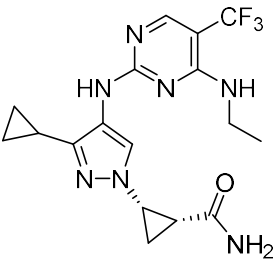
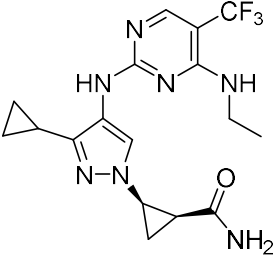
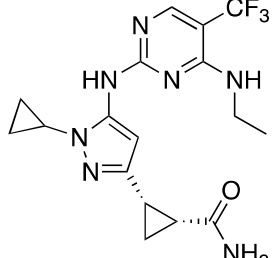


Example No.	LRRK2 G2019S TR-FRET (nM)	HEK293T LRRK2 G2019S pS935 (nM)	HLM Avg mL/min/kg	MDCK- MDR1 Efflux Avg
7 	1.47	1.83	3.6	110
8 	1.11	4.94		
Comparative Example A 	1.41	11.8	2.6	144

[0247] The IC₅₀ values from the cellular assay of Biological Example 4 (HEK293T LRRK2 G2019S pS935) are generally ten times greater than the values from the biochemical assay of Biological Example 1 (LRRK2 G2019S TR-FRET), with the tenfold difference decreasing as the IC₅₀ values approach 10 nM or less. At single digit nanomolar IC₅₀ concentrations, the cellular assay was found to have greater sensitivity than the biochemical assay, and thus more accurately resolves the relative IC₅₀ values of compounds in this range.

[0248] As shown in the table above, Compounds 1-8 were surprisingly found to be more active LRRK2 inhibitors than Comparative Example A when tested according to the cellular assay of Biological Example 4.

[0249] Compounds 1-8 are expected to be P-glycoprotein (P-gp) substrates and have very poor brain penetration (Hitchcock, J. Med. Chem. 2012, 55, 4877-4895) based on their calculated total polar surface area of 110 (Ertl et al., J. Med. Chem. 2000, 43, 3714-3717). Compound 7 was further tested *in vitro* (Biological Example 3, MDR efflux assay) and was found to be a clear P-gp substrate (efflux ratio = 110) suggesting very poor brain penetration. Thus compounds 1-8 would be advantageous in avoiding CNS related side effects in the treatment of non-CNS diseases as compared to LRRK2 inhibitors that can cross the blood brain barrier.

[0250] In particular, Compound 7 was surprisingly found to be a highly potent, stable, and non-brain penetrant LRRK2 inhibitor. Compound 7 was found to be approximately $\frac{12-11.8}{1.83} = 6.4$ times more potent than Comparative Example A.

[0251] Unless otherwise defined, 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.

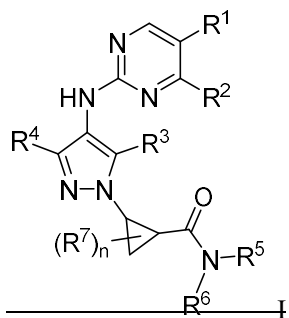
[0252] The inventions illustratively described herein may suitably be practiced in the absence of any element or elements, limitation or limitations, not specifically disclosed herein. Thus, for example, the terms “comprising”, “including,” “containing”, etc. shall be read expansively and without limitation. Additionally, the terms and expressions employed herein have been used as terms of description and not of limitation, and there is no intention in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the invention claimed.

[0253] Thus, it should be understood that although the present invention has been specifically disclosed by preferred embodiments and optional features, modification, improvement and variation of the inventions embodied therein herein disclosed may be resorted to by those skilled in the art, and that such modifications, improvements and variations are considered to be within the scope of this invention. The materials, methods, and examples provided here are representative of preferred embodiments, are exemplary, and are not intended as limitations on the scope of the invention.

[0254] The invention has been described broadly and generically herein. Each of the narrower species and subgeneric groupings falling within the generic disclosure also form part of the invention. This includes the generic description of the invention with a proviso or negative limitation removing any subject matter from the genus, regardless of whether or not the excised material is specifically recited herein.

What is claimed is:

1. — A compound of Formula I:



or a pharmaceutically acceptable salt, isotopically enriched analog, tautomer, stereoisomer, mixture of stereoisomers, or prodrug thereof, wherein:

n is 0, 1, 2, or 3;

R^1 is halo, cyano, C_{1-6} -alkyl, C_{1-6} -alkenyl, C_{1-6} -alkynyl, cycloalkyl, C_{1-6} -alkoxy, cycloalkoxy, C_{1-6} -alkylthio, C_{1-6} -alkylsulfonyl, $-C(O)R^{10}$, or $-C(O)N(R^{11})(R^{12})$, wherein each C_{1-6} -alkyl, C_{1-6} -alkenyl, C_{1-6} -alkynyl, cycloalkyl, C_{1-6} -alkoxy, cycloalkoxy, C_{1-6} -alkylthio, and C_{1-6} -alkylsulfonyl is independently optionally substituted;

R^2 is C_{1-6} -alkoxy, cycloalkyl, cycloalkoxy, C_{1-6} -alkylthio, C_{1-6} -alkylsulfonyl, or $N(R^{13})(R^{14})$, wherein each C_{1-6} -alkoxy, cycloalkyl, cycloalkoxy, C_{1-6} -alkylthio, and C_{1-6} -alkylsulfonyl is independently optionally substituted;

R^3 is hydrogen or halo;

R^4 is hydrogen, halo, cyano, C_{1-6} -alkyl, C_{1-6} -alkenyl, C_{1-6} -alkynyl, cycloalkyl, heterocyclyl, heteroaryl, C_{1-6} -alkylthio, C_{1-6} -alkylsulfonyl, $-C(O)R^{10}$, or $-C(O)N(R^{11})(R^{12})$, wherein each C_{1-6} -alkyl, C_{1-6} -alkenyl, C_{1-6} -alkynyl, cycloalkyl, heterocyclyl, heteroaryl, C_{1-6} -alkylthio, and C_{1-6} -alkylsulfonyl is independently optionally substituted;

R^5 and R^6 are each independently hydrogen, C_{1-6} -alkyl or cycloalkyl, or R^5 and R^6 together form a heterocyclyl, wherein each C_{1-6} -alkyl, cycloalkyl, and heterocyclyl is independently optionally substituted;

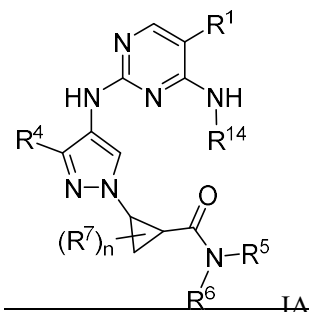
R^7 is halo or C_{1-6} -alkyl, wherein each C_{1-6} -alkyl is independently optionally substituted;

each R^{10} is independently C_{1-6} -alkyl or C_{1-6} -alkoxy, wherein each C_{1-6} -alkyl and C_{1-6} -alkoxy is independently optionally substituted;

each R^{11} and R^{12} are independently hydrogen, C_{1-6} -alkyl, cycloalkyl, or R^{11} and R^{12} together form a heterocyclyl group, wherein each C_{1-6} -alkyl, cycloalkyl, and heterocyclyl is independently optionally substituted; and

R^{13} and R^{14} are each independently hydrogen, C_{1-6} -alkyl, cycloalkyl, or R^{13} and R^{14} together form a heterocyclyl, wherein each C_{1-6} -alkyl, cycloalkyl, and heterocyclyl is independently optionally substituted.

2. ——— A compound of Formula IA:



————— or a pharmaceutically acceptable salt, isotopically enriched analog, tautomer, stereoisomer, mixture of stereoisomers, or prodrug thereof, wherein:

n is 0, 1, 2, or 3;

R^1 is halo or optionally substituted C_{1-6} -alkyl;

R^4 is hydrogen, halo, cyano, C_{1-6} -alkyl, C_{1-6} -alkenyl, C_{1-6} -alkynyl, cycloalkyl, heterocycyl, heteroaryl, C_{1-6} -alkylthio, C_{1-6} -alkylsulfonyl, $C(O)R^{10}$, or $C(O)N(R^{11})(R^{12})$, wherein each C_{1-6} -alkyl, C_{1-6} -alkenyl, C_{1-6} -alkynyl, cycloalkyl, heterocycyl, heteroaryl, C_{1-6} -alkylthio, and C_{1-6} -alkylsulfonyl is independently optionally substituted;

R^5 and R^6 are each independently hydrogen, C_{1-6} -alkyl or cycloalkyl, or R^5 and R^6 together form a heterocycyl, wherein each C_{1-6} -alkyl, cycloalkyl, and heterocycyl is independently optionally substituted;

R^7 is halo or C_{1-6} -alkyl, wherein each C_{1-6} -alkyl is independently optionally substituted;

each R^{10} is independently C_{1-6} -alkyl or C_{1-6} -alkoxy, wherein each C_{1-6} -alkyl and C_{1-6} -alkoxy is independently optionally substituted;

each R^{11} and R^{12} are independently hydrogen, C_{1-6} -alkyl, cycloalkyl, or R^{11} and R^{12} together form an heterocycyl group, wherein each C_{1-6} -alkyl, cycloalkyl, and heterocycyl is independently optionally substituted; and

R^{14} is C_{1-6} -alkyl or cycloalkyl, wherein each C_{1-6} -alkyl and cycloalkyl is independently optionally substituted.

3. ——— The compound of claim 1 or 2, wherein R^4 is other than optionally substituted cycloalkyl.

4. ——— The compound of claim 3, wherein R^4 is methyl.

5. ——— The compound of any preceding claim, wherein n is 1.

6. ——— The compound of any preceding claim, wherein R^7 is optionally substituted C_{1-6} -alkyl.

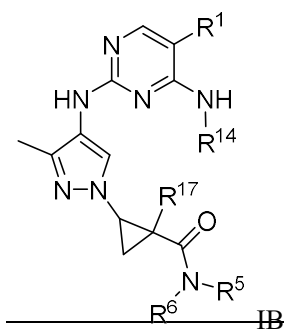
7. ——— The compound of any one of claims 1-5, wherein R^7 is halo.

8. ——— The compound of any one of claims 1-4, wherein n is 0.

9. ——— The compound of any preceding claim, wherein R^2 is optionally substituted C_{1-6} -alkoxy, optionally substituted cycloalkyl, or $N(R^{13})(R^{14})$.

10. ——— The compound of any preceding claim, wherein R^2 is $N(R^{13})(R^{14})$.

11. ——— A compound of Formula IB:



— or a pharmaceutically acceptable salt, isotopically enriched analog, tautomer, stereoisomer, mixture of stereoisomers, or prodrug thereof, wherein:

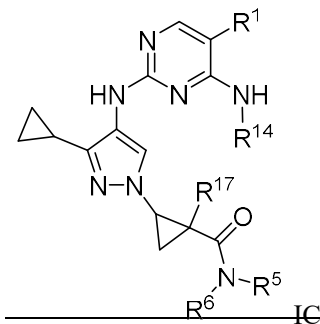
R^1 is halo or optionally substituted C_{1-6} -alkyl;

R^5 and R^6 are each independently hydrogen, C_{1-6} alkyl or cycloalkyl, or R^5 and R^6 together form a heterocyclyl, wherein each C_{1-6} alkyl, cycloalkyl, and heterocyclyl is independently optionally substituted;

R^{14} is C_{1-6} alkyl or cycloalkyl, wherein each C_{1-6} alkyl and cycloalkyl is independently optionally substituted; and

R^{17} is hydrogen, halo or optionally substituted C_{1-6} alkyl.

12. — A compound of Formula IC:



— or a pharmaceutically acceptable salt, isotopically enriched analog, tautomer, stereoisomer, mixture of stereoisomers, or prodrug thereof, wherein:

R^1 is halo or optionally substituted C_{1-6} -alkyl;

R^5 and R^6 are each independently hydrogen, C_{1-6} alkyl or cycloalkyl, or R^5 and R^6 together form a heterocyclyl, wherein each C_{1-6} alkyl, cycloalkyl, and heterocyclyl is independently optionally substituted;

R^{14} is C_{1-6} alkyl or cycloalkyl, wherein each C_{1-6} alkyl and cycloalkyl is independently optionally substituted; and

R^{17} is hydrogen, halo or optionally substituted C_{1-6} alkyl.

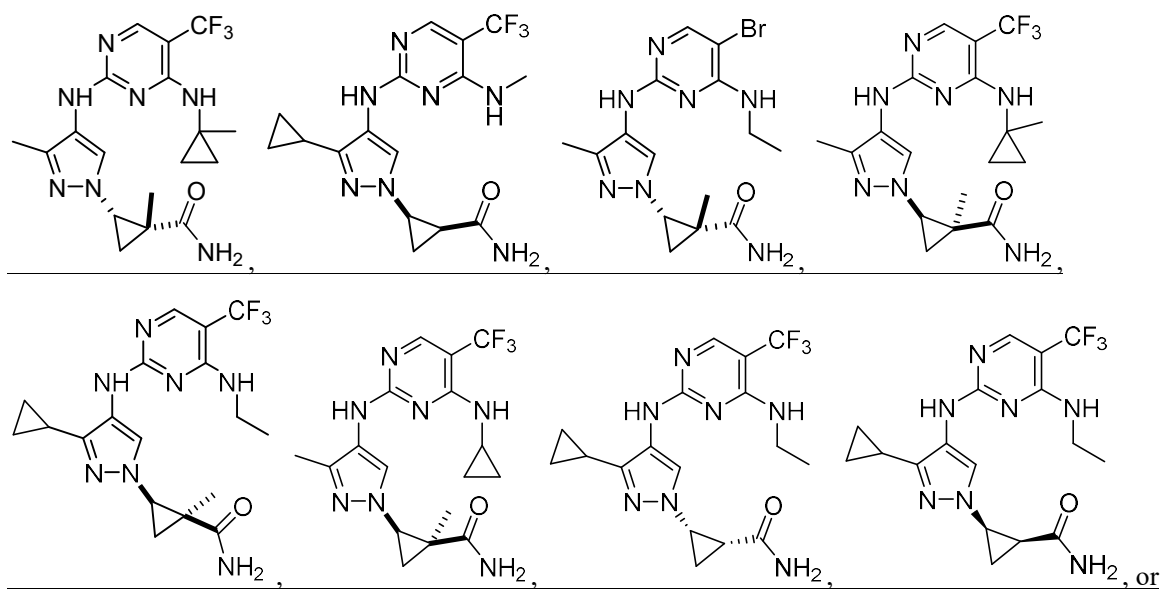
13. — The compound of any preceding claim, wherein R^1 is halo, cyano, or C_{1-6} alkyl optionally substituted with halo.

14. — The compound of claim 13, wherein R^1 is halo.

15. — The compound of claim 14, wherein R^1 is bromo.

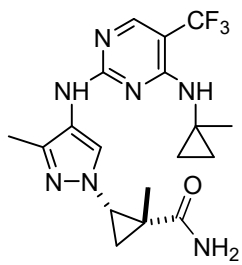
16. — ~~The compound of claim 13, wherein R^1 is C_{1-6} alkyl optionally substituted with one or more halo.~~
17. — ~~The compound of claim 16, wherein R^1 is C_{1-6} haloalkyl.~~
18. — ~~The compound of claim 17, wherein R^1 is $-CF_3$.~~
19. — ~~The compound of any preceding claim, wherein R^{14} is optionally substituted C_{1-6} alkyl.~~
20. — ~~The compound of any preceding claim, wherein R^{14} is methyl or ethyl.~~
21. — ~~The compound of any one of claims 1–18, wherein R^{14} is optionally substituted cycloalkyl.~~
22. — ~~The compound of claim 21, wherein R^{14} is cyclopropyl.~~
23. — ~~The compound of claim 21, wherein R^{14} is methylecyclopropyl.~~
24. — ~~The compound of claim 1, wherein n is 0; R^1 is halo, cyano, or C_{1-6} alkyl optionally substituted with one or more halo; R^2 is $N(R^{13})(R^{14})$, where R^{13} is hydrogen and R^{14} is hydrogen, C_{1-6} alkyl, or cycloalkyl; R^3 is hydrogen or halo; R^4 is methyl or cycloalkyl; and R^5 and R^6 are each independently hydrogen, C_{1-6} alkyl or cycloalkyl.~~
25. — ~~A compound of Table 1 or Table 2, or a pharmaceutically acceptable salt, isotopically enriched analog, tautomer, stereoisomer, mixture of stereoisomers, or prodrug thereof.~~

1. A compound selected from:



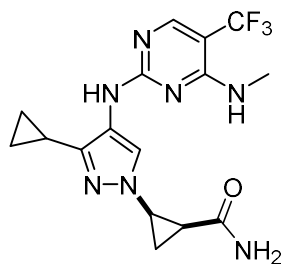
a pharmaceutically acceptable salt, stereoisomer, or a mixture of stereoisomers thereof.

2. A compound according to claim 1 having the structure:



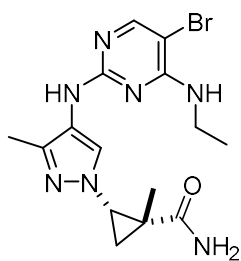
or a pharmaceutically acceptable salt, stereoisomer, or a mixture of stereoisomers thereof.

3. A compound according to claim 1 having the structure:



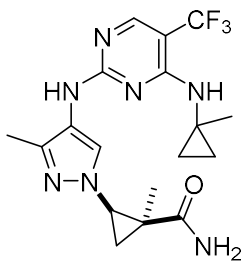
or a pharmaceutically acceptable salt, stereoisomer, or a mixture of stereoisomers thereof.

4. A compound according to claim 1 having the structure:



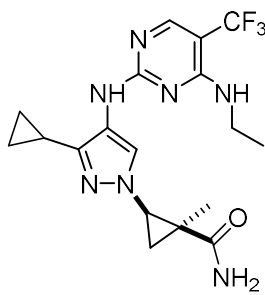
or a pharmaceutically acceptable salt, stereoisomer, or a mixture of stereoisomers thereof.

5. A compound according to claim 1 having the structure:



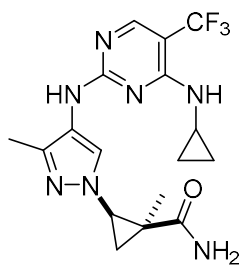
or a pharmaceutically acceptable salt, stereoisomer, or a mixture of stereoisomers thereof.

6. A compound according to claim 1 having the structure:



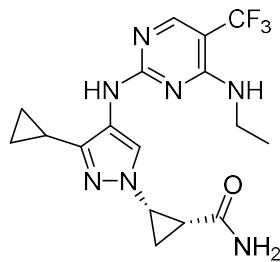
or a pharmaceutically acceptable salt, stereoisomer, or a mixture of stereoisomers thereof.

7. A compound according to claim 1 having the structure:



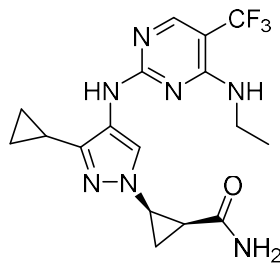
or a pharmaceutically acceptable salt, stereoisomer, or a mixture of stereoisomers thereof.

8. A compound according to claim 1 having the structure:



or a pharmaceutically acceptable salt, stereoisomer, or a mixture of stereoisomers thereof.

9. A compound according to claim 1 having the structure:



or a pharmaceutically acceptable salt, stereoisomer, or a mixture of stereoisomers thereof.

1026. A pharmaceutical composition comprising a compound of any ~~preceding one of~~ claims 1 to 9, or a pharmaceutically acceptable salt, isotopically enriched analog, tautomer, stereoisomer, or mixture of stereoisomers, ~~or prodrug~~ thereof, and a pharmaceutically acceptable carrier, diluent, or excipient.

1127. Use of a compound of any one of claims 1 to ~~925~~ or a pharmaceutical composition of claim 10 for the manufacture of a medicament for treating a neurodegenerative disease, cancer, or an inflammatory disease.

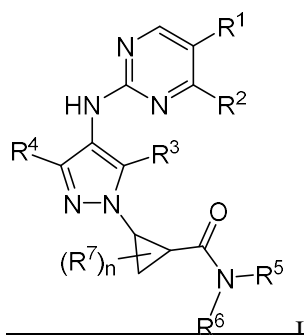
~~1228. Use of a compound~~ The use of claim 1127, wherein the cancer is kidney cancer, breast cancer, prostate cancer, blood cancer, papillary cancer, lung cancer, acute myelogenous leukemia, or multiple myeloma.

~~1329. Use of a compound~~ The use of claim 1127, wherein the inflammatory disease is leprosy, Crohn's disease, inflammatory bowel disease, ulcerative colitis, amyotrophic lateral sclerosis, rheumatoid arthritis, or ankylosing spondylitis.

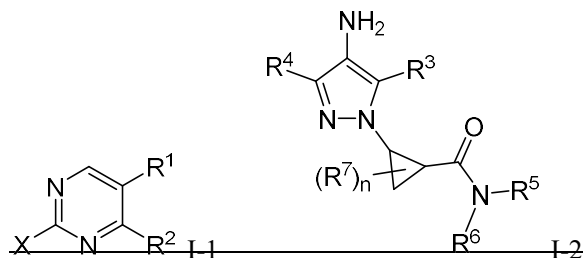
~~1430. Use of a compound~~ The use of claim 1127, wherein the inflammatory disease is Crohn's disease.

~~1531. Use of a compound~~ The use of claim ~~1127~~, wherein the neurodegenerative disease is Parkinson's disease.

~~32. A method of preparing a compound of Formula I, or a salt, isotopically enriched analog, tautomer, stereoisomer, mixture of stereoisomers, or prodrug thereof:~~



~~comprising coupling a compound of Formula I 1 with a compound of Formula I 2:~~



~~under conditions suitable to provide a compound of Formula I, wherein X is a leaving group, under conditions suitable to provide the compound of Formula I, or a salt, isotopically enriched analog, tautomer, stereoisomer, mixture of stereoisomers, or prodrug thereof, wherein:~~

~~n is 0, 1, 2, or 3;~~

~~R¹ is halo, cyano, C₁₋₆-alkyl, C₁₋₆-alkenyl, C₁₋₆-alkynyl, cycloalkyl, C₁₋₆-alkoxy, cycloalkoxy, C₁₋₆-alkylthio, C₁₋₆-alkylsulfonyl, -C(O)R¹⁰, or -C(O)N(R¹¹)(R¹²), wherein each C₁₋₆-alkyl, C₁₋₆-alkenyl, C₁₋₆-alkynyl, cycloalkyl, C₁₋₆-alkoxy, cycloalkoxy, C₁₋₆-alkylthio, and C₁₋₆-alkylsulfonyl is independently optionally substituted;~~

~~R² is C₁₋₆-alkoxy, cycloalkyl, cycloalkoxy, C₁₋₆-alkylthio, C₁₋₆-alkylsulfonyl, or -N(R¹³)(R¹⁴), wherein each C₁₋₆-alkoxy, cycloalkyl, cycloalkoxy, C₁₋₆-alkylthio, and C₁₋₆-alkylsulfonyl is independently optionally substituted;~~

~~R³ is hydrogen or halo;~~

~~R⁴ is hydrogen, halo, cyano, C₁₋₆-alkyl, C₁₋₆-alkenyl, C₁₋₆-alkynyl, cycloalkyl, heterocyclyl, heteroaryl, C₁₋₆-alkylthio, C₁₋₆-alkylsulfonyl, -C(O)R¹⁰, or -C(O)N(R¹¹)(R¹²), wherein each C₁₋₆-alkyl, C₁₋₆-alkenyl, C₁₋₆-alkynyl, cycloalkyl, heterocyclyl, heteroaryl, C₁₋₆-alkylthio, and C₁₋₆-alkylsulfonyl is independently optionally substituted;~~

~~R⁵ and R⁶ are each independently hydrogen, C₁₋₆-alkyl or cycloalkyl, or R⁵ and R⁶ together form a heterocyclyl, wherein each C₁₋₆-alkyl, cycloalkyl, and heterocyclyl is independently optionally substituted;~~

~~R⁷ is halo or C₁₋₆-alkyl, wherein each C₁₋₆-alkyl is independently optionally substituted;~~

~~each R¹⁰ is independently C₁₋₆-alkyl or C₁₋₆-alkoxy, wherein each C₁₋₆-alkyl and C₁₋₆-alkoxy is independently optionally substituted;~~

~~each R¹¹ and R¹² are independently hydrogen, C₁₋₆ alkyl, cycloalkyl, or R¹¹ and R¹² together form an heterocyclyl group, wherein each C₁₋₆ alkyl, cycloalkyl, and heterocyclyl is independently optionally substituted; and~~

~~R¹³ and R¹⁴ are each independently hydrogen, C₁₋₆ alkyl, cycloalkyl, or R¹³ and R¹⁴ together form a heterocyclyl, wherein each C₁₋₆ alkyl, cycloalkyl, and heterocyclyl is independently optionally substituted.~~

~~33. The method of claim 32, wherein X is halo.~~