		2-[2-methyl-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-8-oxa-2-azaspiro[4.5]decane
71		3-[4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]-2-(trifluoromethyl)phenyl]benzenesulfonamide
72		3-[2-cyano-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide
73		3-[2,6-difluoro-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide
74		6-[2-methyl-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-2-oxa-6-azaspiro[3.3]heptane
75		5-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]-2-morpholino-benzonitrile

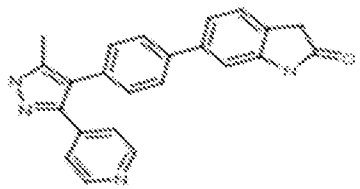
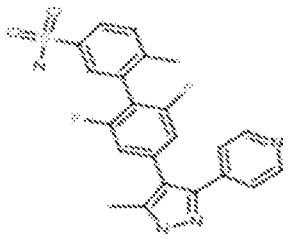
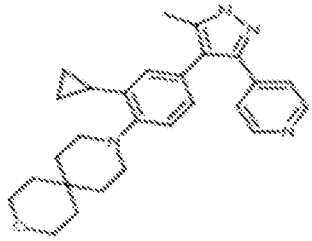
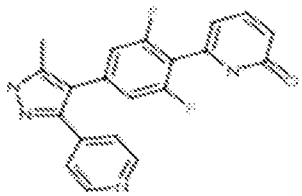
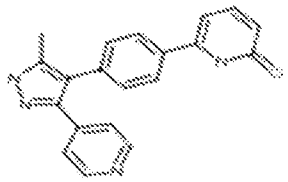
76		4-[2-methyl-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]morpholine
77		2-[2,6-difluoro-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-8-oxa-2-azaspiro[4.5]decane
78		6-[2,6-difluoro-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-2-oxa-6-azaspiro[3.3]heptane
79		2-[4-[5-methyl-3-(2-morpholino-4-pyridyl)-1H-pyrazol-4-yl]phenyl]-8-oxa-2-azaspiro[4.5]decane
80		2-[4-[3-(2,6-dimethyl-4-pyridyl)-5-methyl-1H-pyrazol-4-yl]phenyl]-8-oxa-2-azaspiro[4.5]decane
81		2-[4-[5-methyl-3-(2-methyl-4-pyridyl)-1H-pyrazol-4-yl]phenyl]-8-oxa-2-azaspiro[4.5]decane
82		3-[4-[3-(2-morpholino-4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide
83		4-[5-methyl-4-[3-methyl-4-(4-pyridyl)phenyl]-1H-pyrazol-3-yl]pyridine

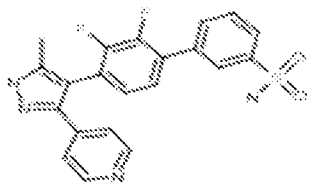
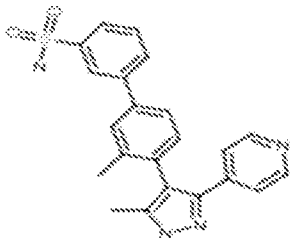
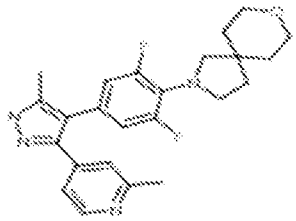
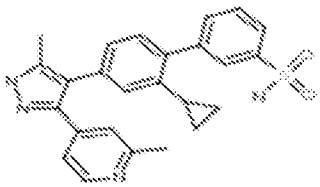
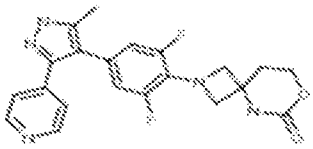
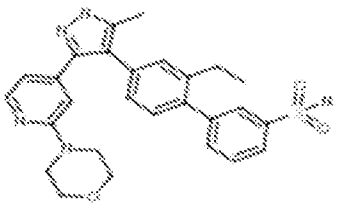
84		2-methoxy-4-[2-methyl-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]pyridine
85		3-[4-(3-phenyl-1H-pyrazol-4-yl)phenyl]benzenesulfonamide
86		3-[4-[3-(2-methoxy-4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide
87		4-[5-methyl-4-[3-methyl-4-(3-methylsulfonylphenyl)phenyl]-1H-pyrazol-3-yl]pyridine
88		3-[2-methyl-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]pyridine
89		2-[2-methyl-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-7-oxa-2-azaspiro[3.5]nonane
90		2-[4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-7-oxa-2-azaspiro[3.5]nonane

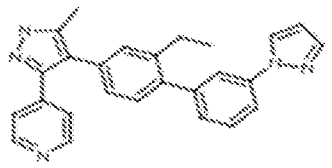
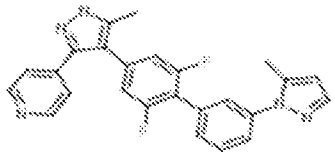
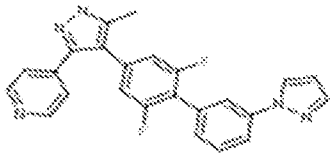
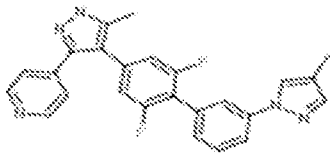
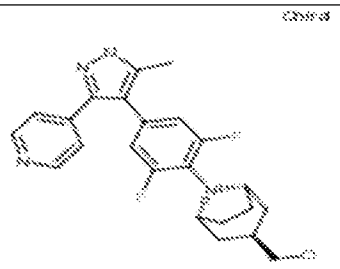
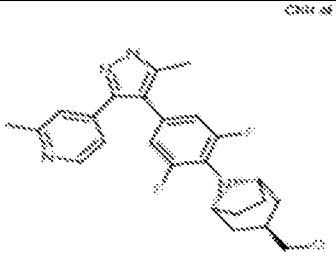
91		2-[2-methoxy-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-7-oxa-2-azaspiro[3.5]nonane
92		2-[2-ethyl-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-7-oxa-2-azaspiro[3.5]nonane
93		4-[2-ethyl-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide
94		4-[2,6-difluoro-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide
95		2-[4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-6-oxa-2-azaspiro[3.4]octane
96		2-[4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-8λ6-thia-2-azaspiro[4.5]decane 8,8-dioxide
97		3-[2-methoxy-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide

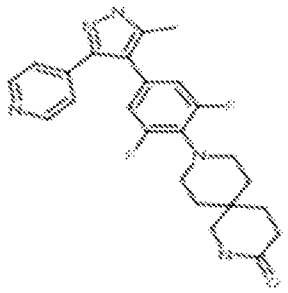
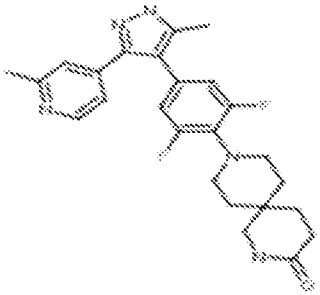
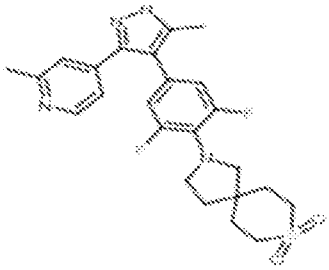
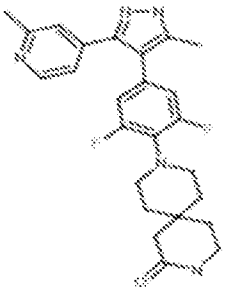
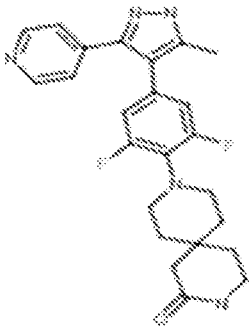
98		5-[2-methyl-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-1H-pyridin-2-one
99		3-[2-cyclopropyl-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide
100		4-[4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzonitrile
101		7-[4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-2-oxa-7-azaspiro[3.4]octane
102		3-[4-[3-(2,6-dimethyl-4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide
103		3-[2-isopropyl-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide
104		6-[2,6-difluoro-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-2λ6-thia-6-azaspiro[3.3]heptane 2,2-dioxide
105		3-[4-[3-(4-pyridyl)-5-(trifluoromethyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide

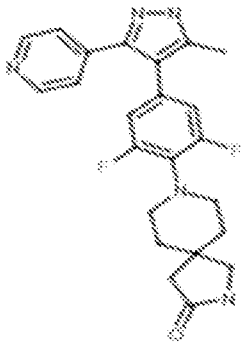
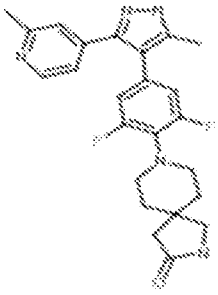
106		6-[2-cyclopropyl-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-2λ6-thia-6-azaspiro[3.3]heptane 2,2-dioxide
107		3-[2,6-dimethyl-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide
108		2-[2,6-difluoro-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-8λ6-thia-2-azaspiro[4.5]decane 8,8-dioxide
109		2-[2-cyclopropyl-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-8λ6-thia-2-azaspiro[4.5]decane 8,8-dioxide
110		2-[2,6-dimethyl-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-8λ6-thia-2-azaspiro[4.5]decane 8,8-dioxide
111		7-[2-cyclopropyl-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-2λ6-thia-7-azaspiro[3.4]octane 2,2-dioxide
112		3-[2-fluoro-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide

113		6-[4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]indolin-2-one
114		3-[2,6-difluoro-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-4-methyl-benzenesulfonamide
115		9-[2-cyclopropyl-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-3-oxa-9-azaspiro[5.5]undecane
116		6-[2,6-difluoro-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-1H-pyridin-2-one
117		6-[4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-1H-pyridin-2-one

118		3-[2,3-difluoro-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide
119		3-[3-methyl-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide
120		2-[2,6-difluoro-4-[5-methyl-3-(2-methyl-4-pyridyl)-1H-pyrazol-4-yl]phenyl]-8-oxa-2-azaspiro[4.5]decane
121		3-[2-cyclopropyl-4-[5-methyl-3-(2-methyl-4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide
122		2-[2,6-difluoro-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-7-oxa-2,5-diazaspiro[3.5]nonan-6-one
123		3-[2-ethyl-4-[5-methyl-3-(2-morpholino-4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide

124		4-[4-[3-ethyl-4-(3-pyrazol-1-ylphenyl)phenyl]-5-methyl-1H-pyrazol-3-yl]pyridine
125		4-[4-[3,5-difluoro-4-[3-(5-methylpyrazol-1-yl)phenyl]phenyl]-5-methyl-1H-pyrazol-3-yl]pyridine
126		4-[4-[3,5-difluoro-4-(3-pyrazol-1-ylphenyl)phenyl]-5-methyl-1H-pyrazol-3-yl]pyridine
127		4-[4-[3,5-difluoro-4-[3-(4-methylpyrazol-1-yl)phenyl]phenyl]-5-methyl-1H-pyrazol-3-yl]pyridine
128		[(1R,5S)-8-[2,6-difluoro-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-8-azabicyclo[3.2.1]octan-3-yl]methanol
129		[(1R,5S)-8-[2,6-difluoro-4-[5-methyl-3-(2-methyl-4-pyridyl)-1H-pyrazol-4-yl]phenyl]-8-azabicyclo[3.2.1]octan-3-yl]methanol

130		9-[2,6-difluoro-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-2,9-diazaspiro[5.5]undecan-3-one
131		9-[2,6-difluoro-4-[5-methyl-3-(2-methyl-4-pyridyl)-1H-pyrazol-4-yl]phenyl]-2,9-diazaspiro[5.5]undecan-3-one
132		2-[2,6-difluoro-4-[5-methyl-3-(2-methyl-4-pyridyl)-1H-pyrazol-4-yl]phenyl]-8λ6-thia-2-azaspiro[4.5]decane 8,8-dioxide
133		3-[2,6-difluoro-4-[5-methyl-3-(2-methyl-4-pyridyl)-1H-pyrazol-4-yl]phenyl]-3,9-diazaspiro[5.5]undecan-10-one
134		3-[2,6-difluoro-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-3,9-diazaspiro[5.5]undecan-10-one

135		8-[2,6-difluoro-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-2,8-diazaspiro[4.5]decan-3-one
136		8-[2,6-difluoro-4-[5-methyl-3-(2-methyl-4-pyridyl)-1H-pyrazol-4-yl]phenyl]-2,8-diazaspiro[4.5]decan-3-one

[0009] In some embodiments a pharmaceutical composition or medicament is provided that includes at least one compound according to formula (I) or Table 1, and a physiologically compatible excipient.

[0010] In an embodiment a method is provided for treating or delaying the progression of a disease alleviated by inhibiting LRRK2 protein kinase activity, the method comprising administering a therapeutically effective amount of at least one compound of formula (I) or Table 1, as described herein. In some In some embodiments the disease is Parkinson's disease (PD), which may be familial or sporadic, e.g. associated with mutations or idiopathic. In some embodiments the PD is familial and associated with LRRK2 Gly2019Ser mutation. In some embodiments the disease is inflammatory diseases such as inflammatory bowel disease or Crohn's disease. In some embodiments the disease is a form of cancer related to germline or somatic variants in LRRK2, e.g. skin cancer, hormone-related cancers, leukemia, colon cancer. In some embodiments the indazole LRRK2 inhibitor selectively inhibits mutated forms of human LRRK2, relative to the wild-type protein, e.g. the inhibitor has an activity against mutated forms that is greater than about 2X, greater than about 5X, greater than about 10X, greater than about 20X, greater than about 50X, greater than about 100X the level of activity relative to the wild-type human LRRK2 protein. In some embodiments the mutated form of human LRRK2 comprises an amino acid modification at residue G2019, including without limitation amino acid substitutions and deletions such as G2019S. In some embodiments the mutated form of human LRRK2 comprises an amino acid modification at one or more of residues G2019, I2020, and R1441, including without limitation the mutations G2019S, I2020T, R1441C, R1441H, and R1141G.

[0011] In certain embodiments, a pharmaceutical composition is administered to an individual having at least one symptom associated with Parkinson's disease, inflammatory diseases such as Crohn's disease, and/or cancer. In some embodiments, the individual has a mutation in the *LRRK2* gene and protein encoded by the mutated gene. Non-limiting examples of such mutants include, but are not limited to, G2019S, I2020T, R1441C, R1441H, or R1141G. In other embodiments, the mutation is any germline or somatic, genetic or epigenetic variation in *LRRK2* associated with Parkinson's disease, inflammatory diseases, or cancer. In certain embodiments, such administration results in amelioration of at least one symptom. In certain embodiments, such administration of the pharmaceutical composition to an individual results in an increase in functional LRRK2 protein or decreased activity of a mutated LRRK2 in a cell. In certain embodiments, the administration delays the onset of symptoms or changes biomarkers of disease (imaging, physiologic, biochemical, or molecular). In certain embodiments, the administration prevents the onset of disease. In certain embodiments, the administration rescues a normal cellular phenotype that had been perturbed by neurodegeneration, inflammation, or cancer.

DETAILED DESCRIPTION

[0012] Before the present methods and compositions are described, it is to be understood that this invention is not limited to a particular method or composition described, as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of the present invention will be limited only by the appended claims.

[0013] Where a range of values is provided, it is understood that each intervening value, to the tenth of the unit of the lower limit unless the context clearly dictates otherwise, between the upper and lower limits of that range is also specifically disclosed. Each smaller range between any stated value or intervening value in a stated range and any other stated or intervening value in that stated range is encompassed within the invention. The upper and lower limits of these smaller ranges may independently be included or excluded in the range, and each range where either, neither or both limits are included in the smaller ranges is also encompassed within the invention, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either or both of those included limits are also included in the invention.

[0014] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, some potential and preferred methods and materials are now described. All publications mentioned herein are incorporated herein by

reference to disclose and describe the methods and/or materials in connection with which the publications are cited. It is understood that the present disclosure supercedes any disclosure of an incorporated publication to the extent there is a contradiction.

[0015] It must be noted that as used herein and in the appended claims, the singular forms "a", "an", and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a cell" includes a plurality of such cells and reference to "the peptide" includes reference to one or more peptides and equivalents thereof, e.g. polypeptides, known to those skilled in the art, and so forth.

[0016] The publications discussed herein are provided solely for their disclosure prior to the filing date of the present application. Nothing herein is to be construed as an admission that the present invention is not entitled to antedate such publication by virtue of prior invention. Further, the dates of publication provided may be different from the actual publication dates which may need to be independently confirmed.

[0017] While an apparatus and method has or will be described for the sake of grammatical fluidity with functional explanations, it is to be expressly understood that the claims, unless expressly formulated under 35 U.S.C. §112, are not to be construed as necessarily limited in any way by the construction of "means" or "steps" limitations, but are to be accorded the full scope of the meaning and equivalents of the definition provided by the claims under the judicial doctrine of equivalents, and in the case where the claims are expressly formulated under 35 U.S.C. §112 are to be accorded full statutory equivalents under 35 U.S.C. §112.In describing and claiming the present invention, certain terminology will be used in accordance with the definitions set out below. It will be appreciated that the definitions provided herein are not intended to be mutually exclusive. Accordingly, some chemical moieties may fall within the definition of more than one term.

[0018] All stereoisomers of the compounds of the invention, either in a mixture or in pure or substantially pure form, are considered to be within the scope of this invention. The compounds of the invention may have asymmetric centers at any of the carbon atoms including any one of the substituents. Consequently, compounds of the invention may exist in enantiomeric or diastereomeric forms or in mixtures thereof. Furthermore, where a stereocenter existing in a compound of the invention is represented as a racemate, it is understood that the stereocenter may encompass the racemic mixture of R and S isomers, the S isomers, and the R isomers. The processes for preparation of such compounds can utilize racemates, enantiomers, or diastereomers as starting materials. When diastereomeric or enantiomeric products are prepared, they can be separated by conventional methods including, chromatographic, chiral HPLC, fractional crystallization, or distillation. Some compounds of the present invention have groups including alkenyls, iminyls, and the like, which may exist as entgegen (E) or zusammen

(Z) conformations, in which case all geometric forms thereof, both E and Z, cis and trans, and mixtures thereof, are within the scope of the present invention. Accordingly, when such geometric isomeric products are prepared, they can be separated by conventional methods for example, chromatographic, HPLC, distillation or crystallization.

[0019] The terms “specific binding,” “specifically binds,” and the like, refer to non-covalent or covalent preferential binding to a molecule relative to other molecules or moieties in a solution or reaction mixture (e.g., an antibody specifically binds to a particular polypeptide or epitope relative to other available polypeptides). In some embodiments, the affinity of one molecule for another molecule to which it specifically binds is characterized by a KD (dissociation constant) of 10^{-5} M or less (e.g., 10^{-6} M or less, 10^{-7} M or less, 10^{-8} M or less, 10^{-9} M or less, 10^{-10} M or less, 10^{-11} M or less, 10^{-12} M or less, 10^{-13} M or less, 10^{-14} M or less, 10^{-15} M or less, or 10^{-16} M or less). "Affinity" refers to the strength of binding, increased binding affinity being correlated with a lower Kd.

[0020] The term “Alkyl” refers to a C1-C20 alkyl that may be linear, branched, or cyclic. “Lower alkyl”, as in “lower alkyl”, or “substituted lower alkyl”, means a C1-C10 alkyl. The term “alkyl”, “lower alkyl” or “cycloalkyl” includes methyl, ethyl, isopropyl, propyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, neopentyl, hexyl, cyclopropyl, cyclopropylmethyl, cyclobutyl, cyclobutylmethyl, cyclopentyl, cyclopentylmethyl, cyclohexyl, cyclohexylmethyl, C6 to C12 spirocycles, cyclopropylethyl, cyclobutylethyl, decalinyl, Bicyclo-[1.1.1]-pentyl, norboranyl, bicylo-[2.2.2]-octyl, cubyl, adamantanyl and related cage hydrocarbon moieties. In certain embodiments, the alkyl is a C1-C20 alkyl. In certain embodiments an alkyl is a lower alkyl.

[0021] A “substituted alkyl” is an alkyl which is typically mono-, di-, or tri-substituted with heterocycloalkyl, aryl, substituted aryl, heteroaryl, nitro, cyano (also referred to herein as nitrile), azido, halo, –OR, -SR, -SF_5, -CHO, –COR, –C(O)OR, -C(O)-NR_2, –OC(O)R, -$OC(O)NR_2$, -OC(O)OR, --$P(O)(OR)_2$, -$OP(O)(OR)_2$, –NR2, -N^+R_3 (wherein a counterion may be present), –$CONR_2$, –NRCOR, -NHC(O)OR, -NHC(O)NR2, -$NHC(NH)NR_2$, SO_3^-, -SO_2OR, -OSO_2R, -SO_2NR_2, or -$NRSO_2R$, where each R is, independently, hydrogen, lower alkyl, R′-substituted lower alkyl, aryl, R′-substituted aryl, heteroaryl, heteroaryl(alkyl), R′-substituted aryl(alkyl), or aryl(alkyl) and each R′ is, independently, hydroxy, halo, alkyloxy, cyano, thio, SF_5, nitro, alkyl, halo- alkyl, or amino. Substituted alkyls which are substituted with one to three of the substituents selected from the group consisting of alkynyl, cyano, halo, alkyloxy, thio, nitro, amino, or hydroxy are particularly of interest.

[0022] The term “Aryl” refers to an aromatic ring having (4n+2) pi electrons that may contain 6 to 20 ring carbon atoms, and be composed of a single ring (e.g., phenyl), or two or more condensed rings, such as 2 to 3 condensed rings (e.g., naphthyl), or two or more aromatic rings, such as 2 to 3 aromatic rings, which are linked by a single bond (e.g., biphenylyl). In certain cases, the aryl

is C6-C16 or C6 to C14. In certain embodiments the alkyl group has one or more hydrogen atoms replaced with deuterium.

[0023] Heteroaryl means an aromatic ring system containing (4n+2)pi electrons and comprised of 1 to 10 ring carbon atoms and 1 to 5 heteroatoms selected from O, N, S, Se, having a single ring (e.g., thiophene, pyridine, pyrazine, imidazole, oxazole, tetrazole, etc.), or two or more condensed rings, for example 2 to 3 condensed rings (e.g., indole, benzimidazole, quinolone, quinoxaline, phenothiazine, etc.), or two or more aromatic rings, such as 2 to 3 aromatic rings, which are linked by a single bond (e.g., bipyridyl). In some cases, the heteroaryl is C1-C16, and a selection of 1 to 5 heteroatoms consisting of S, Se, N, and O.

[0024] The term “heterocycloalkyl”, “heterocycle”, “heterocyclic group” or “heterocyclyl” refers to a saturated or unsaturated nonaromatic ring system containing 1 to 10 ring carbon atoms and 1 to 5 heteroatoms selected from O, N, S, Se, having a single ring (e.g., tetrahydrofuran, aziridine, azetidine, pyrrolidine, piperidine, tetrathiopyran, hexamethylene oxide, oxazepane, etc.), or two or more condensed rings, such as 2 to 3 condensed rings (e.g., indoline, tetrahydrobenzodiazapines, etc., including fused, bridged and spiro ring systems, having 3-15 ring atoms, included 1 to 4 heteroatoms. In certain cases, the heterocycloalky is C1-C16, and a selection of 1 to 5 heteroatoms consisting of S, Se, N, and O. In fused ring systems, one or more of the rings can be cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, provided that the point of attachment is through the non-aromatic ring. In certain embodiments, the nitrogen and/or sulfur atom(s) of the heterocyclic group are optionally oxidized to provide for the N-oxide, -S(O)-, or –SO_2- moieties.

[0025] Examples of heterocycles and heteroaryls include, but are not limited to, azetidine, pyrrole, imidazole, benzimidazole, pyrazole, benzopyrazole, tetrazole, 1,2,3-triazole, benzotriazole, 1,2,4-triazole, pyridine, pyrazine, pyrimidine, pyridazine, indolizine, isoindole, indole, dihydroindole, pyrazole, purine, quinolizine, isoquinoline, quinoline, phthalazine, naphthylpyridine, quinoxaline, quinazoline, cinnoline, pteridine, carbazole, carboline, phenanthridine, acridine, phenanthroline, isothiazole, benzoisothiazole, phenazine, isoxazole, benzoisooxazole, phenoxazine, phenothiazine, imidazolidine, imidazoline, piperidine, piperazine, indoline, phthalimide, 1,2,3,4-tetrahydroisoquinoline, 4,5,6,7-tetrahydrobenzo[b]thiophene, thiazole, benzothiazole, thiazolidine, furan, benzofuran, thiophene, benzothiophene, benzo[b]thiophene, morpholinyl, thiomorpholinyl (also referred to as thiamorpholinyl), 1,1-dioxothiomorpholinyl, piperidinyl, pyrrolidine, tetrahydrofuranyl, benzotetrahydrofuranyl, and the like.

[0026] Substituted heterocycloalkyl, aryl, heteroaryl are optionally substituted with, hydrogen, 1 to 3 alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl(alkyl), aryl, substituted aryl, aryl(alkyl), -$SO_2NR^5R^5$, -PO_3H_2, -$NR^5SO_2R^6$ or –$NR_5C(=O)R^6$, wherein R^5 and R^6 are independently, hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl(alkyl), aryl, optionally

substituted heterocycloalkyl, aryloxy, heteroaryl, heteroaryl(alkyl), or R^5 and R^6 together are $-(CH_2)_{3-6}-$ or $-(CH_2)_{0-3}X(CH_2)_{0-3}-$ where X= NR, O, S, SO_2, substituted aryl(alkyl), halo(alkyl), SF_5, NR^53^+, azido, cyano (also referred to herein as nitrile), $-OR^5$, $-SR^5$, $-NR^5R^6$, halogen, nitro, SCH_3, OCF_3, SO_2CH_3, SCF_3, SO_2CF_3, CF_3, $-SO_2OR^5$, $-OSO_2R^5$, CCl_3, $-C(=O)R^5$, $-C(=O)OR^5$; $-C(=O)NR^5R^6$, $-OC(=O)R^5$.

[0027] By "substituted" as in "substituted alkyl," "substituted aryl," and the like, as alluded to in some of the aforementioned definitions, is meant that in the hydrocarbyl, alkyl, aryl, or other moiety, at least one hydrogen atom bound to a carbon (or other) atom is replaced with one or more non-hydrogen substituents. Examples of such substituents include, without limitation, functional groups, and the hydrocarbyl moieties C1-C24 alkyl (including C1-C18 alkyl, further including C1-C12 alkyl, and further including C1-C6 alkyl), C2-C24 alkenyl (including C2-C18 alkenyl, further including C2-C12 alkenyl, and further including C2-C6 alkenyl), C2-C24 alkynyl (including C2-C18 alkynyl, further including C2-C12 alkynyl, and further including C2-C6 alkynyl), C5-C30 aryl (including C5-C20 aryl, and further including C5-C12 aryl), and C6-C30 aralkyl (including C6-C20 aralkyl, and further including C6-C12 aralkyl). The above-mentioned hydrocarbyl moieties may be further substituted with one or more functional groups or additional hydrocarbyl moieties such as those specifically enumerated. Unless otherwise indicated, any of the groups described herein are to be interpreted as including substituted and/or heteroatom-containing moieties, in addition to unsubstituted groups.

[0028] “Sulfonyl” refers to the group SO_2-alkyl, SO_2-substituted alkyl, SO_2-alkenyl, SO_2-substituted alkenyl, SO_2-alkynyl, SO_2-substituted alkynyl, SO_2-cycloalkyl, SO_2-substituted cylcoalkyl, SO_2-cycloalkenyl, SO_2-substituted cylcoalkenyl, SO_2-aryl, SO_2-substituted aryl, SO_2-heteroaryl, SO_2-substituted heteroaryl, SO_2-heterocyclic, and SO_2-substituted heterocyclic, wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein. Sulfonyl includes, by way of example, methyl-SO_2-, phenyl-SO_2-, and 4-methylphenyl-SO_2-. Sulfonimidoyl refers to S(O)(NH)-bonded as for sulfonyl defined above.

[0029] The term "water-soluble group" refers to a functional group that is well solvated in aqueous environments and that imparts improved water solubility to the compound to which it is attached. Water-soluble groups of interest include, but are not limited to, polyalcohols, straight chain or cyclic saccharides, primary, secondary, tertiary, or quaternary amines and polyamines, sulfate groups, sulfonate groups, sulfinate groups, carboxylate groups, phosphate groups, phosphonate groups, phosphinate groups, ascorbate groups, glycols, including polyethylene glycols (PEG) and modified PEGs, and polyethers. In some instances, water-soluble groups are primary, secondary, tertiary, and quaternary amines, carboxylates, phosphonates, phosphates, sulfonates,

sulfates, -N(H)0-1($CH_2CH_2OH)_{1-2}$, -$NHCH_2CH_2N(CH_3)_{2-3}$, -$NHCH_2CH_2SO_3H$, -$NHCH_2CH_2PO_3H_2$ and -$NHCH_2CH_2CO_2H$, -$(CH_2CH_2O)yyCH_2CH_2XRyy$, -$(CH_2CH_2O)yyCH_2CH_2X$-, -$X(CH_2CH_2O)yy$ CH_2CH_2-, glycol, oligoethylene glycol, and polyethylene glycol, wherein yy is selected from 1 to 1000, X is selected from O, S, and NRZZ, and RZZ and RYY are independently selected from H and C1-3 alkyl.

[0030] The term “carboxy isostere” refers to standard medicinal bioisosteric replacement groups for carboxylic acids, amides and ester. These include, but are not limited to: acyl cyanamide, tetrazoles, hydroxychromes, 3-hydroxy-1,2,4-triazoles, 1-hydroxy pyrazoles, 2,4-dihydroxy imidazoles, 1-hydroxy imidazole, 1-hydroxy 1,2,3-triazole, alkylsulfonyl carboxamides, hydroxy isoxazoles, 5-hydroxy 1,2,4-oxadiazoles, thiazoles, 1,2,4-oxadiazoles, 1,2,4-oxadiazolones, oxazoles, triazoles, thiazoles, others hydroxamic acids, sulfonimide, acylsulfonamide, sulfonylureas, oxadiazolone, thiazolidinediones, oxadiazole, thiadiazole, isothiazoles, difluorophenols, tetramic acids, tetronic acids, squaric acids, hydroxyquinoline-ones, hydroxyquinoline-2-ones, boronic acids and phosphoric acids.

[0031] As used herein the term “PEG” refers to a polyethylene glycol or a modified polyethylene glycol. Modified polyethylene glycol polymers include a methoxypolyethylene glycol, and polymers that are unsubstituted or substituted at one end with an alkyl, a substituted alkyl or a substituent (e.g., as described herein).

[0032] By the term “functional groups” is meant chemical groups such as halo, hydroxyl, sulfhydryl, C1-C24 alkoxy, C2-C24 alkenyloxy, C2-C24 alkynyloxy, C5-C20 aryloxy, acyl (including C2-C24 alkylcarbonyl (-CO-alkyl) and C6-C20 arylcarbonyl (-CO-aryl)), acyloxy (-O-acyl), C2-C24 alkoxycarbonyl (-(CO)-O-alkyl), C6-C20 aryloxycarbonyl (-(CO)-O-aryl), halocarbonyl (-CO)-X where X is halo), C2-C24 alkylcarbonato (-O-(CO)-O-alkyl), C6-C20 arylcarbonato (-O-(CO)-O-aryl), carboxy (-COOH), carboxylato (-COO-), carbamoyl (-(CO)-NH2), mono-substituted C1-C24 alkylcarbamoyl (-(CO)-NH(C1-C24 alkyl)), di-substituted alkylcarbamoyl (-(CO)-N(C1-C24 alkyl)2), mono-substituted arylcarbamoyl (-(CO)-NH-aryl), thiocarbamoyl (-(CS)-NH2), carbamido (-NH-(CO)-NH2), cyano (-C≡N), isocyano (-N+≡C-), cyanato (-O-C≡N), isocyanato (-O-N+≡C-), isothiocyanato (-S-C≡N), azido (-N=N+=N-), formyl (-(CO)-H), thioformyl (-(CS)-H), amino (-NH2), mono- and di-(C1-C24 alkyl)-substituted amino, mono- and di-(C5-C20 aryl)-substituted amino, C2-C24 alkylamido (-NH-(CO)-alkyl), C5-C20 arylamido (-NH-(CO)-aryl), imino (-CR=NH where R = hydrogen, C1-C24 alkyl, C5-C20 aryl, C6-C20 alkaryl, C6-C20 aralkyl, etc.), alkylimino (-CR=N(alkyl), where R = hydrogen, alkyl, aryl, alkaryl, etc.), arylimino (-CR=N(aryl), where R = hydrogen, alkyl, aryl, alkaryl, etc.), nitro (-NO2), nitroso (-NO), sulfo (-SO2-OH), sulfonato (-SO2-O-), C1-C24 alkylsulfanyl (-S-alkyl; also termed "alkylthio"), arylsulfanyl (-S-aryl; also termed "arylthio"), C1-C24 alkylsulfinyl (-(SO)-alkyl), C5-C20 arylsulfinyl (-(SO)-aryl), C1-C24 alkylsulfonyl (-SO2-alkyl), C5-C20 arylsulfonyl (-SO2-aryl), phosphono (-P(O)(OH)2), phosphonato (-P(O)(O-)2), phosphinato (-P(O)(O-)), phospho (-PO2),

and phosphino (-PH2), mono- and di-(C1-C24 alkyl)-substituted phosphino, mono- and di-(C5-C20 aryl)-substituted phosphine. In addition, the aforementioned functional groups may, if a particular group permits, be further substituted with one or more additional functional groups or with one or more hydrocarbyl moieties such as those specifically enumerated above.

[0033] When the term "substituted" appears prior to a list of possible substituted groups, it is intended that the term apply to every member of that group. For example, the phrase "substituted alkyl and aryl" is to be interpreted as "substituted alkyl and substituted aryl."

[0034] In addition to the disclosure herein, the term “substituted,” when used to modify a specified group or radical, can also mean that one or more hydrogen atoms of the specified group or radical are each, independently of one another, replaced with the same or different substituent groups as defined below.

[0035] In addition to the groups disclosed with respect to the individual terms herein, substituent groups for substituting for one or more hydrogens (any two hydrogens on a single carbon can be replaced with =O, $=NR^{70}$, $=N\text{-}OR^{70}$, $=N_2$ or =S) on saturated carbon atoms in the specified group or radical are, unless otherwise specified, $-R^{60}$, halo, =O, -OR70, $-SR^{70}$, $-NR^{80}R^{80}$, trihalomethyl, -CN, -OCN, -SCN, -NO, $-NO_2$, $=N_2$, $-N_3$, $-SO_2R^{70}$, $-SO_2O\text{-}M+$, $-SO_2OR^{70}$, $-OSO_2R^{70}$, $-OSO_2O\text{-}M+$, $-OSO_2OR^{70}$, $-P(O)(O\text{-})2(M+)_2$, $-P(O)(OR^{70})O\text{-}M+$, $-P(O)(OR^{70})_2$, $-C(O)R^{70}$, $-C(S)R^{70}$, $-C(NR^{70})R^{70}$, $-C(O)O\text{-}M+$, $-C(O)OR^{70}$, $-C(S)OR^{70}$, $-C(O)NR^{80}R^{80}$, $-C(NR^{70})NR^{80}R^{80}$, $-OC(O)R^{70}$, $-OC(S)R^{70}$, $-OC(O)O\text{-}M+$, $-OC(O)OR^{70}$, $-OC(S)OR^{70}$, $-NR^{70}C(O)R^{70}$, $-NR^{70}C(S)R^{70}$, $-NR^{70}CO_2\text{-}M+$, $-NR^{70}CO_2R^{70}$, $-NR^{70}C(S)OR^{70}$, $-NR^{70}C(O)NR^{80}R^{80}$, $-NR^{70}C(NR^{70})R^{70}$ and $-NR^{70}C(NR^{70})NR^{80}R^{80}$, where R^{60} is selected from the group consisting of optionally substituted alkyl, cycloalkyl, heteroalkyl, heterocycloalkylalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl and heteroarylalkyl, each R^{70} is independently hydrogen or R^{60}; each R^{80} is independently R^{70} or alternatively, two R^{80}'s, taken together with the nitrogen atom to which they are bonded, form a 5-, 6- or 7-membered heterocycloalkyl which may optionally include from 1 to 4 of the same or different additional heteroatoms selected from the group consisting of O, N and S, of which N may have -H or C1-C3 alkyl substitution; and each M+ is a counter ion with a net single positive charge. Each M+ may independently be, for example, an alkali ion, such as K+, Na+, Li+; an ammonium ion, such as $+N(R^{60})_4$; or an alkaline earth ion, such as [Ca2+]0.5, [Mg2+]0.5, or [Ba2+]0.5 (“subscript 0.5 means that one of the counter ions for such divalent alkali earth ions can be an ionized form of a compound of the invention and the other a typical counter ion such as chloride, or two ionized compounds disclosed herein can serve as counter ions for such divalent alkali earth ions, or a doubly ionized compound of the invention can serve as the counter ion for such divalent alkali earth ions). As specific examples, $-NR^{80}R^{80}$ is meant to include $-NH_2$, -NH-alkyl, N-pyrrolidinyl, N-piperazinyl, 4N-methyl-piperazin-1-yl, N-morpholinyl, $-N(H)0\text{-}1(CH_2CH_2OH)_{1\text{-}2}$, $-NHCH_2CH_2N(CH_3)_{2\text{-}3}$, $-NHCH_2CH_2SO_3H$, $-NHCH_2CH_2PO_3H_2$ and $-NHCH_2CH_2CO_2H$.

[0036] In addition to the disclosure herein, substituent groups for hydrogens on unsaturated carbon atoms in "substituted" alkene, alkyne, aryl and heteroaryl groups are, unless otherwise specified, $-R^{60}$, halo, -O-M+, $-OR^{70}$, $-SR^{70}$, -S–M+, $-NR^{80}R^{80}$, trihalomethyl, $-CF_3$, -CN, -OCN, -SCN, -NO, $-NO_2$, $-N_3$, $-SO_2R^{70}$, $-SO_3$–M+, $-SO_3R^{70}$, $-OSO_2R^{70}$, $-OSO_3$–M+, $-OSO_3R^{70}$, $-PO_3$-2(M+)$_2$, -P(O)(OR^{70})O–M+, -P(O)(OR^{70})$_2$, $-C(O)R^{70}$, $-C(S)R^{70}$, $-C(NR^{70})R^{70}$, $-CO_2$–M+, $-CO_2R^{70}$, $-C(S)OR^{70}$, $-C(O)NR^{80}R^{80}$, $-C(NR^{70})NR^{80}R^{80}$, $-OC(O)R^{70}$, $-OC(S)R^{70}$, $-OCO_2$–M+, $-OCO_2R^{70}$, $-OC(S)OR^{70}$, $-NR^{70}C(O)R^{70}$, $-NR^{70}C(S)R^{70}$, $-NR^{70}CO_2$–M+, $-NR^{70}CO_2R^{70}$, $-NR^{70}C(S)OR^{70}$, $-NR^{70}C(O)NR^{80}R^{80}$, $-NR^{70}C(NR^{70})R^{70}$ and $-NR^{70}C(NR^{70})NR^{80}R^{80}$, where R^{60}, R^{70}, R^{80} and M+ are as previously defined, provided that in case of substituted alkene or alkyne, the substituents are not -O-M+, $-OR^{70}$, $-SR^{70}$, or -S–M+.

[0037] In addition to the groups disclosed with respect to the individual terms herein, substituent groups for hydrogens on nitrogen atoms in "substituted" heteroalkyl and cycloheteroalkyl groups are, unless otherwise specified, $-R^{60}$, -O-M+, $-OR^{70}$, $-SR^{70}$, -S-M+, $-NR^{80}R^{80}$, trihalomethyl, $-CF_3$, -CN, -NO, $-NO_2$, $-S(O)_2R^{70}$, $-S(O)_2$O-M+, $-S(O)_2OR^{70}$, $-OS(O)_2R^{70}$, $-OS(O)_2$O-M+, $-OS(O)_2OR^{70}$, -P(O)(O-)$_2$(M+)$_2$, -P(O)(OR^{70})O-M+, -P(O)(OR^{70})(OR^{70}), $-C(O)R^{70}$, $-C(S)R^{70}$, $-C(NR^{70})R^{70}$, $-C(O)OR^{70}$, $-C(S)OR^{70}$, $-C(O)NR^{80}R^{80}$, $-C(NR^{70})NR^{80}R^{80}$, $-OC(O)R^{70}$, $-OC(S)R^{70}$, $-OC(O)OR^{70}$, $-OC(S)OR^{70}$, $-NR^{70}C(O)R^{70}$, $-NR^{70}C(S)R^{70}$, $-NR^{70}C(O)OR^{70}$, $-NR^{70}C(S)OR^{70}$, $-NR^{70}C(O)NR^{80}R^{80}$, $-NR^{70}C(NR^{70})R^{70}$ and $-NR^{70}C(NR^{70})NR^{80}R^{80}$, where R^{60}, R^{70}, R^{80} and M+ are as previously defined.

[0038] Salts include but are not limited to: Na, K, Ca, Mg, ammonium, tetraalkyl ammonium, aryl and alkyl sulfonates, phosphates, carboxylates, sulfates, Cl, Br, and guanidinium.

[0039] Unless otherwise specified, reference to an atom is meant to include isotopes of that atom. For example, reference to H is meant to include ^1H, ^2H (i.e., D) and ^3H (i.e., T), and reference to C is meant to include ^{12}C and all isotopes of carbon (such as ^{13}C).

[0040] In addition to the disclosure herein, in a certain embodiment, a group that is substituted has 1, 2, 3, or 4 substituents, 1, 2, or 3 substituents, 1 or 2 substituents, or 1 substituent.

[0041] Unless indicated otherwise, the nomenclature of substituents that are not explicitly defined herein are arrived at by naming the terminal portion of the functionality followed by the adjacent functionality toward the point of attachment. For example, the substituent "heterocycloalkyl(alkyl)" refers to the group (heterocycloalkyl)-(alkyl)-.

[0042] As to any of the groups disclosed herein which contain one or more substituents, it is understood, of course, that such groups do not contain any substitution or substitution patterns which are sterically impractical and/or synthetically non-feasible. In addition, the subject compounds include all stereochemical isomers arising from the substitution of these compounds.

[0043] In certain embodiments, a substituent may contribute to optical isomerism and/or stereo isomerism of a compound. Salts, solvates, hydrates, and prodrug forms of a compound are also

of interest. Polymorphic, pseudo-polymorphic, amorphous and co-crystal forms of a compound are also of interest. All such forms are embraced by the present disclosure. Thus, the compounds described herein include salts, solvates, hydrates, prodrug and isomer forms thereof, including the pharmaceutically acceptable salts, solvates, hydrates, prodrugs and isomers thereof. In certain embodiments, a compound may be a metabolized into a pharmaceutically active derivative.

[0044] Turning to the administration of therapeutics, the compounds of the invention may be administered as described herein, or in a form from which the active agent can be derived, such as a prodrug. A "prodrug" is a derivative of a compound described herein, the pharmacologic action of which results from the conversion by chemical or metabolic processes in vivo to the active compound. Prodrugs include compounds wherein an amino acid residue, or a polypeptide chain of two or more (e.g., two, three or four) amino acid residues is covalently joined through an amide or ester bond to a free amino, hydroxyl or carboxylic acid group of the compound. Additional types of prodrugs are also encompassed. For instance, free carboxyl groups can be derivatized as amides or alkyl esters. Prodrug esters as employed herein includes esters and carbonates formed by reacting one or more hydroxyls of compounds of the method of the invention with alkyl, alkoxy, or aryl substituted acylating agents employing procedures known to those skilled in the art to generate acetates, pivalates, methylcarbonates, benzoates and the like. As further examples, free hydroxyl groups may be derivatized using groups including but not limited to hemisuccinates, phosphate esters, dimethylaminoacetates, and phosphoryloxymethyloxycarbonyls, as outlined in Advanced Drug Delivery Reviews, 1996, 19, 115. Carbamate prodrugs of hydroxyl and amino groups are also included, as are carbonate prodrugs, sulfonate prodrugs, sulfonate esters and sulfate esters of hydroxyl groups. Free amines can also be derivatized to amides, sulfonamides or phosphonamides. All of the stated prodrug moieties may incorporate groups including but not limited to ether, amine and carboxylic acid functionalities. Moreover, any compound that can be converted in vivo to provide the bioactive agent (e.g., a compound of formula I) is a prodrug within the scope of the invention. Various forms of prodrugs are well known in the art. A comprehensive description of prodrugs and prodrug derivatives are described in: (a) The Practice of Medicinal Chemistry, Camille G. Wermuth et al., (Academic Press, 1996); (b) Design of Prodrugs, edited by H. Bundgaard, (Elsevier, 1985); (c) A Textbook of Drug Design and Development, P. Krogsgaard-Larson and H. Bundgaard, eds., (Harwood Academic Publishers, 1991).

[0045] In general, prodrugs may be designed to improve the penetration of a drug across biological membranes in order to obtain improved drug absorption, to prolong duration of action of a drug (slow release of the parent drug from a prodrug, decreased first-pass metabolism of the drug), to target the drug action (e.g. organ or tumor-targeting, lymphocyte targeting), to modify or improve aqueous solubility of a drug (e.g., i.v. preparations and eyedrops), to improve topical

drug delivery (e.g. dermal and ocular drug delivery), to improve the chemical/enzymatic stability of a drug, or to decrease off-target drug effects, and more generally in order to improve the therapeutic efficacy of the compounds utilized in the invention.

[0046] "Pharmaceutically acceptable salts and esters" means salts and esters that are pharmaceutically acceptable and have the desired pharmacological properties. Such salts include salts that can be formed where acidic protons present in the compounds are capable of reacting with inorganic or organic bases. Suitable inorganic salts include those formed with the alkali metals, *e.g.* sodium and potassium, magnesium, calcium, and aluminum. Suitable organic salts include those formed with organic bases such as the amine bases, *e.g.*, ethanolamine, diethanolamine, triethanolamine, tromethamine, N methylglucamine, and the like. Such salts also include acid addition salts formed with inorganic acids (*e.g.*, hydrochloric and hydrobromic acids) and organic acids (*e.g.*, acetic acid, citric acid, maleic acid, and the alkane- and arene-sulfonic acids such as methanesulfonic acid and benzenesulfonic acid). Pharmaceutically acceptable esters include esters formed from carboxy, sulfonyloxy, and phosphonoxy groups present in the compounds, *e.g.*, C_{1-6} alkyl esters. When there are two acidic groups present, a pharmaceutically acceptable salt or ester can be a mono-acid-mono-salt or ester or a di-salt or ester; and similarly, where there are more than two acidic groups present, some or all of such groups can be salified or esterified. Compounds named in this invention can be present in unsalified or unesterified form, or in salified and/or esterified form, and the naming of such compounds is intended to include both the original (unsalified and unesterified) compound and its pharmaceutically acceptable salts and esters. Also, certain compounds named in this invention may be present in more than one stereoisomeric form, and the naming of such compounds is intended to include all single stereoisomers and all mixtures (whether racemic or otherwise) of such stereoisomers.

[0047] The terms "pharmaceutically acceptable", "physiologically tolerable" and grammatical variations thereof, as they refer to compositions, carriers, diluents and reagents, are used interchangeably and represent that the materials are capable of administration to or upon a human without the production of undesirable physiological effects to a degree that would prohibit administration of the composition.

[0048] A pharmaceutical formulation is a composition comprising different chemical substances including but not limited to active drugs, excipients, etc. which are combined and formulated to produce a final medicinal product for the treatment of humans or other organisms.

[0049] A sterile formulation is a formulation substantially free of living germs or microorganisms.

[0050] A therapeutically effective amount is that mass of an active drug in a formulation, and the frequency of administration of a formulation, that results in the prevention of the development of symptoms, prevention of development of markers or signs of a disease, prevention of the development of tissue or organ damage, prevention of the progression of a disease, reduction in the severity of a disease, or treatment of disease symptoms as defined above.

[0051] It is within the level of skill of a clinician to determine the preferred route of administration and the corresponding dosage form and amount, as well as the dosing regimen, i.e., the frequency of dosing. Such information may be obtained in a straightforward manner in accordance with the teachings and guidelines contained in the instant specification taken in light of the knowledge and skill of the artisan. The results that are obtained can also be correlated with data from corresponding evaluations of an approved product in the same assays.

[0052] Dosage and frequency may vary depending on the half-life of the agent in the patient. It will be understood by one of skill in the art that such guidelines will be adjusted for the molecular weight of the active agent, the clearance from the blood, the mode of administration, and other pharmacokinetic parameters. The dosage may also be varied for localized administration, e.g. intranasal, inhalation, etc., or for systemic administration, e.g. i.m., i.p., i.v., oral, and the like.

[0053] Dose range for an agent is the range of the mass of active drug in, and frequency of administration of, a formulation which results in the prevention of the development of symptoms, prevention of the development of a disease, prevention of development of abnormal markers or signs of a disease, prevention of the development of tissue or organ damage, prevention of the progression of a disease, reduction in the severity of a disease, or treatment of disease symptoms as defined above.

[0054] Regimen means dose, frequency of administration, for example twice-per day, daily, weekly, bi-weekly etc., and duration of treatment, for example one day, several days, one week, several weeks, one month, several months, one year, several years, etc.

[0055] Unit doses (also called dosage forms) are essentially pharmaceutical products in the form in which they are marketed for use, typically involving a mixture of active drug components and nondrug components (excipients), along with other non-reusable material that may not be considered either ingredient or packaging (such as a capsule shell, for example). Depending on the context, multi(ple) unit dose can refer to distinct drug products packaged together, or to a single drug product containing multiple drugs and/or doses. The term dosage form can also sometimes refer only to the chemical formulation of a drug product's constituent drug substance(s) and any blends involved.

[0056] A dose pack is a premeasured amount of drug to be dispensed to a patient in a set or variable dose and in a package including but not limited to a blister pack or other series of container for the purpose of facilitating a dose regimen. A dose pack can be used to facilitate delivery of an initial and/or loading dose to an individual, followed by a maintenance dose.

[0057] An excipient is generally a pharmacologically inactive substance formulated with the active pharmaceutical ingredient ("API") of a medication. Excipients are commonly used to bulk up formulations that contain potent active ingredients (thus often referred to as "bulking agents," "fillers," or "diluents"), to allow convenient and accurate dispensation of a drug substance when

producing a dosage form. They also can serve various therapeutic-enhancing purposes, such as facilitating drug absorption or solubility, or other pharmacokinetic considerations.

[0058] An active agent can be administered by any suitable means, including topical, oral, parenteral, intrapulmonary, and intranasal. Parenteral infusions include intramuscular, intravenous (bolus or slow drip), intraperitoneal, intrathecal or subcutaneous administration. An agent can be administered in any manner which is medically acceptable. This may include injections, by parenteral routes such as intravenous, intravascular, intraarterial, subcutaneous, intramuscular, intratumor, intraperitoneal, intraventricular, intraepidural, or others as well as oral, nasal, ophthalmic, rectal, or topical. Sustained release administration is also specifically included in the disclosure, by such means as depot injections or erodible implants.

[0059] As noted above, an agent can be formulated with an a pharmaceutically acceptable carrier (one or more organic or inorganic ingredients, natural or synthetic, with which a subject agent is combined to facilitate its application). A suitable carrier includes sterile saline although other aqueous and non-aqueous isotonic sterile solutions and sterile suspensions known to be pharmaceutically acceptable are known to those of ordinary skill in the art. An "effective amount" refers to that amount which is capable of ameliorating or delaying progression of the diseased, degenerative or damaged condition. An effective amount can be determined on an individual basis and will be based, in part, on consideration of the symptoms to be treated and results sought. An effective amount can be determined by one of ordinary skill in the art employing such factors and using no more than routine experimentation.

[0060] An agent can be administered as a pharmaceutical composition comprising a pharmaceutically acceptable excipient. The preferred form depends on the intended mode of administration and therapeutic application. The compositions can also include, depending on the formulation desired, pharmaceutically-acceptable, non-toxic carriers or diluents, which are defined as vehicles commonly used to formulate pharmaceutical compositions for animal or human administration. The diluent is selected so as not to affect the biological activity of the combination. Examples of such diluents are distilled water, physiological phosphate-buffered saline, Ringer's solutions, dextrose solution, and Hank's solution. In addition, the pharmaceutical composition or formulation may also include other carriers, adjuvants, or nontoxic, nontherapeutic, nonimmunogenic stabilizers and the like.

[0061] As used herein, compounds which are "commercially available" may be obtained from commercial sources including but not limited to Acros Organics (Pittsburgh PA), Aldrich Chemical (Milwaukee WI, including Sigma Chemical and Fluka), Apin Chemicals Ltd. (Milton Park UK), Avocado Research (Lancashire U.K.), BDH Inc. (Toronto, Canada), Bionet (Cornwall, U.K.), Chemservice Inc. (West Chester PA), Crescent Chemical Co. (Hauppauge NY), Eastman Organic Chemicals, Eastman Kodak Company (Rochester NY), Fisher Scientific Co. (Pittsburgh PA), Fisons Chemicals (Leicestershire UK), Frontier Scientific (Logan UT), ICN Biomedicals, Inc.

(Costa Mesa CA), Key Organics (Cornwall U.K.), Lancaster Synthesis (Windham NH), Maybridge Chemical Co. Ltd. (Cornwall U.K.), Parish Chemical Co. (Orem UT), Pfaltz & Bauer, Inc. (Waterbury CN), Polyorganix (Houston TX), Pierce Chemical Co. (Rockford IL), Riedel de Haen AG (Hannover, Germany), Spectrum Quality Product, Inc. (New Brunswick, NJ), TCI America (Portland OR), Trans World Chemicals, Inc. (Rockville MD), Wako Chemicals USA, Inc. (Richmond VA), Novabiochem and Argonaut Technology.

[0062] Compounds useful for co-administration with the active agents of the invention can also be made by methods known to one of ordinary skill in the art. As used herein, "methods known to one of ordinary skill in the art" may be identified though various reference books and databases. Suitable reference books and treatises that detail the synthesis of reactants useful in the preparation of compounds of the present invention, or provide references to articles that describe the preparation, include for example, "Synthetic Organic Chemistry", John Wiley & Sons, Inc., New York; S. R. Sandler et al., "Organic Functional Group Preparations," 2nd Ed., Academic Press, New York, 1983; H. O. House, "Modern Synthetic Reactions", 2nd Ed., W. A. Benjamin, Inc. Menlo Park, Calif. 1972; T. L. Gilchrist, “Heterocyclic Chemistry”, 2nd Ed., John Wiley & Sons, New York, 1992; J. March, “Advanced Organic Chemistry: Reactions, Mechanisms and Structure”, 4th Ed., Wiley-Interscience, New York, 1992. Specific and analogous reactants may also be identified through the indices of known chemicals prepared by the Chemical Abstract Service of the American Chemical Society, which are available in most public and university libraries, as well as through on-line databases (the American Chemical Society, Washington, D.C., may be contacted for more details). Chemicals that are known but not commercially available in catalogs may be prepared by custom chemical synthesis houses, where many of the standard chemical supply houses (e.g., those listed above) provide custom synthesis services.

[0063] The active agents of the invention and/or the compounds administered therewith are incorporated into a variety of formulations for therapeutic administration. In one aspect, the agents are formulated into pharmaceutical compositions by combination with appropriate, pharmaceutically acceptable carriers or diluents, and are formulated into preparations in solid, semi-solid, liquid or gaseous forms, such as tablets, capsules, powders, granules, ointments, solutions, suppositories, injections, inhalants, gels, microspheres, and aerosols. As such, administration of the active agents and/or other compounds can be achieved in various ways, usually by oral administration. The active agents and/or other compounds may be systemic after administration or may be localized by virtue of the formulation, or by the use of an implant that acts to retain the active dose at the site of implantation. Localized administration to the brain may be used, e.g. using a pump, convection, etc. as known in the art.

[0064] In pharmaceutical dosage forms, the active agents and/or other compounds may be administered in the form of their pharmaceutically acceptable salts, or they may also be used alone or in appropriate association, as well as in combination with other pharmaceutically active

compounds. The agents may be combined, as previously described, to provide a cocktail of activities. The following methods and excipients are exemplary and are not to be construed as limiting the invention.

[0065] For oral preparations, the agents can be used alone or in combination with appropriate additives to make tablets, powders, granules or capsules, for example, with conventional additives, such as lactose, mannitol, corn starch or potato starch; with binders, such as crystalline cellulose, cellulose derivatives, acacia, corn starch or gelatins; with disintegrators, such as corn starch, potato starch or sodium carboxymethylcellulose; with lubricants, such as talc or magnesium stearate; and if desired, with diluents, buffering agents, moistening agents, preservatives and flavoring agents.

[0066] The pharmaceutically acceptable excipients, such as vehicles, adjuvants, carriers or diluents, are commercially available. Moreover, pharmaceutically acceptable auxiliary substances, such as pH adjusting and buffering agents, tonicity adjusting agents, stabilizers, wetting agents and the like, are commercially available. Any compound useful in the methods and compositions of the invention can be provided as a pharmaceutically acceptable base addition salt. "Pharmaceutically acceptable base addition salt" refers to those salts which retain the biological effectiveness and properties of the free acids, which are not biologically or otherwise undesirable. These salts are prepared from addition of an inorganic base or an organic base to the free acid. Salts derived from inorganic bases include, but are not limited to, the sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Preferred inorganic salts are the ammonium, sodium, potassium, calcium, and magnesium salts. Salts derived from organic bases include, but are not limited to, salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, N-ethylpiperidine, polyamine resins and the like. Particularly preferred organic bases are isopropylamine, diethylamine, ethanolamine, trimethylamine, dicyclohexylamine, choline and caffeine.

[0067] Depending on the patient and condition being treated and on the administration route, the active agent may be administered in dosages of 0.001 mg to 500 mg /kg body weight per day, for example at least about 1 μg/kg, at least about 5 μg/kg; at least about 10 μg/kg; at least about 25 μg/kg; at least about 50 μg/kg; at least about 100 μg/kg; at least about 250 μg/kg; at least about 500 μg/kg; at least about 750 μg/kg; at least about 1 mg/kg; at least about 5 mg/kg; at least about 10 mg/kg; at least about 25 mg/kg; at least about 50 mg/kg; at least about 100 mg/kg; at least about 250 mg/kg; up to about 500 mg/kg; up to about 250 mg/kg; up to about 100 mg/kg;

up to about 50 mg/kg; up to about 25 mg/kg; up to about 10 mg/kg; up to about 5 mg/kg; up to about 1 mg/kg. Ranges may be, for example, from about 1 μg/ml to about 1 mg/ml, from about 100 μg/ml to about 1 mg/ml, from about 100 μg/ml to about 10 mg/ml, from about 500 μg/ml to about 10 mg/ml, from about 500 μg/ml to about 1100 mg/ml,, and intervening values thereof. Dosages will be appropriately adjusted for pediatric formulation.

[0068] An effective dose may be administered at suitable intervals, e.g. every 4 hours, every 6 hours, every 12 hours, daily, every 2 days, every 3 days, semi-weekly, weekly, bi-weekly, monthly, and for a period of time sufficient for the desired effect, e.g. 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 3 months, 4 months, 5 months, 6 months, and may be continued for extended periods of time, e.g. over the course of years.

[0069] Acceptable excipients, or stabilizers are non-toxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid and methionine; preservatives (such as octadecyidimethylbenzyl ammonium chloride; hexamethonium chloride; benzalkonium chloride, benzethonium chloride; phenol, butyl or benzyl alcohol; alkyl parabens such as methyl or propyl paraben; catechol; resorcinol; cyclohexanol; 3-pentanol; and m-cresol); low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, histidine, arginine, or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrins; chelating agents such as EDTA; sugars such as sucrose, mannitol, trehalose or sorbitol; salt-forming counter-ions such as sodium; metal complexes (e.g., Zn-protein complexes); and/or non-ionic surfactants such as TWEEN™, PLURONICS™ or polyethylene glycol (PEG). Formulations to be used for in vivo administration must be sterile. This is readily accomplished by filtration through sterile filtration membranes.

[0070] The active ingredients may also be entrapped in microcapsule prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsule and poly-(methylmethacylate) microcapsule, respectively, in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nano-particles and nanocapsules) or in macroemulsions. Such techniques are disclosed in Remington's Pharmaceutical Sciences 16th edition, Osol, A. Ed. (1980).

[0071] Compositions can be prepared as injectables, either as liquid solutions or suspensions; solid forms suitable for solution in, or suspension in, liquid vehicles prior to injection can also be prepared. The preparation also can be emulsified or encapsulated in liposomes or micro particles such as polylactide, polyglycolide, or copolymer for enhanced adjuvant effect, as discussed above. Langer, Science 249: 1527, 1990 and Hanes, Advanced Drug Delivery Reviews 28: 97-119, 1997. The agents of this invention can be administered in the form of a depot injection or

implant preparation which can be formulated in such a manner as to permit a sustained or pulsatile release of the active ingredient. The pharmaceutical compositions are generally formulated as sterile, substantially isotonic and in full compliance with all Good Manufacturing Practice (GMP) regulations of the U.S. Food and Drug Administration.

[0072] Toxicity of the active agents can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., by determining the LD50 (the dose lethal to 50% of the population) or the LD100 (the dose lethal to 100% of the population). The dose ratio between toxic and therapeutic effect is the therapeutic index. The data obtained from these cell culture assays and animal studies can be used in further optimizing and/or defining a therapeutic dosage range and/or a sub-therapeutic dosage range (e.g., for use in humans). The exact formulation, route of administration and dosage can be chosen by the individual physician in view of the patient's condition.

[0073] The terms “subject,” “individual,” and “patient” are used interchangeably herein to refer to a mammal being assessed for treatment and/or being treated. In some embodiments, the mammal is a human. The terms “subject,” “individual,” and “patient” encompass, without limitation, individuals having a disease. Subjects may be human, but also include other mammals, particularly those mammals useful as laboratory models for human disease, e.g., mice, rats, etc.

[0074] The term “sample” with reference to a patient encompasses blood and other liquid samples of biological origin, solid tissue samples such as a biopsy specimen or tissue cultures or cells derived therefrom and the progeny thereof. The term also encompasses samples that have been manipulated in any way after their procurement, such as by treatment with reagents; washed; or enrichment for certain cell populations, such as diseased cells. The definition also includes samples that have been enriched for particular types of molecules, e.g., nucleic acids, polypeptides, etc. The term “biological sample” encompasses a clinical sample, and also includes tissue obtained by surgical resection, tissue obtained by biopsy, cells in culture, cell supernatants, cell lysates, tissue samples, organs, bone marrow, blood, plasma, serum, and the like. A “biological sample” includes a sample obtained from a patient’s diseased cell, e.g., a sample comprising polynucleotides and/or polypeptides that is obtained from a patient’s diseased cell (e.g., a cell lysate or other cell extract comprising polynucleotides and/or polypeptides); and a sample comprising diseased cells from a patient. A biological sample comprising a diseased cell from a patient can also include non-diseased cells.

[0075] The term “diagnosis” is used herein to refer to the identification of a molecular or pathological state, disease or condition in a subject, individual, or patient.

[0076] The term “prognosis” is used herein to refer to the prediction of the likelihood of death or disease progression, including recurrence, spread, and drug resistance, in a subject, individual, or patient. The term “prediction” is used herein to refer to the act of foretelling or estimating, based on observation, experience, or scientific reasoning, the likelihood of a subject, individual, or

patient experiencing a particular event or clinical outcome. In one example, a physician may attempt to predict the likelihood that a patient will survive.

[0077] As used herein, the terms “treatment,” “treating,” and the like, refer to administering an agent, or carrying out a procedure, for the purposes of obtaining an effect on or in a subject, individual, or patient. The effect may be prophylactic in terms of completely or partially preventing a disease or symptom thereof and/or may be therapeutic in terms of effecting a partial or complete cure for a disease and/or symptoms of the disease. “Treatment,” as used herein, may include treatment of a disease in a mammal, particularly in a human, and includes: (a) inhibiting the disease, i.e., arresting its development; and (b) relieving the disease or its symptoms, i.e., causing regression of the disease or its symptoms.

[0078] Treating may refer to any indicia of success in the treatment or amelioration or prevention of a disease, including any objective or subjective parameter such as abatement; remission; diminishing of symptoms or making the disease condition more tolerable to the patient; slowing in the rate of degeneration or decline, or tumor growth as appropriate for the condition; or making the final point of degeneration less debilitating. The treatment or amelioration of symptoms can be based on objective or subjective parameters; including the results of an examination by a physician. The term "therapeutic effect" refers to the reduction, elimination, or prevention of the disease, symptoms of the disease, or side effects of the disease in the subject.

[0079] As used herein, a "therapeutically effective amount" refers to that amount of the therapeutic agent sufficient to treat or manage a disease or disorder. A therapeutically effective amount may refer to the amount of therapeutic agent sufficient to delay or minimize the onset of disease, e.g., to delay or minimize the growth and spread of cancer. A therapeutically effective amount may also refer to the amount of the therapeutic agent that provides a therapeutic benefit in the treatment or management of a disease. Further, a therapeutically effective amount with respect to a therapeutic agent of the invention means the amount of therapeutic agent alone, or in combination with other therapies, that provides a therapeutic benefit in the treatment or management of a disease.

[0080] As used herein, the term “dosing regimen” refers to a set of unit doses (typically more than one) that are administered individually to a subject, typically separated by periods of time. In some embodiments, a given therapeutic agent has a recommended dosing regimen, which may involve one or more doses. In some embodiments, a dosing regimen comprises a plurality of doses each of which are separated from one another by a time period of the same length; in some embodiments, a dosing regimen comprises a plurality of doses and at least two different time periods separating individual doses. In some embodiments, all doses within a dosing regimen are of the same unit dose amount. In some embodiments, different doses within a dosing regimen are of different amounts. In some embodiments, a dosing regimen comprises a first dose in a first dose amount, followed by one or more additional doses in a second dose amount

different from the first dose amount. In some embodiments, a dosing regimen comprises a first dose in a first dose amount, followed by one or more additional doses in a second dose amount same as the first dose amount. In some embodiments, a dosing regimen is correlated with a desired or beneficial outcome when administered across a relevant population (i.e., is a therapeutic dosing regimen).

[0081] "In combination with", "combination therapy" and "combination products" refer, in certain embodiments, to the concurrent administration to a patient of the agents described herein in combination with additional therapies, e.g. surgery, radiation, chemotherapy, and the like. When administered in combination, each component can be administered at the same time or sequentially in any order at different points in time. Thus, each component can be administered separately but sufficiently closely in time so as to provide the desired therapeutic effect.

[0082] "Concomitant administration" means administration of one or more components, such as the pyrazole agents, known therapeutic agents, etc. at such time that the combination will have a therapeutic effect. Such concomitant administration may involve concurrent (*i.e.* at the same time), prior, or subsequent administration of components. A person of ordinary skill in the art would have no difficulty determining the appropriate timing, sequence and dosages of administration.

[0083] The use of the term "in combination" does not restrict the order in which prophylactic and/or therapeutic agents are administered to a subject with a disorder. A first prophylactic or therapeutic agent can be administered prior to (e.g., 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks 6 weeks, 8 weeks, or 12 weeks before), concomitantly with, or subsequent to (e.g., 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks after) the administration of a second prophylactic or therapeutic agent to a subject with a disorder.

Methods of Treatment

[0084] The present invention relates generally to compounds, and methods of using such compounds, that selectively inhibit LRRK2 protein kinase activity. More specifically, the compounds may be used in treating diseases that implicate LRRK2, such as, for example neuroinflammatory and neurodegenerative disorders (e.g., Parkinson's Disease, HIV-induced brain inflammation, Amyotrophic Lateral Sclerosis (ALS), Multiple Sclerosis (MS), Alzheimer's Disease (AD), Traumatic Brain Injury (TBI), and the like), inflammatory disorders (e.g., Crohn's disease, other forms of inflammatory bowel disease, or leprosy), or cancer. Specifically, the compounds of the invention may be used for treating or delaying the progression of a disorder or disease that may be alleviated by inhibiting LRRK2 kinase activity; and/or preventing or deterring

mutant LRRK2 activity, in a person in need of such treatment, by administering a therapeutically effective amount of at least one compound disclosed herein.

[0085] The *LRRK2* gene encodes a member of the leucine-rich repeat kinase family and encodes a protein with an ankryin repeat region, a leucine-rich repeat (LRR) domain, a kinase domain, a DFG-like motif, a RAS domain, a GTPase domain, a kinase domain, and a WD40 domain. The protein is present largely in the cytoplasm but also associates with the mitochondrial outer membrane. Mutations in *LRRK2* are the most common known genetic cause of familial and sporadic PD, accounting for approximately 5% of individuals with a family history of the disease and 3% of sporadic cases. It has been suggested that the G2019S mutation results in hyperphosphorylation of downstream targets leading to disruption of membrane flux and mitochondrial, lysosomal and synaptic signaling defects. Phosphorylation of membrane associated Rab substrates is inhanced by at least 2 fold by the LRRK2 G2019S mutation (i.e. gain of function mutation) which suggests that (G2019S) mutant LRRK2-induced neurodegeneration in PD may be partly mediated by increased phosphorylation of Rabs which may interfere with neurite outgrowth, axonal transport, and synapse formation.

[0086] Human (Homo sapiens) leucine-rich repeat kinase 2 (LRRK2) is located on chromosome 12 (genomic coordinates (GRCh38): 12:40, 224,894-40,369, 284). The gene is 9239 bp mRNA (RefSeq Gene ID: 120892; Official Symbol: LRRK2; Official Full Name: leucine rich repeat kinase 2) and is assigned NCBI Reference Sequence: NM_198578.3 (SEQ ID NO: 3); ACCESSION: NM_198578; Ensembl: ENSG00000188906. LRRK2 is also known as: PARK8; RIPK7; ROCO2; AURA17; DARDARIN; FLJ45829; DKFZp434H2111. Human LRRK2 protein is assigned NCBI Reference Sequence: NP_940980.3 (2527 aa; SEQ ID NO: 4).

[0087] Genotyping of an individual for disease-associated polymorphisms may be performed prior to treatment. Such methods and polymorphisms are known in the art, for a review see, for example, Fatahian et al. (2019) Folia Neuropathol 57(1):1-5; Paisán-Ruíz et al. (2005) Neurology 65 (5) 696-700. In some embodiments the mutated form of human LRRK2 comprises an amino acid modification at residue G2019, including without limitation amino acid substitutions and deletions such as G2019S. In some embodiments the mutated form of human LRRK2 comprises an amino acid modification at one or more of residues G2019, I2020, and R1441, including without limitation the mutations G2019S, I2020T, R1441C, R1441H, and R1141G.

[0088] For example, the compounds of the disclosure may be used in methods of treating Parkinson's Disease (PD), Crohn's disease, and cancer.

[0089] Parkinson disease is a slowly progressive, degenerative disorder characterized by resting tremor, stiffness (rigidity), slow and decreased movement (bradykinesia), and eventually gait and/or postural instability. Diagnosis is clinical. Currently treatment aims to restore dopaminergic function in the brain with levodopa plus carbidopa and/or other drugs, e.g. dopamine agonists, monoamine oxidase type B [MAO-B] inhibitors, amantadine. For refractory, disabling symptoms

in patients without dementia, stereotactic deep brain stimulation or lesional surgery and levodopa and an apomorphine pump may help.

[0090] The pathologic hallmark of Parkinson disease is synuclein-filled Lewy bodies in the nigrostriatal system; however, synuclein can accumulate in many other parts of the nervous system, including the dorsal motor nucleus of the vagus nerve, basal nucleus of Meynert, hypothalamus, neocortex, olfactory bulb, sympathetic ganglia, and myenteric plexus of the gastrointestinal tract. Lewy bodies appear in a sequence, and many experts think that signs and symptoms of Parkinson disease is a relatively late development in a systemic synucleinopathy. Other synucleinopathies (synuclein deposition disorders) include dementia with Lewy bodies and multiple system atrophy. Parkinson disease may share features of other synucleinopathies, such as autonomic dysfunction and dementia.

[0091] In Parkinson disease, pigmented neurons of the substantia nigra, locus ceruleus, and other brain stem dopaminergic cell groups degenerate. Loss of substantia nigra neurons results in depletion of dopamine in the striatum (part of the basal ganglia) and causes many of the motor manifestations of Parkinson disease.

[0092] A genetic predisposition is likely in at least in some cases of Parkinson disease. About 10% of patients have a family history of Parkinson disease. Several abnormal genes have been identified. Inheritance is autosomal dominant for some genes and autosomal recessive for others. Mutations in *LRRK2* are the most prevalent mutation in sporadic cases of Parkinson disease in patients, and it is the most prevalent autosomal dominant mutation of the inherited forms of the disease.

[0093] Diagnosis of Parkinson disease is clinical. Parkinson disease is suspected in patients with characteristic unilateral resting tremor, decreased movement, or rigidity. During finger-to-nose coordination testing, the tremor disappears (or attenuates) in the limb being tested. During the neurologic examination, patients cannot perform rapidly alternating or rapid successive movements well. Sensation and strength are usually normal. Reflexes are normal but may be difficult to elicit because of marked tremor or rigidity. Slowed and decreased movement due to Parkinson disease must be differentiated from decreased movement and spasticity due to lesions of the corticospinal tracts. To help distinguish Parkinson disease from secondary or atypical parkinsonism, clinicians often test responsiveness to levodopa. A large, sustained response strongly supports Parkinson disease.

[0094] Levodopa is the most effective current treatment. However, when Parkinson disease is advanced, sometimes soon after diagnosis, response to levodopa can wear off, causing fluctuations in motor symptoms and dyskinesias. To reduce the time levodopa is taken and thus minimize these effects, clinicians can consider treating younger patients who have mild disability with MAO-B inhibitors (selegiline, rasagiline), Dopamine agonists (eg, pramipexole, ropinirole, rotigotine), Amantadine (which is also the best option when trying to decrease peak-dose

dyskinesias). However, if these drugs do not sufficiently control symptoms, clinicians should promptly initiate levodopa because it can usually greatly improve quality of life. Evidence now suggests that levodopa becomes ineffective because of disease progression rather than cumulative exposure to levodopa.

[0095] Deep brain stimulation of the subthalamic nucleus or globus pallidus interna is often recommended for patients with levodopa-induced dyskinesias or significant motor fluctuations; this procedure can modulate overactivity in the basal ganglia and thus decrease parkinsonian symptoms in patients with Parkinson disease. For patients with tremor only, stimulation of the ventralis intermediate nucleus of the thalamus is sometimes recommended; however, because most patients also have other symptoms, stimulation of the subthalamic nucleus, which relieves tremor as well as other symptoms, is usually preferred. When the main problem is inadequate control of dyskinesias or when patients have an increased risk of cognitive decline, the globus pallidus interna is a good target.

[0096] In some embodiments, an LRRK2 inhibitor of the disclosure is administered in combination with a dopaminergic agent or deep brain stimulation. Examples of dopaminergic agents include, but are not limited to, levodopa, bromocriptine, pergolide, pramipexole, cabergoline, ropinorole, apomorphine or a combination thereof.

[0097] In some embodiments the invention provides compositions or methods that combine a compound disclosed herein and a dopaminergic agent, where the dopaminergic agent is present in an amount sufficient to exert a therapeutic effect when the composition is administered to an animal. In some embodiments, the compositions of the invention include an agent such as carbidopa, which blocks the conversion of levodopa to dopamine in the blood. In some embodiments, the compositions of the invention include a COMT Inhibitor, such as entacapone. In some embodiments, the compositions of the invention include a monoamine oxidase type B (MAO-B) inhibitor such as selegiline. In some embodiments, the compositions of the invention include amantadine.

[0098] In some embodiments, an LRRK2 inhibitor of the disclosure is administered in combination with a therapy that inhibits, decreases, reverses, or prevents α-synuclein fibrillation and/or aggregation or inhibits MAO and at least one other agent that is anti-emetic, 1-dihydroxyphenylalanine, aromatic acid decarboxylase inhibitor, catechol-O-methyltransferase inhibitor, monoamine oxidase-B inhibitor, a different dopamine agonist, otigotine, lisuride, nicotinic receptor agonist, amantadine, carbidopa, entacapone, levodopa, bromocriptine, pergolide, pramixpexole, cabergoline or ropinorole.

[0099] LRRK2 has also been connected genetically to a number of chronic inflammatory conditions, including Crohn's disease (CD) and inflammatory bowel disease. In the context of LRRK2 function in immune cells, LRRK2 has been implicated in regulating the calcium activated transcription factor NFAT. NFAT is of central importance to the innate immune response, but also

relevant to neuronal biology. Under basal conditions NFAT is retained in the cytoplasm by an inhibitory NRON complex, but is activated via dephosphorylation by the calcium-activated phosphatase calcineurin, which allows NFAT to dissociate from the NRON complex and enter the nucleus, driving subsequent gene expression. LRRK2 appears to form part of this complex, where it strengthens the repression of NFAT.

[00100] LRRK2 mutations are associated with cancers including, for example, skin cancers, such as melanoma; hormone-related cancers, such as breast cancer, leukemia, and colon cancer. In some embodiments an individual with a cancer is treated with an effective dose of a compound of the invention.

EXPERIMENTAL

[00101] The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the present invention, and are not intended to limit the scope of what the inventors regard as their invention nor are they intended to represent that the experiments below are all or the only experiments performed. Efforts have been made to ensure accuracy with respect to numbers used (e.g. amounts, temperature, etc.) but some experimental errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, molecular weight is weight average molecular weight, temperature is in degrees Centigrade, and pressure is at or near atmospheric.

[00102] Experimental procedures for compounds of the invention are provided below. Further experimental procedures can be found in Lesniak et al., ACS Med Chem Lett 2022. Where the preparation of starting materials is not described, these are commercially available, known in the literature, or readily obtainable by those skilled in the art using standard procedures. Where it is stated that compounds were prepared analogously to earlier examples or intermediates, it will be appreciated by the skilled person that the reaction time, number of equivalents of reagents and temperature can be modified for each specific reaction and that it may be necessary or desirable to employ different work-up or purification techniques. Where reactions are carried out using microwave irradiation, the microwave used is a Biotage Initiator. The actual power supplied varies during the course of the reaction in order to maintain a constant temperature. All solvents used were commercially available and were used without further purification. Reactions were typically run using anhydrous solvents under an inert atmosphere of nitrogen.

[00103] Liquid Chromatography-Mass Spectrometry Method A. 1H Nuclear magnetic resonance (NMR) spectroscopy was carried out using one of the following instruments: a Bruker Avance 400 instrument equipped with probe DUAL 400MHz SI, a Bruker Avance 400 instrument equipped with probe 6 SI 400 MHz 5mm 1H-13C ID, a Bruker Avance III 400 instrument with nanobay equipped with probe Broadband BBFO 5 mm direct, a 400 MHz Agilent Direct Drive instrument with ID AUTO-X PFG probe, all operating at 400 MHz, or an Agilent VNMRS500 Direct

Drive instrument equipped with a 5 mm Triple Resonance 1H(13CZ15N) cryoprobe operating at 500 MHz . The spectra were acquired in the stated solvent at around room temperature unless otherwise stated. In all cases, NMR data were consistent with the proposed structures. Characteristic chemical shifts (δ) are given in parts-per-million using conventional abbreviations for designation of major peaks: e.g. s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; dt, doublet of triplets; br, broad. Where thin layer chromatography (TLC) has been used it refers to silica gel TLC using silica gel F254 (Merck) plates, Rf is the distance travelled by the compound divided by the distance travelled by the solvent on a TLC plate. Column chromatography was performed using an automatic flash chromatography (Isolera) system over Biotage silica gel cartridges (Sfär) or in the case of reverse phase chromatography over Biotage Cl8 cartridges (Sfär-C18).

Example 1

[00104] Here, we have pursued a precision medicine approach to the treatment of PD from G2019S *LRRK2* by creating novel compounds that selectively and potently inhibit G2019S LRRK2 kinase activity in vitro and in cells. The compounds are tested for activity in an animal model including knockin mice.

Results

[00105] The results of a LRRK2 kinase activity screen are shown in Table 2. Inhibition data are presented as follows: A is $IC_{50} \leq 20$ nM; B is 20 nM < $IC_{50} \leq 50$ nM; C is 50 nM < $IC_{50} \leq 100$ nM; D is 100 nM < $IC_{50} \leq 1000$ nM; E is $IC_{50} > 1000$ nM

Table 2 LRRK2 kinase activity

Entry	WT IC_{50}	G2019S IC_{50}
1	E	E
2	D	A
3	E	E
4	E	D
5	E	E
6	E	E
7	E	E
8	E	E

9	E	D
10	E	D
11	E	E
12	E	E
13	D	D
14	D	D
15	E	E
16	E	E
17	C	C
18	E	D
19	E	E
20	E	E
21	E	C
22	E	D
23	E	E
24	E	D
25	C	B
26	E	D
27	D	C
28	E	E
29	E	E
30	E	E
31	D	A
32	D	D
33	E	D

34	C	A
35	E	D
36	D	B
37	D	C
38	E	E
39	E	D
40	D	C
41	E	D
42	E	E
43	D	D
44	D	D
45	D	D
46	D	A
47	E	D
48	D	C
49	D	D
50	D	D
51	D	B
52	D	D
53	D	D
54	C	A
55	D	D
56	D	B
57	D	D
58	E	D

59	C	B
60	B	A
61	D	A
62	A	A
63	D	C
64	B	A
65	C	A
66	E	D
67	A	A
68	E	D
69	D	D
70	C	B
71	D	C
72	E	D
73	C	A
74	D	D
75	E	E
76	D	D
77	D	B
78	D	D
79	A	A
80	B	A
81	B	A
82	B	A
83	E	D

84	E	D
85	E	D
86	D	B
87	D	C
88	D	D
89	D	C
90	D	D
91	D	B
92	D	B
93	D	D
94	D	D
95	E	E
96	C	A
97	D	A
98	E	D
99	B	A
100	E	E
101	D	B
102	B	A
103	B	A
104	D	C
105	E	D
106	D	D
107	D	A
108	C	A

109	A	A
110	B	A
111	D	B
112	C	A
113	D	D
114	D	A
115	E	D
116	E	E
117	E	E
118	C	A
119	E	D
120	B	A
121	A	A

The results of a LRRK2 cellular activity screen are shown in Table 3. Inhibition data are presented as follows: A is $EC_{50} \leq 250$ nM; B is 250 nM < $EC_{50} \leq 2000$ nM; C is 2000 nM < $EC_{50} \leq 10000$ nM; D $EC_{50} > 10000$

Table 3 LRRK2 kinase activity

Entry	WT EC_{50}	G2019S EC_{50}
1	D	D
2	D	C
3	D	D
4	D	D
5	D	D
6	D	D
7	D	D

8	D	D
9	D	D
10	D	D
11	D	D
12	D	D
13	D	D
14	D	D
15	D	D
16	D	D
17	D	D
18	D	D
19	D	D
20	D	D
21	D	D
22	D	D
23	D	D
24	D	D
25	D	D
26	D	D
27	D	D
28	D	D
29	D	D
30	D	D
31	D	B
32	D	D

33	D	D
34	D	C
35	D	D
36	D	B
37	D	C
38	D	D
39	D	D
40	D	C
41	D	C
42	D	D
43	D	D
44	D	D
45	D	D
46	D	B
47	D	D
48	D	C
49	D	D
50	D	D
51	D	D
52	D	D
53	D	C
54	D	B
55	D	D
56	D	B
57	D	D

58	D	C
59	D	B
60	D	B
61	D	B
62	D	A
63	D	C
64	D	B
65	D	B
66	D	C
67	D	A
68	D	D
69	D	D
70	C	B
71	D	C
72	D	C
73	D	A
74	D	C
75	D	D
76	D	D
77	B	A
78	D	B
79	B	A
80	B	B
81	C	B
82	C	A

83	D	C
84	D	D
85	D	C
86	D	B
87	D	C
88	D	C
89	D	B
90	D	C
91	C	B
92	D	C
93	D	B
94	D	C
95	D	C
96	D	B
97	D	B
98	D	D
99	D	A
100	D	D
101	D	B
102	C	B
103	D	B
104	D	C
105	D	D
106	D	D
107	D	B

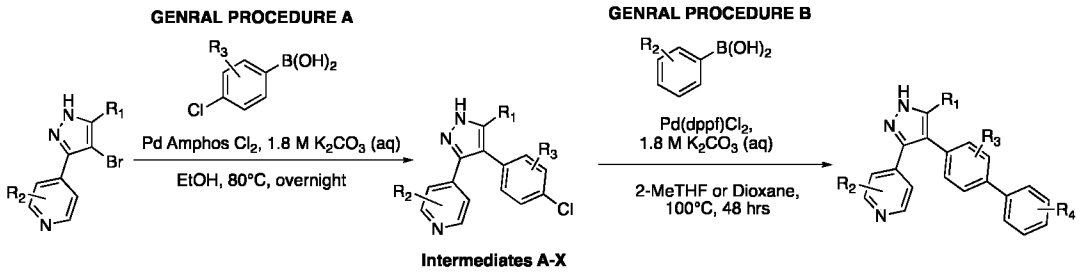
108	D	A
109	C	A
110	D	B
111	D	B
112	D	B
113	D	C
114	D	B
115	D	D
116	D	D
117	D	D
118	D	C
119	D	C
120	C	B
121	C	B
122	D	D
123	D	C
124	D	D
125	D	D
126	D	D
127	D	D
128	D	C
129	D	C
131	D	D
132	D	A
133	D	D

134	D	D
135	D	D
136	D	B

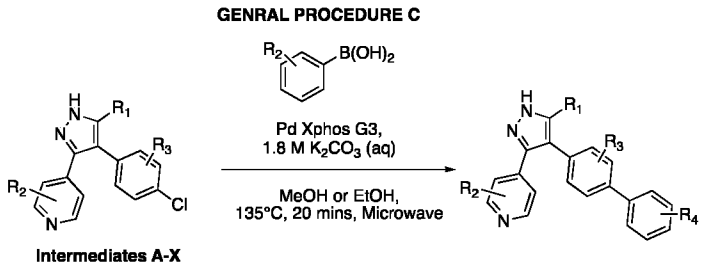
SYNTHETIC CHEMISTRY

GENERAL SCHEMES

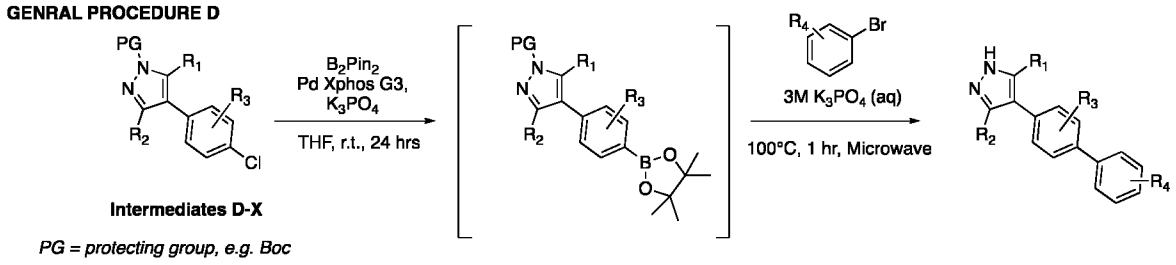
ROUTE1



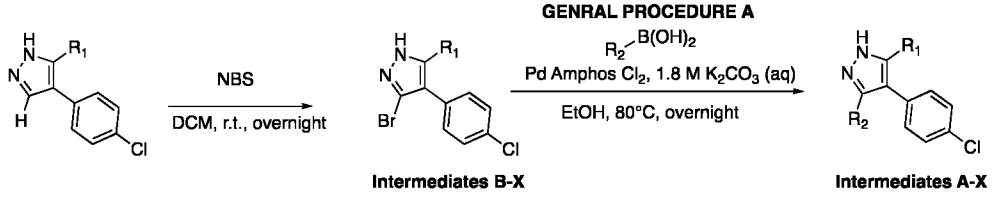
ROUTE 2

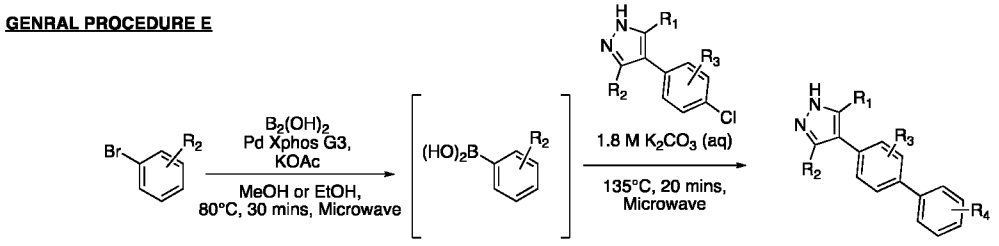


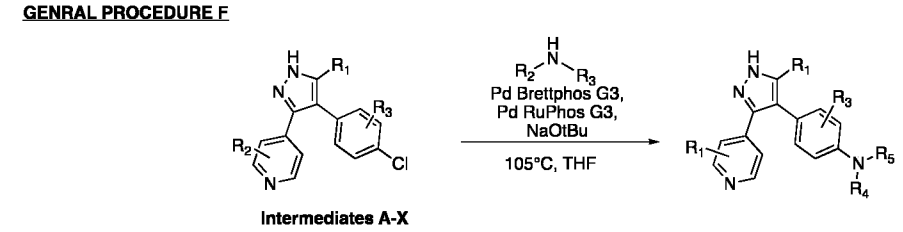
ROUTE 3

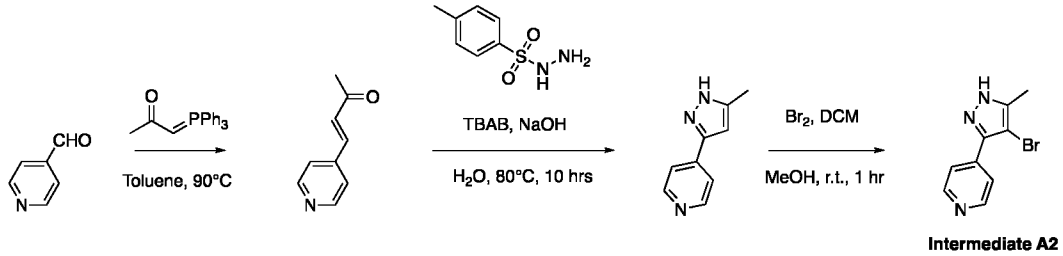


ROUTE 4







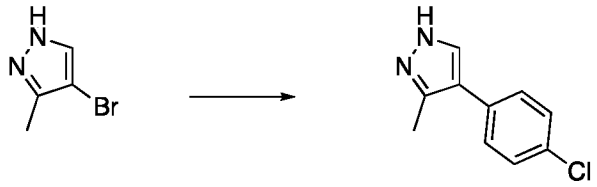


GENERAL PROCEDURES

General procedure A

Example

[00106] 4-(4-chlorophenyl)-3-methyl-1H-pyrazole (**Intermediate A1**)

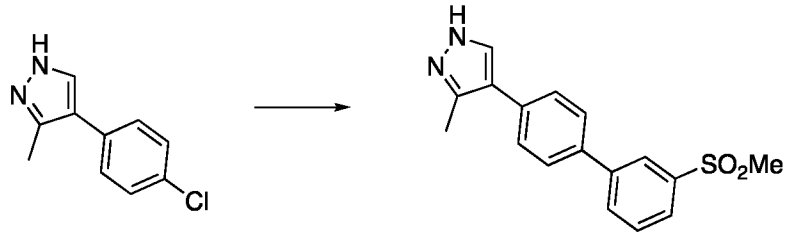


[00107] 4-Bromo-3-methyl-1H-pyrazole (2g, 12.4 mmol), 2-(4-chlorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.5g, 14.9 mmol), Pd Amphos Cl_2 (1.75 g, 2.48 mmol) and K_2CO_3 (3.42 g, 24.8 mmol) were added to a round-bottom flask equipped with stirrer bar. The flask was sealed and evacuated and re-filled with nitrogen gas three times, before water (11.2 mL) and 1,4-dioxane (33.5 mL) were added. The mixture was heated in a sand bath at 100°C until complete conversion was observed. After 6 hours the reaction was concentrated and then diluted with EtOAc and washed with sat. NH_4Cl. The organic phase was dried over MgSO4, filtered and concentrated onto silica gel and purified by FCC (50g SiO_2 0-100% EtOAc in hexanes) which gave a an orange oil. Trituration with cold DCM gave a yellow solid (1290 mg, 51%). LCMS ESI (m/z) FOUND $[M+H]^+$ = 193.10

General procedure B

Example

[00108] 3-methyl-4-[4-(3-methylsulfonylphenyl)phenyl]-1*H*-pyrazole (**1**)

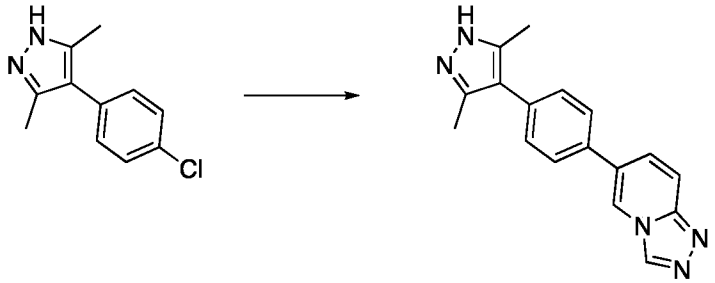


[00109] 4-(4-chlorophenyl)-3-methyl-1*H*-pyrazole (50 mg, 0.26 mmol), 4,4,5,5-tetramethyl-2-(3-methylsulfonylphenyl)-1,3,2-dioxaborolane (110 mg, 0.39 mmol) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (64mg, 0.08 mmol) were added to a microwave vial equipped with stir bar. The vessel was sealed and evacuated under vacuo and re-filled with N_2 gas. This was repeated 3 times before 2-MeTHF (2.6 mL) and K_2CO_3 (0.29 mL, 0.52 mmol) were added and the mixture was degassed with N_2 gas for 5 minutes with stirring. The reaction was then heated at 100°C in a sand bath for 48 hrs. The reaction was then concentrated and purified by FCC to give the product (21 mg, 25%). LCMS ESI (m/z) found $[M+H]^+ = 313.10$

General procedure C

Example

[00110] 6-[4-(3,5-dimethyl-1H-pyrazol-4-yl)phenyl]-[1,2,4]triazolo[4,3-a]pyridine (**8**)

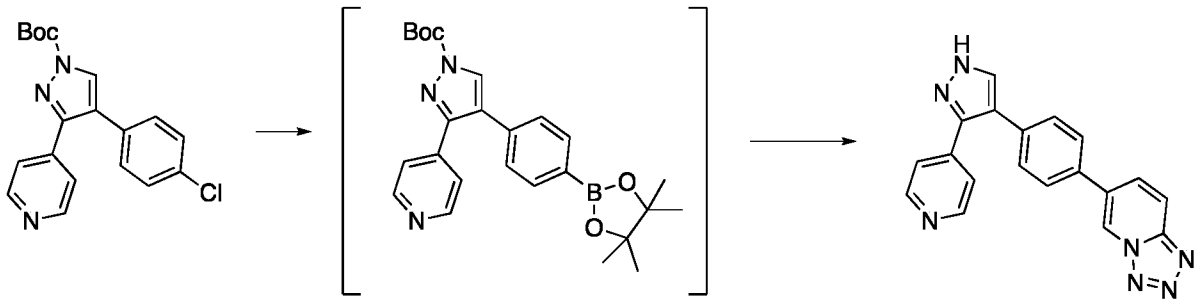


[00111] XPhos Pd G3 (4.91 mg, 0.01 mmol), 4-(4-chlorophenyl)-3,5-dimethyl-1H-pyrazole (60 mg, 0.29 mmol), [1,2,4]triazolo[4,3-a]pyridin-6-ylboronic acid (95 mg, 0.58 mmol) and were added to a microwave vial equipped with stir bar. The vessel was purged with N_2 gas before ethanol (1.2 mL) and K_2CO_3 (0.32 mL, 0.58 mmol) solution were added. The reaction was heated in a microwave reactor for 20 mins at 135 °C. The reaction was then diluted with EtOAc and sat. brine solution and extracted with 3 x EtOAc. The organic layers were combined, dried over MgSO4, filtered and concentrated before the resulting residue was purified by FCC (5g SiO_2, 0-100% EtOAc in hexanes, then 12g C18, 0-100% MeOH in water) to give the product as a white solid (46 mg, 52%). LCMS ESI (m/z) found $[M+H]^+ = 290.10$

General procedure D

Example

[00112] 6-[4-[3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]tetrazolo[1,5-a]pyridine (**7**)



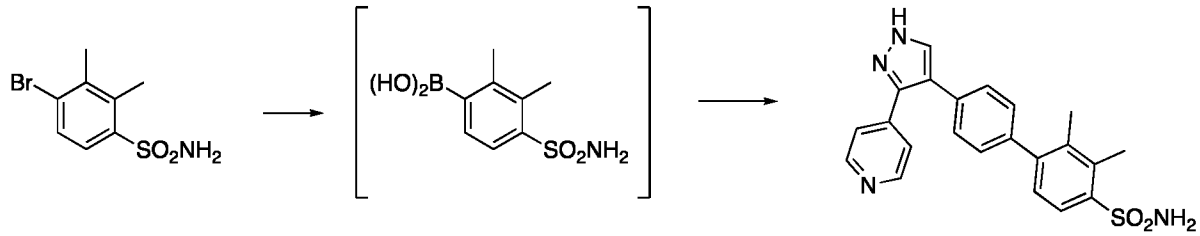
[00113] To a microwave vial equipped with stir bar was added tert-butyl 4-(4-chlorophenyl)-3-(4-pyridyl)pyrazole-1-carboxylate (100 mg, 0.28 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (107 mg, 0.42 mmol), XPhos Pd G3 (12 mg, 0.01 mmol) and K_3PO_4 (0.28 mL, 0.84 mmol). THF (0.56 mL) was then added and the system was degassed. The mixture was stirred at room temperature until complete conversion was observed (~24-48 hrs). 6-bromotetrazolo[1,5-a]pyridine (56 mg, 0.28 mmol) before 3M potassium phosphate tribasic (0.28 mL, 0.84 mmol) was added and the reaction was heated for 1 hr in a microwave reactor at 100°C. The reaction was diluted with EtOAc and sat. brine solution and extracted with 3 x EtOAc. The organic phases were combined, dried over MgSO4, filtered, and concentrated before the mixture was re-suspended in a minimal amount of DCM and TFA was added. The resulting mixture was stirred at room temperature for 1 hour. The reaction was concentrated and purified by reverse phase FCC (12g, C18, 0-100% MeOH in water) to give the product as a solid (8.3 mg, 8%).

LCMS ESI (m/z) found $[M+H]^+$ = 340.10

General procedure E

Example

[00114] 2,3-dimethyl-4-[4-[3-(4-pyridyl)-1*H*-pyrazol-4-yl]phenyl]benzenesulfonamide (**21**)



[00115] To a 2-5 ml microwave vial equipped with stir bar was added 4-bromo-2,3-dimethyl-benzenesulfonamide (116.21 mg, 0.44 mmol), tetrahydroxydiboron (118 mg, 1.32 mmol), XPhos Pd G3 (10 mg, 0.01 mmol) and KOAc (130 mg, 1.32 mmol). The vial was sealed and evacuated under *vacuo* and re-filled with nitrogen. This was repeated three times before ethanol (1.2 mL) was then added and the mixture was degassed with a stream of nitrogen.. After 5 minutes, the mixture was stirred in a microwave reactor at 80°C for 30 minutes. Then, potassium carbonate (0.73 mL, 1.32 mmol) solution was added followed by 4-[4-(4-chlorophenyl)-1*H*-pyrazol-3-yl]pyridine (75 mg, 0.29 mmol) and the mixture was heated in a microwave reactor at 135°C for

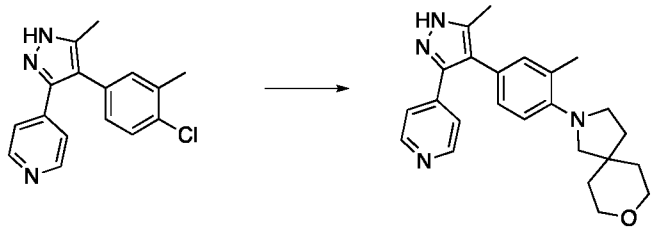
30 mins. The reaction was concentrated and purified by FCC (5 g SiO_2, 0-100% EtOAc in hexanes then 12 g Sfär C18, 0-100% MeOH in water) to give the product as a solid (24 mg, 19%).

LCMS ESI (m/z) found $[M+H]^+$ = 405.10

General procedure F

Example

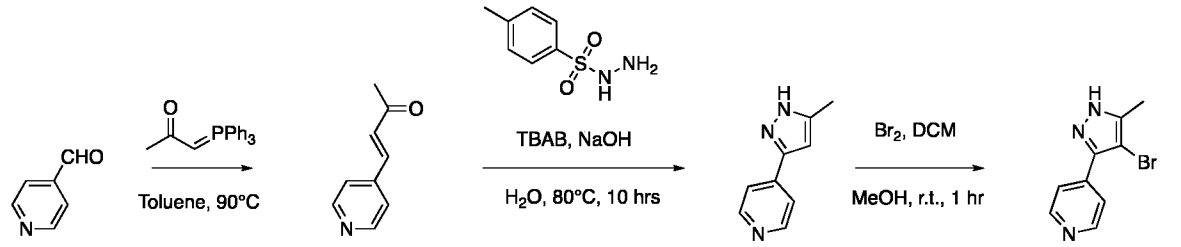
[00116] 2-[2-methyl-4-[5-methyl-3-(4-pyridyl)-1*H*-pyrazol-4-yl]phenyl]-8-oxa-2-azaspiro[4.5]decane (**70**)



[00117] To a 2-5 ml microwave vial equipped with stir bar was added BrettPhos Pd G3 (13.6 mg, 0.01 mmol), RuPhos Pd G3 (12.5 mg, 0.01 mmol), 4-[4-(4-chloro-3-methyl-phenyl)-5-methyl-1*H*-pyrazol-3-yl]pyridine (85 mg, 0.3 mmol), sodium tert-butoxide (80.6 mg, 0.84 mmol). THF (0.80 mL) and 8-oxa-2-azaspiro[4.5]decane (59 mg, 0.42 mmol) were then added and the resulting mixture was heated in a sand bath at 100°C overnight. The mixture was then diluted with MeOH and filtered through a cotton wool plug, and the filtrate was concentrated and purified by FCC (5 g SiO_2, 50-100% EtOAc in hexanes, then 12 g Sfär C18, 0-100% MeOH in water) to give the product as a solid (65 mg, 53%). LCMS ESI (m/z) found $[M+H]^+$ = 389.30

SYNTHESIS OF INTERMEDIATES

[00118] 4-(4-bromo-5-methyl-1*H*-pyrazol-3-yl)pyridine (**Intermediate A2**)



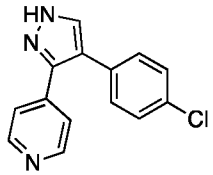
Intermediate A2

[00119] **Step1:** To a solution of isonicotinaldehyde (24 g, 0.224 mol, 1.0 eq) in toluene (150 mL) was added 1-(triphenylphosphoranylidene)-2-propanone (74.9 g, 0.235 mol, 1.05 eq). The reaction mixture was stirred at 90-95 °C for 2 h. The reaction mixture was concentrated. Ether (300 mL) was added to the above residue and stirred at -70 °C for 1 h. The suspension was filtered and the filtrate washed with ether (100 mL). The filtrate was concentrated under reduced pressure at 40 °C to give (*E*)-4-(pyridin-4-yl)but-3-en-2-one (32 g, 97%) as yellow oil. LCMS ESI (m/z) found $[M+H]^+$ = 148.2

[00120] **Step 2**: A mixture of (*E*)-4-(pyridin-4-yl)but-3-en-2-one (16 g, 0.109 mol, 1.0 eq), toluene-4-sulfonic acid hydrazide (24.3 g, 0.13 mol, 1.2 eq), TBAB (52.5 g, 0.164 mol, 1.5 eq) and NaOH (6.55 g, 0.164 mol, 1.5 eq) in water (300 mL) was stirred for 4 h at 80°C. The reaction mixture was then cooled to room temperature and extracted with DCM (500 mL x 3). The organic phases were combined and concentrated. The residue was dissolved in water (100 mL) and cooled to 0 °C and stirred for 0.5 h. The precipitate was filtered and washed with water (100 mL). The filter cake was dried under reduced pressure to give crude 4-(5-methyl-1*H*-pyrazol-3-yl)pyridine as white solid. The filtrate was extracted with DCM (200 mL x 3). The organic phases were combined and concentrated. The residue was purified by FCC (5% MeOH in DCM) to give 4-(5-methyl-1*H*-pyrazol-3-yl)pyridine (6 g, total yield: 35%) as a white solid. LCMS ESI (m/z) found $[M+H]^+$ = 160.2.

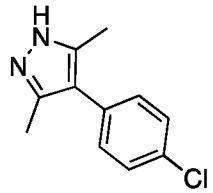
[00121] **Step 3**: To a solution of 4-(5-methyl-1*H*-pyrazol-3-yl)pyridine (6 g, 0.377 mol, 1.0 eq) in DCM (50 mL) and MeOH (30 mL) at 0 °C was added bromine (6.0 g, 0.377 mol, 1.0 eq). The reaction mixture was stirred for 2 h at 10-15 °C. The reaction mixture was concentrated and the residue was stirred with saturated $NaHCO_3$ aqueous solution for 0.5 h. The precipitate was filtered and washed with water, dried under reduced pressure at 40 °C to give 4-(4-bromo-5-methyl-1*H*-pyrazol-3-yl)pyridine (5.5 g, 61%) as a solid. LCMS ESI (m/z) found $[M+H]^+$ = 238.10.

[00122] 4-[4-(4-Chlorophenyl)-1H-pyrazol-3-yl]pyridine (**Intermediate A3**)



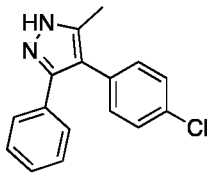
[00123] Synthesized according to ***general procedure A.*** Obtained as a light yellow solid (2000 mg, 83%). LCMS ESI (m/z) FOUND $[M+H]^+$ = 256.10

[00124] 4-(4-chlorophenyl)-3,5-dimethyl-1*H*-pyrazole (**Intermediate A4**)



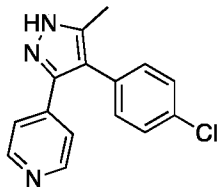
[00125] Synthesized according to ***general procedure A***. (2100 mg, 68%). LCMS (m/z) FOUND [M+H]+ = 207.00

[00126] 4-(4-chlorophenyl)-5-methyl-3-phenyl-1H-pyrazole (**Intermediate A5**)



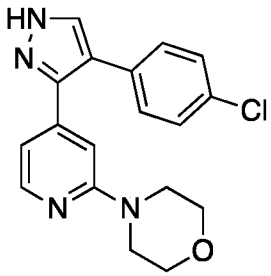
[00127] Synthesized according to ***general procedure A*** .(1000 mg, 84%). LCMS (m/z) FOUND $[M+H]^+$ = 269.10

[00128] 4-[4-(4-chlorophenyl)-5-methyl-1H-pyrazol-3-yl]pyridine (**Intermediate A6**)



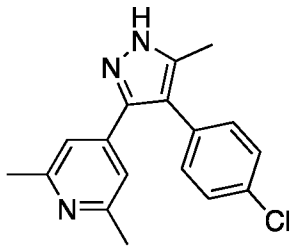
[00129] Synthesized according to a modification to ***general procedure A*** (750 mg, 63%). LCMS ESI (m/z) FOUND [M+H]+ = 270.00

[00130] 4-[4-[4-(4-Chlorophenyl)-1*H*-pyrazol-3-yl]-2-pyridyl]morpholine (**Intermediate A7**)



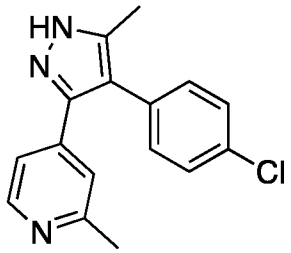
Synthesized according to ***general procedure A***. (88 mg, 43%). LCMS (m/z) FOUND $[M+H]^+$ = 341.10

[00131] 4-[4-(4-chlorophenyl)-5-methyl-1H-pyrazol-3-yl]-2,6-dimethyl-pyridine (**Intermediate A8**)



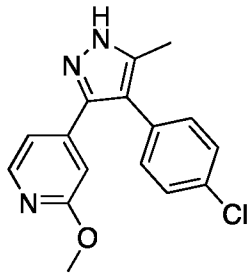
Synthesized according to ***general procedure A***. Obtained as a pale-yellow solid (100 mg, 35%). LCMS ESI (m/z) FOUND $[M+H]^+$ = 298.10

[00132] 4-[4-(4-chlorophenyl)-5-methyl-1*H*-pyrazol-3-yl]-2-methyl-pyridine (**Intermediate A9**)



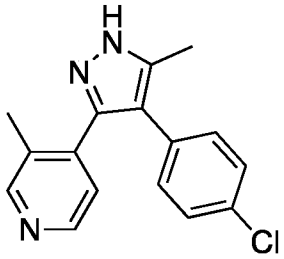
Synthesized according to ***general procedure A***. Obtained as a pale-yellow solid (172 mg, 62%). LCMS ESI (m/z) FOUND $[M+H]^+$ = 284.10

[00133] 4-[4-(4-chlorophenyl)-5-methyl-1*H*-pyrazol-3-yl]-2-methoxy-pyridine (**Intermediate A10**)



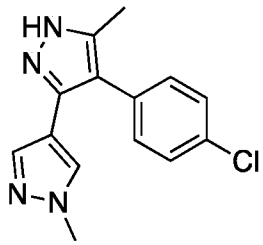
Synthesized according to ***general procedure A***. Obtained as a pale-yellow solid (158 mg, 54%). LCMS ESI (m/z) FOUND $[M+H]^+$ = 300.10

[00134] 4-[4-(4-chlorophenyl)-5-methyl-1*H*-pyrazol-3-yl]-3-methyl-pyridine (**Intermediate A11**)



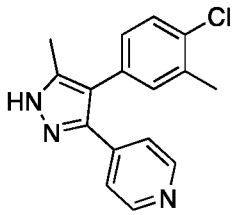
Synthesized according to ***general procedure A***. Obtained as a white solid (210 mg, 73%). LCMS ESI (m/z) FOUND $[M+H]^+$ = 284.10

[00135] 4-(4-chlorophenyl)-5-methyl-3-(1-methylpyrazol-4-yl)-1*H*-pyrazole (**Intermediate A12**)



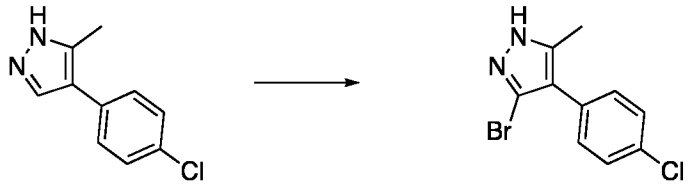
Synthesized according to ***general procedure A***. Obtained as a pale-yellow solid (198 mg, 75%).
LCMS ESI (m/z) FOUND $[M+H]^+$ = 273.00

[00136] 4-[4-(4-chloro-3-methyl-phenyl)-5-methyl-1*H*-pyrazol-3-yl]pyridine (**Intermediate A13**)



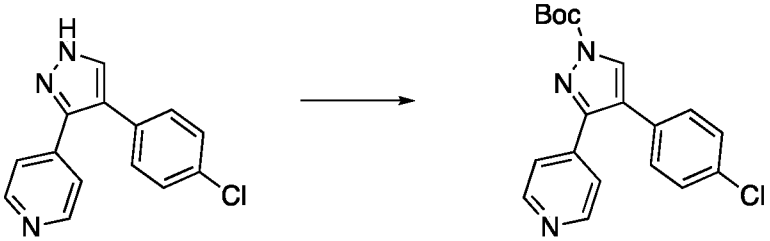
Synthesized according to ***general procedure A***. Obtained as a pale-yellow solid (247 mg, 66%).
LCMS ESI (m/z) FOUND $[M+H]^+$ = 284.10

[00137] 3-bromo-4-(4-chlorophenyl)-5-methyl-1*H*-pyrazole (**Intermediate B1**)



[00138] To a 50 ml round-bottom flask equipped with stir bar was added 4-(4-chlorophenyl)-3-methyl-1*H*-pyrazole (471 mg, 2.44 mmol) and DCM (24.4 mL). The solution was cooled to 0°C and *N*-bromosuccinimide (522 mg, 2.93 mmol) was then added portion-wise. The mixture was the stirred at room temperature for 3 hrs, before water was added and the resulting biphasic mixture stirred vigorously for 5 mins before being extracted with 3 x DCM. The organic phases were combined, dried over MgSO4, filtered and concentrated onto silica gel before being purified by FCC (25 g SiO_2, 25% EtOAc in hexanes) to give the product as a white solid.
LCMS ESI (m/z) FOUND $[M+H]^+$ = 270.90 and 272.90 as the major product isotopes.

[00139] Tert-butyl 4-(4-chlorophenyl)-3-(4-pyridyl)pyrazole-1-carboxylate (**Intermediate D1**)



[00140] 4-[4-(4-chlorophenyl)-1*H*-pyrazol-3-yl]pyridine (933 mg, 3.65 mmol) was dissolved in DMSO (18.2 mL). Tert-butoxycarbonyl tert-butyl carbonate (1.2 g, 5.47 mmol), DBU (0.82 mL, 5.47 mmol) and DMAP (22.3 mg, 0.18 mmol) were added and the mixture stirred at room temperature for 3 hours. The mixture was poured into an excess of sat. NH_4Cl solution, before the solution was extracted with 3 x EtOAc. The organic phases were combined, washed with brine, dried over MgSO4, filtered and purified by FCC (40g SiO_2 0-100% EtOAc in hexnaes). The product was isolated as a pale yellow powder (1.2 g, 88%).
LCMS (m/z) FOUND $[M+H]^+$ = 356.20

[00141] 3-[4-[3-(4-pyridyl)-1*H*-pyrazol-4-yl]phenyl]benzenesulfonamide (**2**)

Synthesized according to ***general procedure B***. Obtained as a white solid (23 mg, 30%). LCMS ESI (m/z) found = $[M+H]^+$ = 377.10

[00142] 3-[4-[3-(4-pyridyl)-1*H*-pyrazol-4-yl]phenyl]benzonitrile (**3**)

Synthesized according to ***general procedure B.*** Obtained as an off-white solid (15 mg, 23%). LCMS ESI (m/z) found $[M+H]^+$ = 323.20

[00143] 2-(4'-(3-(pyridin-4-yl)-1*H*-pyrazol-4-yl)-[1,1'-biphenyl]-3-yl)acetonitrile (**4**)

Synthesized according to ***general procedure B.*** Obtained as a light-yellow solid (49 mg, 71%). LCMS ESI (m/z) found $[M+H]^+$ = 337.10

[00144] 1-methyl-5-[4-[3-(4-pyridyl)-1*H*-pyrazol-4-yl]phenyl]indazole (**5**)

Synthesized according to ***general procedure B.*** Obtained as an off-white solid (13 mg, 18%). LCMS ESI (m/z) FOUND $[M+H]^+$ = 352.10

[00145] 4-[4-[3-(4-pyridyl)-1*H*-pyrazol-4-yl]phenyl]-1*H*-pyridin-2-one (**6**)

Synthesized according to ***general procedure B***.Obtained as a solid (6 mg, 9.3%) LCMS (m/z) found $[M+H]^+$ = 315.10

[00146] 4-[4-(3,5-dimethyl-1*H*-pyrazol-4-yl)phenyl]-3-methyl-benzenesulfonamide (**9**)

Synthesized according to ***general procedure C***. Obtained as a solid (60 mg, 58%). LCMS ESI (m/z) found $[M+H]^+$ = 342.10

[00147] 2-[2-[4-[3-(4-pyridyl)-1*H*-pyrazol-4-yl]phenyl]phenyl]acetonitrile (**10**)

Synthesized according to ***general procedure D.*** Obtained as a white solid (14 mg, 14%). LCMS ESI (m/z) FOUND $[M+H]^+$ = 337.10

[00148] 2-[4-[4-[3-(4-pyridyl)-1*H*-pyrazol-4-yl]phenyl]phenyl]acetonitrile **(11)**

Synthesized according to ***general procedure B***. Obtained as a white solid (23 mg, 15%). LCMS (m/z) FOUND $[M+H]^+$ = 337.10

[00149] 4-[4-(3-methyl-1*H*-pyrazol-4-yl)phenyl]benzenesulfonamide (**12**)

Synthesized according to ***general procedure B***. Obtained as a solid (4 mg, 5%). LCMS (m/z) FOUND $[M+H]^+$ = 314.10

[00150] 4-[4-[3-(4-pyridyl)-1*H*-pyrazol-4-yl]phenyl]benzenesulfonamide (**13**)

Synthesized according to ***general procedure C*** obtained as a solid (66 mg, 57%). LCMS ESI (m/z) found [M+H]+ = 377.10

[00151] 3-methyl-4-[4-[3-(4-pyridyl)-1*H*-pyrazol-4-yl]phenyl]benzenesulfonamide (**14)**

Synthesized according to ***general procedure C***. Obtained as a white solid (31 mg, 25%). LCMS ESI (m/z) found $[M+H]^+$ = 391.10

[00152] 2-methyl-4-[4-[3-(4-pyridyl)-1*H*-pyrazol-4-yl]phenyl]benzenesulfonamide (**15**)

Synthesized according to ***general procedure C.*** Obtained as a white solid (82 mg, 68%). LCMS ESI (m/z) found $[M+H]^+$ = 391.10

[00153] 4-[4-[4-(2,3-dimethylphenyl)phenyl]-1*H*-pyrazol-3-yl]pyridine (**16**)

Synthesized according to ***general procedure C.*** Obtained as a white solid (80 mg, 79%). LCMS ESI (m/z) found $[M+H]^+$ = 326.20

[00154] 2-[4-[3-(4-pyridyl)-1*H*-pyrazol-4-yl]phenyl]benzonitrile (**17**)

Synthesized according to ***general procedure C.*** Obtained as a white solid (51 mg, 52%). LCMS ESI (m/z) found $[M+H]^+$ = 323.20

[00155] 4-[4-[3-(4-pyridyl)-1*H*-pyrazol-4-yl]phenyl]benzonitrile (**18**)

Synthesized according to ***general procedure C.*** Obtained as a white solid (69 mg, 69%). LCMS ESI (m/z) found $[M+H]^+$ = 323.20

[00156] 3-methyl-4-[4-[3-(4-pyridyl)-1*H*-pyrazol-4-yl]phenyl]benzonitrile (**19**)

Synthesized according to ***general procedure C.*** Obtained as a white solid (88 mg, 85%). LCMS ESI (m/z) found $[M+H]^+$ = 337.20

[00157] 2-methyl-4-[4-[3-(4-pyridyl)-1*H*-pyrazol-4-yl]phenyl]benzonitrile (**20**)

Synthesized according to ***general procedure C.*** Obtained as a white solid (72 mg, 69%).

LCMS ESI (m/z) found $[M+H]^+$ = 337.10

[00158] 3-[4-(3,5-dimethyl-1*H*-pyrazol-4-yl)phenyl]benzonitrile (**22**)

Synthesized according to ***general procedure C.*** Obtained as a white solid (37 mg, 38%).

LCMS ESI (m/z) found $[M+H]^+$ = 274.10

[00159] 3-[4-(5-methyl-3-phenyl-1*H*-pyrazol-4-yl)phenyl]benzonitrile (**23**)

Synthesized according to ***general procedure C.*** Obtained as a white solid (85 mg, 81%). LCMS ESI (m/z) found $[M+H]^+$ = 336.10

[00160] 2,3-dimethyl-4-[4-[3-(4-pyridyl)-1*H*-pyrazol-4-yl]phenyl]benzonitrile (**24**)

Synthesized according to ***general procedure E.*** Obtained as a white solid (84 mg, 78%). LCMS ESI (m/z) found $[M+H]^+$ = 351.20

[00161] 4-methyl-3-[4-[3-(4-pyridyl)-1*H*-pyrazol-4-yl]phenyl]benzenesulfonamide (**25**)

Synthesized according to ***general procedure C.*** Obtained as a white solid (49 mg, 41%). LCMS ESI (m/z) found $[M+H]^+$ = 391.10

2,3-dimethyl-4-[4-(5-methyl-3-phenyl-1*H*-pyrazol-4-yl)phenyl]benzenesulfonamide (**26**)
Synthesized according to ***general procedure E.*** Product obtained as a white solid (73 mg, 56%). LCMS ESI (m/z) found $[M+H]^+$ = 418.10

[00162] 4-methyl-3-[4-(5-methyl-3-phenyl-1*H*-pyrazol-4-yl)phenyl]benzenesulfonamide (**27**)

Synthesized according to ***general procedure C***. Obtained as a white solid (66 mg, 53%). LCMS ESI (m/z) found $[M+H]^+$ = 404.10

[00163] 2,3-dimethyl-4-[4-(5-methyl-3-phenyl-1H-pyrazol-4-yl)phenyl]benzonitrile (**28**)

Synthesized according to ***general procedure E***. Obtained as a white solid (30 mg, 26%). LCMS ESI (m/z) found $[M+H]^+$ = 364.20

[00164] 4-methyl-3-[4-(5-methyl-3-phenyl-1*H*-pyrazol-4-yl)phenyl]benzonitrile (**29**)

Synthesized according to ***general procedure C***. Obtained as a white solid (53 mg, 49%). LCMS ESI (m/z) found $[M+H]^+$ = 350.20

[00165] 3-methyl-4-[4-(5-methyl-3-phenyl-1*H*-pyrazol-4-yl)phenyl]benzonitrile (**30**)

Synthesized according to ***general procedure C***. Obtained as a white solid (52 mg, 48%). LCMS ESI (m/z) found $[M+H]^+$ = 350.20

[00166] 2,3-dimethyl-4-[4-[3-(2-morpholino-4-pyridyl)-1*H*-pyrazol-4-yl]phenyl]benzenesulfonamide (**31**)

Synthesized according to ***general procedure E***. Obtained as a white solid (8 mg, 6%) LCMS ESI (m/z) found $[M+H]^+$ = 490.30

[00167] 2-[4-(5-methyl-3-phenyl-1*H*-pyrazol-4-yl)phenyl]-8-oxa-2-azaspiro[4.5]decane (**32**)

Synthesized according to ***general procedure F***. Obtained as a white solid (9 mg, 7%) LCMS ESI (m/z) found $[M+H]^+$ = 374.20

[00168] 5-[4-(5-methyl-3-phenyl-1*H*-pyrazol-4-yl)phenyl]-1,3-dihydropyrrolo[2,3-b]pyridin-2-one (**33**)

Synthesized according to ***general procedure C***. Obtained as a white solid (23 mg, 20%). LCMS ESI (m/z) found $[M+H]^+$ = 367.20

[00169] 4-Methyl-3-[4-[5-methyl-3-(4-pyridyl)-1*H*-pyrazol-4-yl]phenyl]benzenesulfonamide (**34**)

Synthesized according to ***general procedure C***. Obtained as a white solid (50 mg, 40%). LCMS ESI (m/z) found $[M+H]^+$ = 405.20

[00170] 2,3-dimethyl-4-[4-[5-methyl-3-(4-pyridyl)-1*H*-pyrazol-4-yl]phenyl]benzenesulfonamide (**35**)

Synthesized according to ***general procedure E***. Obtained as a white solid (7 mg, 5%). LCMS ESI (m/z) found $[M+H]^+$ = 419.20

[00171] 2,3-dimethyl-4-[4-[5-methyl-3-(2-morpholino-4-pyridyl)-1*H*-pyrazol-4-yl]phenyl]benzenesulfonamide (**36**)

Synthesized according to ***general procedure E***. Obtained as a white solid (67 mg, 45%). ESI LCMS (m/z) found $[M+H]^+$ = 504.20

[00172] 4-[4-[3-(2,6-dimethyl-4-pyridyl)-5-methyl-1*H*-pyrazol-4-yl]phenyl]-2,3-dimethyl-benzenesulfonamide (**37**)

Synthesized according to ***general procedure E***. Obtained as a white solid (79 mg, 59%). ESI LCMS (m/z) found $[M+H]^+$ = 447.20

[00173] 6-methyl-5-[4-[3-(4-pyridyl)-1*H*-pyrazol-4-yl]phenyl]pyridine-3-carbonitrile (**38**)

Synthesized according to ***general procedure E***. Obtained as a white solid (6 mg, 5%). LCMS ESI (m/z) found $[M+H]^+$ = 338.20

[00174] 6-Methyl-5-[4-[5-methyl-3-(4-pyridyl)-1*H*-pyrazol-4-yl]phenyl]pyridine-2-carbonitrile (**39**)

Synthesized according to ***general procedure C***. Obtained as a white solid (44 mg, 40%). LCMS ESI (m/z) found $[M+H]^+$ = 352.20

[00175] 2,3-dimethyl-4-[4-[5-methyl-3-(2-methyl-4-pyridyl)-1*H*-pyrazol-4-yl]phenyl]benzenesulfonamide (**40**)

Synthesized according to ***general procedure E***. Obtained as a white solid (77 mg, 60%). LCMS ESI (m/z) found $[M+H]^+$ = 433.20

[00176] 4-[4-[3-(2-methoxy-4-pyridyl)-5-methyl-1*H*-pyrazol-4-yl]phenyl]-2,3-dimethyl-benzenesulfonamide (**41**)

Synthesized according to ***general procedure E***. Obtained as a white solid (90 mg, 67%). LCMS ESI (m/z) found $[M+H]^+$ = 449.20

[00177] 2,3-dimethyl-4-[4-[5-methyl-3-(3-methyl-4-pyridyl)-1*H*-pyrazol-4-yl]phenyl]benzenesulfonamide (**42**)

Synthesized according to ***general procedure E***. Obtained as a white solid (102 mg, 79%). LCMS ESI (m/z) found $[M+H]^+$ = 433.20

[00178] 2,3-dimethyl-4-[4-[5-methyl-3-(1-methylpyrazol-4-yl)-1*H*-pyrazol-4-yl]phenyl]benzenesulfonamide (**43**)

Synthesized according to ***general procedure E***. Obtained as a white solid (72 mg, 58%). LCMS ESI (m/z) found $[M+H]^+$ = 422.20

[00179] 4-[4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzene-1,3-dicarbonitrile (**44**)

Synthesized according to ***general procedure E***. Obtained as a white solid (7 mg, 6%). LCMS ESI (m/z) found $[M+H]^+$ = 362.20

[00180] 3,4-dimethyl-5-[4-[5-methyl-3-(4-pyridyl)-1*H*-pyrazol-4-yl]phenyl]benzenesulfonamide (**45**)

Synthesized according to ***general procedure E***. Obtained as a white solid (20 mg, 17%). LCMS ESI (m/z) found $[M+H]^+$ = 419.20

[00181] 3-[4-[5-Methyl-3-(4-pyridyl)-1*H*-pyrazol-4-yl]phenyl]benzenesulfonamide (**46**)

Synthesized according to ***general procedure C***. Obtained as a white solid (35 mg, 33%). LCMS ESI (m/z) found $[M+H]^+$ = 399.10

[00182] *N*,3-Dimethyl-4-[4-[5-methyl-3-(4-pyridyl)-1*H*-pyrazol-4-yl]phenyl]benzenesulfonamide (**47**)

Synthesized according to ***general procedure C***. Obtained as a white solid (25 mg, 22%). LCMS ESI (m/z) FOUND $[M+H]^+$= 419.20

[00183] 2-Methyl-3-[4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide (**48**)

Synthesized according to ***general procedure C***. Obtained as a white solid (83 mg, 66%). LCMS ESI (m/z) FOUND $[M+H]^+$ = 405.10

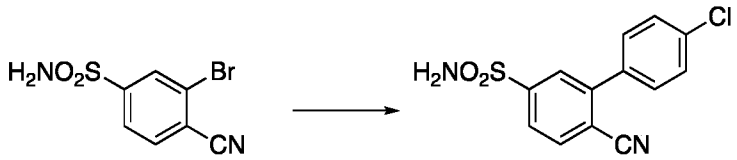
[00184] 5-[4-[5-Methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-1,3-dihydropyrrolo[2,3-b]pyridin-2-one (**49**)

Synthesized according to ***general procedure C***. Obtained as a white solid (43 mg, 38%). LCMS ESI (m/z) found $[M+H]^+$ = 368.20

[00185] 2-Methyl-6-[4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzonitrile (**50**)

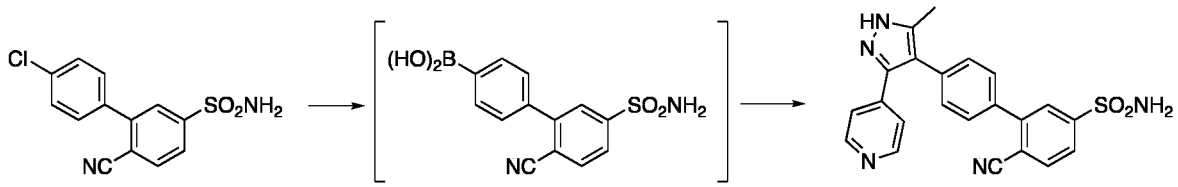
Synthesized according to ***general procedure C***. Obtained as a white solid (25 mg, 26%). LCMS ESI (m/z) found $[M+H]^+$ = 351.20

[00186] 3-(4-chlorophenyl)-4-cyano-benzenesulfonamide (**51a**)



Synthesized according to ***general procedure A***. Obtained as a yellow solid (221 mg, 62%). LCMS ESI (m/z) found $[M+H]^+$ = 293.00

[00187] 4-cyano-3-[4-[5-methyl-3-(4-pyridyl)-1*H*-pyrazol-4-yl]phenyl]benzenesulfonamide (**51**)



[00188] To a 2-5 ml microwave vial equipped with stir bar was added 3-(4-chlorophenyl)-4-cyano-benzenesulfonamide (62 mg, 0.21 mmol), tetrahydroxydiboron (57 mg, 0.63 mmol), XPhos Pd G3 (6 mg, 0.01 mmol) and potassium acetate (62 mg, 0.63 mmol). The vial was sealed,

evacuated under vacuo and re-filled with N_2. This was repeated three times before methanol (1.4 mL) was added and the reaction was heated at 80°C in a sand bath for 2 hours. Then 4-(4-bromo-5-methyl-1*H*-pyrazol-3-yl)pyridine (34 mg, 0.14 mmol) followed by a potassium carbonate (0.35 mL, 0.63 mmol) (1.8 M aq) was added and the reaction stirred at 125°C in a microwave reactor for 20 minutes. The reaction was then diluted with MeOH and filtered, and purified by FCC to give the product. LCMS (m/z) ESI found $[M+H]^+$ = 416.10

[00189] 4-methyl-3-[4-[5-methyl-3-(4-pyridyl)-1*H*-pyrazol-4-yl]phenyl]benzamide (**52**)

Synthesized according to ***general procedure E***. Obtained as a white solid (52 mg, 45%). ESI LCMS (m/z) found $[M+H]^+$ = 369.20

[00190] 4-[4-[5-methyl-3-(4-pyridyl)-1*H*-pyrazol-4-yl]phenyl]pyridine-3-carbonitrile (**53**)

Synthesized according to ***general procedure C***. Obtained as a white solid (27 mg, 24%). LCMS ESI (m/z) found $[M+H]^+$ = 338.10

[00191] 3-[2-Methyl-4-[5-methyl-3-(4-pyridyl)-1*H*-pyrazol-4-yl]phenyl]benzenesulfonamide (**54**)

Synthesized according to ***general procedure C***. Obtained as a white solid (61 mg, 61%). LCMS ESI (m/z) FOUND $[M+H]^+$ = 405.20

[00192] 3-[2-Methyl-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzamide (**55**)

Synthesized according to ***general procedure C***. Obtained as a white solid (61 mg, 59%). LCMS ESI (m/z) FOUND $[M+H]^+$ = 367.20

[00193] 2-[4-[5-methyl-3-(4-pyridyl)-1*H*-pyrazol-4-yl]phenyl]-8-oxa-2-azaspiro[4.5]decane (**56**)

Synthesized according to ***general procedure F***. Obtained as a white solid (17 mg, 15%). LCMS ESI (m/z) found $[M+H]^+$ = 375.20

[00194] (3*R*)-3-methyl-2-[4-[5-methyl-3-(4-pyridyl)-1*H*-pyrazol-4-yl]phenyl]-8-oxa-2-azaspiro[4.5]decane (**57**)

Synthesized according to ***general procedure F***. Obtained as a white solid (64 mg, 58%). LCMS ESI (m/z) found $[M+H]^+$ = 389.20

[00195] 8-[4-[5-methyl-3-(4-pyridyl)-1*H*-pyrazol-4-yl]phenyl]-2,8-diazaspiro[4.5]decan-3-one (**58**)

Synthesized according to ***general procedure F***. Obtained as a white solid (19 mg, 18%). LCMS ESI (m/z) found $[M+H]^+$ = 388.20

[00196] (3*S*)-3-methyl-2-[4-[5-methyl-3-(4-pyridyl)-1*H*-pyrazol-4-yl]phenyl]-8-oxa-2-azaspiro[4.5]decane (**59**)

Synthesized according to ***general procedure F***. Obtained as a white solid (55 mg, 45%). LCMS ESI (m/z) found $[M+H]^+$ = 389.20

[00197] 3-[4-[5-methyl-3-(2-methyl-4-pyridyl)-1*H*-pyrazol-4-yl]phenyl]benzenesulfonamide (**60**)
Synthesized according to ***general procedure C***. Obtained as a white solid (59.1 mg, 75%).

[00198] 3-[4-[3-(2-methoxy-4-pyridyl)-5-methyl-1*H*-pyrazol-4-yl]phenyl]benzenesulfonamide (**61**)
Synthesized according to ***general procedure C***. Obtained as a white solid (81 mg, 67%).

[00199] 3-[4-[5-methyl-3-(2-morpholino-4-pyridyl)-1*H*-pyrazol-4-yl]phenyl]benzenesulfonamide (**62**)
Synthesized according to ***general procedure C***. Obtained as a white solid (106 mg, 28%).

[00200] 3-[4-(5-methyl-3-phenyl-1*H*-pyrazol-4-yl)phenyl]benzenesulfonamide (**63**)
Synthesized according to ***general procedure C***. Obtained as a white solid (143 mg, 58%).

[00201] 3-[4-[3-(2,6-dimethyl-4-pyridyl)-5-methyl-1*H*-pyrazol-4-yl]phenyl]benzenesulfonamide (**64**)

[00202] Synthesized according to ***general procedure C***. Obtained as a white solid (32 mg, 46%).

[00203] 3-[4-[3-(2-methyl-4-pyridyl)-1*H*-pyrazol-4-yl]phenyl]benzenesulfonamide (**65**)
Synthesized according to ***general procedure C***. Obtained as a white solid (40 mg, 47%).

[00204] 4-[2-methyl-4-[5-methyl-3-(4-pyridyl)-1*H*-pyrazol-4-yl]phenyl]benzonitrile (**66**)
Synthesized according to ***general procedure C***. Obtained as a white solid (41 mg, 38%).
LCMS ESI (m/z) FOUND $[M+H]^+$ = 351.20

[00205] 3-[2-ethyl-4-[5-methyl-3-(4-pyridyl)-1*H*-pyrazol-4-yl]phenyl]benzenesulfonamide (**67**)
Synthesized according to ***general procedure C***. Obtained as a white solid (64 mg, 54%).
LCMS ESI (m/z) FOUND $[M+H]^+$ = 419.20

[00206] 4-[2-ethyl-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzonitrile (**68**)
Synthesized according to ***general procedure C***. Obtained as a white solid (53 mg, 51%).
LCMS ESI (m/z) FOUND $[M+H]^+$ = 365.20

[00207] 4-[2-ethyl-4-[5-methyl-3-(4-pyridyl)-1*H*-pyrazol-4-yl]phenyl]pyridine (**69**)
Synthesized according to ***general procedure C***. Obtained as a white solid (37 mg, 39%).
LCMS ESI (m/z) FOUND $[M+H]^+$ = 341.20

[00208] 2-[2-methyl-4-[5-methyl-3-(4-pyridyl)-1*H*-pyrazol-4-yl]phenyl]-8-oxa-2-azaspiro[4.5]decane (**70**)

Synthesized according to ***general procedure F***. Obtained as a white solid (65 mg, 53%). LCMS ESI (m/z) found $[M+H]^+$ = 389.30

[00209] 3-[4-[5-Methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]-2-(trifluoromethyl)phenyl]benzenesulfonamide (**71**)

Synthesized according to ***general procedure C***. Obtained as a white solid (46 mg, 40%). LCMS ESI (m/z) FOUND $[M+H]^+$ = 459.10

[00210] 3-[2-cyano-4-[5-methyl-3-(4-pyridyl)-1*H*-pyrazol-4-yl]phenyl]benzenesulfonamide (**72**)

Synthesized according to ***general procedure C***. Obtained as a white solid (53 mg, 44%). LCMS ESI (m/z) FOUND $[M+H]^+$ = 416.10

[00211] 3-[2,6-difluoro-4-[5-methyl-3-(4-pyridyl)-1*H*-pyrazol-4-yl]phenyl]benzenesulfonamide (**73**)

Synthesized according to ***general procedure C***. Obtained as a white solid (47 mg, 40%). LCMS ESI (m/z) FOUND $[M+H]^+$ = 427.10

[00212] 6-[2-methyl-4-[5-methyl-3-(4-pyridyl)-1*H*-pyrazol-4-yl]phenyl]-2-oxa-6-azaspiro[3.3]heptane (**74**)

Synthesized according to ***general procedure F***. Obtained as a white solid (55 mg, 61%). LCMS ESI (m/z) found $[M+H]^+$ = 347.10

[00213] 5-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]-2-morpholino-benzonitrile (**75**)

Synthesized according to ***general procedure F***. LCMS ESI (m/z) found $[M+H]^+$ = 346.20

[00214] 4-[2-methyl-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]morpholine (**76**)

Synthesized according to ***general procedure F***. LCMS ESI (m/z) found $[M+H]^+$ = 335.20

[00215] 2-[2,6-difluoro-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-8-oxa-2-azaspiro[4.5]decane (**77**)

Synthesized according to ***general procedure F***. LCMS ESI (m/z) found $[M+H]^+$ = 411.20

[00216] 6-[2,6-difluoro-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-2-oxa-6-azaspiro[3.3]heptane (**78**)

Synthesized according to ***general procedure F***. LCMS ESI (m/z) found $[M+H]^+$ = 369.20

[00217] 2-[4-[5-methyl-3-(2-morpholino-4-pyridyl)-1H-pyrazol-4-yl]phenyl]-8-oxa-2-azaspiro[4.5]decane (**79**)

Synthesized according to ***general procedure F***. LCMS ESI (m/z) found $[M+H]^+$ = 460.20

[00218] 2-[4-[3-(2,6-dimethyl-4-pyridyl)-5-methyl-1H-pyrazol-4-yl]phenyl]-8-oxa-2-azaspiro[4.5]decane (**80**)

Synthesized according to ***general procedure F***. LCMS ESI (m/z) found $[M+H]^+$ = 403.30

[00219] 2-[4-[5-methyl-3-(2-methyl-4-pyridyl)-1H-pyrazol-4-yl]phenyl]-8-oxa-2-azaspiro[4.5]decane (**81**)

Synthesized according to ***general procedure F***. LCMS ESI (m/z) found $[M+H]^+$ = 389.20

[00220] 3-[4-[3-(2-morpholino-4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide (**82**)

Synthesized according to ***general procedure C***. LCMS ESI (m/z) found $[M+H]^+$ = 476

[00221] 4-[5-methyl-4-[3-methyl-4-(4-pyridyl)phenyl]-1H-pyrazol-3-yl]pyridine (**83**)

Synthesized according to ***general procedure C***. LCMS ESI (m/z) found $[M+H]^+$= 327; $[M-H]^-$ = 325.

[00222] 2-methoxy-4-[2-methyl-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]pyridine (**84**)

Synthesized according to ***general procedure C***. LCMS ESI (m/z) found $[M+H]^+$= 357; $[M-H]^-$ = 355.

[00223] 3-[4-(3-phenyl-1H-pyrazol-4-yl)phenyl]benzenesulfonamide (**85**)

Synthesized according to ***general procedure C***. LCMS ESI (m/z) found $[M+H]^+$= 376.

[00224] 3-[4-[3-(2-methoxy-4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide (**86**)

Synthesized according to ***general procedure C***. LCMS ESI (m/z) found $[M+H]^+$= 407.

[00225] 4-[5-methyl-4-[3-methyl-4-(3-methylsulfonylphenyl)phenyl]-1H-pyrazol-3-yl]pyridine (**87**)

Synthesized according to ***general procedure C***. LCMS ESI (m/z) found $[M+H]^+$= 404; $[M-H]^-$ = 402.

[00226] 3-[2-methyl-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]pyridine (**88**)

Synthesized according to ***general procedure C***. LCMS ESI (m/z) found $[M+H]^+$= 327.

[00227] 2-[2-methyl-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-7-oxa-2-azaspiro[3.5]nonane (**89**)

Synthesized according to ***general procedure F***. LCMS ESI (m/z) found $[M+H]^+$ = 375.30.

[00228] 2-[4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-7-oxa-2-azaspiro[3.5]nonane (**90**)

Synthesized according to ***general procedure F***. LCMS ESI (m/z) found $[M+H]^+$ = 361.20.

[00229] 2-[2-methoxy-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-7-oxa-2-azaspiro[3.5]nonane (**91**)

Synthesized according to ***general procedure F***. LCMS ESI (m/z) found $[M+H]^+$ = 391.10.

[00230] 2-[2-ethyl-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-7-oxa-2-azaspiro[3.5]nonane (**92**)

Synthesized according to ***general procedure F***. LCMS ESI (m/z) found $[M+H]^+$ = 389.30.

[00231] 4-[2-ethyl-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide (**93**)

Synthesized according to ***general procedure C***. LCMS ESI (m/z) found $[M+H]^+$= 419.10.

[00232] 4-[2,6-difluoro-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide (**94**)

Synthesized according to ***general procedure C***. LCMS ESI (m/z) found $[M+H]^+$= 427.10

[00233] 2-[4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-6-oxa-2-azaspiro[3.4]octane (**95**)

Synthesized according to ***general procedure F***. LCMS ESI (m/z) found $[M+H]^+$= 347.10

[00234] 2-[4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-8λ6-thia-2-azaspiro[4.5]decane 8,8-dioxide (**96**)

Synthesized according to ***general procedure F***. LCMS ESI (m/z) found $[M+H]^+$= 423.10.

7-[4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-2-oxa-7-azaspiro[3.4]octane (**101**)

Synthesized according to ***general procedure F***. LCMS ESI (m/z) found $[M+H]^+$= 347.10.

[00235] 6-[2,6-difluoro-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-2λ6-thia-6-azaspiro[3.3]heptane 2,2-dioxide (**104**)

Synthesized according to ***general procedure F***. LCMS ESI (m/z) found $[M+H]^+$= 417.10.

[00236] 3-[4-[3-(4-pyridyl)-5-(trifluoromethyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide (**105**)

Synthesized according to ***general procedure C***. LCMS ESI (m/z) found $[M+H]^+$= 445.10

[00237] 6-[2-cyclopropyl-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-2λ6-thia-6-azaspiro[3.3]heptane 2,2-dioxide (**106**)

Synthesized according to ***general procedure F***. LCMS ESI (m/z) found $[M+H]^+$= 421.20.

[00238] 3-[2,6-dimethyl-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide (**107**)

Synthesized according to ***general procedure C***. LCMS ESI (m/z) found $[M+H]^+$= 419.20.

General procedure G

Example

2-[2,6-difluoro-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-8λ6-thia-2-azaspiro[4.5]decane 8,8-dioxide (**108**)

[00239] To a microwave vial equipped with stir bar was added 1,2,3-trifluoro-5-nitro-benzene (0.23 mL, 1.94 mmol), 8-thia-2-azaspiro[4.5]decane 8,8-dioxide hydrochloride (526 mg, 2.33 mmol), K_2CO_3 (805 mg, 5.83 mmol), and DMSO (3.89 mL). The vial was sealed and heated to 90 ˚C for 20 mins. An excess water was added and the resulting bright yellow precipitate was isolated by Büchnner filtration and dried. This solid was then suspended in EtOH (5 mL) and solid $Na_2S_2O_4$ (1.0 g, 5.83 mmol) was added. Water (3 mL) was added dropwise with vigorous stirring. The resulting mixture was was left to stir until complete conversion of the starting material was observed. The reaction was then diluted with excess sat. $NaHCO_3$, and the resulting yellow solid (366 mg, 57%, 4-(8,8-dioxo-8λ6-thia-2-azaspiro[4.5]decan-2-yl)-3,5-difluoro-aniline) was isolated by Büchner filtration and washed with water. LCMS: (ESI MS) found $[M+H]^+$ = 317.10.

[00240] To a flask equipped with stir bar was added 4-(8,8-dioxo-8λ6-thia-2-azaspiro[4.5]decan-2-yl)-3,5-difluoro-aniline (430 mg, 1.36 mmol) and MeOH (2.3 mL). This solution was cooled with an ice bath and 1.5 M aqueous HCl (2.72 mL, 4.08 mmol) was added followed by a 2M solution of $NaNO_2$ (0.68 mL, 1.36 mmol) in water. The resulting mixture was stirred on ice for 30 min before B_2Pin_2 (1.03 g, 4.08 mmol) was added as a solution in MeOH (2.31 mL) and the resulting mixture was stirred overnight at room temp. The resulting mixture was then diluted with water and extracted with DCM. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated before FCC purification (25g SiO_2, EtOAc/DCM) to give the product as an oil (180 mg, 25%, observed as a 85:15 mixture of BPin ester and free $B(OH)_2$). The material was used directly for the next step without further purification.

[00241] To a flask equipped with stir-bar was added crude 2-[2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-8λ6-thia-2-azaspiro[4.5]decane 8,8-dioxide (180 mg, 0.42 mmol), 4-(4-bromo-5-methyl-1*H*-pyrazol-3-yl)pyridine (50 mg, 0.21 mmol), Pd XPhos G3 (9 mg, 0.01 mmol) followed by K_2CO_3 (0.23 mL, 0.42 mmol) and EtOH (2.1 mL). The resulting mixture was heated in a microwave reactor at 125 ˚C for 20 mins. The reaction was then diluted with MeOH and concentrated before being purified by FCC (25g SiO_2, MeOH/DCM, then 30g C18, MeCN/water) to give the desired product as a white solid (73 mg, 72 %). LCMS: (ESI MS) *m/z* calcd for $C_{23}H_{24}F_2N_4O_2S$ found $[M+H]^+$ = 459.20.

Entry	Name	LCMS ESI (m/z) found $[M+H]^+$=	Method used
111	2-[2-cyclopropyl-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-8λ6-thia-2-azaspiro[4.5]decane 8,8-dioxide	463.20	F
110	2-[2,6-dimethyl-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-8λ6-thia-2-azaspiro[4.5]decane 8,8-dioxide	451.20	F
111	7-[2-cyclopropyl-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-2λ6-thia-7-azaspiro[3.4]octane 2,2-dioxide	435.20	F
112	3-[2-fluoro-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide	409.10	C
113	6-[4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]indolin-2-one	367.20	C
114	3-[2,6-difluoro-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-4-methyl-benzenesulfonamide	441.20	C
115	9-[2-cyclopropyl-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-3-oxa-9-azaspiro[5.5]undecane	429.20	F
116	6-[2,6-difluoro-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-1H-pyridin-2-one	365.20	C
117	6-[4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-1H-pyridin-2-one	329.20	C
119	3-[3-methyl-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide	405.20	C
120	2-[2,6-difluoro-4-[5-methyl-3-(2-methyl-4-pyridyl)-1H-pyrazol-4-yl]phenyl]-8-oxa-2-azaspiro[4.5]decane	425.20	F
121	3-[2-cyclopropyl-4-[5-methyl-3-(2-methyl-4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide	445.20	C
122	2-[2,6-difluoro-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-7-oxa-2,5-diazaspiro[3.5]nonan-6-one	412.20	G
123	3-[2-ethyl-4-[5-methyl-3-(2-morpholino-4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide	504.20	C
124	4-[4-[3-ethyl-4-(3-pyrazol-1-ylphenyl)phenyl]-5-methyl-1H-pyrazol-3-yl]pyridine	406.20	C
125	4-[4-[3,5-difluoro-4-[3-(5-methylpyrazol-1-yl)phenyl]phenyl]-5-methyl-1H-pyrazol-3-yl]pyridine	428.20	C
126	4-[4-[3,5-difluoro-4-(3-pyrazol-1-ylphenyl)phenyl]-5-methyl-1H-pyrazol-3-yl]pyridine	414.20	C
127	4-[4-[3,5-difluoro-4-[3-(4-methylpyrazol-1-yl)phenyl]phenyl]-5-methyl-1H-pyrazol-3-yl]pyridine	428.20	C
128	[(1R,5S)-8-[2,6-difluoro-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-8-azabicyclo[3.2.1]octan-3-yl]methanol	411.20	G
129	[(1R,5S)-8-[2,6-difluoro-4-[5-methyl-3-(2-methyl-4-pyridyl)-1H-pyrazol-4-yl]phenyl]-8-azabicyclo[3.2.1]octan-3-yl]methanol	425.20	G
130	9-[2,6-difluoro-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-2,9-diazaspiro[5.5]undecan-3-one	438.20	G
131	9-[2,6-difluoro-4-[5-methyl-3-(2-methyl-4-pyridyl)-1H-pyrazol-4-yl]phenyl]-2,9-diazaspiro[5.5]undecan-3-one	452.20	G
132	2-[2,6-difluoro-4-[5-methyl-3-(2-methyl-4-pyridyl)-1H-pyrazol-4-yl]phenyl]-8λ6-thia-2-azaspiro[4.5]decane 8,8-dioxide	473.20	G

133	3-[2,6-difluoro-4-[5-methyl-3-(2-methyl-4-pyridyl)-1H-pyrazol-4-yl]phenyl]-3,9-diazaspiro[5.5]undecan-10-one	452.20	G
134	3-[2,6-difluoro-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-3,9-diazaspiro[5.5]undecan-10-one	438.20	G
135	8-[2,6-difluoro-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-2,8-diazaspiro[4.5]decan-3-one	424.20	G
136	8-[2,6-difluoro-4-[5-methyl-3-(2-methyl-4-pyridyl)-1H-pyrazol-4-yl]phenyl]-2,8-diazaspiro[4.5]decan-3-one	438.20	G

Biochemical Assays

[00242] *LRRKtide Adapta Assay.* A 2X Full length LRRK2 wild-type or LRRK2 G2019S/ERM (LRRKtide) mixture was prepared in 50 mM Tris pH 8.5, 0.01% BRIJ-35, 10 mM $MgCl_2$, 1 mM EGTA, 0.02% NaN_3. The final 10 µL Kinase Reaction consists of 7.5 - 60 ng LRRK2 FL and 200 µM ERM (LRRKtide) in 25 mM Tris / 7.5 mM HEPES pH 8.2, 0.005% BRIJ-35, 5 mM MgCl2, 0.5 mM EGTA, 0.01% NaN3. After 1 hour kinase reaction incubation, 5 µL of Detection Mix is added. The Detection Mix was prepared in TR-FRET Dilution Buffer and consisted of EDTA (30mM), Eu-anti-ADP antibody (6 nM) and ADP tracer at the EC60 concentration (5-150 uM ATP). Test Compounds were screened in 1% DMSO (final) per well in 10 point titrations of 3-fold serial dilutions.

[00243] *GFP-nanobody capture based ELISA for LRRK2 and LRRK2 pSer935*- GST fused GFP-nanobody (GST-GFPnb) was used as the capture antibody and was expressed from pGEX6p-GFPnb (Addgene#61838) in BL21rosetta cells. Cells were grown to an OD600 of 0.5 and induced with 1mM IPTG overnight at 16°C. Cell pellets were lysed in PBS/1%TritonX100/10% glycerol plus cOmplete protease inhibitors (Roche) by sonication and protein was purified by glutathione agarose chromatography (Gold Bio cat. no. G-250-10). GSH bound protein was eluted with 20mM glutathione in PBS and dialyzed against PBS/10%glycerol and snap frozen in aliquots.

[00244] *LRRK2 pSer935 Enzyme Linked Immunosorbant Assay*- Greiner Bio plates (781074) were coated with 30ng/well GST-GFPnb in 100mM Carbonate buffer pH11 overnight. Plates were washed twice with TBS/0.05% Tween and blocked in 1%BSA/TBS/0.05% Tween for 2 hours. HEK293 cells at 80% confluence in 10cm dishes were transfected with pcDNA5FRT-TO-LRRK2 or pcDNA5FRT-TO LRRK2 G2019S overnight (15ug DNA / 30ul p3000 / 23ul Lipofectamine 3000; Thermofisher cat. no. L3000015). Cells were replated at 100,000 cells per well of a 48well in 200ul media. 24 hours after plating, cells were treated with compounds in 7-point, 3-fold serial dilutions for 24hrs. Cells were lysed in-situ with 85ul Lanthascreen Lysis buffer (Invitrogen cat. no. PV5598) containing protease and phosphatase inhibitors Gold Bio ProBlock™ Gold Mammalian Protease Inhibitor Cocktail cat. no. GB-331-5; Sigma Phosphatase Inhibitor Cocktail 2 & 3 cat. no. P5726-5ML and P0044-5ML; microcystin; Enzo Life Sci. ALX-350-012-C100; Sigma, Benzamidine cat. no. 12072-10G and PMSF cat. no. P7626-5G) and (10ul) added to GST-GFPnb coated plates and allowed to bind overnight at 4°C. Plates were washed twice with TBST and incubated with anti-LRRK2 pSer935 (1:2000 UDD2; abcam ab133450) or anti-Total

LRRK2 (1:2000 Neuromab Anti-Dardarin/LRRK2, C-terminus (N241A/34) cat. no. 75-253) for 2.5 hours. Plates were washed and incubated with goat anti-rabbit HRP (Thermofisher cat. no. 31439) or goat anti-mouse HRP (Thermofisher cat. no. 31460) at 1:15,000 for 2.5 hours. Plates were washed three times and incubated with SuperSignal ELISA Pico ECL substrate (Pierce cat. no. 37069) and read on a Molecular Devices Spectramax iD5 plate reader.

[00245] *Statistics.* SelectScreen Kinase Profiling Service uses XLfit from IDBS. The ATP/ADP standard curve is fit to model number 205 (sigmoidal dose-response model). The dose response curve is also curve fit to model number 205. If the bottom of the curve does not fit between -20% & 20% inhibition, it is set to 0% inhibition. If the top of the curve does not fit between 70% and 130% inhibition, it is set to 100% inhibition. Effective concentrations of inhibitors were generated in Graphpad Prism 8.0, setting no inhibition at 100% and complete inhibition at 0% and fitting to 3-parameter inhibitor response curves.

[00246] *Kinome Selectivity Profiling,* compounds are profiled against protein kinases using the SelectScreen Profiling Services (Thermofisher Scientific, Madison WI). All assays are performed at ATP concentrations near K_mATP. Compounds were tested at 1 μM or 0.1 μM as indicated.

[00247] *Cell Culture and Plasmids*-HEK293 cells are acquired from ATCC for this study (CRL-1573) and are cultured in DMEM supplemented with 10% FBS, 2 mM glutamine, 1x antimycotic/antibiotic. pcDNA5FRT-TO-GFP-LRRK2 G2019S was generated by subcloning the LRRK2-G2019S cDNA from pCMV5-FLAG-LRRK2 G2019S (DU48064, kind gift from Prof. Dario Alessi, University of Dundee) into pcDNA5FRT-TO-GFP vector (DU41455, kind gift from Prof. Dario Alessi, University of Dundee) using standard protocols and sequence verified by Sanger sequencing.

[00248] *MEFs*-Mice are used in accordance with an approved Institutional Animal Care and Use Committee protocol at Stanford University. Mice are housed with free access to water and food according to the university's guidelines in a 12 h light/12 h dark cycles. Mouse embryonic fibroblasts (MEFs) are prepared from WT or LRRK2 G2019S knock-in mice (Jackson Laboratories; 030961). Embryos (dpc 13.5-14.5) are used to generate the MEFs through standard published protocols. Spontaneously immortalized lines are derived from serial passaging according to Xu.

[00249] *Immunoblot analyses*-HEK293 cells are transfected as above and re-plated in 6-well dishes. 24 h after plating, cells were dosed as indicated for 24 h. Confluent 6-well plates of Wild-type and G2019S MEFs are treated with inhibitors for 24 h. Cells are rinsed with PBS and lysed in situ and clarified by centrifugation at 15,000 x g for 15 min at 4 ˚C. Lysis Buffer contained 1% TritonX-100, 50 mM Tris/HCl, pH 7.4, 1 mM EGTA, 1 mM EDTA, 1 mM sodium orthovanadate, 10 mM sodium β-glycerophosphate, 50 mM NaF, 5 mM sodium pyrophosphate, 0.27 M sucrose with protease and phosphatase inhibitors. Clarified lysates are resolved on 4-12% Nupage Bis-Tris Gels (Thermoscientific) and transferred to nitrocellulose. Membranes are probed with anti-

LRRK2 pSer935 (1:2000 UDD2; abcam ab133450) or anti-LRRK2 pSer973 (1:1000; abcam ab181364), anti-LRRK2 pSer1292 (1:1000; ab203181)anti-Rab10 pThr73 (1:1000; abcam ab230261), Total Rab10 (1:1000; abcam 4E10 ab104859), anti-tubulin (1:1000; Cell Signaling 3873S). Immunoblots are developed with LiCor goat anti-mouse CW800 (NC9401841) and goat-anti-Rabbit LT680 (NC9030093) secondaries and read on a Sapphire Scanner (Azure) or blots were developed with BioRad goat anti-rabbit HRP 1706515 and exposed to film.

[00250] *Microsomal stability assays*. Method was adapted from Obach 1999. Incubation mixtures consisted of liver microsomes (0.5 mg microsomal protein/mL), substrates (1.0 μM), $MgCl_2$ (10 mM), and NADPH (1 mM) in a total volume of 0.5 mL in potassium phosphate buffer (100 mM, pH 7.5). Reactions are started with the addition of NADPH and shaken in a water bath open to the air at 37 ˚C. Aliquots (50 μl) are removed and added to termination mixtures containing internal standard at time points between 0 and 40 min. The samples are mixed and precipitated by centrifugation; the resulting supernatant was diluted with mobile phase and analyzed by HPLC-MS.

[00251] *Caco-2 permeability assays.* Caco-2 cells are maintained in DMEM in an atmosphere of 5% CO_2. For transport experiments 50,000 cells/well were seeded on 12-well plate with polycarbonate filter inserts and allowed to grow and differentiate for 25 ± 4 days before the cell monolayers were used for experiments. Apparent permeability coefficients are determined for apical to basolateral and basolateral to apical directions with and without 2 μM elacridar as a P-glycoprotein transporter inhibitor. Test articles and reference compounds are dissolved in Hank's balanced salt solution (HBSS) containing 25 mM HEPES to yield a final concentration of 10 μM. The assays were performed in HBSS at pH 7.4 for the basolateral side and pH 6.5 for apical side at 37˚C. Prior to the study, the monolayers are washed in prewarmed HBSS. At the start of the experiments, prewarmed HBSS containing the test articles is added to the donor side of the monolayer and HBSS without test articles was added to the receiver side. Aliquots of the receiver side are taken over the 2 h incubation period; aliquots of the donor side are taken at 0 h and 2 h. Aliquots are diluted with an equal volume of methanol/water with 0.1% formic acid containing the internal standard. The mixture is analyzed by LC–MS/MS. The apparent permeability coefficients (P_{app}) are calculated using the formula: $P_{app} = (dC_{rec}/dt)/(A \times C_{0,donor})] \times 10^6$ with dC_{rec}/dt being the change in concentration in the receiver compartment with time; $C_{0,donor}$ the concentration in the donor compartment at time 0; and A the area of the cells monolayer.

[00252] *Animal Studies. Pharmacokinetics.* A mouse PK is performed at Bayside Biosciences Inc (Santa Clara, CA, US). The animal study protocol is approved by Institutional Animal Care and Use Committee (IACUC) of Bayside Biosciences Inc. before the animal study was initiated. In the PK study, male CD-1 mice at age of 7 weeks are purchased from Charles River Laboratories (US). The mice are divided into two groups (n=15); mice in Group 1 are IV dosed via tail vein

injection at 0.5 mg/kg/each, and mice in Group 2 are oral gavage dosed with the cassette of two compounds at 5 mg/kg/each.

[00253] Mouse PK studies are performed by Concept Life Sciences LLC (UK) in a cassette format. For cassette dosing - equal volumes compounds are aliquoted together to ensure a final concentration of 1 mg/mL per compound in DMSO. Analytical standards are prepared from an initial 1mg/ml stock of compound, a 12-point standard curve range is from 0.5 ng/mL to 2000 ng/mL. Independent quality controls are prepared from 1 ng/ml to 1000 ng/ml to validate the standards. All standards and quality controls are matrix matched to eliminate any possible suppression. Plasma samples are prepared neat and diluted (diluted 1:10 in plasma). Brain tissue samples are homogenised in 0.1M phosphate buffer at a ratio of 1:4 and prepared neat. Dose solutions are diluted in control matrix to a relative concentration that will fall on the standard curve. Cold acetonitrile containing internal standard is added to all samples, dose samples, standards and QCs. Samples are then centrifuged at 4000 rpm for 30 min. Following centrifugation, supernatant is transferred to a new 96-well plate and diluted with an equal amount of water. Samples are mixed thoroughly before LC-MS/MS analysis.

[00254] For quantitation, the supernatants are analysed by LC-MS/MS using Concept Life Sciences generic analytical methods with matrix matched standard curve to quantify the concentration of test compound in each sample.

[00255] For data analysis, for each test compound injection; Response ratio = (Test peak area/Internal standard peak area). From the standard curve, the response ratio is converted to concentration of test compound. Back calculated concentrations are determined using linear regression, applying the minimum weighting possible. Over the calibration range, 75% of the calibration standards are required to meet the acceptance criterion of ± 25% of nominal concentration. The acceptance criterion for quality control samples must be two thirds of samples within ± 25% of nominal concentration.

[00256] *In vivo target engagement.* Compounds are dissolved in (EtOH/Cremophor at 1:1) + 75% saline and wild-type or GS-LRRK2 mice are dosed intraperitoneally with 30 mg/kg for 2 h. Animals are sacrificed by cervical dislocation and tissues are dissected and snap frozen in liquid nitrogen. Frozen tissue is thawed into a 10X volume of lysis buffer in 2 mL screwcap microtubes with 1.4 mm ceramic beads (#19-627, Omni International). Lysis buffer is 1% TritonX-100, 0.1% SDS, 50 mM Tris/HCl, pH 7.4, 1 mM EGTA, 1 mM EDTA, 1 mM sodium orthovanadate, 10 mM sodium β-glycerophosphate, 50 mM NaF, 5 mM sodium pyrophosphate, 0.27 M sucrose, with Halt protease and phosphatase inhibitors (Thermofisher 78446) with microcystin (Enzo Life Sci. ALX-350-012-C100); Benzamidine (Sigma 12072) and PMSF (Sigma P7626). Tissues are homogenized in a Bead Ruptor 12 at 4°C and protein concentrations determined by Bradford assay. Lysates of Brain, Kidney, Spleen and Lung are analyzed by immunoblot as above for cell lysate assays.

[00257] Included in this disclosure is evidence published as Leśniak et al. (2022) Eur J Med Chem 229:114080, herein specifically incorporated by reference.

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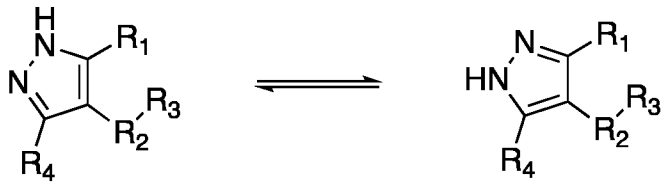
[00282] The preceding merely illustrates the principles of the invention. It will be appreciated that those skilled in the art will be able to devise various arrangements which, although not explicitly described or shown herein, embody the principles of the invention and are included within its spirit and scope. Furthermore, all examples and conditional language recited herein are principally intended to aid the reader in understanding the principles of the invention and the concepts contributed by the inventors to furthering the art, and are to be construed as being without limitation to such specifically recited examples and conditions. Moreover, all statements herein reciting principles, aspects, and embodiments of the invention as well as specific examples thereof, are intended to encompass both structural and functional equivalents thereof. Additionally, it is intended that such equivalents include both currently known equivalents and equivalents developed in the future, i.e., any elements developed that perform the same function, regardless of structure. The scope of the present invention, therefore, is not intended to be limited to the exemplary embodiments shown and described herein. Rather, the scope and spirit of the present invention is embodied by the appended claims.

THAT WHICH IS CLAIMED IS:

1. A compound that inhibits human LRRK2 protein, of formula (I) or derivatives or prodrugs thereof:



where

R_1 is H, F, Cl, Br, I Me, alkyl, OMe, O-alkyl, OCF_3, CF_3, CH_2F, or CHF_2;

R_2, R_3 and R_4 are an aryl or alkyl composed of a single ring (e.g., phenyl), or two or more condensed rings, such as 2 to 3 condensed rings (e.g., naphthyl), or two or more aromatic rings, such as 2 to 3 aromatic rings, which are linked by a single bond (e.g., biphenylyl), or a substituted aryl, that is mono-, di-, or tri-substituted with heterocycloalkyl, aryl, substituted aryl, heteroaryl, nitro, cyano (also referred to herein as nitrile), azido, halo, –OR, -SR, -SF5, -CHO, –COR, –C(O)OR, -C(O)-NR_2, –OC(O)R, -OC(O)NR_2, -OC(O)OR, --P(O)$(OR)_2$, -OP(O)$(OR)_2$, –NR2, -N+R_3 (wherein a counterion may be present), –$CONR_2$, –NRCOR, -NHC(O)OR, -NHC(O)NR_2, -NHC(NH)NR_2, SO_3^-, -SO_2OR, -OSO_2R, -SO_2NR_2, or -$NRSO_2$R, where each R is, independently, hydrogen, lower alkyl, R′-substituted lower alkyl, aryl, R′-substituted aryl, heteroaryl, heteroaryl(alkyl), R′-substituted aryl(alkyl), or aryl(alkyl) and each R′ is, independently, hydroxy, halo, alkyloxy, cyano, thio, SF5, nitro, alkyl, halo- alkyl, or amino;

R_4 is heterocycloalkyl, aryl, substituted aryl, heteroaryl, nitro, cyano (also referred to herein as nitrile), azido, halo, –OR, -SR, -SF5, -CHO, –COR, –C(O)OR, -C(O)-NR_2, –OC(O)R, -OC(O)NR_2, -OC(O)OR, --P(O)$(OR)_2$, -OP(O)$(OR)_2$, –NR_2, -N^+R_3, –$CONR_2$, –NRCOR, -NHC(O)OR, -NHC(O)NR_2, -NHC(NH)NR_2, SO_3^-, -SO_2OR, -OSO_2R, -SO_2NR_2, or -$NRSO_2$R, where each R is, independently, hydrogen, lower alkyl, R′-substituted lower alkyl, aryl, R′-substituted aryl, heteroaryl, heteroaryl(alkyl), R′-substituted aryl(alkyl), or aryl(alkyl) and each R′ is, independently, hydroxy, halo, alkyloxy, cyano, thio, SF5, nitro, alkyl, halo- alkyl, or amino.

2. The compound of claim 1, selected from:
3-methyl-4-[4-(3-methylsulfonylphenyl)phenyl]-1H-pyrazole; 3-[4-[3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide; 3-[4-[3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzonitrile; 2-[3-[4-[3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]phenyl]acetonitrile; 1-methyl-5-[4-[3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]indazole; 4-[4-[3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-1H-pyridin-2-one; 6-[4-[3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]tetrazolo[1,5-a]pyridine; 6-[4-(3,5-dimethyl-1H-pyrazol-4-yl)phenyl]-[1,2,4]triazolo[4,3-a]pyridine; 4-[4-(3,5-dimethyl-1H-pyrazol-4-yl)phenyl]-3-methyl-benzenesulfonamide; 2-[2-[4-[3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]phenyl]acetonitrile; 2-[4-[4-[3-

(4-pyridyl)-1H-pyrazol-4-yl]phenyl]phenyl]acetonitrile; 4-[4-(3-methyl-1H-pyrazol-4-yl)phenyl]benzenesulfonamide; 4-[4-[3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide; 3-methyl-4-[4-[3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide; 2-methyl-4-[4-[3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide; 4-[4-[4-(2,3-dimethylphenyl)phenyl]-1H-pyrazol-3-yl]pyridine; 2-[4-[3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzonitrile; 4-[4-[3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzonitrile; 3-methyl-4-[4-[3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzonitrile; 2-methyl-4-[4-[3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzonitrile; 2,3-dimethyl-4-[4-[3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide; 3-[4-(3,5-dimethyl-1H-pyrazol-4-yl)phenyl]benzonitrile; 3-[4-(5-methyl-3-phenyl-1H-pyrazol-4-yl)phenyl]benzonitrile; 2,3-dimethyl-4-[4-[3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzonitrile; 4-methyl-3-[4-[3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide; 2,3-dimethyl-4-[4-(5-methyl-3-phenyl-1H-pyrazol-4-yl)phenyl]benzenesulfonamide; 4-methyl-3-[4-(5-methyl-3-phenyl-1H-pyrazol-4-yl)phenyl]benzenesulfonamide; 2,3-dimethyl-4-[4-(5-methyl-3-phenyl-1H-pyrazol-4-yl)phenyl]benzonitrile; 4-methyl-3-[4-(5-methyl-3-phenyl-1H-pyrazol-4-yl)phenyl]benzonitrile; 3-methyl-4-[4-(5-methyl-3-phenyl-1H-pyrazol-4-yl)phenyl]benzonitrile; 2,3-dimethyl-4-[4-[3-(2-morpholino-4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide; 2-[4-(5-methyl-3-phenyl-1H-pyrazol-4-yl)phenyl]-8-oxa-2-azaspiro[4.5]decane; 5-[4-(5-methyl-3-phenyl-1H-pyrazol-4-yl)phenyl]-1,3-dihydropyrrolo[2,3-b]pyridin-2-one; 4-methyl-3-[4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide; 2,3-dimethyl-4-[4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide; 2,3-dimethyl-4-[4-[5-methyl-3-(2-morpholino-4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide; 4-[4-[3-(2,6-dimethyl-4-pyridyl)-5-methyl-1H-pyrazol-4-yl]phenyl]-2,3-dimethyl-benzenesulfonamide; 6-methyl-5-[4-[3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]pyridine-3-carbonitrile; 6-methyl-5-[4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]pyridine-2-carbonitrile; 2,3-dimethyl-4-[4-[5-methyl-3-(2-methyl-4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide; 4-[4-[3-(2-methoxy-4-pyridyl)-5-methyl-1H-pyrazol-4-yl]phenyl]-2,3-dimethyl-benzenesulfonamide; 2,3-dimethyl-4-[4-[5-methyl-3-(3-methyl-4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide; 2,3-dimethyl-4-[4-[5-methyl-3-(1-methylpyrazol-4-yl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide; 4-[4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzene-1,3-dicarbonitrile; 3,4-dimethyl-5-[4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide; 3-[4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide; N,3-dimethyl-4-[4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide; 2-methyl-3-[4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide; 5-[4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-1,3-dihydropyrrolo[2,3-b]pyridin-2-one; 2-methyl-6-[4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzonitrile; 4-cyano-3-[4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide; 4-methyl-3-[4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzamide; 4-[4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]pyridine-3-carbonitrile;

3-[2-methyl-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide; 3-[2-methyl-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzamide; 2-[4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-8-oxa-2-azaspiro[4.5]decane; rac-(3R)-3-methyl-2-[4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-8-oxa-2-azaspiro[4.5]decane; 8-[4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-2,8-diazaspiro[4.5]decan-3-one; rac-(3S)-3-methyl-2-[4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-8-oxa-2-azaspiro[4.5]decane; 3-[4-[5-methyl-3-(2-methyl-4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide; 3-[4-[3-(2-methoxy-4-pyridyl)-5-methyl-1H-pyrazol-4-yl]phenyl]benzenesulfonamide; 3-[4-[5-methyl-3-(2-morpholino-4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide; 3-[4-(5-methyl-3-phenyl-1H-pyrazol-4-yl)phenyl]benzenesulfonamide; 3-[4-[3-(2,6-dimethyl-4-pyridyl)-5-methyl-1H-pyrazol-4-yl]phenyl]benzenesulfonamide; 3-[4-[3-(2-methyl-4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide; 4-[2-methyl-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzonitrile; 3-[2-ethyl-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide; 4-[2-ethyl-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzonitrile; 4-[2-ethyl-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]pyridine; 2-[2-methyl-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-8-oxa-2-azaspiro[4.5]decane; 3-[4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]-2-(trifluoromethyl)phenyl]benzenesulfonamide; 3-[2-cyano-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide; 3-[2,6-difluoro-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide; 6-[2-methyl-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-2-oxa-6-azaspiro[3.3]heptane; 5-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]-2-morpholino-benzonitrile; 4-[2-methyl-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]morpholine; 2-[2,6-difluoro-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-8-oxa-2-azaspiro[4.5]decane; 6-[2,6-difluoro-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-2-oxa-6-azaspiro[3.3]heptane; 2-[4-[5-methyl-3-(2-morpholino-4-pyridyl)-1H-pyrazol-4-yl]phenyl]-8-oxa-2-azaspiro[4.5]decane; 2-[4-[3-(2,6-dimethyl-4-pyridyl)-5-methyl-1H-pyrazol-4-yl]phenyl]-8-oxa-2-azaspiro[4.5]decane; 2-[4-[5-methyl-3-(2-methyl-4-pyridyl)-1H-pyrazol-4-yl]phenyl]-8-oxa-2-azaspiro[4.5]decane; 3-[4-[3-(2-morpholino-4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide; 4-[5-methyl-4-[3-methyl-4-(4-pyridyl)phenyl]-1H-pyrazol-3-yl]pyridine; 2-methoxy-4-[2-methyl-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]pyridine; 3-[4-(3-phenyl-1H-pyrazol-4-yl)phenyl]benzenesulfonamide; 3-[4-[3-(2-methoxy-4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide; 4-[5-methyl-4-[3-methyl-4-(3-methylsulfonylphenyl)phenyl]-1H-pyrazol-3-yl]pyridine; 3-[2-methyl-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]pyridine; 2-[2-methyl-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-7-oxa-2-azaspiro[3.5]nonane; 2-[4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-7-oxa-2-azaspiro[3.5]nonane; 2-[2-methoxy-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-7-oxa-2-azaspiro[3.5]nonane; 2-[2-ethyl-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-7-oxa-2-azaspiro[3.5]nonane; 4-[2-ethyl-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-

yl]phenyl]benzenesulfonamide; 4-[2,6-difluoro-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide; 2-[4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-6-oxa-2-azaspiro[3.4]octane; 2-[4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-8λ6-thia-2-azaspiro[4.5]decane 8,8-dioxide; 3-[2-methoxy-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide; 5-[2-methyl-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-1H-pyridin-2-one; 3-[2-cyclopropyl-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide; 4-[4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzonitrile; 7-[4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-2-oxa-7-azaspiro[3.4]octane; 3-[4-[3-(2,6-dimethyl-4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide; 3-[2-isopropyl-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide; 6-[2,6-difluoro-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-2λ6-thia-6-azaspiro[3.3]heptane 2,2-dioxide; 3-[4-[3-(4-pyridyl)-5-(trifluoromethyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide; 6-[2-cyclopropyl-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-2λ6-thia-6-azaspiro[3.3]heptane 2,2-dioxide; 3-[2,6-dimethyl-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide; 2-[2,6-difluoro-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-8λ6-thia-2-azaspiro[4.5]decane 8,8-dioxide; 2-[2-cyclopropyl-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-8λ6-thia-2-azaspiro[4.5]decane 8,8-dioxide; 2-[2,6-dimethyl-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-8λ6-thia-2-azaspiro[4.5]decane 8,8-dioxide; 7-[2-cyclopropyl-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-2λ6-thia-7-azaspiro[3.4]octane 2,2-dioxide; 3-[2-fluoro-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide; 6-[4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]indolin-2-one; 3-[2,6-difluoro-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-4-methyl-benzenesulfonamide; 9-[2-cyclopropyl-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-3-oxa-9-azaspiro[5.5]undecane; 6-[2,6-difluoro-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-1H-pyridin-2-one; 6-[4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-1H-pyridin-2-one; 3-[2,3-difluoro-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide; 3-[3-methyl-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide; 2-[2,6-difluoro-4-[5-methyl-3-(2-methyl-4-pyridyl)-1H-pyrazol-4-yl]phenyl]-8-oxa-2-azaspiro[4.5]decane; 3-[2-cyclopropyl-4-[5-methyl-3-(2-methyl-4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide; 2-[2,6-difluoro-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-7-oxa-2,5-diazaspiro[3.5]nonan-6-one; 3-[2-ethyl-4-[5-methyl-3-(2-morpholino-4-pyridyl)-1H-pyrazol-4-yl]phenyl]benzenesulfonamide; 4-[4-[3-ethyl-4-(3-pyrazol-1-ylphenyl)phenyl]-5-methyl-1H-pyrazol-3-yl]pyridine; 4-[4-[3,5-difluoro-4-[3-(5-methylpyrazol-1-yl)phenyl]phenyl]-5-methyl-1H-pyrazol-3-yl]pyridine; 4-[4-[3,5-difluoro-4-(3-pyrazol-1-ylphenyl)phenyl]-5-methyl-1H-pyrazol-3-yl]pyridine; 4-[4-[3,5-difluoro-4-[3-(4-methylpyrazol-1-yl)phenyl]phenyl]-5-methyl-1H-pyrazol-3-yl]pyridine; [(1R,5S)-8-[2,6-difluoro-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-8-azabicyclo[3.2.1]octan-3-yl]methanol; [(1R,5S)-8-[2,6-difluoro-4-[5-methyl-3-(2-methyl-4-pyridyl)-1H-pyrazol-4-yl]phenyl]-8-azabicyclo[3.2.1]octan-3-yl]methanol; 9-[2,6-difluoro-4-[5-

methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-2,9-diazaspiro[5.5]undecan-3-one; 9-[2,6-difluoro-4-[5-methyl-3-(2-methyl-4-pyridyl)-1H-pyrazol-4-yl]phenyl]-2,9-diazaspiro[5.5]undecan-3-one; 2-[2,6-difluoro-4-[5-methyl-3-(2-methyl-4-pyridyl)-1H-pyrazol-4-yl]phenyl]-8λ6-thia-2-azaspiro[4.5]decane 8,8-dioxide; 3-[2,6-difluoro-4-[5-methyl-3-(2-methyl-4-pyridyl)-1H-pyrazol-4-yl]phenyl]-3,9-diazaspiro[5.5]undecan-10-one; 3-[2,6-difluoro-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-3,9-diazaspiro[5.5]undecan-10-one; 8-[2,6-difluoro-4-[5-methyl-3-(4-pyridyl)-1H-pyrazol-4-yl]phenyl]-2,8-diazaspiro[4.5]decan-3-one; and 8-[2,6-difluoro-4-[5-methyl-3-(2-methyl-4-pyridyl)-1H-pyrazol-4-yl]phenyl]-2,8-diazaspiro[4.5]decan-3-one.

3. The compound of claim 1 or claim 2, wherein the compound selectively inhibits human LRRK2 with a Gly2019Ser mutation greater than about 2X relative to wild-type human LRRK2.

4. A pharmaceutical formulation comprising a compound of any of claims 1-3.

5. A method of treating or delaying the progression of a disease in an individual by inhibiting LRRK2 protein kinase activity, the method comprising administering a therapeutically effective amount of a pharmaceutical formulation of claim 4.

6. The method of claim 8, wherein the individual has a mutated allele of human LRRK2.

7. The method of claim 6, wherein the mutated allele comprises an amino acid modification at one or more of residues G2019, I2020, and R1441, Y1699, and N1437.

8. The method of claim 6 or claim 7, wherein the mutated allele is G2019S.

9. The method of any of claims 6-8, wherein the disease is Parkinson's Disease.

10. The method of claim 9, wherein the disease is familial Parkinson's Disfease.

11. The method of claim 9, wherein the disease is idiopathic Parkinson's Disease.

12. The method of any of claims 6-8, wherein the disease is cancer.

13. The method of claim 12, wherein the cancer is a skin cancer.

14. The method of claim 13, wherein the skin cancer is melanoma.

15. The method of any of claims 6-8, wherein the disease is an inflammatory disease.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US22/73830

A. CLASSIFICATION OF SUBJECT MATTER

IPC - INV. A61K 31/415; A61K 31/4155; A61P 25/16; C07D 231/02; C07D 231/10 (2022.01)
ADD.

CPC - INV. A61K 31/415; A61K 31/4155; A61P 25/16; C07D 231/02; C07D 231/10
ADD.

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)
See Search History document

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

Electronic database consulted during the international search (name of database and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y --- A	US 2005/0222230 A1 (DRYSDALE, MJ et al.) 5 October 2005; paragraphs [0031]-[0032], [0938]-[0939]	1, 3/1 --- 2, 3/2
Y	WO 2012/162254 A1 (ELAN PHARMACEUTICALS, INC.) 29 November 2012; paragraphs [0008], [0010]-[0011], [0033], [0036], [0110], [0123], [0157]	1, 3/1
A	WO 2007/002559 A1 (EXELIXIS, INC., et al) 4 January 2007; page 294, lines 8-10	2, 3/2
A	WO 200031063 A (G.D. SEARLE and CO, et al.) 2 June 2000; page 221, second paragraph	2, 3/2
A	WO 2019/222173 A1 (E-SCAPE BIO, INC) 21 November 2019; entire publication	3

☐ 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
"D" document cited by the applicant in the international application
"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
03 September 2022 (03.09.2022)	OCT 05 2022
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Shane Thomas Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US22/73830

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.:
because they relate to subject matter not required to be searched by this Authority, namely:

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.: 4-15
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 additional fees, this Authority did not invite payment of additional fees.

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.