

PIPERAZINE INDAZOLE GLUCOCORTICOID RECEPTOR ANTAGONISTS

CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application Nos. 63/368,413, filed July 14, 2022, and 63/292,104, filed December 21, 2021, each of which is incorporated
5 herein in its entirety.

BACKGROUND OF THE INVENTION

[0002] In most species, including man, the physiological glucocorticoid is cortisol (hydrocortisone). In rodents, the physiological glucocorticoid is corticosterone.
10 Glucocorticoids are secreted in response to ACTH (corticotropin), which shows both circadian rhythm variation and elevations in response to stress and food. Cortisol levels are responsive within minutes to many physical and psychological stresses, including trauma, surgery, exercise, anxiety and depression. Cortisol is a steroid and acts by binding to an intracellular, glucocorticoid receptor (GR). In man, glucocorticoid receptors are present in
15 two forms: a ligand-binding GR-alpha of 777 amino acids; and, a GR-beta isoform which lacks the 50 carboxy terminal residues. Since these residues include the ligand binding domain, GR-beta is unable to bind the natural ligand, and is constitutively localized in the nucleus.

[0003] The biologic effects of cortisol, including those caused by hypercortisolemia, can be
20 modulated at the GR level using receptor modulators, such as agonists, partial agonists and antagonists. Several different classes of agents are able to block the physiologic effects of GR-agonist binding. These antagonists include compositions which, by binding to GR, inhibit the ability of an agonist to effectively bind to and/or activate the GR. One such known GR antagonist, mifepristone, has been found to be an effective anti-glucocorticoid
25 agent in humans (Bertagna (1984) *J. Clin. Endocrinol. Metab.* **59**:25). Mifepristone binds to the GR with high affinity, with a dissociation constant (K_d) of 10^{-9} M (Cadepond (1997) *Annu. Rev. Med.* **48**:129).

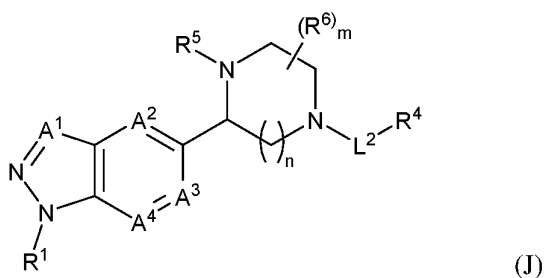
[0004] Cortisol (and corticosterone) also bind to the mineralocorticoid receptor, MR. Cortisol has higher affinity for MR than it does for GR, and MR is usually considered to be
30 fully occupied under normal physiological conditions. Under conditions of stress, cortisol concentrations are increased and GR becomes occupied. MR also binds to the

mineralocorticoid aldosterone, and aldosterone and cortisol have similar affinity for MR. However, glucocorticoids circulate at roughly 100 times the level of mineralocorticoids. An enzyme (11- β hydroxysteroid dehydrogenase 1), which deactivates cortisol (and corticosterone) exists in mineralocorticoid target tissues to prevent overstimulation by glucocorticoids.

[0005] When administered to subjects in need thereof, steroids can provide both intended therapeutic effects as well as negative side effects. What is needed in the art are new compositions and methods for selectively modulating GR. Surprisingly, the present invention meets these and other needs.

BRIEF SUMMARY OF THE INVENTION

[0006] In one embodiment, the present invention provides a compound of Formula J:



- or a pharmaceutically acceptable salt thereof, wherein
- R¹ is heterocycloalkyl having 3 to 12 ring members and 1 to 4 heteroatoms each N, O or S, phenyl or heteroaryl having 5 to 10 ring members and 1 to 5 heteroatoms each N, O or S, each independently substituted with 0 to 5 R^{1a} groups;
- each R^{1a} is independently C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkoxyalkyl, C₁₋₆ hydroxyalkyl, halogen, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, -OH, oxo, -CN, -C(O)N(R^{1b})(R^{1c}), C₃₋₁₀ cycloalkyl, or heterocycloalkyl having 3 to 12 ring members and 1 to 4 heteroatoms each N, O or S;
- each R^{1b} and R^{1c} is independently hydrogen, C₁₋₆ alkyl or a 3 to 8 membered heterocycloalkyl having 1 to 3 heteroatoms each independently N, O or S;
- A¹, A², A³ and A⁴ are each independently =CR²- or =N-;
- each R² is independently hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₂₋₆ alkoxyalkyl, halogen, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, hydroxy or -CN;

L^2 is $-C(O)-$, $-C(O)O-$, $-C(O)N(R^3)-$, $-S(O)_2-$ or $-S(O)_2N(R^3)-$;
 R^3 is hydrogen, or C_{1-6} alkyl;
 R^4 is C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{2-6} alkoxyalkyl, C_{1-6} hydroxyalkyl, C_{1-6} haloalkyl, C_{3-8} cycloalkyl, C_{1-6} alkyl- C_{3-8} cycloalkyl, heterocycloalkyl, C_{1-6} alkyl-heterocycloalkyl, C_{6-12} aryl, C_{1-6} alkyl- C_{6-12} aryl, $-O-C_{6-12}$ aryl, heteroaryl, or C_{1-6} alkyl-heteroaryl,
 wherein each heterocycloalkyl independently has 3 to 12 ring members and 1 to 3 heteroatoms each independently N, O or S,
 wherein each heteroaryl independently has 5 to 10 ring members and 1 to 4 heteroatoms each independently N, O or S, and
 wherein the cycloalkyl, heterocycloalkyl, aryl and heteroaryl are each independently substituted with 0 to 5 R^{4a} groups;
 alternatively, R^3 and R^4 are combined with the atoms to which they are attached to form a heterocycloalkyl having 3 to 12 ring members and 1 to 3 additional heteroatoms each independently N, O or S, wherein the heterocycloalkyl is substituted with 0, 1 or 2 C_{1-6} alkyl groups;
 each R^{4a} is independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, C_{2-6} alkoxyalkyl, C_{1-6} hydroxyalkyl, halogen, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, $-CN$, $-OH$, oxo , $-C(O)R^{4b}$, $-C(O)OR^{4b}$, $-OC(O)R^{4b}$, $-OC(O)OR^{4b}$, $-C(O)N(R^{4b})(R^{4c})$, $-N(R^{4b})C(O)R^{4c}$, $-OC(O)N(R^{4b})(R^{4c})$, $-N(R^{4b})C(O)OR^{4c}$, $-S(O)_2R^{4b}$, $-S(O)_2N(R^{4b})(R^{4c})$, $-N(R^{4b})S(O)_2R^{4c}$, C_{3-8} cycloalkyl, C_{1-6} alkyl- C_{3-8} cycloalkyl, heterocycloalkyl, C_{1-6} alkyl-heterocycloalkyl, C_{6-12} aryl, C_{1-6} alkyl- C_{6-12} aryl, $-O-C_{6-12}$ aryl, heteroaryl, or C_{1-6} alkyl-heteroaryl, wherein each heterocycloalkyl independently has 3 to 12 ring members and 1 to 3 heteroatoms each independently N, O or S, wherein each heteroaryl independently has 5 to 10 ring members and 1 to 4 heteroatoms each independently N, O or S, and wherein each cycloalkyl, heterocycloalkyl, aryl and heteroaryl is substituted with 0, 1 or 2 C_{1-6} alkyl groups;
 each R^{4b} and R^{4c} is hydrogen or C_{1-6} alkyl;
 R^5 is C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{2-6} alkoxyalkyl, C_{1-6} hydroxyalkyl, C_{1-6} haloalkyl, C_{1-6} alkyl- OR^{5a} , $-C(O)R^{5a}$, C_{1-6} alkyl- $C(O)R^{5a}$, $-C(O)OR^{5a}$, $-C(O)N(R^{5a})(R^{5b})$, $-S(O)_2R^{5a}$, $-S(O)_2N(R^{5a})(R^{5b})$, C_{3-8} cycloalkyl, C_{1-6} alkyl- C_{3-8} cycloalkyl, heterocycloalkyl, C_{1-6} alkyl-heterocycloalkyl, C_{6-12} aryl, C_{1-6} alkyl- C_{6-12} aryl, heteroaryl, or C_{1-6} alkyl-heteroaryl,

wherein each heterocycloalkyl independently has 3 to 12 ring members and 1 to 3 heteroatoms each independently N, O or S,
 wherein each heteroaryl independently has 5 to 10 ring members and 1 to 4 heteroatoms each independently N, O or S, and
 wherein each cycloalkyl, heterocycloalkyl, aryl and heteroaryl is independently substituted with 0 to 4 R^{5c} groups;
 each R^{5a} and R^{5b} is independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₂₋₆ alkoxyalkyl, hydroxy, C₁₋₆ hydroxyalkyl, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, C₃₋₈ cycloalkyl, C₁₋₆ alkyl-C₃₋₈ cycloalkyl, heterocycloalkyl, C₁₋₆ alkyl-heterocycloalkyl, C₆₋₁₂ aryl, C₁₋₆ alkyl-C₆₋₁₂ aryl, heteroaryl, or C₁₋₆ alkyl-heteroaryl, wherein each heterocycloalkyl independently has 3 to 12 ring members and 1 to 3 heteroatoms each independently N, O or S, wherein each heteroaryl independently has 5 to 10 ring members and 1 to 4 heteroatoms each independently N, O or S, and wherein each cycloalkyl, heterocycloalkyl, aryl and heteroaryl is substituted with 0 to 4 R^{5d} groups;
 alternatively, R^{5a} and R^{5b} are combined with the atoms to which they are attached to form a heterocycloalkyl having 3 to 12 ring members and 1 to 3 additional heteroatoms each independently N, O or S, wherein the heterocycloalkyl is substituted with 0, 1 or 2 C₁₋₆ alkyl groups;
 each R^{5c} is independently C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ alkoxy, C₂₋₆ alkoxyalkyl, C₁₋₆ hydroxyalkyl, halogen, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, -CN, oxo, -OH, -C(O)R^{5c1}, -C(O)OR^{5c1}, -OC(O)R^{5c1}, -OC(O)OR^{5c1}, -C(O)N(R^{5c1})(R^{5c2}), -N(R^{5c1})C(O)R^{5c2}, -OC(O)N(R^{5c1})(R^{5c2}), -N(R^{5c1})C(O)OR^{5c2}, -S(O)₂R^{5c1}, -S(O)₂N(R^{5c1})(R^{5c2}), -N(R^{5c1})S(O)₂R^{5c2}, C₃₋₈ cycloalkyl, C₁₋₆ alkyl-C₃₋₈ cycloalkyl, heterocycloalkyl, C₁₋₆ alkyl-heterocycloalkyl, C₆₋₁₂ aryl, C₁₋₆ alkyl-C₆₋₁₂ aryl, heteroaryl, or C₁₋₆ alkyl-heteroaryl, wherein each heterocycloalkyl independently has 3 to 12 ring members and 1 to 3 heteroatoms each independently N, O or S, wherein each heteroaryl independently has 5 to 10 ring members and 1 to 4 heteroatoms each independently N, O or S, and wherein each heterocycloalkyl and heteroaryl is substituted with 0, 1 or 2 C₁₋₆ alkyl groups;
 each R^{5c1} and R^{5c2} is independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₂₋₆ alkoxyalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ haloalkyl, C₃₋₈ cycloalkyl, C₁₋₆ alkyl-C₃₋₈ cycloalkyl, heterocycloalkyl, C₁₋₆ alkyl-heterocycloalkyl, C₆₋₁₂ aryl, C₁₋₆

alkyl-C₆₋₁₂ aryl, heteroaryl, or C₁₋₆ alkyl-heteroaryl, wherein each heterocycloalkyl independently has 3 to 12 ring members and 1 to 3 heteroatoms each independently N, O or S, wherein each heteroaryl independently has 5 to 10 ring members and 1 to 4 heteroatoms each independently N, O or S, and wherein each heterocycloalkyl and heteroaryl is substituted with 0, 1 or 2 C₁₋₆ alkyl groups;

alternatively, R^{5c1} and R^{5c2} are combined with the atoms to which they are attached to form a heterocycloalkyl having 3 to 12 ring members and 1 to 3 heteroatoms each independently N, O or S, wherein the heterocycloalkyl is substituted with 0, 1 or 2 C₁₋₆ alkyl groups;

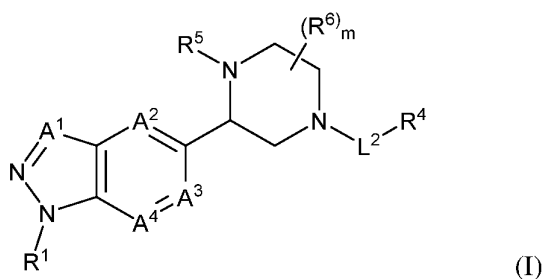
each R^{5d} is independently C₁₋₆ alkyl or halogen;

each R⁶ is independently hydrogen, C₁₋₆ alkyl, halogen, C₁₋₆ haloalkyl, or oxo;

subscript m is 0, 1, 2, 3, 4, or 5; and

subscript n is 1 or 2.

[0007] In another embodiment, the present invention provides a compound of Formula I:



or a pharmaceutically acceptable salt thereof, wherein

R¹ is heterocycloalkyl having 3 to 12 ring members and 1 to 4 heteroatoms each N, O or S, phenyl or heteroaryl having 5 to 10 ring members and 1 to 5 heteroatoms each N, O or S, each independently substituted with 0 to 5 R^{1a} groups;

each R^{1a} is independently C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkoxyalkyl, C₁₋₆ hydroxyalkyl, halogen, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, -OH, oxo, -CN, -C(O)N(R^{1b})(R^{1c}), C₃₋₁₀ cycloalkyl, or heterocycloalkyl having 3 to 12 ring members and 1 to 4 heteroatoms each N, O or S;

each R^{1b} and R^{1c} is independently hydrogen, C₁₋₆ alkyl or a 3 to 8 membered heterocycloalkyl having 1 to 3 heteroatoms each independently N, O or S;

A¹, A², A³ and A⁴ are each independently =CR²- or =N-;

each R² is independently hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₂₋₆ alkoxyalkyl, halogen, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, hydroxy or -CN;
L² is -C(O)-, -C(O)O-, -C(O)N(R³)-, -S(O)₂- or -S(O)₂N(R³)-;
R³ is hydrogen, or C₁₋₆ alkyl;
5 R⁴ is C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₂₋₆ alkoxyalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ haloalkyl, C₃₋₈ cycloalkyl, C₁₋₆ alkyl-C₃₋₈ cycloalkyl, heterocycloalkyl, C₁₋₆ alkyl-heterocycloalkyl, C₆₋₁₂ aryl, C₁₋₆ alkyl-C₆₋₁₂ aryl, -O-C₆₋₁₂ aryl, heteroaryl, or C₁₋₆ alkyl-heteroaryl,
wherein each heterocycloalkyl independently has 3 to 12 ring members and 1
10 to 3 heteroatoms each independently N, O or S,
wherein each heteroaryl independently has 5 to 10 ring members and 1 to 4 heteroatoms each independently N, O or S, and
wherein the cycloalkyl, heterocycloalkyl, aryl and heteroaryl are each independently substituted with 0 to 5 R^{4a} groups;
15 alternatively, R³ and R⁴ are combined with the atoms to which they are attached to form a heterocycloalkyl having 3 to 12 ring members and 1 to 3 additional heteroatoms each independently N, O or S, wherein the heterocycloalkyl is substituted with 0, 1 or 2 C₁₋₆ alkyl groups;
each R^{4a} is independently C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ alkoxy, C₂₋₆
20 alkoxyalkyl, C₁₋₆ hydroxyalkyl, halogen, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, -CN, -OH, oxo, -C(O)R^{4b}, -C(O)OR^{4b}, -OC(O)R^{4b}, -OC(O)OR^{4b}, -C(O)N(R^{4b})(R^{4c}), -N(R^{4b})C(O)R^{4c}, -OC(O)N(R^{4b})(R^{4c}), -N(R^{4b})C(O)OR^{4c}, -S(O)₂R^{4b}, -S(O)₂N(R^{4b})(R^{4c}), -N(R^{4b})S(O)₂R^{4c}, C₃₋₈ cycloalkyl, C₁₋₆ alkyl-C₃₋₈ cycloalkyl, heterocycloalkyl, C₁₋₆ alkyl-heterocycloalkyl, C₆₋₁₂ aryl, C₁₋₆ alkyl-C₆₋₁₂ aryl, -O-C₆₋₁₂ aryl, heteroaryl, or C₁₋₆ alkyl-heteroaryl, wherein each
25 heterocycloalkyl independently has 3 to 12 ring members and 1 to 3 heteroatoms each independently N, O or S, wherein each heteroaryl independently has 5 to 10 ring members and 1 to 4 heteroatoms each independently N, O or S, and wherein each cycloalkyl, heterocycloalkyl, aryl
30 and heteroaryl is substituted with 0, 1 or 2 C₁₋₆ alkyl groups;
each R^{4b} and R^{4c} is hydrogen or C₁₋₆ alkyl;
R⁵ is C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₂₋₆ alkoxyalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ haloalkyl, C₁₋₆ alkyl-OR^{5a}, -C(O)R^{5a}, C₁₋₆ alkyl-C(O)R^{5a}, -C(O)OR^{5a}, -C(O)N(R^{5a})(R^{5b}), -S(O)₂R^{5a}, -S(O)₂N(R^{5a})(R^{5b}), C₃₋₈ cycloalkyl, C₁₋₆ alkyl-C₃₋₈

cycloalkyl, heterocycloalkyl, C₁₋₆ alkyl-heterocycloalkyl, C₆₋₁₂ aryl, C₁₋₆ alkyl-C₆₋₁₂ aryl, heteroaryl, or C₁₋₆ alkyl-heteroaryl,
 wherein each heterocycloalkyl independently has 3 to 12 ring members and 1 to 3 heteroatoms each independently N, O or S,
 5 wherein each heteroaryl independently has 5 to 10 ring members and 1 to 4 heteroatoms each independently N, O or S, and
 wherein each cycloalkyl, heterocycloalkyl, aryl and heteroaryl is independently substituted with 0 to 4 R^{5c} groups;
 each R^{5a} and R^{5b} is independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₂₋₆ alkoxyalkyl, hydroxy, C₁₋₆ hydroxyalkyl, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, C₃₋₈
 10 cycloalkyl, C₁₋₆ alkyl-C₃₋₈ cycloalkyl, heterocycloalkyl, C₁₋₆ alkyl-heterocycloalkyl, C₆₋₁₂ aryl, C₁₋₆ alkyl-C₆₋₁₂ aryl, heteroaryl, or C₁₋₆ alkyl-heteroaryl, wherein each heterocycloalkyl independently has 3 to 12 ring members and 1 to 3 heteroatoms each independently N, O or S, wherein each
 15 heteroaryl independently has 5 to 10 ring members and 1 to 4 heteroatoms each independently N, O or S, and wherein each cycloalkyl, heterocycloalkyl, aryl and heteroaryl is substituted with 0 to 4 R^{5d} groups;
 alternatively, R^{5a} and R^{5b} are combined with the atoms to which they are attached to form a heterocycloalkyl having 3 to 12 ring members and 1 to 3 additional
 20 heteroatoms each independently N, O or S, wherein the heterocycloalkyl is substituted with 0, 1 or 2 C₁₋₆ alkyl groups;
 each R^{5c} is independently C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ alkoxy, C₂₋₆ alkoxyalkyl, C₁₋₆ hydroxyalkyl, halogen, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, -CN, oxo, -OH, -C(O)R^{5c1}, -C(O)OR^{5c1}, -OC(O)R^{5c1}, -OC(O)OR^{5c1}, -
 25 C(O)N(R^{5c1})(R^{5c2}), -N(R^{5c1})C(O)R^{5c2}, -OC(O)N(R^{5c1})(R^{5c2}), -N(R^{5c1})C(O)OR^{5c2}, -S(O)₂R^{5c1}, -S(O)₂N(R^{5c1})(R^{5c2}), -N(R^{5c1})S(O)₂R^{5c2}, C₃₋₈ cycloalkyl, C₁₋₆ alkyl-C₃₋₈ cycloalkyl, heterocycloalkyl, C₁₋₆ alkyl-heterocycloalkyl, C₆₋₁₂ aryl, C₁₋₆ alkyl-C₆₋₁₂ aryl, heteroaryl, or C₁₋₆ alkyl-heteroaryl, wherein each heterocycloalkyl independently has 3 to 12 ring
 30 members and 1 to 3 heteroatoms each independently N, O or S, wherein each heteroaryl independently has 5 to 10 ring members and 1 to 4 heteroatoms each independently N, O or S, and wherein each heterocycloalkyl and heteroaryl is substituted with 0, 1 or 2 C₁₋₆ alkyl groups;

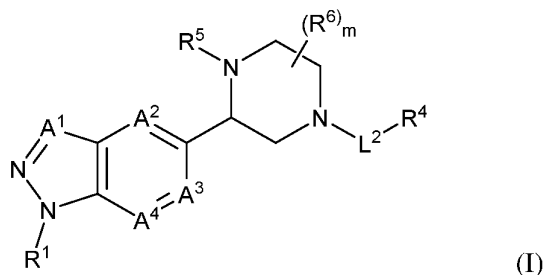
each R^{5c1} and R^{5c2} is independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₂₋₆ alkoxyalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ haloalkyl, C₃₋₈ cycloalkyl, C₁₋₆ alkyl-C₃₋₈ cycloalkyl, heterocycloalkyl, C₁₋₆ alkyl-heterocycloalkyl, C₆₋₁₂ aryl, C₁₋₆ alkyl-C₆₋₁₂ aryl, heteroaryl, or C₁₋₆ alkyl-heteroaryl, wherein each heterocycloalkyl independently has 3 to 12 ring members and 1 to 3 heteroatoms each independently N, O or S, wherein each heteroaryl independently has 5 to 10 ring members and 1 to 4 heteroatoms each independently N, O or S, and wherein each heterocycloalkyl and heteroaryl is substituted with 0, 1 or 2 C₁₋₆ alkyl groups;

alternatively, R^{5c1} and R^{5c2} are combined with the atoms to which they are attached to form a heterocycloalkyl having 3 to 12 ring members and 1 to 3 heteroatoms each independently N, O or S, wherein the heterocycloalkyl is substituted with 0, 1 or 2 C₁₋₆ alkyl groups;

each R^{5d} is independently C₁₋₆ alkyl or halogen;

each R⁶ is independently hydrogen, C₁₋₆ alkyl, halogen, C₁₋₆ haloalkyl, or oxo; and subscript m is 0, 1, 2, 3, 4, or 5.

[0008] In another embodiment, the present invention provides a compound of Formula I:



or a pharmaceutically acceptable salt thereof, wherein

R¹ is heterocycloalkyl having 3 to 12 ring members and 1 to 4 heteroatoms each N, O or S, phenyl or heteroaryl having 5 to 10 ring members and 1 to 5 heteroatoms each N, O or S, each independently substituted with 0 to 5 R^{1a} groups;

each R^{1a} is independently C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkoxyalkyl, C₁₋₆ hydroxyalkyl, halogen, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, -OH, oxo, -CN, -C(O)N(R^{1b})(R^{1c}), C₃₋₁₀ cycloalkyl, or heterocycloalkyl having 3 to 12 ring members and 1 to 4 heteroatoms each N, O or S;

each R^{1b} and R^{1c} is independently hydrogen, C₁₋₆ alkyl or a 3 to 8 membered heterocycloalkyl having 1 to 3 heteroatoms each independently N, O or S;

A^1 , A^2 , A^3 and A^4 are each independently $=CR^2-$ or $=N-$;
each R^2 is independently hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{2-6} alkoxyalkyl, halogen,
 C_{1-6} haloalkyl, C_{1-6} haloalkoxy, hydroxy or $-CN$;
 L^2 is $-C(O)-$, $-C(O)O-$, $-C(O)N(R^3)-$, $-S(O)_2-$ or $-S(O)_2N(R^3)-$;
5 R^3 is hydrogen, or C_{1-6} alkyl;
 R^4 is C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{2-6} alkoxyalkyl, C_{1-6} hydroxyalkyl, C_{1-6}
haloalkyl, C_{3-8} cycloalkyl, C_{1-6} alkyl- C_{3-8} cycloalkyl, heterocycloalkyl, C_{1-6}
alkyl-heterocycloalkyl, C_{6-12} aryl, C_{1-6} alkyl- C_{6-12} aryl, $-O-C_{6-12}$ aryl,
heteroaryl, or C_{1-6} alkyl-heteroaryl, wherein each heterocycloalkyl
10 independently has 3 to 12 ring members and 1 to 3 heteroatoms each
independently N, O or S, wherein each heteroaryl independently has 5 to 10
ring members and 1 to 4 heteroatoms each independently N, O or S, and
wherein the cycloalkyl, heterocycloalkyl, aryl and heteroaryl are each
independently substituted with 0 to 5 R^{4a} groups;
15 alternatively, R^3 and R^4 are combined with the atoms to which they are attached to
form a heterocycloalkyl having 3 to 12 ring members and 1 to 3 additional
heteroatoms each independently N, O or S, wherein the heterocycloalkyl is
substituted with 0, 1 or 2 C_{1-6} alkyl groups;
each R^{4a} is independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, C_{2-6}
20 alkoxyalkyl, C_{1-6} hydroxyalkyl, halogen, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, $-CN$,
 $-OH$, oxo, $-C(O)R^{4b}$, $-C(O)OR^{4b}$, $-OC(O)R^{4b}$, $-OC(O)OR^{4b}$, $-C(O)N(R^{4b})(R^{4c})$,
 $-N(R^{4b})C(O)R^{4c}$, $-OC(O)N(R^{4b})(R^{4c})$, $-N(R^{4b})C(O)OR^{4c}$, $-S(O)_2R^{4b}$, $-$
 $S(O)_2N(R^{4b})(R^{4c})$, $-N(R^{4b})S(O)_2R^{4c}$, C_{3-8} cycloalkyl, C_{1-6} alkyl- C_{3-8} cycloalkyl,
heterocycloalkyl, C_{1-6} alkyl-heterocycloalkyl, C_{6-12} aryl, C_{1-6} alkyl- C_{6-12} aryl, $-$
25 $O-C_{6-12}$ aryl, heteroaryl, or C_{1-6} alkyl-heteroaryl, wherein each
heterocycloalkyl independently has 3 to 12 ring members and 1 to 3
heteroatoms each independently N, O or S, wherein each heteroaryl
independently has 5 to 10 ring members and 1 to 4 heteroatoms each
independently N, O or S, and wherein each cycloalkyl, heterocycloalkyl, aryl
30 and heteroaryl is substituted with 0, 1 or 2 C_{1-6} alkyl groups;
each R^{4b} and R^{4c} is hydrogen or C_{1-6} alkyl;
 R^5 is C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{2-6} alkoxyalkyl, C_{1-6} hydroxyalkyl, C_{1-6}
haloalkyl, C_{1-6} alkyl- OR^{5a} , $-C(O)R^{5a}$, $-C(O)OR^{5a}$, $-C(O)N(R^{5a})(R^{5b})$, $-$
 $S(O)_2R^{5a}$, $-S(O)_2N(R^{5a})(R^{5b})$, C_{3-8} cycloalkyl, C_{1-6} alkyl- C_{3-8} cycloalkyl,

heterocycloalkyl, C₁₋₆ alkyl-heterocycloalkyl, C₆₋₁₂ aryl, C₁₋₆ alkyl-C₆₋₁₂ aryl, heteroaryl, or C₁₋₆ alkyl-heteroaryl, wherein each heterocycloalkyl independently has 3 to 12 ring members and 1 to 3 heteroatoms each independently N, O or S, wherein each heteroaryl independently has 5 to 10 ring members and 1 to 4 heteroatoms each independently N, O or S, and wherein each cycloalkyl, heterocycloalkyl, aryl and heteroaryl is independently substituted with 0 to 4 R^{5c} groups;

each R^{5a} and R^{5b} is independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₂₋₆ alkoxyalkyl, hydroxy, C₁₋₆ hydroxyalkyl, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, C₃₋₈ cycloalkyl, C₁₋₆ alkyl-C₃₋₈ cycloalkyl, heterocycloalkyl, C₁₋₆ alkyl-heterocycloalkyl, C₆₋₁₂ aryl, C₁₋₆ alkyl-C₆₋₁₂ aryl, heteroaryl, or C₁₋₆ alkyl-heteroaryl, wherein each heterocycloalkyl independently has 3 to 12 ring members and 1 to 3 heteroatoms each independently N, O or S, wherein each heteroaryl independently has 5 to 10 ring members and 1 to 4 heteroatoms each independently N, O or S, and wherein each cycloalkyl, heterocycloalkyl, aryl and heteroaryl is substituted with 0 to 4 R^{5d} groups;

alternatively, R^{5a} and R^{5b} are combined with the atoms to which they are attached to form a heterocycloalkyl having 3 to 12 ring members and 1 to 3 additional heteroatoms each independently N, O or S, wherein the heterocycloalkyl is substituted with 0, 1 or 2 C₁₋₆ alkyl groups;

each R^{5c} is independently C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ alkoxy, C₂₋₆ alkoxyalkyl, C₁₋₆ hydroxyalkyl, halogen, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, -CN, oxo, -OH, -C(O)R^{5c1}, -C(O)OR^{5c1}, -OC(O)R^{5c1}, -OC(O)OR^{5c1}, -C(O)N(R^{5c1})(R^{5c2}), -N(R^{5c1})C(O)R^{5c2}, -OC(O)N(R^{5c1})(R^{5c2}), -N(R^{5c1})C(O)OR^{5c2}, -S(O)₂R^{5c1}, -S(O)₂N(R^{5c1})(R^{5c2}), -N(R^{5c1})S(O)₂R^{5c2}, C₃₋₈ cycloalkyl, C₁₋₆ alkyl-C₃₋₈ cycloalkyl, heterocycloalkyl, C₁₋₆ alkyl-heterocycloalkyl, C₆₋₁₂ aryl, C₁₋₆ alkyl-C₆₋₁₂ aryl, heteroaryl, or C₁₋₆ alkyl-heteroaryl, wherein each heterocycloalkyl independently has 3 to 12 ring members and 1 to 3 heteroatoms each independently N, O or S, wherein each heteroaryl independently has 5 to 10 ring members and 1 to 4 heteroatoms each independently N, O or S, and wherein each heterocycloalkyl and heteroaryl is substituted with 0, 1 or 2 C₁₋₆ alkyl groups;

each R^{5c1} and R^{5c2} is independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₂₋₆ alkoxyalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ haloalkyl, C₃₋₈ cycloalkyl, C₁₋₆ alkyl-

- C₃₋₈ cycloalkyl, heterocycloalkyl, C₁₋₆ alkyl-heterocycloalkyl, C₆₋₁₂ aryl, C₁₋₆ alkyl-C₆₋₁₂ aryl, heteroaryl, or C₁₋₆ alkyl-heteroaryl, wherein each heterocycloalkyl independently has 3 to 12 ring members and 1 to 3 heteroatoms each independently N, O or S, wherein each heteroaryl independently has 5 to 10 ring members and 1 to 4 heteroatoms each independently N, O or S, and wherein each heterocycloalkyl and heteroaryl is substituted with 0, 1 or 2 C₁₋₆ alkyl groups;
- alternatively, R^{5c1} and R^{5c2} are combined with the atoms to which they are attached to form a heterocycloalkyl having 3 to 12 ring members and 1 to 3 heteroatoms each independently N, O or S, wherein the heterocycloalkyl is substituted with 0, 1 or 2 C₁₋₆ alkyl groups;
- each R^{5d} is independently C₁₋₆ alkyl or halogen;
- each R⁶ is independently hydrogen, C₁₋₆ alkyl, halogen, C₁₋₆ haloalkyl, or oxo; and subscript m is 0, 1, 2, 3, 4, or 5.
- 15 **[0009]** In another embodiment, the present invention provides a pharmaceutical composition comprising a compound of the present invention and a pharmaceutically acceptable excipient.
- [0010]** In another embodiment, the present invention provides a method of treating a disorder or condition through modulating a glucocorticoid receptor, the method comprising
- 20 administering to a subject in need of such treatment, a therapeutically effective amount of a compound or a pharmaceutical composition of the present invention, thereby treating the disorder or condition.
- [0011]** In another embodiment, the present invention provides a method of treating a disorder or condition through antagonizing a glucocorticoid receptor, the method comprising
- 25 administering to a subject in need of such treatment, an effective amount of the compound or a pharmaceutical composition of the present invention.
- [0012]** In another embodiment, the present invention provides a compound or pharmaceutical composition for use in a method of treating a disorder or condition through modulating a glucocorticoid receptor.
- 30 **[0013]** In another embodiment, the present invention provides a compound or pharmaceutical composition for use in a method of treating a disorder or condition through antagonizing the glucocorticoid receptor.

[0014] In another embodiment, the present invention provides use of a compound or pharmaceutical composition of the present invention in the manufacture of a medicament for treating a disorder or condition through modulating a glucocorticoid receptor.

5 [0015] In another embodiment, the present invention provides a use of a compound or pharmaceutical composition of the present invention in the manufacture of a medicament for treating a disorder or condition through antagonizing a glucocorticoid receptor.

DETAILED DESCRIPTION OF THE INVENTION

I. GENERAL

10 [0016] The present invention provides compounds of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic or Id capable of modulating and/or antagonizing a glucocorticoid receptor, and thereby providing beneficial therapeutic effects. The present invention also provides methods of treating disorders and conditions by modulating a glucocorticoid receptor or by antagonizing a glucocorticoid receptor. The present invention also provides use of a compound of the
15 present invention in the manufacture of a medicament for treating a disorder or condition through modulating a glucocorticoid receptor, agonizing a glucocorticoid receptor or antagonizing a glucocorticoid receptor.

II. DEFINITIONS

[0017] Unless specifically indicated otherwise, all technical and scientific terms used
20 herein have the same meaning as commonly understood by those of ordinary skill in the art to which this invention belongs. In addition, any method or material similar or equivalent to a method or material described herein can be used in the practice of the present invention. For purposes of the present invention, the following terms are defined.

[0018] “A,” “an,” or “the” as used herein not only include aspects with one member, but
25 also include aspects with more than one member. For instance, 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 agent” includes reference to one or more agents known to those skilled in the art, and so forth.

[0019] “Alkyl” refers to a straight or branched, saturated, aliphatic radical having the
30 number of carbon atoms indicated. Alkyl can include any number of carbons, such as C₁₋₂,

C₁₋₃, C₁₋₄, C₁₋₅, C₁₋₆, C₁₋₇, C₁₋₈, C₁₋₉, C₁₋₁₀, C₂₋₃, C₂₋₄, C₂₋₅, C₂₋₆, C₃₋₄, C₃₋₅, C₃₋₆, C₄₋₅, C₄₋₆ and C₅₋₆. For example, C₁₋₆ alkyl includes, but is not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, hexyl, etc. Alkyl can also refer to alkyl groups having up to 20 carbons atoms, such as, but not limited to heptyl, octyl, nonyl, decyl, etc. Alkyl groups can be substituted or unsubstituted.

[0020] “Alkylene” refers to a straight or branched, saturated, aliphatic radical having the number of carbon atoms indicated (i.e., C₁₋₆ means one to six carbons), and linking at least two other groups, *i.e.*, a divalent hydrocarbon radical. The two moieties linked to the alkylene can be linked to the same atom or different atoms of the alkylene group. For instance, a straight chain alkylene can be the bivalent radical of $-(CH_2)_n-$, where n is 1, 2, 3, 4, 5 or 6. Representative C₁₋₄ alkylene groups include, but are not limited to, methylene, ethylene, propylene, isopropylene, butylene, isobutylene, and sec-butylene.

[0021] “Alkenyl” refers to a straight chain or branched hydrocarbon having at least 2 carbon atoms and at least one double bond. Alkenyl can include any number of carbons, such as C₂, C₂₋₃, C₂₋₄, C₂₋₅, C₂₋₆, C₂₋₇, C₂₋₈, C₂₋₉, C₂₋₁₀, C₃, C₃₋₄, C₃₋₅, C₃₋₆, C₄, C₄₋₅, C₄₋₆, C₅, C₅₋₆, and C₆. Alkenyl groups can have any suitable number of double bonds, including, but not limited to, 1, 2, 3, 4, 5 or more. Examples of alkenyl groups include, but are not limited to, vinyl (ethenyl), propenyl, isopropenyl, 1-butenyl, 2-butenyl, isobutenyl, butadienyl, 1-pentenyl, 2-pentenyl, isopentenyl, 1,3-pentadienyl, 1,4-pentadienyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 1,3-hexadienyl, 1,4-hexadienyl, 1,5-hexadienyl, 2,4-hexadienyl, or 1,3,5-hexatrienyl. Alkenyl groups can be substituted or unsubstituted.

[0022] “Alkynyl” refers to either a straight chain or branched hydrocarbon having at least 2 carbon atoms and at least one triple bond. Alkynyl can include any number of carbons, such as C₂, C₂₋₃, C₂₋₄, C₂₋₅, C₂₋₆, C₂₋₇, C₂₋₈, C₂₋₉, C₂₋₁₀, C₃, C₃₋₄, C₃₋₅, C₃₋₆, C₄, C₄₋₅, C₄₋₆, C₅, C₅₋₆, and C₆. Examples of alkynyl groups include, but are not limited to, acetylenyl, propynyl, 1-butyne, 2-butyne, butadiynyl, 1-pentyne, 2-pentyne, isopentyne, 1,3-pentadiynyl, 1,4-pentadiynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 1,3-hexadiynyl, 1,4-hexadiynyl, 1,5-hexadiynyl, 2,4-hexadiynyl, or 1,3,5-hexatriynyl. Alkynyl groups can be substituted or unsubstituted.

[0023] “Deuteroalkyl” refers to an alkyl group, as defined above, where at least one of the hydrogen atoms is replaced with a deuterium. As for the alkyl group, deuteroalkyl groups can have any suitable number of carbon atoms, such as C₁₋₆. Exemplary C₁₋₄ deuteroalkyl

groups include, but are not limited to, -CH₂D, -CHD₂, -CD₃, -CH₂CH₂D, -CH₂CHD₂, -CH₂CD₃, and the like.

[0024] “Alkoxy” refers to an alkyl group having an oxygen atom that connects the alkyl group to the point of attachment: alkyl-O-. As for alkyl groups, alkoxy groups can have any
5 suitable number of carbon atoms, such as C₁₋₆. Alkoxy groups include, for example, methoxy, ethoxy, propoxy, iso-propoxy, butoxy, 2-butoxy, iso-butoxy, sec-butoxy, tert-butoxy, pentoxy, hexoxy, etc. The alkoxy groups can be further substituted with a variety of substituents described within. Alkoxy groups can be substituted or unsubstituted.

[0025] “Alkoxyalkyl” refers to a radical having an alkyl component and an alkoxy
10 component, where the alkyl component links the alkoxy component to the point of attachment. The alkyl component is as defined above, except that the alkyl component is at least divalent, an alkylene, to link to the alkoxy component and to the point of attachment. The alkyl component can include any number of carbons, such as C₁₋₆, C₁₋₂, C₁₋₃, C₁₋₄, C₁₋₅, C₁₋₆, C₂₋₃, C₂₋₄, C₂₋₅, C₂₋₆, C₃₋₄, C₃₋₅, C₃₋₆, C₄₋₅, C₄₋₆ and C₅₋₆. The alkoxy component is as
15 defined above. Examples of the alkyl-alkoxy group include, but are not limited to, 2-ethoxyethyl and methoxymethyl.

[0026] “Hydroxyalkyl” or “alkylhydroxy” refers to an alkyl group, as defined above, where at least one of the hydrogen atoms is replaced with a hydroxy group. As for the alkyl group, hydroxyalkyl or alkylhydroxy groups can have any suitable number of carbon atoms, such as
20 C₁₋₆. Exemplary C₁₋₄ hydroxyalkyl groups include, but are not limited to, hydroxymethyl, hydroxyethyl (where the hydroxy is in the 1- or 2-position), hydroxypropyl (where the hydroxy is in the 1-, 2- or 3-position), hydroxybutyl (where the hydroxy is in the 1-, 2-, 3- or 4-position), 1,2-dihydroxyethyl, and the like.

[0027] “Halogen” refers to fluorine, chlorine, bromine and iodine.

[0028] “Haloalkyl” refers to alkyl, as defined above, where some or all of the hydrogen
25 atoms are replaced with halogen atoms. As for alkyl groups, haloalkyl groups can have any suitable number of carbon atoms, such as C₁₋₆. For example, haloalkyl includes trifluoromethyl, fluoromethyl, etc. In some instances, the term “perfluoro” can be used to define a compound or radical where all the hydrogens are replaced with fluorine. For
30 example, perfluoromethyl refers to 1,1,1-trifluoromethyl.

[0029] “Haloalkoxy” refers to an alkoxy group where some or all of the hydrogen atoms are substituted with halogen atoms. As for an alkyl group, haloalkoxy groups can have any suitable number of carbon atoms, such as C₁₋₆. The alkoxy groups can be substituted with 1, 2, 3, or more halogens. When all the hydrogens are replaced with a halogen, for example by fluorine, the compounds are per-substituted, for example, perfluorinated. Haloalkoxy includes, but is not limited to, trifluoromethoxy, 2,2,2-trifluoroethoxy, perfluoroethoxy, etc.

[0030] “Amino” refers to an -N(R)₂ group where the R groups can be hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, among others. The R groups can be the same or different. The amino groups can be primary (each R is hydrogen), secondary (one R is hydrogen) or tertiary (each R is other than hydrogen).

[0031] “Oxo” refers to a carbonyl group, =O.

[0032] “Cycloalkyl” refers to a saturated or partially unsaturated, monocyclic, fused bicyclic or bridged polycyclic ring assembly containing from 3 to 12 ring atoms, or the number of atoms indicated. Cycloalkyl can include any number of carbons, such as C₃₋₆, C₄₋₆, C₅₋₆, C₃₋₈, C₄₋₈, C₅₋₈, C₆₋₈, C₃₋₉, C₃₋₁₀, C₃₋₁₁, and C₃₋₁₂. Saturated monocyclic cycloalkyl rings include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cyclooctyl. Saturated bicyclic and polycyclic cycloalkyl rings include, for example, norbornane, [2.2.2] bicyclooctane, decahydronaphthalene and adamantane. Cycloalkyl groups can also be partially unsaturated, having one or more double or triple bonds in the ring. Representative cycloalkyl groups that are partially unsaturated include, but are not limited to, cyclobutene, cyclopentene, cyclohexene, cyclohexadiene (1,3- and 1,4-isomers), cycloheptene, cycloheptadiene, cyclooctene, cyclooctadiene (1,3-, 1,4- and 1,5-isomers), norbornene, and norbornadiene. When cycloalkyl is a saturated monocyclic C₃₋₈ cycloalkyl, exemplary groups include, but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl. When cycloalkyl is a saturated monocyclic C₃₋₆ cycloalkyl, exemplary groups include, but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. Cycloalkyl groups can be substituted or unsubstituted.

[0033] “Alkyl-cycloalkyl” refers to a radical having an alkyl component and a cycloalkyl component, where the alkyl component links the cycloalkyl component to the point of attachment. The alkyl component is as defined above, except that the alkyl component is at least divalent, an alkylene, to link to the cycloalkyl component and to the point of attachment. The alkyl component can include any number of carbons, such as C₁₋₆, C₁₋₂, C₁₋₃, C₁₋₄, C₁₋₅,

C₂₋₃, C₂₋₄, C₂₋₅, C₂₋₆, C₃₋₄, C₃₋₅, C₃₋₆, C₄₋₅, C₄₋₆ and C₅₋₆. The cycloalkyl component is as defined within. Exemplary alkyl-cycloalkyl groups include, but are not limited to, methyl-cyclopropyl, methyl-cyclobutyl, methyl-cyclopentyl and methyl-cyclohexyl.

[0034] “Heterocycloalkyl” or “heterocyclyl” refers to a saturated ring system having from 3 to 12 ring members and from 1 to 5 heteroatoms of N, O and S. The heteroatoms can also be oxidized, such as, but not limited to, -S(O)- and -S(O)₂-. Heterocycloalkyl groups can include any number of ring atoms, such as, 3 to 6, 4 to 6, 5 to 6, 3 to 8, 4 to 8, 5 to 8, 6 to 8, 3 to 9, 3 to 10, 3 to 11, or 3 to 12 ring members. Any suitable number of heteroatoms can be included in the heterocycloalkyl groups, such as 1, 2, 3, 4, or 5, or 1 to 2, 1 to 3, 1 to 4, 1 to 5, 2 to 3, 2 to 4, 2 to 5, 3 to 4 or 3 to 5. The heterocycloalkyl group can include any number of carbons, such as C₃₋₆, C₄₋₆, C₅₋₆, C₃₋₈, C₄₋₈, C₅₋₈, C₆₋₈, C₃₋₉, C₃₋₁₀, C₃₋₁₁, and C₃₋₁₂. The heterocycloalkyl group can include groups such as aziridine, azetidine, pyrrolidine, piperidine, azepane, diazepane, azocane, quinuclidine, pyrazolidine, imidazolidine, piperazine (1,2-, 1,3- and 1,4-isomers), oxirane, oxetane, tetrahydrofuran, oxane (tetrahydropyran), oxepane, thiirane, thietane, thiolane (tetrahydrothiophene), thiane (tetrahydrothiopyran), oxazolidine, isoxazolidine, thiazolidine, isothiazolidine, dioxolane, dithiolane, morpholine, thiomorpholine, dioxane, or dithiane. The heterocycloalkyl groups can also be fused to aromatic or non-aromatic ring systems to form members including, but not limited to, indoline. The heterocycloalkyl groups can also form spiro structures such as, but not limited to, diazabicycloheptane, diazabicyclooctane, diazaspirooctane or diazaspirononane. Heterocycloalkyl groups can be unsubstituted or substituted. For example, heterocycloalkyl groups can be substituted with C₁₋₆ alkyl or oxo (=O), among many others. Heterocycloalkyl groups can also include a double bond or a triple bond, such as, but not limited to dihydropyridine or 1,2,3,6-tetrahydropyridine.

[0035] The heterocycloalkyl groups can be linked via any position on the ring. For example, aziridine can be 1- or 2-aziridine, azetidine can be 1- or 2- azetidine, pyrrolidine can be 1-, 2- or 3-pyrrolidine, piperidine can be 1-, 2-, 3- or 4-piperidine, pyrazolidine can be 1-, 2-, 3-, or 4-pyrazolidine, imidazolidine can be 1-, 2-, 3- or 4-imidazolidine, piperazine can be 1-, 2-, 3- or 4-piperazine, tetrahydrofuran can be 1- or 2-tetrahydrofuran, oxazolidine can be 2-, 3-, 4- or 5-oxazolidine, isoxazolidine can be 2-, 3-, 4- or 5-isoxazolidine, thiazolidine can be 2-, 3-, 4- or 5-thiazolidine, isothiazolidine can be 2-, 3-, 4- or 5- isothiazolidine, and morpholine can be 2-, 3- or 4-morpholine.

[0036] When heterocycloalkyl includes 3 to 8 ring members and 1 to 3 heteroatoms, representative members include, but are not limited to, pyrrolidine, piperidine, tetrahydrofuran, oxane, tetrahydrothiophene, thiane, pyrazolidine, imidazolidine, piperazine, oxazolidine, isoxazolidine, thiazolidine, isothiazolidine, morpholine, thiomorpholine, dioxane and dithiane. Heterocycloalkyl can also form a ring having 5 to 6 ring members and 1 to 2 heteroatoms, with representative members including, but not limited to, pyrrolidine, piperidine, tetrahydrofuran, tetrahydrothiophene, pyrazolidine, imidazolidine, piperazine, oxazolidine, isoxazolidine, thiazolidine, isothiazolidine, and morpholine.

[0037] "Alkyl-heterocycloalkyl" refers to a radical having an alkyl component and a heterocycloalkyl component, where the alkyl component links the heterocycloalkyl component to the point of attachment. The alkyl component is as defined above, except that the alkyl component is at least divalent, an alkylene, to link to the heterocycloalkyl component and to the point of attachment. The alkyl component can include any number of carbons, such as C₀₋₆, C₁₋₂, C₁₋₃, C₁₋₄, C₁₋₅, C₁₋₆, C₂₋₃, C₂₋₄, C₂₋₅, C₂₋₆, C₃₋₄, C₃₋₅, C₃₋₆, C₄₋₅, C₄₋₆ and C₅₋₆. The heterocycloalkyl component is as defined above. Alkyl-heterocycloalkyl groups can be substituted or unsubstituted.

[0038] "Aryl" refers to an aromatic ring system having any suitable number of ring atoms and any suitable number of rings. Aryl groups can include any suitable number of ring atoms, such as 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16 ring atoms, as well as from 6 to 10, 6 to 12, or 6 to 14 ring members. Aryl groups can be monocyclic, fused to form bicyclic or tricyclic groups, or linked by a bond to form a biaryl group. Representative aryl groups include phenyl, naphthyl and biphenyl. Other aryl groups include benzyl, having a methylene linking group. Some aryl groups have from 6 to 12 ring members, such as phenyl, naphthyl or biphenyl. Other aryl groups have from 6 to 10 ring members, such as phenyl or naphthyl. Some other aryl groups have 6 ring members, such as phenyl. Aryl groups can be substituted or unsubstituted.

[0039] "Alkyl-aryl" refers to a radical having an alkyl component and an aryl component, where the alkyl component links the aryl component to the point of attachment. The alkyl component is as defined above, except that the alkyl component is at least divalent, an alkylene, to link to the aryl component and to the point of attachment. The alkyl component can include any number of carbons, such as C₀₋₆, C₁₋₂, C₁₋₃, C₁₋₄, C₁₋₅, C₁₋₆, C₂₋₃, C₂₋₄, C₂₋₅, C₂₋₆, C₃₋₄, C₃₋₅, C₃₋₆, C₄₋₅, C₄₋₆ and C₅₋₆. The aryl component is as defined above. Examples

of alkyl-aryl groups include, but are not limited to, benzyl and ethyl-benzene. Alkyl-aryl groups can be substituted or unsubstituted.

[0040] “Heteroaryl” refers to a monocyclic or fused bicyclic or tricyclic aromatic ring assembly containing 5 to 16 ring atoms, where from 1 to 5 of the ring atoms are a heteroatom such as N, O or S. The heteroatoms can also be oxidized, such as, but not limited to, -N(O)-, -S(O)- and -S(O)₂-. Heteroaryl groups can include any number of ring atoms, such as, 5 to 6, 3 to 8, 4 to 8, 5 to 8, 6 to 8, 3 to 9, 3 to 10, 3 to 11, or 3 to 12 ring members. Any suitable number of heteroatoms can be included in the heteroaryl groups, such as 1, 2, 3, 4, or 5, or 1 to 2, 1 to 3, 1 to 4, 1 to 5, 2 to 3, 2 to 4, 2 to 5, 3 to 4, or 3 to 5. Heteroaryl groups can have from 5 to 8 ring members and from 1 to 4 heteroatoms, or from 5 to 8 ring members and from 1 to 3 heteroatoms, or from 5 to 6 ring members and from 1 to 4 heteroatoms, or from 5 to 6 ring members and from 1 to 3 heteroatoms. The heteroaryl group can include groups such as pyrrole, pyridine, imidazole, pyrazole, triazole, tetrazole, pyrazine, pyrimidine, pyridazine, triazine (1,2,3-, 1,2,4- and 1,3,5-isomers), thiophene, furan, thiazole, isothiazole, oxazole, and isoxazole. The heteroaryl groups can also be fused to aromatic ring systems, such as a phenyl ring, to form members including, but not limited to, benzopyrroles such as indole and isoindole, benzopyridines such as quinoline and isoquinoline, benzopyrazine (quinoxaline), benzopyrimidine (quinazoline), benzopyridazines such as phthalazine and cinnoline, benzothiophene, and benzofuran. Other heteroaryl groups include heteroaryl rings linked by a bond, such as bipyridine. Heteroaryl groups can be substituted or unsubstituted.

[0041] The heteroaryl groups can be linked via any position on the ring. For example, pyrrole includes 1-, 2- and 3-pyrrole, pyridine includes 2-, 3- and 4-pyridine, imidazole includes 1-, 2-, 4- and 5-imidazole, pyrazole includes 1-, 3-, 4- and 5-pyrazole, triazole includes 1-, 4- and 5-triazole, tetrazole includes 1- and 5-tetrazole, pyrimidine includes 2-, 4-, 5- and 6- pyrimidine, pyridazine includes 3- and 4-pyridazine, 1,2,3-triazine includes 4- and 5-triazine, 1,2,4-triazine includes 3-, 5- and 6-triazine, 1,3,5-triazine includes 2-triazine, thiophene includes 2- and 3-thiophene, furan includes 2- and 3-furan, thiazole includes 2-, 4- and 5-thiazole, isothiazole includes 3-, 4- and 5-isothiazole, oxazole includes 2-, 4- and 5-oxazole, isoxazole includes 3-, 4- and 5-isoxazole, indole includes 1-, 2- and 3-indole, isoindole includes 1- and 2-isoindole, quinoline includes 2-, 3- and 4-quinoline, isoquinoline includes 1-, 3- and 4-isoquinoline, quinazoline includes 2- and 4-quinazoline, cinnoline includes 3- and 4-cinnoline, benzothiophene includes 2- and 3-benzothiophene, and benzofuran includes 2- and 3-benzofuran.

- [0042] Some heteroaryl groups include those having from 5 to 10 ring members and from 1 to 3 ring atoms including N, O or S, such as pyrrole, pyridine, imidazole, pyrazole, triazole, pyrazine, pyrimidine, pyridazine, triazine (1,2,3-, 1,2,4- and 1,3,5-isomers), thiophene, furan, thiazole, isothiazole, oxazole, isoxazole, indole, isoindole, quinoline, isoquinoline, quinoxaline, quinazoline, phthalazine, cinnoline, benzothiophene, and benzofuran. Other heteroaryl groups include those having from 5 to 8 ring members and from 1 to 3 heteroatoms, such as pyrrole, pyridine, imidazole, pyrazole, triazole, pyrazine, pyrimidine, pyridazine, triazine (1,2,3-, 1,2,4- and 1,3,5-isomers), thiophene, furan, thiazole, isothiazole, oxazole, and isoxazole. Some other heteroaryl groups include those having from 9 to 12 ring members and from 1 to 3 heteroatoms, such as indole, isoindole, quinoline, isoquinoline, quinoxaline, quinazoline, phthalazine, cinnoline, benzothiophene, benzofuran and bipyridine. Still other heteroaryl groups include those having from 5 to 6 ring members and from 1 to 2 ring atoms including N, O or S, such as pyrrole, pyridine, imidazole, pyrazole, pyrazine, pyrimidine, pyridazine, thiophene, furan, thiazole, isothiazole, oxazole, and isoxazole.
- 15 [0043] “Alkyl-heteroaryl” refers to a radical having an alkyl component and a heteroaryl component, where the alkyl component links the heteroaryl component to the point of attachment. The alkyl component is as defined above, except that the alkyl component is at least divalent, an alkylene, to link to the heteroaryl component and to the point of attachment. The alkyl component can include any number of carbons, such as C₀₋₆, C₁₋₂, C₁₋₃, C₁₋₄, C₁₋₅, C₁₋₆, C₂₋₃, C₂₋₄, C₂₋₅, C₂₋₆, C₃₋₄, C₃₋₅, C₃₋₆, C₄₋₅, C₄₋₆ and C₅₋₆. The heteroaryl component is as defined within. Alkyl-heteroaryl groups can be substituted or unsubstituted.
- 20 [0044] “Pharmaceutically acceptable excipient” refers to a substance that aids the administration of an active agent to and absorption by a subject. Pharmaceutical excipients useful in the present invention include, but are not limited to, binders, fillers, disintegrants, lubricants, surfactants, coatings, sweeteners, flavors and colors. One of skill in the art will recognize that other pharmaceutical excipients are useful in the present invention.
- 25 [0045] “Treat”, “treating” and “treatment” refer to any indicia of success in the treatment or amelioration of an injury, pathology or condition, including any objective or subjective parameter such as abatement; remission; diminishing of symptoms or making the injury, pathology or condition more tolerable to the patient; slowing in the rate of degeneration or decline; making the final point of degeneration less debilitating; improving a patient's physical or mental well-being. The treatment or amelioration of symptoms can be based on
- 30

objective or subjective parameters; including the results of a physical examination, neuropsychiatric exams, and/or a psychiatric evaluation.

- [0046]** “Administering” refers to oral administration, administration as a suppository, topical contact, parenteral, intravenous, intraperitoneal, intramuscular, intralesional, intranasal or subcutaneous administration, intrathecal administration, or the implantation of a slow-release device e.g., a mini-osmotic pump, to the subject.

- [0047]** “Therapeutically effective amount” refers to a dose that produces therapeutic effects for which it is administered. The exact dose will depend on the purpose of the treatment, and will be ascertainable by one skilled in the art using known techniques (*see, e.g.,* Lieberman, *Pharmaceutical Dosage Forms* (vols. 1-3, 1992); Lloyd, *The Art, Science and Technology of Pharmaceutical Compounding* (1999); Pickar, *Dosage Calculations* (1999); and *Remington: The Science and Practice of Pharmacy*, 20th Edition, 2003, Gennaro, Ed., Lippincott, Williams & Wilkins). In sensitized cells, the therapeutically effective dose can often be lower than the conventional therapeutically effective dose for non-sensitized cells.

- [0048]** “Glucocorticoid receptor” (“GR”) refers to one of the family of intracellular receptors which specifically bind to cortisol and/or cortisol analogs such as dexamethasone (*See, e.g.,* Turner & Muller, *J. Mol. Endocrinol.* October 1, 2005 35 283-292). The glucocorticoid receptor is also referred to as the cortisol receptor. The term includes isoforms of GR, recombinant GR and mutated GR.

- [0049]** A cortisol receptor is a glucocorticoid receptor (GR), specifically the type II GR, which specifically binds cortisol and/or cortisol analogs such as dexamethasone (*See, e.g.,* Turner & Muller, *J. Mol. Endocrinol.* October 1, 2005 35 283-292).

[0050] “Mineralocorticoid receptor” (MR) refers to a type I glucocorticoid receptor (GR I), which is activated by aldosterone in humans.

- [0051]** “Glucocorticoid receptor modulator” (GRM) refers to any compound which modulates any biological response associated with the binding of a glucocorticoid receptor to an agonist. As used herein, with respect to a GRM, the glucocorticoid receptor may be GR. For example, a GRM that acts as an agonist, such as dexamethasone, increases the activity of tyrosine aminotransferase (TAT) in HepG2 cells (a human liver hepatocellular carcinoma cell line; ECACC, UK). A GRM that acts as an antagonist, such as mifepristone, inhibits the agonist-induced increase in the activity of tyrosine aminotransferase (TAT) in HepG2 cells.

TAT activity can be measured as outlined in the literature by A. Ali *et al.*, J. Med. Chem., 2004, 47, 2441-2452.

[0052] “Glucocorticoid receptor antagonist” (GRA) refers to any compound which inhibits any biological response associated with the binding of a glucocorticoid receptor to an agonist.

5 As used herein, with respect to a GRA, the glucocorticoid receptor may be GR. Accordingly, GR antagonists can be identified by measuring the ability of a compound to inhibit the effect of dexamethasone. TAT activity can be measured as outlined in the literature by A. Ali *et al.*, J. Med. Chem., 2004, 47, 2441-2452. An inhibitor is a compound with an IC₅₀ (half maximal inhibition concentration) of less than 10 micromolar. See Example 1 of U.S. Patent
10 8,685,973, the entire contents of which is hereby incorporated by reference in its entirety.

[0053] “Modulate” and “modulating” are used in accordance with its plain ordinary meaning and refer to the act of changing or varying one or more properties. “Modulation” refers to the process of changing or varying one or more properties. For example, as applied to the effects of a modulator on a target protein, to modulate means to change by increasing
15 or decreasing a property or function of the target molecule or the amount of the target molecule.

[0054] “Modulator” refers to a composition that increases or decreases the level of a target molecule or the function of a target molecule or the physical state of the target of the molecule.

20 **[0055]** “Antagonize” and “antagonizing” refer to inhibiting the binding of an agonist at a receptor molecule or to inhibiting the signal produced by a receptor-agonist. A receptor antagonist inhibits or dampens agonist-mediated responses, such as gene expression.

[0056] “Antagonist” refers to a substance capable of detectably lowering expression or activity of a given gene or protein. The antagonist can inhibit expression or activity 10%,
25 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100% or less in comparison to a control in the absence of the antagonist. In some embodiments, the inhibition is 1.5-fold, 2-fold, 3-fold, 4-fold, 5-fold, 10-fold, or more than the expression or activity in the absence of the antagonist.

[0057] “Inhibition”, “inhibits” and “inhibitor” refer to a compound that prohibits or a method of prohibiting, a specific action or function.

30 **[0058]** “Disorder” or “condition” refers to a state of being or health status of a patient or subject capable of being treated with the glucocorticoid receptor modulators of the present

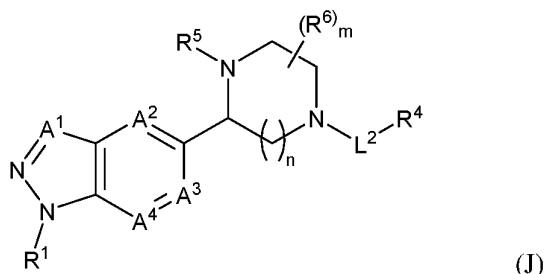
invention. In some embodiments, examples of disorders or conditions include, but are not limited to, Alzheimer's disease, amyotrophic lateral sclerosis (ALS), antipsychotic induced weight gain, cancer, Cushing Disease, Cushing's Syndrome, major psychotic depression, Nonalcoholic steatohepatitis, and obesity. In some embodiments, the disorders or conditions include nonalcoholic liver disease and/or nonalcoholic steatohepatitis. In some embodiments, the disorders or conditions include cancer.

[0059] "Medicament" refers to a composition or substance used for treatment of a disease or condition.

[0060] "Subject" refers to a living organism suffering from or prone to a disease or condition that can be treated by administration of a pharmaceutical composition as provided herein. Non-limiting examples include humans, other mammals, bovines, rats, mice, dogs, monkeys, goat, sheep, cows, deer, horse, and other non-mammalian animals. In some embodiments, the patient is human.

III. COMPOUNDS

[0061] The present invention provides compounds of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic, and Id, or a pharmaceutically acceptable salt thereof. In some embodiments, the present invention provides a compound of Formula J:



or a pharmaceutically acceptable salt thereof, wherein

R¹ is heterocycloalkyl having 3 to 12 ring members and 1 to 4 heteroatoms each N, O or S, phenyl or heteroaryl having 5 to 10 ring members and 1 to 5 heteroatoms each N, O or S, each independently substituted with 0 to 5 R^{1a} groups; each R^{1a} is independently C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkoxyalkyl, C₁₋₆ hydroxyalkyl, halogen, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, -OH, oxo, -CN, -C(O)N(R^{1b})(R^{1c}), C₃₋₁₀ cycloalkyl, or heterocycloalkyl having 3 to 12 ring members and 1 to 4 heteroatoms each N, O or S;

each R^{1b} and R^{1c} is independently hydrogen, C₁₋₆ alkyl or a 3 to 8 membered
 heterocycloalkyl having 1 to 3 heteroatoms each independently N, O or S;
 A¹, A², A³ and A⁴ are each independently =CR²- or =N-;
 each R² is independently hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₂₋₆ alkoxyalkyl, halogen,
 5 C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, hydroxy or -CN;
 L² is -C(O)-, -C(O)O-, -C(O)N(R³)-, -S(O)₂- or -S(O)₂N(R³)-;
 R³ is hydrogen, or C₁₋₆ alkyl;
 R⁴ is C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₂₋₆ alkoxyalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆
 haloalkyl, C₃₋₈ cycloalkyl, C₁₋₆ alkyl-C₃₋₈ cycloalkyl, heterocycloalkyl, C₁₋₆
 10 alkyl-heterocycloalkyl, C₆₋₁₂ aryl, C₁₋₆ alkyl-C₆₋₁₂ aryl, -O-C₆₋₁₂ aryl,
 heteroaryl, or C₁₋₆ alkyl-heteroaryl,
 wherein each heterocycloalkyl independently has 3 to 12 ring members and 1
 to 3 heteroatoms each independently N, O or S,
 wherein each heteroaryl independently has 5 to 10 ring members and 1 to 4
 15 heteroatoms each independently N, O or S, and
 wherein the cycloalkyl, heterocycloalkyl, aryl and heteroaryl are each
 independently substituted with 0 to 5 R^{4a} groups;
 alternatively, R³ and R⁴ are combined with the atoms to which they are attached to
 form a heterocycloalkyl having 3 to 12 ring members and 1 to 3 additional
 20 heteroatoms each independently N, O or S, wherein the heterocycloalkyl is
 substituted with 0, 1 or 2 C₁₋₆ alkyl groups;
 each R^{4a} is independently C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ alkoxy, C₂₋₆
 alkoxyalkyl, C₁₋₆ hydroxyalkyl, halogen, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, -CN,
 -OH, oxo, -C(O)R^{4b}, -C(O)OR^{4b}, -OC(O)R^{4b}, -OC(O)OR^{4b}, -C(O)N(R^{4b})(R^{4c}),
 25 -N(R^{4b})C(O)R^{4c}, -OC(O)N(R^{4b})(R^{4c}), -N(R^{4b})C(O)OR^{4c}, -S(O)₂R^{4b}, -
 S(O)₂N(R^{4b})(R^{4c}), -N(R^{4b})S(O)₂R^{4c}, C₃₋₈ cycloalkyl, C₁₋₆ alkyl-C₃₋₈ cycloalkyl,
 heterocycloalkyl, C₁₋₆ alkyl-heterocycloalkyl, C₆₋₁₂ aryl, C₁₋₆ alkyl-C₆₋₁₂ aryl, -
 O-C₆₋₁₂ aryl, heteroaryl, or C₁₋₆ alkyl-heteroaryl, wherein each
 heterocycloalkyl independently has 3 to 12 ring members and 1 to 3
 30 heteroatoms each independently N, O or S, wherein each heteroaryl
 independently has 5 to 10 ring members and 1 to 4 heteroatoms each
 independently N, O or S, and wherein each cycloalkyl, heterocycloalkyl, aryl
 and heteroaryl is substituted with 0, 1 or 2 C₁₋₆ alkyl groups;
 each R^{4b} and R^{4c} is hydrogen or C₁₋₆ alkyl;

R^5 is C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{2-6} alkoxyalkyl, C_{1-6} hydroxyalkyl, C_{1-6} haloalkyl, C_{1-6} alkyl-OR^{5a}, -C(O)R^{5a}, C_{1-6} alkyl-C(O)R^{5a}, -C(O)OR^{5a}, -C(O)N(R^{5a})(R^{5b}), -S(O)₂R^{5a}, -S(O)₂N(R^{5a})(R^{5b}), C_{3-8} cycloalkyl, C_{1-6} alkyl- C_{3-8} cycloalkyl, heterocycloalkyl, C_{1-6} alkyl-heterocycloalkyl, C_{6-12} aryl, C_{1-6} alkyl- C_{6-12} aryl, heteroaryl, or C_{1-6} alkyl-heteroaryl,

5 wherein each heterocycloalkyl independently has 3 to 12 ring members and 1 to 3 heteroatoms each independently N, O or S, wherein each heteroaryl independently has 5 to 10 ring members and 1 to 4 heteroatoms each independently N, O or S, and

10 wherein each cycloalkyl, heterocycloalkyl, aryl and heteroaryl is independently substituted with 0 to 4 R^{5c} groups;

each R^{5a} and R^{5b} is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{2-6} alkoxyalkyl, hydroxy, C_{1-6} hydroxyalkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{3-8} cycloalkyl, C_{1-6} alkyl- C_{3-8} cycloalkyl, heterocycloalkyl, C_{1-6} alkyl-

15 heterocycloalkyl, C_{6-12} aryl, C_{1-6} alkyl- C_{6-12} aryl, heteroaryl, or C_{1-6} alkyl-heteroaryl, wherein each heterocycloalkyl independently has 3 to 12 ring members and 1 to 3 heteroatoms each independently N, O or S, wherein each heteroaryl independently has 5 to 10 ring members and 1 to 4 heteroatoms each independently N, O or S, and wherein each cycloalkyl, heterocycloalkyl,

20 aryl and heteroaryl is substituted with 0 to 4 R^{5d} groups;

alternatively, R^{5a} and R^{5b} are combined with the atoms to which they are attached to form a heterocycloalkyl having 3 to 12 ring members and 1 to 3 additional heteroatoms each independently N, O or S, wherein the heterocycloalkyl is substituted with 0, 1 or 2 C_{1-6} alkyl groups;

25 each R^{5c} is independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, C_{2-6} alkoxyalkyl, C_{1-6} hydroxyalkyl, halogen, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, -CN, oxo, -OH, -C(O)R^{5c1}, -C(O)OR^{5c1}, -OC(O)R^{5c1}, -OC(O)OR^{5c1}, -C(O)N(R^{5c1})(R^{5c2}), -N(R^{5c1})C(O)R^{5c2}, -OC(O)N(R^{5c1})(R^{5c2}), -N(R^{5c1})C(O)OR^{5c2}, -S(O)₂R^{5c1}, -S(O)₂N(R^{5c1})(R^{5c2}), -N(R^{5c1})S(O)₂R^{5c2}, C_{3-8}

30 cycloalkyl, C_{1-6} alkyl- C_{3-8} cycloalkyl, heterocycloalkyl, C_{1-6} alkyl-heterocycloalkyl, C_{6-12} aryl, C_{1-6} alkyl- C_{6-12} aryl, heteroaryl, or C_{1-6} alkyl-heteroaryl, wherein each heterocycloalkyl independently has 3 to 12 ring members and 1 to 3 heteroatoms each independently N, O or S, wherein each heteroaryl independently has 5 to 10 ring members and 1 to 4 heteroatoms

each independently N, O or S, and wherein each heterocycloalkyl and heteroaryl is substituted with 0, 1 or 2 C₁₋₆ alkyl groups;

each R^{5c1} and R^{5c2} is independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₂₋₆ alkoxyalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ haloalkyl, C₃₋₈ cycloalkyl, C₁₋₆ alkyl-C₃₋₈ cycloalkyl, heterocycloalkyl, C₁₋₆ alkyl-heterocycloalkyl, C₆₋₁₂ aryl, C₁₋₆ alkyl-C₆₋₁₂ aryl, heteroaryl, or C₁₋₆ alkyl-heteroaryl, wherein each heterocycloalkyl independently has 3 to 12 ring members and 1 to 3 heteroatoms each independently N, O or S, wherein each heteroaryl independently has 5 to 10 ring members and 1 to 4 heteroatoms each independently N, O or S, and wherein each heterocycloalkyl and heteroaryl is substituted with 0, 1 or 2 C₁₋₆ alkyl groups;

alternatively, R^{5c1} and R^{5c2} are combined with the atoms to which they are attached to form a heterocycloalkyl having 3 to 12 ring members and 1 to 3 heteroatoms each independently N, O or S, wherein the heterocycloalkyl is substituted with 0, 1 or 2 C₁₋₆ alkyl groups;

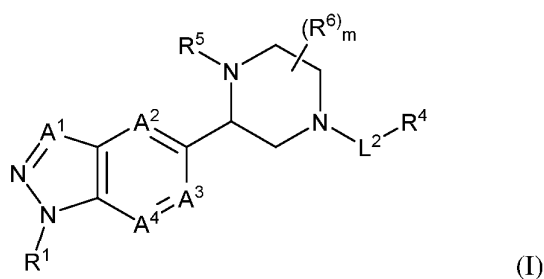
each R^{5d} is independently C₁₋₆ alkyl or halogen;

each R⁶ is independently hydrogen, C₁₋₆ alkyl, halogen, C₁₋₆ haloalkyl, or oxo;

subscript m is 0, 1, 2, 3, 4, or 5; and

subscript n is 1 or 2.

[0062] In some embodiments, the present invention provides a compound of Formula I:



or a pharmaceutically acceptable salt thereof, wherein

R¹ is heterocycloalkyl having 3 to 12 ring members and 1 to 4 heteroatoms each N, O or S, phenyl or heteroaryl having 5 to 10 ring members and 1 to 5 heteroatoms each N, O or S, each independently substituted with 0 to 5 R^{1a} groups;

each R^{1a} is independently C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkoxyalkyl, C₁₋₆ hydroxyalkyl, halogen, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, -OH, oxo, -CN, -C(O)N(R^{1b})(R^{1c}),

C₃₋₁₀ cycloalkyl, or heterocycloalkyl having 3 to 12 ring members and 1 to 4 heteroatoms each N, O or S;
 each R^{1b} and R^{1c} is independently hydrogen, C₁₋₆ alkyl or a 3 to 8 membered heterocycloalkyl having 1 to 3 heteroatoms each independently N, O or S;
 5 A¹, A², A³ and A⁴ are each independently =CR²- or =N-;
 each R² is independently hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₂₋₆ alkoxyalkyl, halogen, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, hydroxy or -CN;
 L² is -C(O)-, -C(O)O-, -C(O)N(R³)-, -S(O)₂- or -S(O)₂N(R³)-;
 R³ is hydrogen, or C₁₋₆ alkyl;
 10 R⁴ is C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₂₋₆ alkoxyalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ haloalkyl, C₃₋₈ cycloalkyl, C₁₋₆ alkyl-C₃₋₈ cycloalkyl, heterocycloalkyl, C₁₋₆ alkyl-heterocycloalkyl, C₆₋₁₂ aryl, C₁₋₆ alkyl-C₆₋₁₂ aryl, -O-C₆₋₁₂ aryl, heteroaryl, or C₁₋₆ alkyl-heteroaryl,
 wherein each heterocycloalkyl independently has 3 to 12 ring members and 1 to 3 heteroatoms each independently N, O or S,
 15 wherein each heteroaryl independently has 5 to 10 ring members and 1 to 4 heteroatoms each independently N, O or S, and
 wherein the cycloalkyl, heterocycloalkyl, aryl and heteroaryl are each independently substituted with 0 to 5 R^{4a} groups;
 20 alternatively, R³ and R⁴ are combined with the atoms to which they are attached to form a heterocycloalkyl having 3 to 12 ring members and 1 to 3 additional heteroatoms each independently N, O or S, wherein the heterocycloalkyl is substituted with 0, 1 or 2 C₁₋₆ alkyl groups;
 each R^{4a} is independently C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ alkoxy, C₂₋₆ alkoxyalkyl, C₁₋₆ hydroxyalkyl, halogen, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, -CN, -OH, oxo, -C(O)R^{4b}, -C(O)OR^{4b}, -OC(O)R^{4b}, -OC(O)OR^{4b}, -C(O)N(R^{4b})(R^{4c}), -N(R^{4b})C(O)R^{4c}, -OC(O)N(R^{4b})(R^{4c}), -N(R^{4b})C(O)OR^{4c}, -S(O)₂R^{4b}, -S(O)₂N(R^{4b})(R^{4c}), -N(R^{4b})S(O)₂R^{4c}, C₃₋₈ cycloalkyl, C₁₋₆ alkyl-C₃₋₈ cycloalkyl, heterocycloalkyl, C₁₋₆ alkyl-heterocycloalkyl, C₆₋₁₂ aryl, C₁₋₆ alkyl-C₆₋₁₂ aryl, -O-C₆₋₁₂ aryl, heteroaryl, or C₁₋₆ alkyl-heteroaryl, wherein each
 25 heterocycloalkyl independently has 3 to 12 ring members and 1 to 3 heteroatoms each independently N, O or S, wherein each heteroaryl independently has 5 to 10 ring members and 1 to 4 heteroatoms each
 30

independently N, O or S, and wherein each cycloalkyl, heterocycloalkyl, aryl and heteroaryl is substituted with 0, 1 or 2 C₁₋₆ alkyl groups;

each R^{4b} and R^{4c} is hydrogen or C₁₋₆ alkyl;

R⁵ is C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₂₋₆ alkoxyalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ haloalkyl, C₁₋₆ alkyl-OR^{5a}, -C(O)R^{5a}, C₁₋₆ alkyl-C(O)R^{5a}, -C(O)OR^{5a}, -C(O)N(R^{5a})(R^{5b}), -S(O)₂R^{5a}, -S(O)₂N(R^{5a})(R^{5b}), C₃₋₈ cycloalkyl, C₁₋₆ alkyl-C₃₋₈ cycloalkyl, heterocycloalkyl, C₁₋₆ alkyl-heterocycloalkyl, C₆₋₁₂ aryl, C₁₋₆ alkyl-C₆₋₁₂ aryl, heteroaryl, or C₁₋₆ alkyl-heteroaryl, wherein each heterocycloalkyl independently has 3 to 12 ring members and 1 to 3 heteroatoms each independently N, O or S, wherein each heteroaryl independently has 5 to 10 ring members and 1 to 4 heteroatoms each independently N, O or S, and wherein each cycloalkyl, heterocycloalkyl, aryl and heteroaryl is independently substituted with 0 to 4 R^{5c} groups;

each R^{5a} and R^{5b} is independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₂₋₆ alkoxyalkyl, hydroxy, C₁₋₆ hydroxyalkyl, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, C₃₋₈ cycloalkyl, C₁₋₆ alkyl-C₃₋₈ cycloalkyl, heterocycloalkyl, C₁₋₆ alkyl-heterocycloalkyl, C₆₋₁₂ aryl, C₁₋₆ alkyl-C₆₋₁₂ aryl, heteroaryl, or C₁₋₆ alkyl-heteroaryl, wherein each heterocycloalkyl independently has 3 to 12 ring members and 1 to 3 heteroatoms each independently N, O or S, wherein each heteroaryl independently has 5 to 10 ring members and 1 to 4 heteroatoms each independently N, O or S, and wherein each cycloalkyl, heterocycloalkyl, aryl and heteroaryl is substituted with 0 to 4 R^{5d} groups;

alternatively, R^{5a} and R^{5b} are combined with the atoms to which they are attached to form a heterocycloalkyl having 3 to 12 ring members and 1 to 3 additional heteroatoms each independently N, O or S, wherein the heterocycloalkyl is substituted with 0, 1 or 2 C₁₋₆ alkyl groups;

each R^{5c} is independently C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ alkoxy, C₂₋₆ alkoxyalkyl, C₁₋₆ hydroxyalkyl, halogen, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, -CN, oxo, -OH, -C(O)R^{5c1}, -C(O)OR^{5c1}, -OC(O)R^{5c1}, -OC(O)OR^{5c1}, -C(O)N(R^{5c1})(R^{5c2}), -N(R^{5c1})C(O)R^{5c2}, -OC(O)N(R^{5c1})(R^{5c2}), -N(R^{5c1})C(O)OR^{5c2}, -S(O)₂R^{5c1}, -S(O)₂N(R^{5c1})(R^{5c2}), -N(R^{5c1})S(O)₂R^{5c2}, C₃₋₈ cycloalkyl, C₁₋₆ alkyl-C₃₋₈ cycloalkyl, heterocycloalkyl, C₁₋₆ alkyl-heterocycloalkyl, C₆₋₁₂ aryl, C₁₋₆ alkyl-C₆₋₁₂ aryl, heteroaryl, or C₁₋₆ alkyl-

heteroaryl, wherein each heterocycloalkyl independently has 3 to 12 ring members and 1 to 3 heteroatoms each independently N, O or S, wherein each heteroaryl independently has 5 to 10 ring members and 1 to 4 heteroatoms each independently N, O or S, and wherein each heterocycloalkyl and heteroaryl is substituted with 0, 1 or 2 C₁₋₆ alkyl groups;

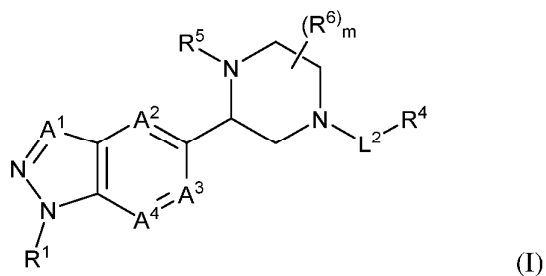
each R^{5c1} and R^{5c2} is independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₂₋₆ alkoxyalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ haloalkyl, C₃₋₈ cycloalkyl, C₁₋₆ alkyl-C₃₋₈ cycloalkyl, heterocycloalkyl, C₁₋₆ alkyl-heterocycloalkyl, C₆₋₁₂ aryl, C₁₋₆ alkyl-C₆₋₁₂ aryl, heteroaryl, or C₁₋₆ alkyl-heteroaryl, wherein each heterocycloalkyl independently has 3 to 12 ring members and 1 to 3 heteroatoms each independently N, O or S, wherein each heteroaryl independently has 5 to 10 ring members and 1 to 4 heteroatoms each independently N, O or S, and wherein each heterocycloalkyl and heteroaryl is substituted with 0, 1 or 2 C₁₋₆ alkyl groups;

alternatively, R^{5c1} and R^{5c2} are combined with the atoms to which they are attached to form a heterocycloalkyl having 3 to 12 ring members and 1 to 3 heteroatoms each independently N, O or S, wherein the heterocycloalkyl is substituted with 0, 1 or 2 C₁₋₆ alkyl groups;

each R^{5d} is independently C₁₋₆ alkyl or halogen;

each R⁶ is independently hydrogen, C₁₋₆ alkyl, halogen, C₁₋₆ haloalkyl, or oxo; and subscript m is 0, 1, 2, 3, 4, or 5.

[0063] In some embodiments, the present invention provides a compound of Formula I:



or a pharmaceutically acceptable salt thereof, wherein R¹ is heterocycloalkyl having 3 to 12 ring members and 1 to 4 heteroatoms each N, O or S, phenyl or heteroaryl having 5 to 10 ring members and 1 to 5 heteroatoms each N, O or S, each independently substituted with 0 to 5 R^{1a} groups;

each R^{1a} is independently C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkoxyalkyl, C₁₋₆ hydroxyalkyl, halogen, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, -OH, oxo, -CN, -C(O)N(R^{1b})(R^{1c}), C₃₋₁₀ cycloalkyl, or heterocycloalkyl having 3 to 12 ring members and 1 to 4 heteroatoms each N, O or S;

5 each R^{1b} and R^{1c} is independently hydrogen, C₁₋₆ alkyl or a 3 to 8 membered heterocycloalkyl having 1 to 3 heteroatoms each independently N, O or S;

A¹, A², A³ and A⁴ are each independently =CR²- or =N-;

each R² is independently hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₂₋₆ alkoxyalkyl, halogen, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, hydroxy or -CN;

10 L² is -C(O)-, -C(O)O-, -C(O)N(R³)-, -S(O)₂- or -S(O)₂N(R³)-;

R³ is hydrogen, or C₁₋₆ alkyl;

R⁴ is C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₂₋₆ alkoxyalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ haloalkyl, C₃₋₈ cycloalkyl, C₁₋₆ alkyl-C₃₋₈ cycloalkyl, heterocycloalkyl, C₁₋₆ alkyl-heterocycloalkyl, C₆₋₁₂ aryl, C₁₋₆ alkyl-C₆₋₁₂ aryl, -O-C₆₋₁₂ aryl,

15 heteroaryl, or C₁₋₆ alkyl-heteroaryl, wherein each heterocycloalkyl independently has 3 to 12 ring members and 1 to 3 heteroatoms each independently N, O or S, wherein each heteroaryl independently has 5 to 10 ring members and 1 to 4 heteroatoms each independently N, O or S, and wherein the cycloalkyl, heterocycloalkyl, aryl and heteroaryl are each

20 independently substituted with 0 to 5 R^{4a} groups;

alternatively, R³ and R⁴ are combined with the atoms to which they are attached to form a heterocycloalkyl having 3 to 12 ring members and 1 to 3 additional heteroatoms each independently N, O or S, wherein the heterocycloalkyl is substituted with 0, 1 or 2 C₁₋₆ alkyl groups;

25 each R^{4a} is independently C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ alkoxy, C₂₋₆ alkoxyalkyl, C₁₋₆ hydroxyalkyl, halogen, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, -CN, -OH, oxo, -C(O)R^{4b}, -C(O)OR^{4b}, -OC(O)R^{4b}, -OC(O)OR^{4b}, -C(O)N(R^{4b})(R^{4c}), -N(R^{4b})C(O)R^{4c}, -OC(O)N(R^{4b})(R^{4c}), -N(R^{4b})C(O)OR^{4c}, -S(O)₂R^{4b}, -S(O)₂N(R^{4b})(R^{4c}), -N(R^{4b})S(O)₂R^{4c}, C₃₋₈ cycloalkyl, C₁₋₆ alkyl-C₃₋₈ cycloalkyl, heterocycloalkyl, C₁₋₆ alkyl-heterocycloalkyl, C₆₋₁₂ aryl, C₁₋₆ alkyl-C₆₋₁₂ aryl, -O-C₆₋₁₂ aryl, heteroaryl, or C₁₋₆ alkyl-heteroaryl, wherein each

30 heterocycloalkyl independently has 3 to 12 ring members and 1 to 3 heteroatoms each independently N, O or S, wherein each heteroaryl independently has 5 to 10 ring members and 1 to 4 heteroatoms each

independently N, O or S, and wherein each cycloalkyl, heterocycloalkyl, aryl and heteroaryl is substituted with 0, 1 or 2 C₁₋₆ alkyl groups;

each R^{4b} and R^{4c} is hydrogen or C₁₋₆ alkyl;

R⁵ is C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₂₋₆ alkoxyalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ haloalkyl, C₁₋₆ alkyl-OR^{5a}, -C(O)R^{5a}, -C(O)OR^{5a}, -C(O)N(R^{5a})(R^{5b}), -S(O)₂R^{5a}, -S(O)₂N(R^{5a})(R^{5b}), C₃₋₈ cycloalkyl, C₁₋₆ alkyl-C₃₋₈ cycloalkyl, heterocycloalkyl, C₁₋₆ alkyl-heterocycloalkyl, C₆₋₁₂ aryl, C₁₋₆ alkyl-C₆₋₁₂ aryl, heteroaryl, or C₁₋₆ alkyl-heteroaryl, wherein each heterocycloalkyl independently has 3 to 12 ring members and 1 to 3 heteroatoms each independently N, O or S, wherein each heteroaryl independently has 5 to 10 ring members and 1 to 4 heteroatoms each independently N, O or S, and wherein each cycloalkyl, heterocycloalkyl, aryl and heteroaryl is independently substituted with 0 to 4 R^{5c} groups;

each R^{5a} and R^{5b} is independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₂₋₆ alkoxyalkyl, hydroxy, C₁₋₆ hydroxyalkyl, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, C₃₋₈ cycloalkyl, C₁₋₆ alkyl-C₃₋₈ cycloalkyl, heterocycloalkyl, C₁₋₆ alkyl-heterocycloalkyl, C₆₋₁₂ aryl, C₁₋₆ alkyl-C₆₋₁₂ aryl, heteroaryl, or C₁₋₆ alkyl-heteroaryl, wherein each heterocycloalkyl independently has 3 to 12 ring members and 1 to 3 heteroatoms each independently N, O or S, wherein each heteroaryl independently has 5 to 10 ring members and 1 to 4 heteroatoms each independently N, O or S, and wherein each cycloalkyl, heterocycloalkyl, aryl and heteroaryl is substituted with 0 to 4 R^{5d} groups;

alternatively, R^{5a} and R^{5b} are combined with the atoms to which they are attached to form a heterocycloalkyl having 3 to 12 ring members and 1 to 3 additional heteroatoms each independently N, O or S, wherein the heterocycloalkyl is substituted with 0, 1 or 2 C₁₋₆ alkyl groups;

each R^{5c} is independently C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ alkoxy, C₂₋₆ alkoxyalkyl, C₁₋₆ hydroxyalkyl, halogen, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, -CN, oxo, -OH, -C(O)R^{5c1}, -C(O)OR^{5c1}, -OC(O)R^{5c1}, -OC(O)OR^{5c1}, -C(O)N(R^{5c1})(R^{5c2}), -N(R^{5c1})C(O)R^{5c2}, -OC(O)N(R^{5c1})(R^{5c2}), -N(R^{5c1})C(O)OR^{5c2}, -S(O)₂R^{5c1}, -S(O)₂N(R^{5c1})(R^{5c2}), -N(R^{5c1})S(O)₂R^{5c2}, C₃₋₈ cycloalkyl, C₁₋₆ alkyl-C₃₋₈ cycloalkyl, heterocycloalkyl, C₁₋₆ alkyl-heterocycloalkyl, C₆₋₁₂ aryl, C₁₋₆ alkyl-C₆₋₁₂ aryl, heteroaryl, or C₁₋₆ alkyl-heteroaryl, wherein each heterocycloalkyl independently has 3 to 12 ring

members and 1 to 3 heteroatoms each independently N, O or S, wherein each heteroaryl independently has 5 to 10 ring members and 1 to 4 heteroatoms each independently N, O or S, and wherein each heterocycloalkyl and heteroaryl is substituted with 0, 1 or 2 C₁₋₆ alkyl groups;

5 each R^{5c1} and R^{5c2} is independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₂₋₆ alkoxyalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ haloalkyl, C₃₋₈ cycloalkyl, C₁₋₆ alkyl-C₃₋₈ cycloalkyl, heterocycloalkyl, C₁₋₆ alkyl-heterocycloalkyl, C₆₋₁₂ aryl, C₁₋₆ alkyl-C₆₋₁₂ aryl, heteroaryl, or C₁₋₆ alkyl-heteroaryl, wherein each heterocycloalkyl independently has 3 to 12 ring members and 1 to 3

10 heteroatoms each independently N, O or S, wherein each heteroaryl independently has 5 to 10 ring members and 1 to 4 heteroatoms each independently N, O or S, and wherein each heterocycloalkyl and heteroaryl is substituted with 0, 1 or 2 C₁₋₆ alkyl groups;

alternatively, R^{5c1} and R^{5c2} are combined with the atoms to which they are attached to

15 form a heterocycloalkyl having 3 to 12 ring members and 1 to 3 heteroatoms each independently N, O or S, wherein the heterocycloalkyl is substituted with 0, 1 or 2 C₁₋₆ alkyl groups;

each R^{5d} is independently C₁₋₆ alkyl or halogen;

each R⁶ is independently hydrogen, C₁₋₆ alkyl, halogen, C₁₋₆ haloalkyl, or oxo; and

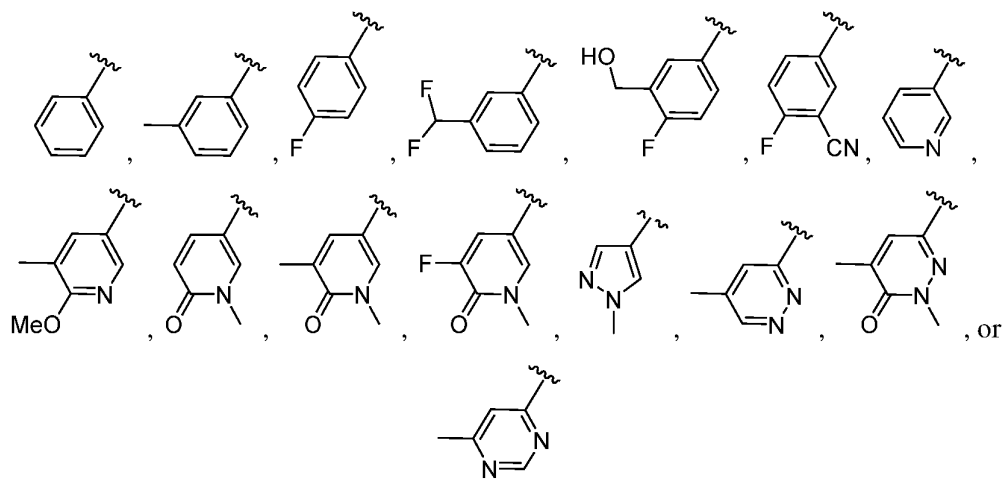
20 subscript m is 0, 1, 2, 3, 4, or 5.

[0064] In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic, or Id, or the pharmaceutically acceptable salt thereof, is the compound wherein R¹ is heterocycloalkyl having 3 to 12 ring members and 1 to 4 heteroatoms each N, O or S, phenyl or heteroaryl having 5 to 10 ring members and 1 to 5 heteroatoms each N, O or S, each independently

25 substituted with 0 to 5 R^{1a} groups; each R^{1a} is independently C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkoxyalkyl, C₁₋₆ hydroxyalkyl, halogen, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, -OH, oxo, -CN, -C(O)N(R^{1b})(R^{1c}), C₃₋₁₀ cycloalkyl, or heterocycloalkyl having 3 to 12 ring members and 1 to 4 heteroatoms each N, O or S; and each R^{1b} and R^{1c} is independently hydrogen, C₁₋₆ alkyl or a 3 to 8 membered heterocycloalkyl having 1 to 3 heteroatoms each independently N, O or S.

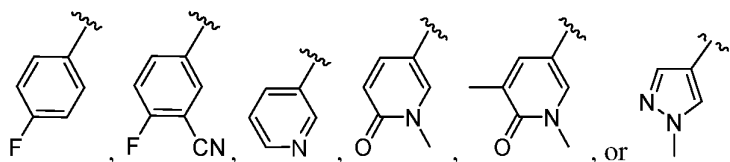
30 **[0065]** In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic, or Id, or the pharmaceutically acceptable salt thereof, is the compound wherein R¹ is phenyl or heteroaryl having 5 to 6 ring members and 1 to 3 heteroatoms each N, each independently substituted with 0 to 3 R^{1a} groups; each R^{1a} is independently C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆

hydroxyalkyl, halogen, C₁₋₆ haloalkyl, -OH, oxo, or -CN; and each R^{1b} and R^{1c} is independently hydrogen or C₁₋₆ alkyl. In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic, or Id, or the pharmaceutically acceptable salt thereof, is the compound wherein R¹ is phenyl, pyrrole, pyrazole, imidazole, pyridine, pyrazine, pyrimidine, or pyridazine, each independently substituted with 0 to 3 R^{1a} groups; and each R^{1a} is independently methyl, ethyl, n-propyl, isopropyl, -OMe, -CH₂OH, fluoro, chloro, bromo, -CHF₂, -OH, oxo, or -CN. In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic, or Id, or the pharmaceutically acceptable salt thereof, is the compound wherein R¹ is phenyl, substituted with 0 to 2 R^{1a} groups each independently methyl, -CH₂OH, fluoro, -CHF₂, or -CN, pyridyl, substituted with 0 to 3 R^{1a} groups each independently methyl, -OMe, F, -OH or oxo, pyrazole, substituted with 1 to 2 R^{1a} groups each independently methyl, pyridazine, substituted with 1 to 3 R^{1a} groups each independently methyl or oxo, or pyrazine, substituted with 1 to 2 R^{1a} groups each methyl. In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic, or Id, or the pharmaceutically acceptable salt thereof, is the compound wherein R¹ is

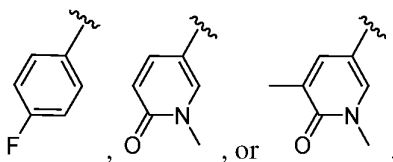


[0066] In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic, or Id, or the pharmaceutically acceptable salt thereof, is the compound wherein R¹ is phenyl or heteroaryl having 5 to 6 ring members and 1 to 3 heteroatoms each N, each independently substituted with 0 to 3 R^{1a} groups; and each R^{1a} is independently C₁₋₆ alkyl, halogen, -OH, oxo, or -CN. In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic, or Id, or the pharmaceutically acceptable salt thereof, is the compound wherein R¹ is phenyl, pyrrole, pyrazole, imidazole, pyridine, pyrazine, pyrimidine, or pyridazine, each independently substituted with 0 to 3 R^{1a} groups; and each R^{1a} is independently methyl, ethyl,

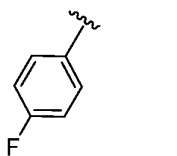
n-propyl, isopropyl, fluoro, chloro, bromo, -OH, oxo, or -CN. In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic, or Id, or the pharmaceutically acceptable salt thereof, is the compound wherein R¹ is phenyl, substituted with 1 to 2 R^{1a} groups each independently fluoro or -CN, pyridyl, substituted with 0 to 3 R^{1a} groups each independently methyl, -OH or oxo, or pyrazole, substituted with 1 to 2 R^{1a} groups each independently methyl. In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic, or Id, or the pharmaceutically acceptable salt thereof, is the compound wherein R¹ is



[0067] In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic, or Id, or the pharmaceutically acceptable salt thereof, is the compound wherein R¹ is



[0068] In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic, or Id, or the pharmaceutically acceptable salt thereof, is the compound wherein R¹ is phenyl substituted with halogen. In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic, or Id, or the pharmaceutically acceptable salt thereof, is the compound wherein R¹ is



[0069] In some embodiments, the compound of Formula J, I, or the pharmaceutically acceptable salt thereof, is the compound wherein A¹, A², A³ and A⁴ are each independently =CR²- or =N-; and each R² is independently hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₂₋₆ alkoxyalkyl, halogen, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, hydroxy or -CN.

[0070] In some embodiments, the compound of Formula J, I, or the pharmaceutically acceptable salt thereof, is the compound wherein each of A¹, A², A³, and A⁴ is =CR²-. In some embodiments, the compound of Formula J, I, or the pharmaceutically acceptable salt thereof, is the compound wherein each of A¹, A², A³, and A⁴ is =N-.

thereof, is the compound wherein at least one R² is C₁₋₆ alkyl, C₁₋₆ alkoxy, C₂₋₆ alkoxyalkyl, halogen, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, hydroxy or -CN.

[0071] In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic, or Id, or the pharmaceutically acceptable salt thereof, is the compound wherein each R² is

5 independently hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, halogen or C₁₋₆ haloalkyl. In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic, or Id, or the pharmaceutically acceptable salt thereof, is the compound wherein each R² is independently hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy or halogen. In some embodiments, the compound of

10 Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic, or Id, or the pharmaceutically acceptable salt thereof, is the compound wherein each R² is independently hydrogen, methyl, ethyl, n-propyl, iso-propyl, methoxy, ethoxy, n-propoxy, iso-propoxy, fluoro, chloro, bromo, -CH₂F, -CHF₂, -CF₃, -CH₂CH₂F, -CH₂CHF₂, or -CH₂CF₃. In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic, or Id, or the pharmaceutically acceptable salt thereof, is the compound wherein each R² is independently hydrogen, methyl, ethyl, n-propyl, iso-propyl, methoxy,

15 ethoxy, n-propoxy, iso-propoxy, fluoro, chloro or bromo. In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic, or Id, or the pharmaceutically acceptable salt thereof, is the compound wherein each R² is independently hydrogen, methyl, methoxy, fluoro, chloro, or CF₃. In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic, or Id, or the pharmaceutically acceptable salt thereof, is the compound wherein each R²

20 is independently hydrogen, methyl, methoxy, or chloro. In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic, or Id, or the pharmaceutically acceptable salt thereof, is the compound wherein each R² is hydrogen or methyl.

[0072] In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic, or Id, or the pharmaceutically acceptable salt thereof, is the compound wherein R² is hydrogen or

25 methyl. In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic, or Id, or the pharmaceutically acceptable salt thereof, is the compound wherein R² is methyl.

[0073] In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic, or Id, or the pharmaceutically acceptable salt thereof, is the compound wherein A¹, A² and A⁴ are each =CH-; and A³ is =C(Me)-, =C(OMe)-, =C(F)-, =C(Cl)-, or =C(CF₃)-. In some embodiments,

30 the compound of Formula J, I, or the pharmaceutically acceptable salt thereof, is the compound wherein A¹, A² and A⁴ are each =CH-; and A³ is =C(Me)-, =C(OMe)- or =C(Cl)-.

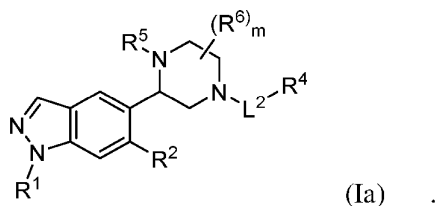
In some embodiments, the compound of Formula J, I, or the pharmaceutically acceptable salt thereof, is the compound wherein A^1 , A^2 and A^4 are each $=CH-$; and A^3 is $=C(Me)-$.

[0074] Each embodiment of A^1 , A^2 , A^3 , A^4 and R^2 described herein can be combined with each embodiment of R^1 described herein.

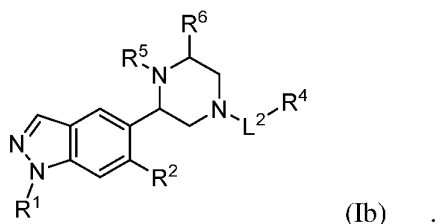
- 5 [0075] In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic, or Id, or the pharmaceutically acceptable salt thereof, is the compound wherein subscript n is 2. In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic, or Id, or the pharmaceutically acceptable salt thereof, is the compound wherein subscript n is 1.

- [0076] Each embodiment of subscript n described herein can be combined with each
10 embodiment of R^1 , A^1 , A^2 , A^3 , A^4 , and R^2 described herein.

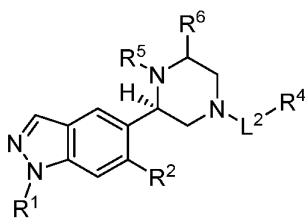
[0077] In some embodiments, the compound of Formula J, I, or the pharmaceutically acceptable salt thereof, is the compound having the structure of Formula Ia:



- [0078] In some embodiments, the compound of Formula J, I, or Ia, or the pharmaceutically
15 acceptable salt thereof, is the compound having the structure of Formula Ib:

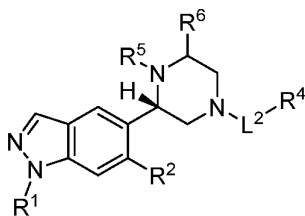


[0079] In some embodiments, the compound of Formula J, I, Ia, or Ib, or the pharmaceutically acceptable salt thereof, is the compound having the structure of Formula Ib-1:



(Ib-1) .

[0080] In some embodiments, the compound of Formula J, I, Ia, or Ib, or the pharmaceutically acceptable salt thereof, is the compound having the structure of Formula Ib-2:

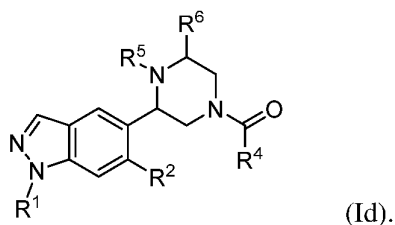
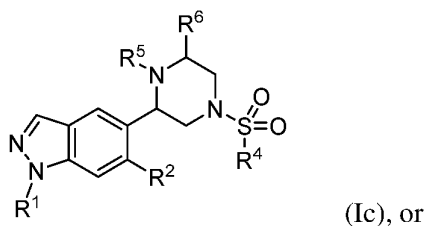


(Ib-2) .

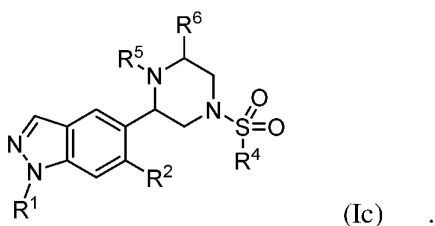
[0081] In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, or Ib-2, or the pharmaceutically acceptable salt thereof, is the compound wherein L^2 is $-C(O)-$, $-C(O)O-$, $-C(O)N(R^3)-$, $-S(O)_2-$ or $-S(O)_2N(R^3)-$; and R^3 is hydrogen, or C_{1-6} alkyl. In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, or Ib-2, or the pharmaceutically acceptable salt thereof, is the compound wherein L^2 is $-C(O)-$, $-S(O)_2-$ or $-S(O)_2N(R^3)-$; and R^3 is C_{1-6} alkyl. In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, or Ib-2, or the pharmaceutically acceptable salt thereof, is the compound wherein L^2 is $-C(O)-$, $-S(O)_2-$ or $-S(O)_2N(Me)-$. In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, or Ib-2, or the pharmaceutically acceptable salt thereof, is the compound wherein L^2 is $-C(O)-$, or $-S(O)_2-$. In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, or Ib-2, or the pharmaceutically acceptable salt thereof, is the compound wherein L^2 is $-S(O)_2-$.

[0082] Each embodiment of L^2 and R^3 described herein can be combined with each embodiment of R^1 , A^1 , A^2 , A^3 , A^4 , R^2 and subscript n described herein.

[0083] In some embodiments, the compound of Formula J, I, Ia, or Ib, or the pharmaceutically acceptable salt thereof, is the compound having the structure of Formula Ic or Formula Id:



[0084] In some emodiments, the compound of Formula J, I, Ia, or Ib, or the pharmaceutically acceptable salt thereof, is the compound having the structure of Formula Ic:



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[0085] In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic, or Id, or the pharmaceutically acceptable salt thereof, is the compound wherein

- R⁴ is C₁₋₆ alkyl, C₂₋₆ alkoxyalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ haloalkyl, C₃₋₈ cycloalkyl, C₁₋₆ alkyl-C₃₋₈ cycloalkyl, heterocycloalkyl, C₁₋₆ alkyl-heterocycloalkyl, C₆₋₁₂ aryl, C₁₋₆ alkyl-C₆₋₁₂ aryl, heteroaryl, or C₁₋₆ alkyl-heteroaryl, wherein each heterocycloalkyl independently has 3 to 6 ring members and 1 to 3 heteroatoms each independently N, O or S, wherein each heteroaryl independently has 5 to 6 ring members and 1 to 4 heteroatoms each independently N, O or S, and wherein the cycloalkyl, heterocycloalkyl, aryl and heteroaryl are each independently substituted with 0 to 5 R^{4a} groups;
- 15 alternatively, R³ and R⁴ are combined with the atoms to which they are attached to form a heterocycloalkyl having 5 to 6 ring members and 1 additional heteroatom N, O or S; and each R^{4a} is independently C₁₋₆ alkyl, C₁₋₆ alkoxy, C₂₋₆ alkoxyalkyl, C₁₋₆ hydroxyalkyl, halogen, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, -CN, C₃₋₈ cycloalkyl, C₁₋₆ alkyl-C₃₋₈ cycloalkyl, heterocycloalkyl, C₁₋₆ alkyl-heterocycloalkyl, C₆₋₁₂ aryl, C₁₋₆ alkyl-C₆₋₁₂ aryl, heteroaryl, or
- 20 C₁₋₆ alkyl-heteroaryl, wherein each heterocycloalkyl independently has 3 to 6 ring members

and 1 to 3 heteroatoms each independently N, O or S, wherein each heteroaryl independently has 5 to 6 ring members and 1 to 4 heteroatoms each independently N, O or S, and wherein each cycloalkyl, heterocycloalkyl, aryl and heteroaryl is substituted with 0, 1 or 2 C₁₋₆ alkyl groups.

- 5 **[0086]** In some emodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic or Id, or the pharmaceutically acceptable salt thereof, is the compound wherein R⁴ is C₁₋₆ alkyl, C₂₋₆ alkoxyalkyl, C₁₋₆ hydroxyalkyl, C₃₋₈ cycloalkyl, C₁₋₆ alkyl-C₃₋₈ cycloalkyl, heterocycloalkyl, C₁₋₆ alkyl-heterocycloalkyl, C₆₋₁₂ aryl, C₁₋₆ alkyl-C₆₋₁₂ aryl, heteroaryl, or C₁₋₆ alkyl-heteroaryl, wherein each heterocycloalkyl independently has 3 to 6
10 ring members and 1 to 3 heteroatoms each independently N, O or S, wherein each heteroaryl independently has 5 to 6 ring members and 1 to 4 heteroatoms each independently N, O or S, and wherein the cycloalkyl, heterocycloalkyl, aryl and heteroaryl are each independently substituted with 0 to 5 R^{4a} groups;
alternatively, R³ and R⁴ are combined with the atoms to which they are attached to form a
15 heterocycloalkyl having 5 to 6 ring members and 1 additional heteroatom N, O or S; and each R^{4a} is independently C₁₋₆ alkyl, C₁₋₆ alkoxy, C₂₋₆ alkoxyalkyl, C₁₋₆ hydroxyalkyl, halogen, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, C₃₋₈ cycloalkyl, C₁₋₆ alkyl-C₃₋₈ cycloalkyl, heterocycloalkyl, C₁₋₆ alkyl-heterocycloalkyl, C₆₋₁₂ aryl, C₁₋₆ alkyl-C₆₋₁₂ aryl, heteroaryl, or C₁₋₆ alkyl-heteroaryl, wherein each heterocycloalkyl independently has 3 to 6 ring members
20 and 1 to 3 heteroatoms each independently N, O or S, wherein each heteroaryl independently has 5 to 6 ring members and 1 to 4 heteroatoms each independently N, O or S, and wherein each cycloalkyl, heterocycloalkyl, aryl and heteroaryl is substituted with 0, 1 or 2 C₁₋₆ alkyl groups.

- [0087]** In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic, or Id, or
25 the pharmaceutically acceptable salt thereof, is the compound wherein R⁴ is C₁₋₆ alkyl, C₂₋₃ alkoxyalkyl, C₁₋₃ hydroxyalkyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, C₁₋₂ alkyl-C₃₋₆ cycloalkyl, heterocycloalkyl, C₁₋₂ alkyl-heterocycloalkyl, C₆₋₁₂ aryl, C₁₋₂ alkyl-aryl, heteroaryl, or C₁₋₂ alkyl-heteroaryl, wherein each heterocycloalkyl independently has 5 to 6 ring members and 1 to 3 heteroatoms each independently N or O, wherein each heteroaryl
30 independently has 5 to 6 ring members and 1 to 3 heteroatoms each independently N, O or S, and wherein the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl are each independently substituted with 0 to 3 R^{4a} groups; and each R^{4a} is independently C₁₋₃ alkyl, C₁₋₃ alkoxy, C₂₋₃ alkoxyalkyl, halogen, C₁₋₃ haloalkyl, -

CN, or heterocycloalkyl, wherein each heterocycloalkyl independently has 5 to 6 ring members and 1 to 2 heteroatoms each independently N or O.

[0088] In some emodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic or Id, or the pharmaceutically acceptable salt thereof, is the compound wherein

- 5 R⁴ is C₁₋₆ alkyl, C₂₋₃ alkoxyalkyl, C₁₋₃ hydroxyalkyl, C₃₋₆ cycloalkyl, C₁₋₂ alkyl-C₃₋₆ cycloalkyl, heterocycloalkyl, or heteroaryl, wherein each heterocycloalkyl independently has 5 to 6 ring members and 1 to 3 heteroatoms each independently N or O, wherein each heteroaryl independently has 5 to 6 ring members and 1 to 3 heteroatoms each independently N, O or S, and wherein the cycloalkyl, heterocycloalkyl, and heteroaryl are each
- 10 independently substituted with 0 to 2 R^{4a} groups; and
- each R^{4a} is independently C₁₋₃ alkyl, C₂₋₃ alkoxyalkyl, halogen, C₁₋₃ haloalkyl, or heterocycloalkyl, wherein each heterocycloalkyl independently has 5 to 6 ring members and 1 to 2 heteroatoms each independently N or O.

[0089] In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic, or Id, or the pharmaceutically acceptable salt thereof, is the compound wherein

- 15 R⁴ is methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, methoxymethyl, methoxyethyl, isopropoxyethyl, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, -CH₂F, -CHF₂, -CF₃, -CH₂CH₂F, -CH₂CHF₂, -CH₂CF₃, C₃₋₆ cycloalkyl, C₁₋₂ alkyl-C₃₋₆ cycloalkyl, heterocycloalkyl, C₁₋₂ alkyl-heterocycloalkyl, C₆₋₁₂ aryl, C₁₋₂ alkyl-C₆₋₁₂ aryl, or heteroaryl,
- 20 wherein each cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl, where each heterocycloalkyl is oxetane, tetrahydrofuran, pyrrolidine, tetrahydropyran, piperidine, or morpholine, wherein each aryl is phenyl, wherein each heteroaryl is pyrrole, pyridine, pyrazole, imidazole, pyridazine, pyrimidine,
- 25 pyrazine, isoxazole, oxazole, isothiazole, thiazole, or triazole, and wherein the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl are each independently substituted with 0 to 3 R^{4a} groups; and
- R^{4a} is independently methyl, ethyl, n-propyl, iso-propyl, methoxy, ethoxy, isopropoxy, methoxymethyl, methoxyethyl, ethoxymethyl, fluoro, chloro, bromo, -CH₂F, -CHF₂, -CF₃, -
- 30 CH₂CH₂F, -CH₂CHF₂, -CH₂CF₃, -CN, tetrahydrofuran, pyrrolidine, tetrahydropyran, piperidine, or morpholine.

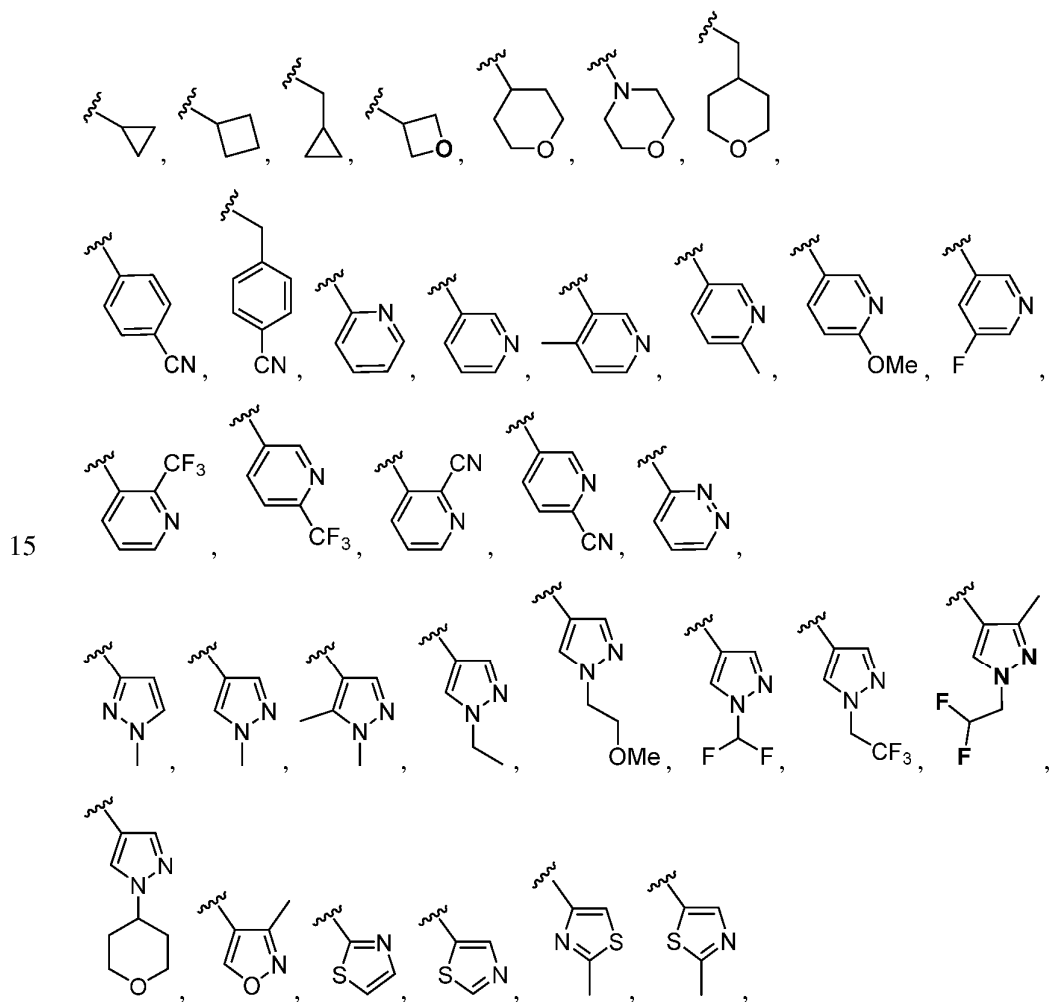
[0090] In some emodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic or Id, or the pharmaceutically acceptable salt thereof, is the compound wherein
R⁴ is methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, methoxymethyl, methoxyethyl, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, C₃₋₆ cycloalkyl, C₁₋₂ alkyl-
5 C₃₋₆ cycloalkyl, heterocycloalkyl, or heteroaryl,
wherein each cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl,
where each heterocycloalkyl is tetrahydrofuran, pyrrolidine, tetrahydropyran, piperidine, or morpholine,
wherein each heteroaryl is pyrrole, pyridine, pyrazole, imidazole, pyridazine, pyrimidine,
10 pyrazine, isoxazole, oxazole, isothiazole, thiazole, or triazole, and
wherein the cycloalkyl, heterocycloalkyl, and heteroaryl are each independently substituted with 0 to 2 R^{4a} groups; and
each R^{4a} is independently methyl, ethyl, n-propyl, iso-propyl, methoxymethyl, methoxyethyl, ethoxymethyl, fluoro, chloro, bromo, -CH₂F, -CHF₂, -CF₃, -CH₂CF₃, tetrahydrofuran,
15 pyrrolidine, tetrahydropyran, piperidine, or morpholine.

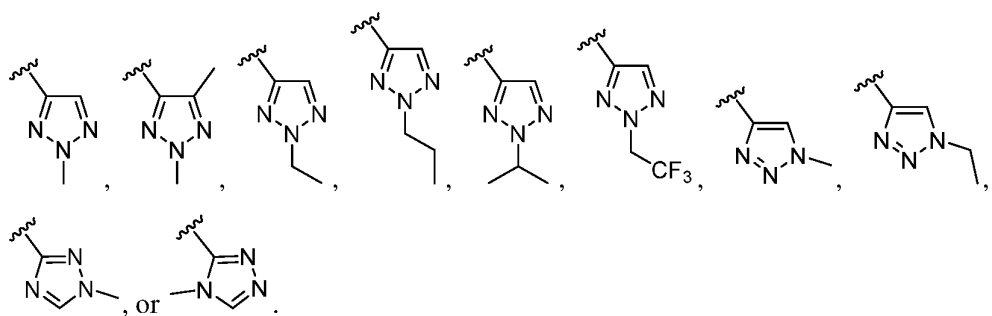
[0091] In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic, or Id, or the pharmaceutically acceptable salt thereof, is the compound wherein
R⁴ is methyl, n-propyl, iso-butyl, -CH(OH)CH₃, methoxyethyl, isopropoxyethyl, CH₂CF₃, C₃₋₆ cycloalkyl, C₁₋₂ alkyl-C₃₋₆ cycloalkyl, heterocycloalkyl, C₁₋₂ alkyl-heterocycloalkyl, C₆₋₁₂
20 aryl, C₁₋₂ alkyl-C₆₋₁₂ aryl, or heteroaryl,
wherein each cycloalkyl is cyclopropyl or cyclobutyl,
where each heterocycloalkyl is oxetane, tetrahydrofuran or morpholine,
wherein each aryl is phenyl,
wherein each heteroaryl is pyridine, pyrazole, isoxazole, thiazole, or triazole, wherein the
25 heteroaryl is substituted with 0 to 2 R^{4a} groups; and
each R^{4a} is independently methyl, ethyl, n-propyl, iso-propyl, methoxy, methoxyethyl, fluoro, -CHF₂, -CF₃, -CH₂CHF₂, -CH₂CF₃, -CN, or tetrahydropyran.

[0092] In some emodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic or Id, or the pharmaceutically acceptable salt thereof, is the compound wherein
30 R⁴ is methyl, n-propyl, iso-butyl, -CH(OH)CH₃, methoxyethyl, C₃₋₆ cycloalkyl, C₁₋₂ alkyl-C₃₋₆ cycloalkyl, heterocycloalkyl, or heteroaryl,
wherein each cycloalkyl is cyclopropyl,
where each heterocycloalkyl is tetrahydrofuran or morpholine,

wherein each heteroaryl is pyridine, pyrazole, isoxazole, thiazole, or triazole, wherein the heteroaryl is substituted with 0 to 2 R^{4a} groups; and
each R^{4a} is independently methyl, ethyl, n-propyl, iso-propyl, methoxyethyl, fluoro, -CHF₂, or tetrahydropyran.

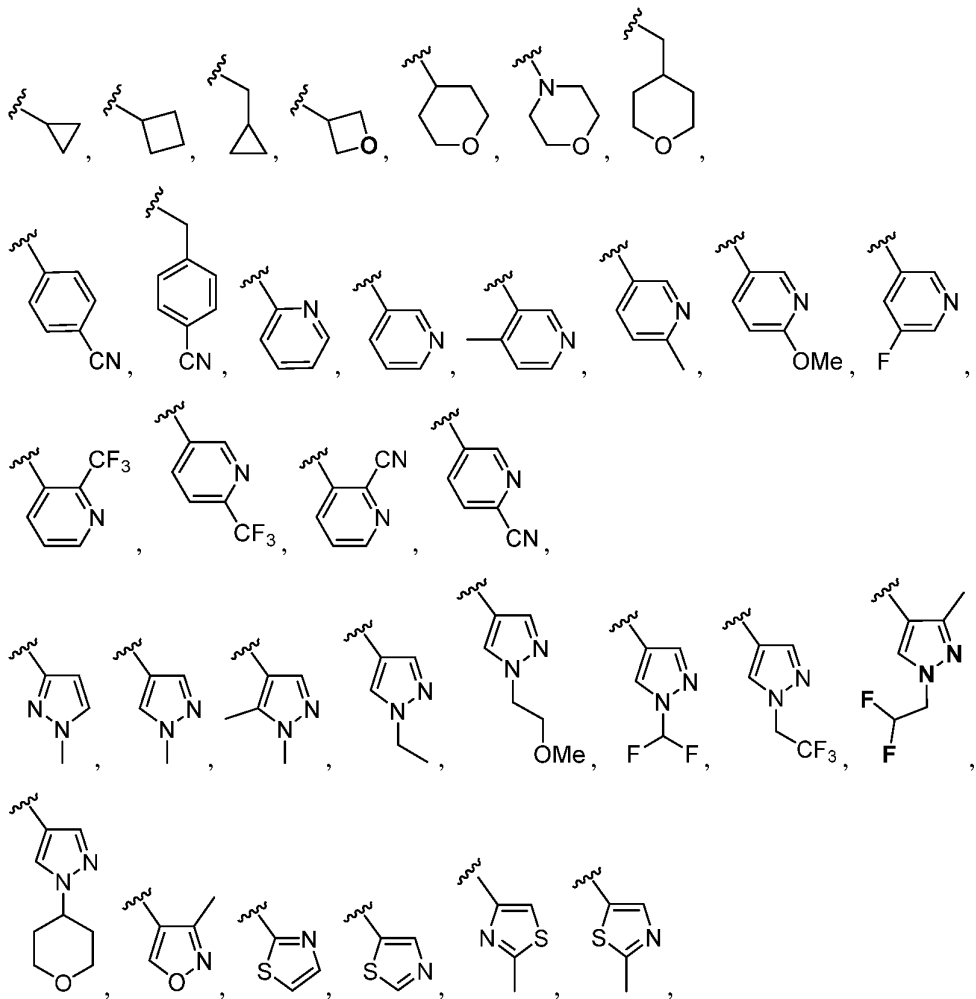
- 5 **[0093]** In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic, or Id, or the pharmaceutically acceptable salt thereof, is the compound wherein R⁴ is pyridine, pyrazole, thiazole, or triazole, each substituted with 0 to 2 R^{4a} groups; and each R^{4a} is independently methyl, ethyl, n-propyl, iso-propyl, methoxy, methoxyethyl, fluoro, -CHF₂, -CF₃, -CH₂CHF₂, -CH₂CF₃, -CN, or tetrahydropyran.
- 10 **[0094]** In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic, or Id, or the pharmaceutically acceptable salt thereof, is the compound wherein R⁴ is methyl, n-propyl, iso-butyl, -CH(OH)CH₃, methoxyethyl, isopropoxyethyl, CH₂CF₃,



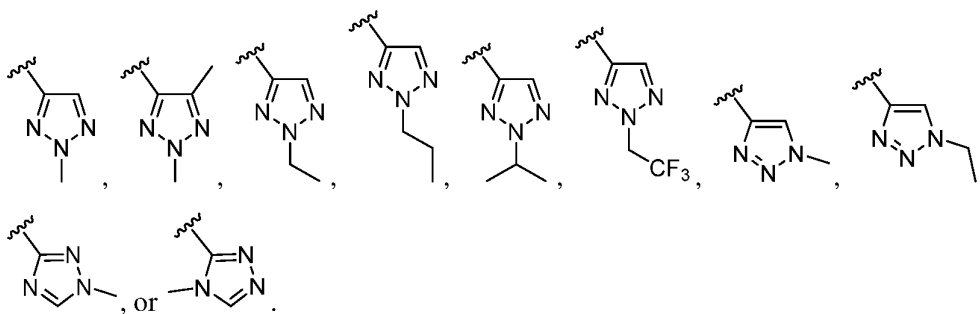


[0095] In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic, or Id, or the pharmaceutically acceptable salt thereof, is the compound wherein

- 5 R⁴ is methyl, n-propyl, iso-butyl, -CH(OH)CH₃, methoxyethyl, isopropoxyethyl, CH₂CF₃,

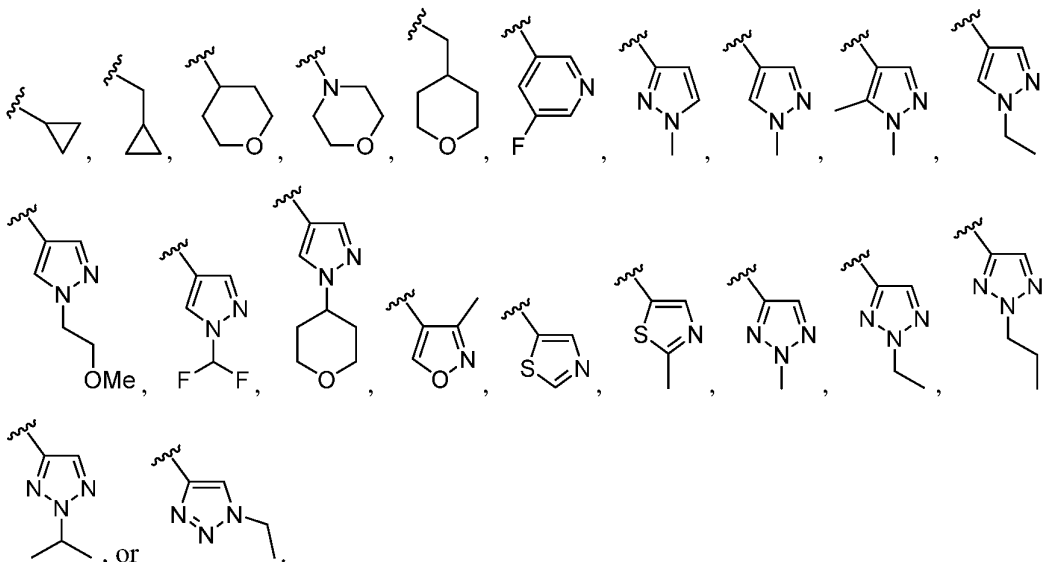


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[0096] In some emodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic or Id, or the pharmaceutically acceptable salt thereof, is the compound wherein

- 5 R^4 is methyl, n-propyl, iso-butyl, $-\text{CH}(\text{OH})\text{CH}_3$, methoxyethyl,

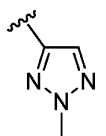


- 10 **[0097]** Each embodiment of R^4 , R^{4a} , R^{4b} , and R^{4c} described herein can be combined with each embodiment of R^1 , A^1 , A^2 , A^3 , A^4 , R^2 , subscript n, L^2 and R^3 described herein.

[0098] In some emodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, or Id, or the pharmaceutically acceptable salt thereof, is the compound wherein

L^2 is $-\text{C}(\text{O})-$; and

R^4 is methyl, $-\text{CH}(\text{OH})\text{CH}_3$, or



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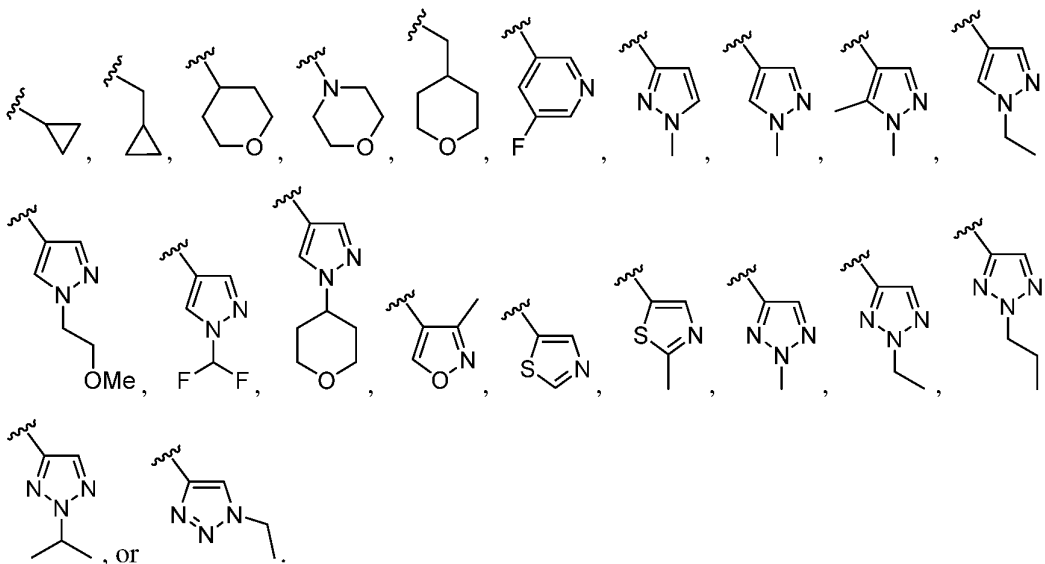
R⁴ is methyl, n-propyl, iso-butyl, -methoxyethyl, isopropoxyethyl, CH₂CF₃,



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- independently N, O or S, wherein the heterocycloalkyl is substituted with 0, 1 or 2 C₁₋₆ alkyl groups; and
- each R^{5c} is independently C₁₋₆ alkyl, C₁₋₆ alkoxy, C₂₋₆ alkoxyalkyl, hydroxy, C₁₋₆ hydroxyalkyl, halogen, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, -CN, oxo or -OH.
- 5 **[0103]** In some emodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic or Id, or the pharmaceutically acceptable salt thereof, is the compound wherein
- R⁵ is C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₂₋₆ alkoxyalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ haloalkyl, -C(O)R^{5a}, -S(O)₂R^{5a}, C₃₋₈ cycloalkyl, C₁₋₆ alkyl-C₃₋₈ cycloalkyl, heterocycloalkyl, C₁₋₆ alkyl-heterocycloalkyl, C₆₋₁₂ aryl, C₁₋₆ alkyl-C₆₋₁₂ aryl, heteroaryl, or C₁₋₆ alkyl-heteroaryl, wherein
- 10 each heterocycloalkyl independently has 3 to 6 ring members and 1 to 3 heteroatoms each independently N, O or S, wherein each heteroaryl independently has 5 to 6 ring members and 1 to 4 heteroatoms each independently N, O or S, and wherein each cycloalkyl, heterocycloalkyl, aryl and heteroaryl is independently substituted with 0 to 4 R^{5c} groups; each R^{5a} and R^{5b} is independently hydrogen or C₁₋₆ alkyl;
- 15 alternatively, R^{5a} and R^{5b} are combined with the atoms to which they are attached to form a heterocycloalkyl having 3 to 12 ring members and 1 to 3 additional heteroatoms each independently N, O or S, wherein the heterocycloalkyl is substituted with 0, 1 or 2 C₁₋₆ alkyl groups; and
- each R^{5c} is independently C₁₋₆ alkyl, C₁₋₆ alkoxy, C₂₋₆ alkoxyalkyl, hydroxy, C₁₋₆ hydroxyalkyl, halogen, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, or -CN.
- 20 **[0104]** In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic, or Id, or the pharmaceutically acceptable salt thereof, is the compound wherein
- R⁵ is C₁₋₆ alkyl, C₂₋₆ alkenyl, C₁₋₆ hydroxyalkyl, C₁₋₆ haloalkyl, -C(O)R^{5a}, C₁₋₂ alkyl-C(O)R^{5a}, C₃₋₆ cycloalkyl, C₁₋₂ alkyl-C₃₋₆ cycloalkyl, heterocycloalkyl, C₁₋₂ alkyl-heterocycloalkyl, C₆₋₁₂ aryl, C₁₋₂ alkyl-C₆₋₁₂ aryl, or C₁₋₂ alkyl-heteroaryl, wherein each heterocycloalkyl
- 25 independently has 3 to 6 ring members and 1 to 2 heteroatoms each independently N or O, wherein each heteroaryl independently has 5 to 6 ring members and 1 to 3 heteroatoms each independently N, O or S, and wherein each cycloalkyl, heterocycloalkyl, aryl and heteroaryl is independently substituted with 0 to 2 R^{5c} groups;
- 30 each R^{5a} is independently C₁₋₆ alkyl; and
- each R^{5c} is independently C₁₋₃ alkyl, C₁₋₃ alkoxy, halogen, C₁₋₃ haloalkyl, -CN, oxo or -OH.

[0105] In some emodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic or Id, or the pharmaceutically acceptable salt thereof, is the compound wherein R⁵ is C₁₋₆ alkyl, C₂₋₆ alkenyl, C₁₋₆ hydroxyalkyl, C₁₋₆ haloalkyl, -C(O)R^{5a}, C₃₋₆ cycloalkyl, C₁₋₂ alkyl-C₃₋₆ cycloalkyl, heterocycloalkyl, C₁₋₂ alkyl-heterocycloalkyl, C₆₋₁₂ aryl, C₁₋₂ alkyl-C₆₋₁₂ aryl, or C₁₋₂ alkyl-heteroaryl, wherein each heterocycloalkyl independently has 3 to 6 ring members and 1 to 2 heteroatoms each independently N or O, wherein each heteroaryl independently has 5 to 6 ring members and 1 to 3 heteroatoms each independently N, O or S, and wherein each cycloalkyl, heterocycloalkyl, aryl and heteroaryl is independently substituted with 0 to 2 R^{5c} groups;

10 each R^{5a} is independently C₁₋₆ alkyl; and
each R^{5c} is independently C₁₋₃ alkyl, C₁₋₃ alkoxy, halogen, C₁₋₃ haloalkyl, or -CN.

[0106] In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic, or Id, or the pharmaceutically acceptable salt thereof, is the compound wherein R⁵ is C₁₋₆ alkyl, C₁₋₆ haloalkyl, or C₁₋₂ alkyl-C₃₋₆ cycloalkyl, wherein each cycloalkyl is independently substituted with 0 to 2 R^{5c} groups; and each R^{5c} is independently C₁₋₃ alkyl, C₁₋₃ alkoxy, halogen, C₁₋₃ haloalkyl, -CN, oxo or -OH. In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic, or Id, or the pharmaceutically acceptable salt thereof, is the compound wherein R⁵ is C₁₋₆ alkyl. In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic, or Id, or the pharmaceutically acceptable salt thereof, is the compound wherein R⁵ is C₁₋₆ haloalkyl.

15 with 0 to 2 R^{5c} groups; and each R^{5c} is independently C₁₋₃ alkyl, C₁₋₃ alkoxy, halogen, C₁₋₃ haloalkyl, -CN, oxo or -OH. In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic, or Id, or the pharmaceutically acceptable salt thereof, is the compound wherein R⁵ is C₁₋₆ haloalkyl.

20 In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic, or Id, or the pharmaceutically acceptable salt thereof, is the compound wherein R⁵ is C₁₋₂ alkyl-C₃₋₆ cycloalkyl, wherein each cycloalkyl is independently substituted with 0 to 2 R^{5c} groups; and each R^{5c} is independently C₁₋₃ alkyl, C₁₋₃ alkoxy, halogen, C₁₋₃ haloalkyl, -CN, oxo or -OH.

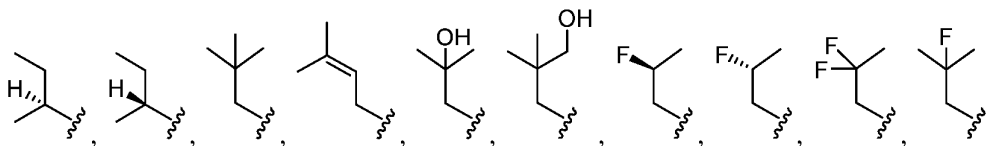
[0107] In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic, or Id, or the pharmaceutically acceptable salt thereof, is the compound wherein R⁵ is methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, C₄₋₆ alkenyl, C₄₋₆ hydroxyalkyl, -CH₂F, -CHF₂, -CF₃, -CH₂CH₂F, -CH₂CHF₂, -CH₂CF₃, -CH₂CHFCH₃, -CH₂CF₂CH₃, -CH₂CH₂CF₃, -CH₂CF(CH₃)₂, -CH₂CH₂CH₂CF₃, -CH₂CH(CH₃)(CF₃), -CH₂C(CH₃)₂(CF₃), -C(O)R^{5a}, C₁₋₂ alkyl-C(O)R^{5a}, C₃₋₆ cycloalkyl, C₁₋₂ alkyl-C₃₋₆ cycloalkyl, heterocycloalkyl, C₁₋₂ alkyl-heterocycloalkyl, C₆₋₁₂ aryl, C₁₋₂ alkyl-C₆₋₁₂ aryl, or C₁₋₂ alkyl-heteroaryl,

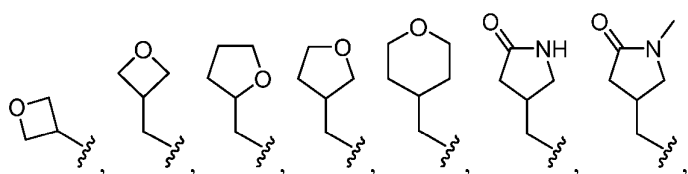
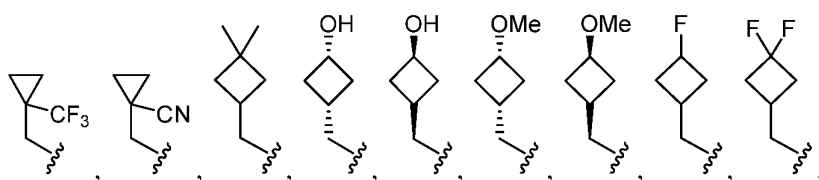
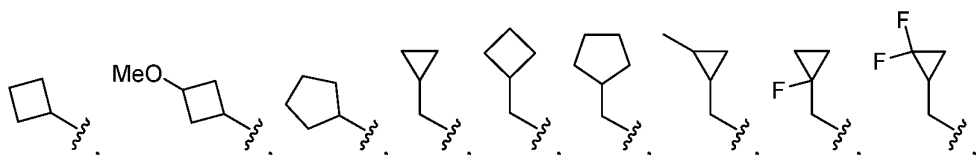
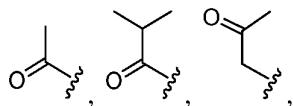
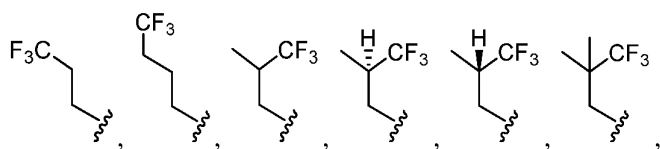
25 the pharmaceutically acceptable salt thereof, is the compound wherein R⁵ is methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, C₄₋₆ alkenyl, C₄₋₆ hydroxyalkyl, -CH₂F, -CHF₂, -CF₃, -CH₂CH₂F, -CH₂CHF₂, -CH₂CF₃, -CH₂CHFCH₃, -CH₂CF₂CH₃, -CH₂CH₂CF₃, -CH₂CF(CH₃)₂, -CH₂CH₂CH₂CF₃, -CH₂CH(CH₃)(CF₃), -CH₂C(CH₃)₂(CF₃), -C(O)R^{5a}, C₁₋₂ alkyl-C(O)R^{5a}, C₃₋₆ cycloalkyl, C₁₋₂ alkyl-C₃₋₆ cycloalkyl, heterocycloalkyl, C₁₋₂ alkyl-heterocycloalkyl, C₆₋₁₂ aryl, C₁₋₂ alkyl-C₆₋₁₂ aryl, or C₁₋₂ alkyl-heteroaryl,

30 heterocycloalkyl, C₁₋₂ alkyl-heterocycloalkyl, C₆₋₁₂ aryl, C₁₋₂ alkyl-C₆₋₁₂ aryl, or C₁₋₂ alkyl-heteroaryl,

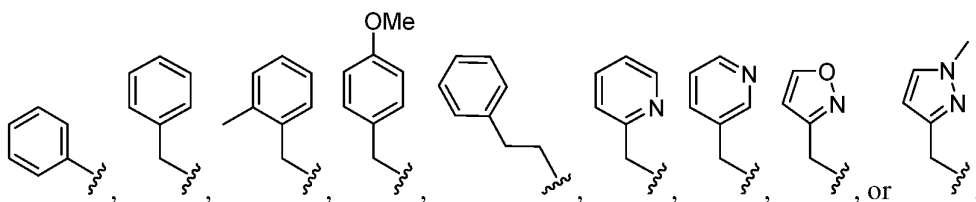
wherein each cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl, wherein each heterocycloalkyl is oxetane, tetrahydrofuran, or tetrahydropyran,

- wherein each aryl is phenyl,
 wherein each heteroaryl is pyrrole, pyridine, pyrazole, imidazole, pyridazine, pyrimidine, pyrazine, isoxazole, oxazole, isothiazole, thiazole, or triazole, and
 wherein each cycloalkyl, aryl and heteroaryl is independently substituted with 0 to 2 R^{5c} groups;
- 5 each R^{5a} is independently methyl, ethyl, n-propyl or iso-propyl; and
 each R^{5c} is independently methyl, ethyl, n-propyl, iso-propyl, methoxy, ethoxy, n-propoxy, iso-propoxy, fluoro, chloro, bromo, -CH₂F, -CHF₂, -CF₃, -CH₂CF₃, -CN, oxo or -OH.
- [0108]** In some emodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic or Id, or
 10 the pharmaceutically acceptable salt thereof, is the compound wherein
 R⁵ is methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, C₄₋₆ alkenyl, C₄₋₆ hydroxyalkyl, -CH₂F, -CHF₂, -CF₃, -CH₂CF₃, -CH₂CH₂CF₃, -CH₂CH₂CH₂CF₃, -CH₂CH(CH₃)(CF₃), -C(O)R^{5a}, C₃₋₆ cycloalkyl, C₁₋₂ alkyl-C₃₋₆ cycloalkyl, heterocycloalkyl, C₁₋₂ alkyl-heterocycloalkyl, C₆₋₁₂ aryl, C₁₋₂ alkyl-C₆₋₁₂ aryl, or C₁₋₂ alkyl-heteroaryl,
 15 wherein each cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl,
 wherein each heterocycloalkyl is oxetane, tetrahydrofuran, or tetrahydropyran,
 wherein each aryl is phenyl,
 wherein each heteroaryl is pyrrole, pyridine, pyrazole, imidazole, pyridazine, pyrimidine, pyrazine, isoxazole, oxazole, isothiazole, thiazole, or triazole, and
 20 wherein each cycloalkyl, aryl and heteroaryl is independently substituted with 0 to 2 R^{5c} groups;
 each R^{5a} is independently methyl, ethyl, n-propyl or iso-propyl; and
 each R^{5c} is independently methyl, ethyl, n-propyl, iso-propyl, methoxy, ethoxy, n-propoxy, iso-propoxy, fluoro, chloro, bromo, -CH₂F, -CHF₂, -CF₃, -CH₂CF₃, or -CN.
- 25 **[0109]** In some emobidiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic, or Id, or the pharmaceutically acceptable salt thereof, is the compound wherein
 R⁵ is ethyl, iso-propyl, iso-butyl,



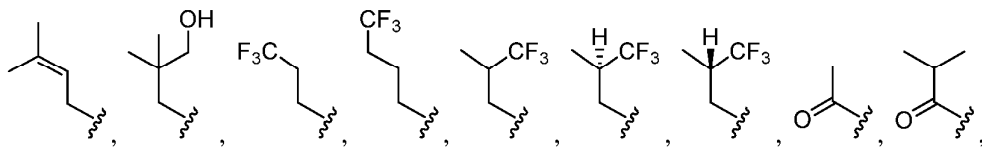


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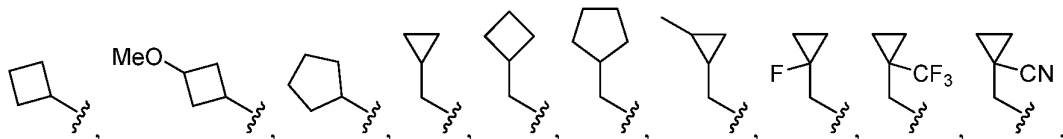


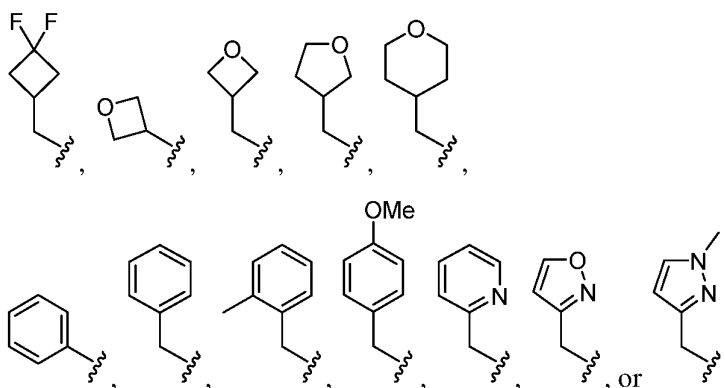
[0110] In some emodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic or Id, or the pharmaceutically acceptable salt thereof, is the compound wherein

R⁵ is ethyl, iso-propyl, iso-butyl,



10





[0111] Each embodiment of R^5 , R^{5a} , R^{5b} , R^{5c} , R^{5c1} , R^{5c2} , and R^{5d} described herein can be combined with each embodiment of R^1 , A^1 , A^2 , A^3 , A^4 , R^2 , subscript n, L^2 , R^3 , R^4 , R^{4a} , R^{4b} , and R^{4c} described herein.

[0112] In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic, or Id, or the pharmaceutically acceptable salt thereof, is the compound wherein R^6 is hydrogen, C_{1-6} alkyl or oxo; and subscript m is 0, 1 or 2. In some emodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic or Id, or the pharmaceutically acceptable salt thereof, is the compound wherein R^6 is hydrogen or C_{1-6} alkyl; and subscript m is 0 or 1. In some emodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic or Id, or the pharmaceutically acceptable salt thereof, is the compound wherein R^6 is hydrogen or methyl; and subscript m is 0 or 1. In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic, or Id, or the pharmaceutically acceptable salt thereof, is the compound wherein R^6 is hydrogen, methyl, or oxo; and subscript m is 0, 1 or 2. In some emodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic or Id, or the pharmaceutically acceptable salt thereof, is the compound wherein subscript m is 0.

[0113] Each embodiment of R^6 and subscript m described herein can be combined with each embodiment of R^1 , A^1 , A^2 , A^3 , A^4 , R^2 , subscript n, L^2 , R^3 , R^4 , R^{4a} , R^{4b} , R^{4c} , R^5 , R^{5a} , R^{5b} , R^{5c} , R^{5c1} , R^{5c2} , and R^{5d} described herein.

[0114] In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic, or Id, or the pharmaceutically acceptable salt thereof, is the compound wherein R^1 is phenyl or heteroaryl having 5 to 6 ring members and 1 to 3 heteroatoms each N, each independently substituted with 0 to 3 R^{1a} groups; each R^{1a} is independently C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} hydroxyalkyl, halogen, C_{1-6} haloalkyl, -OH, oxo, or -CN; each R^{1b} and R^{1c} is independently hydrogen or C_{1-6} alkyl;

A¹, A² and A⁴ are each =CH-;

A³ is =C(Me)-, =C(OMe)-, =C(F)-, =C(Cl)-, or =C(CF₃)-; and

subscript n is 1.

[0115] In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic, or Id, or

5 the pharmaceutically acceptable salt thereof, is the compound wherein

R¹ is phenyl or heteroaryl having 5 to 6 ring members and 1 to 3 heteroatoms each N, each independently substituted with 0 to 3 R^{1a} groups; each R^{1a} is independently C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ hydroxyalkyl, halogen, C₁₋₆ haloalkyl, -OH, oxo, or -CN;

each R^{1b} and R^{1c} is independently hydrogen or C₁₋₆ alkyl;

10 A¹, A² and A⁴ are each =CH-;

A³ is =C(Me)-, =C(OMe)-, =C(F)-, =C(Cl)-, or =C(CF₃)-;

subscript n is 1;

L² is -C(O)-, -S(O)₂- or -S(O)₂N(R³)-;

R³ is C₁₋₆ alkyl;

15 R⁴ is C₁₋₆ alkyl, C₂₋₃ alkoxyalkyl, C₁₋₃ hydroxyalkyl, C₃₋₆ cycloalkyl, C₁₋₂ alkyl-C₃₋₆ cycloalkyl, heterocycloalkyl, or heteroaryl, wherein each heterocycloalkyl independently has 5 to 6 ring members and 1 to 3 heteroatoms each independently N or O, wherein each heteroaryl independently has 5 to 6 ring members and 1 to 3 heteroatoms each independently N, O or S, and wherein the cycloalkyl, heterocycloalkyl, and heteroaryl are each

20 independently substituted with 0 to 2 R^{4a} groups; and

each R^{4a} is independently C₁₋₃ alkyl, C₂₋₃ alkoxyalkyl, halogen, C₁₋₃ haloalkyl, or heterocycloalkyl, wherein each heterocycloalkyl independently has 5 to 6 ring members and 1 to 2 heteroatoms each independently N or O.

[0116] In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic, or Id, or

25 the pharmaceutically acceptable salt thereof, is the compound wherein

R¹ is phenyl or heteroaryl having 5 to 6 ring members and 1 to 3 heteroatoms each N, each independently substituted with 0 to 3 R^{1a} groups; each R^{1a} is independently C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ hydroxyalkyl, halogen, C₁₋₆ haloalkyl, -OH, oxo, or -CN;

each R^{1b} and R^{1c} is independently hydrogen or C₁₋₆ alkyl;

30 A¹, A² and A⁴ are each =CH-;

A³ is =C(Me)-, =C(OMe)-, =C(F)-, =C(Cl)-, or =C(CF₃)-;

subscript n is 1;

L² is -C(O)-, -S(O)₂- or -S(O)₂N(R³)-;

R^3 is C_{1-6} alkyl;
 R^4 is C_{1-6} alkyl, C_{2-3} alkoxyalkyl, C_{1-3} hydroxyalkyl, C_{3-6} cycloalkyl, C_{1-2} alkyl- C_{3-6} cycloalkyl, heterocycloalkyl, or heteroaryl, wherein each heterocycloalkyl independently has 5 to 6 ring members and 1 to 3 heteroatoms each independently N or O, wherein each heteroaryl independently has 5 to 6 ring members and 1 to 3 heteroatoms each independently N, O or S, and wherein the cycloalkyl, heterocycloalkyl, and heteroaryl are each independently substituted with 0 to 2 R^{4a} groups;
each R^{4a} is independently C_{1-3} alkyl, C_{2-3} alkoxyalkyl, halogen, C_{1-3} haloalkyl, or heterocycloalkyl, wherein each heterocycloalkyl independently has 5 to 6 ring members and 1 to 2 heteroatoms each independently N or O;
 R^5 is C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} hydroxyalkyl, C_{1-6} haloalkyl, $-C(O)R^{5a}$, C_{1-2} alkyl- $C(O)R^{5a}$, C_{3-6} cycloalkyl, C_{1-2} alkyl- C_{3-6} cycloalkyl, heterocycloalkyl, C_{1-2} alkyl-heterocycloalkyl, C_{6-12} aryl, C_{1-2} alkyl- C_{6-12} aryl, or C_{1-2} alkyl-heteroaryl, wherein each heterocycloalkyl independently has 3 to 6 ring members and 1 to 2 heteroatoms each independently N or O, wherein each heteroaryl independently has 5 to 6 ring members and 1 to 3 heteroatoms each independently N, O or S, and wherein each cycloalkyl, heterocycloalkyl, aryl and heteroaryl is independently substituted with 0 to 2 R^{5c} groups;
each R^{5a} is independently C_{1-6} alkyl;
each R^{5c} is independently C_{1-3} alkyl, C_{1-3} alkoxy, halogen, C_{1-3} haloalkyl, $-CN$, oxo or $-OH$;
and
subscript m is 0.

[0117] In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic, or Id, or the pharmaceutically acceptable salt thereof, is the compound wherein
 R^1 is phenyl, substituted with 0 to 2 R^{1a} groups each independently methyl, $-CH_2OH$, fluoro, $-CHF_2$, or $-CN$, pyridyl, substituted with 0 to 3 R^{1a} groups each independently methyl, $-OMe$, F, $-OH$ or oxo, pyrazole, substituted with 1 to 2 R^{1a} groups each independently methyl, pyridazine, substituted with 1 to 2 R^{1a} groups each independently methyl or oxo, or pyrazine, substituted with 1 to 2 R^{1a} groups each methyl;
 A^1 , A^2 and A^4 are each $=CH-$;
 A^3 is $=C(Me)-$, $=C(OMe)-$, $=C(F)-$, $=C(Cl)-$, or $=C(CF_3)-$;
 L^2 is $-C(O)-$, $-S(O)_2-$ or $-S(O)_2N(Me)-$;
 R^4 is C_{1-6} alkyl, C_{2-3} alkoxyalkyl, C_{1-3} hydroxyalkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, C_{1-2} alkyl- C_{3-6} cycloalkyl, heterocycloalkyl, C_{1-2} alkyl-heterocycloalkyl, C_{6-12} aryl, C_{1-2} alkyl-aryl,

- heteroaryl, or C₁₋₂ alkyl-heteroaryl, wherein each heterocycloalkyl independently has 5 to 6 ring members and 1 to 3 heteroatoms each independently N or O, wherein each heteroaryl independently has 5 to 6 ring members and 1 to 3 heteroatoms each independently N, O or S, and wherein the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl are each independently substituted with 0 to 3 R^{4a} groups;
- each R^{4a} is independently C₁₋₃ alkyl, C₁₋₃ alkoxy, C₂₋₃ alkoxyalkyl, halogen, C₁₋₃ haloalkyl, -CN, or heterocycloalkyl, wherein each heterocycloalkyl independently has 5 to 6 ring members and 1 to 2 heteroatoms each independently N or O;
- R⁵ is C₁₋₆ alkyl, C₂₋₆ alkenyl, C₁₋₆ hydroxyalkyl, C₁₋₆ haloalkyl, -C(O)R^{5a}, C₁₋₂ alkyl-C(O)R^{5a}, C₃₋₆ cycloalkyl, C₁₋₂ alkyl-C₃₋₆ cycloalkyl, heterocycloalkyl, C₁₋₂ alkyl-heterocycloalkyl, C₆₋₁₂ aryl, C₁₋₂ alkyl-C₆₋₁₂ aryl, or C₁₋₂ alkyl-heteroaryl, wherein each heterocycloalkyl independently has 3 to 6 ring members and 1 to 2 heteroatoms each independently N or O, wherein each heteroaryl independently has 5 to 6 ring members and 1 to 3 heteroatoms each independently N, O or S, and wherein each cycloalkyl, heterocycloalkyl, aryl and heteroaryl is independently substituted with 0 to 2 R^{5c} groups;
- each R^{5a} is independently C₁₋₆ alkyl;
- each R^{5c} is independently C₁₋₃ alkyl, C₁₋₃ alkoxy, halogen, C₁₋₃ haloalkyl, -CN, oxo or -OH;
- R⁶ is hydrogen, methyl, or oxo;
- subscript m is 0, 1 or 2; and
- subscript n is 1.

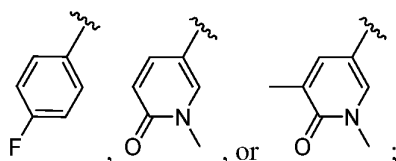
- [0118]** In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic, or Id, or the pharmaceutically acceptable salt thereof, is the compound wherein
- R¹ is phenyl, substituted with 1 to 2 R^{1a} groups each independently fluoro or -CN, pyridyl, substituted with 0 to 3 R^{1a} groups each independently methyl, -OH or oxo, or pyrazole, substituted with 1 to 2 R^{1a} groups each independently methyl;
- A¹, A² and A⁴ are each =CH-;
- A³ is =C(Me)-, =C(OMe)-, =C(F)-, =C(Cl)-, or =C(CF₃)-;
- L² is -C(O)-, -S(O)₂- or -S(O)₂N(Me)-;
- R⁴ is C₁₋₆ alkyl, C₂₋₃ alkoxyalkyl, C₁₋₃ hydroxyalkyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, C₁₋₂ alkyl-C₃₋₆ cycloalkyl, heterocycloalkyl, C₁₋₂ alkyl-heterocycloalkyl, C₆₋₁₂ aryl, C₁₋₂ alkyl-aryl, heteroaryl, or C₁₋₂ alkyl-heteroaryl, wherein each heterocycloalkyl independently has 5 to 6 ring members and 1 to 3 heteroatoms each independently N or O, wherein each heteroaryl independently has 5 to 6 ring members and 1 to 3 heteroatoms each independently N, O or S,

- and wherein the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl are each independently substituted with 0 to 3 R^{4a} groups;
 each R^{4a} is independently C₁₋₃ alkyl, C₁₋₃ alkoxy, C₂₋₃ alkoxyalkyl, halogen, C₁₋₃ haloalkyl, -CN, or heterocycloalkyl, wherein each heterocycloalkyl independently has 5 to 6 ring members and 1 to 2 heteroatoms each independently N or O;
 R⁵ is C₁₋₆ alkyl, C₂₋₆ alkenyl, C₁₋₆ hydroxyalkyl, C₁₋₆ haloalkyl, -C(O)R^{5a}, C₁₋₂ alkyl-C(O)R^{5a}, C₃₋₆ cycloalkyl, C₁₋₂ alkyl-C₃₋₆ cycloalkyl, heterocycloalkyl, C₁₋₂ alkyl-heterocycloalkyl, C₆₋₁₂ aryl, C₁₋₂ alkyl-C₆₋₁₂ aryl, or C₁₋₂ alkyl-heteroaryl, wherein each heterocycloalkyl independently has 3 to 6 ring members and 1 to 2 heteroatoms each independently N or O,
 wherein each heteroaryl independently has 5 to 6 ring members and 1 to 3 heteroatoms each independently N, O or S, and wherein each cycloalkyl, heterocycloalkyl, aryl and heteroaryl is independently substituted with 0 to 2 R^{5c} groups;
 each R^{5a} is independently C₁₋₆ alkyl;
 each R^{5c} is independently C₁₋₃ alkyl, C₁₋₃ alkoxy, halogen, C₁₋₃ haloalkyl, -CN, oxo or -OH;
 R⁶ is hydrogen, methyl, or oxo; and
 subscript m is 0, 1 or 2.

- [0119]** In some emodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic or Id, or the pharmaceutically acceptable salt thereof, is the compound wherein
 R¹ is phenyl substituted with halogen;
 A¹, A² and A⁴ are each =CH-;
 A³ is =C(Me)-, =C(OMe)- or =C(Cl)-;
 L² is -C(O)-, -S(O)₂- or -S(O)₂N(Me)-;
 R⁴ is C₁₋₆ alkyl, C₂₋₃ alkoxyalkyl, C₁₋₃ hydroxyalkyl, C₃₋₆ cycloalkyl, C₁₋₂ alkyl-C₃₋₆ cycloalkyl, heterocycloalkyl, or heteroaryl, wherein each heterocycloalkyl independently has 5 to 6 ring members and 1 to 3 heteroatoms each independently N or O, wherein each heteroaryl independently has 5 to 6 ring members and 1 to 3 heteroatoms each independently N, O or S, and wherein the cycloalkyl, heterocycloalkyl, and heteroaryl are each independently substituted with 0 to 2 R^{4a} groups;
 each R^{4a} is independently C₁₋₃ alkyl, C₂₋₃ alkoxyalkyl, halogen, C₁₋₃ haloalkyl, or heterocycloalkyl, wherein each heterocycloalkyl independently has 5 to 6 ring members and 1 to 2 heteroatoms each independently N or O;
 R⁵ is C₁₋₆ alkyl, C₂₋₆ alkenyl, C₁₋₆ hydroxyalkyl, C₁₋₆ haloalkyl, -C(O)R^{5a}, C₃₋₆ cycloalkyl, C₁₋₂ alkyl-C₃₋₆ cycloalkyl, heterocycloalkyl, C₁₋₂ alkyl-heterocycloalkyl, C₆₋₁₂ aryl, C₁₋₂ alkyl-C₆₋₁₂

- aryl, or C₁₋₂ alkyl-heteroaryl, wherein each heterocycloalkyl independently has 3 to 6 ring members and 1 to 2 heteroatoms each independently N or O, wherein each heteroaryl independently has 5 to 6 ring members and 1 to 3 heteroatoms each independently N, O or S, and wherein each cycloalkyl, heterocycloalkyl, aryl and heteroaryl is independently
- 5 substituted with 0 to 2 R^{5c} groups;
 each R^{5a} is independently C₁₋₆ alkyl;
 each R^{5c} is independently C₁₋₃ alkyl, C₁₋₃ alkoxy, halogen, C₁₋₃ haloalkyl, or -CN;
 R⁶ is hydrogen or methyl; and
 subscript m is 0 or 1.
- 10 **[0120]** In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic, or Id, or the pharmaceutically acceptable salt thereof, is the compound wherein
 R¹ is phenyl or heteroaryl having 5 to 6 ring members and 1 to 3 heteroatoms each N, each independently substituted with 0 to 3 R^{1a} groups;
 each R^{1a} is independently C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ hydroxyalkyl, halogen, C₁₋₆ haloalkyl, -
 15 OH, oxo, -CN, or C₁₋₆ alkyl-C(O)N(R^{1b})(R^{1c});
 each R^{1b} and R^{1c} is independently hydrogen or C₁₋₆ alkyl;
 A¹, A² and A⁴ are each =CH-;
 A³ is =C(Me)-, =C(OMe)-, =C(F)-, =C(Cl)-, or =C(CF₃)-;
 R⁴ is heteroaryl, having 5 to 6 ring members and 1 to 3 heteroatoms each independently N, O
 20 or S, and substituted with 0 to 3 R^{4a} groups;
 each R^{4a} is independently C₁₋₃ alkyl, C₁₋₃ alkoxy, C₂₋₃ alkoxyalkyl, halogen, C₁₋₃ haloalkyl, -CN, or heterocycloalkyl, wherein each heterocycloalkyl independently has 5 to 6 ring members and 1 to 2 heteroatoms each independently N or O;
 R⁵ is C₁₋₆ alkyl, C₁₋₆ haloalkyl, or C₁₋₂ alkyl-C₃₋₆ cycloalkyl, wherein each cycloalkyl is
 25 independently substituted with 0 to 2 R^{5c} groups;
 each R^{5c} is independently C₁₋₃ alkyl, C₁₋₃ alkoxy, halogen, C₁₋₃ haloalkyl, -CN, oxo or -OH;
 subscript m is 0; and
 subscript n is 1.
- [0121]** In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic, or Id, or
 30 the pharmaceutically acceptable salt thereof, is the compound wherein

R¹ is



A¹, A² and A⁴ are each =CH-;

A³ is =C(Me)-;

5 L² is -S(O)₂-;

R⁴ is pyridine, pyrazole, thiazole, or triazole, each substituted with 0 to 2 R^{4a} groups;
each R^{4a} is independently methyl, ethyl, n-propyl, iso-propyl, methoxy, methoxyethyl,
fluoro, -CHF₂, -CF₃, -CH₂CHF₂, -CH₂CF₃, -CN, or tetrahydropyran;

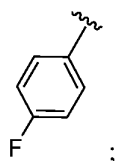
10 R⁵ is C₁₋₆ alkyl, C₁₋₆ haloalkyl, or C₁₋₂ alkyl-C₃₋₆ cycloalkyl, wherein each
cycloalkyl is independently substituted with 0 to 2 R^{5c} groups;
each R^{5c} is independently C₁₋₃ alkyl, C₁₋₃ alkoxy, halogen, C₁₋₃ haloalkyl, -CN, oxo or
-OH;

subscript m is 0; and

subscript n is 1.

15 **[0122]** In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic, or Id, or
the pharmaceutically acceptable salt thereof, is the compound wherein

R¹ is



A¹, A² and A⁴ are each =CH-;

20 A³ is =C(Me)-;

L² is -S(O)₂-;

R⁴ is pyrazole or triazole, each substituted with 1 R^{4a} groups;

R^{4a} is methyl, ethyl, n-propyl, or iso-propyl;

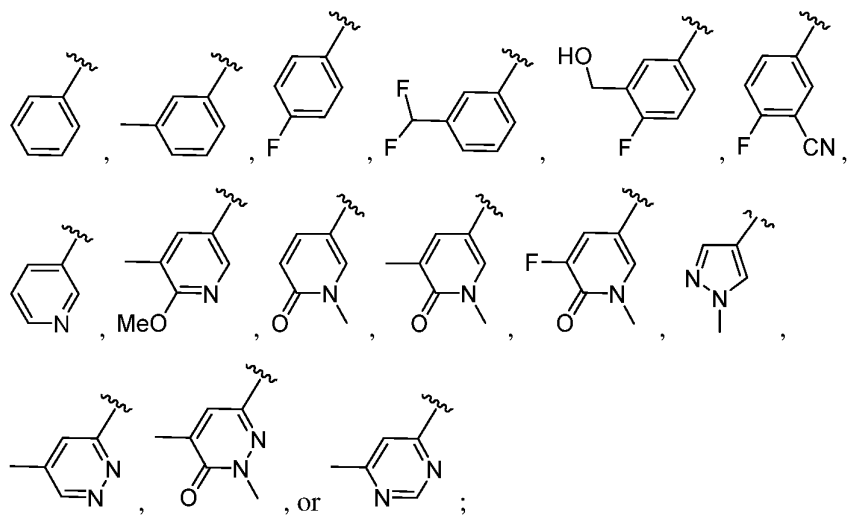
R⁵ is C₁₋₆ haloalkyl;

25 subscript m is 0; and

subscript n is 1.

[0123] In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic, or Id, or
the pharmaceutically acceptable salt thereof, is the compound wherein

R¹ is



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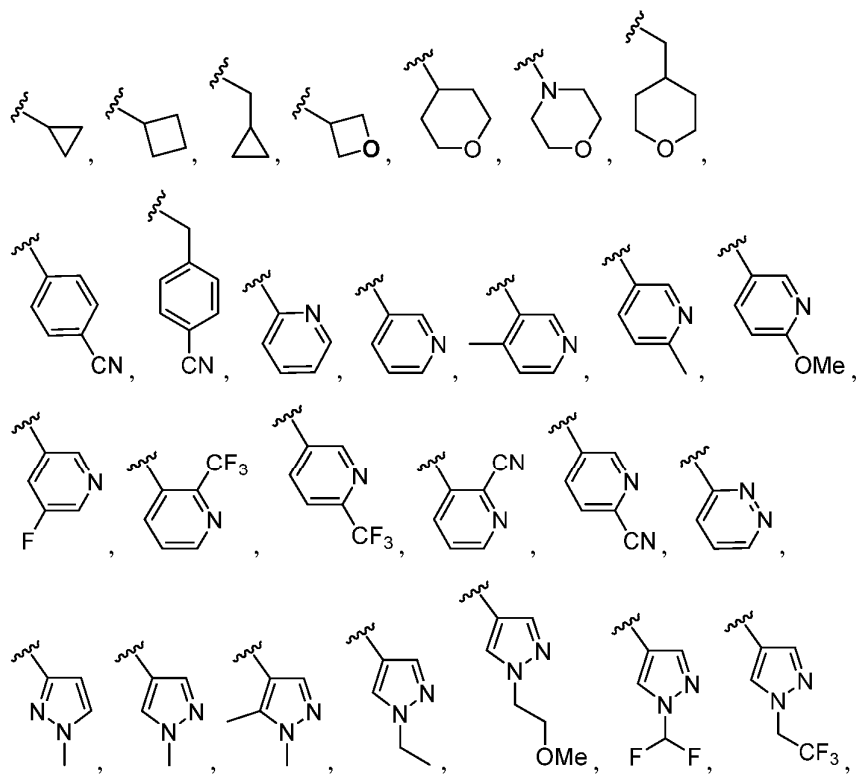
A¹, A² and A⁴ are each =CH-;

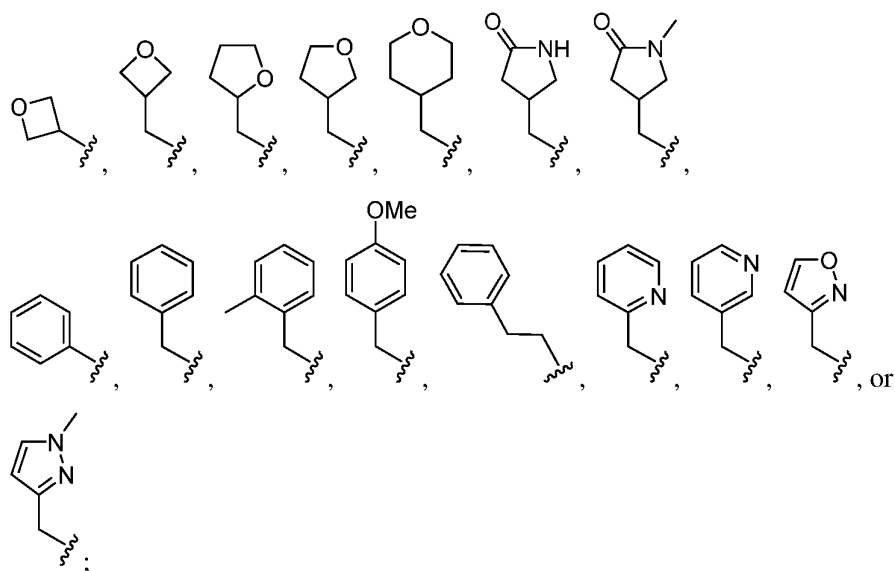
A³ is =C(Me)-, =C(OMe)-, =C(F)-, =C(Cl)-, or =C(CF₃)-;

L² is -C(O)-, -S(O)₂- or -S(O)₂N(Me)-;

R⁴ is methyl, n-propyl, iso-butyl, -CH(OH)CH₃, methoxyethyl, isopropoxyethyl, CH₂CF₃,

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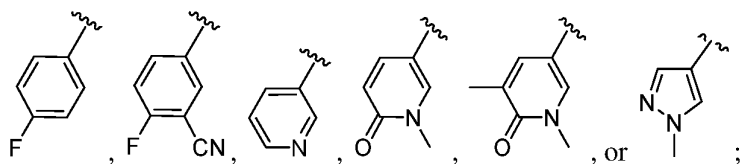


R⁶ is hydrogen, methyl, or oxo; and

5 subscript m is 0, 1 or 2.

[0124] In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic, or Id, or the pharmaceutically acceptable salt thereof, is the compound wherein

R¹ is

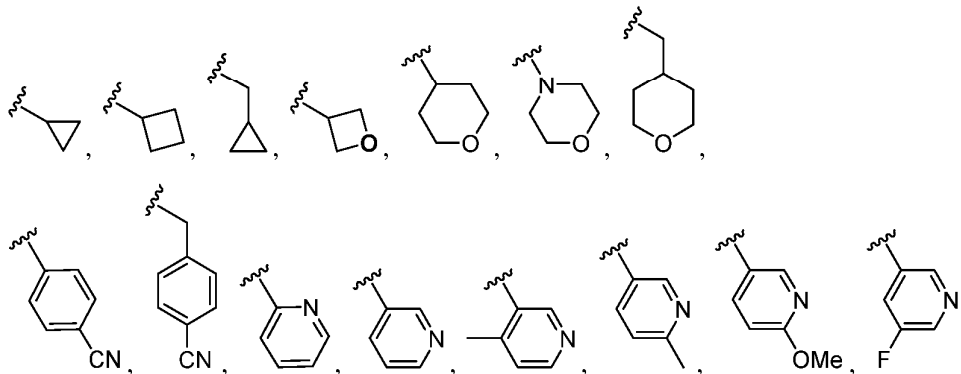


10 A¹, A² and A⁴ are each =CH-;

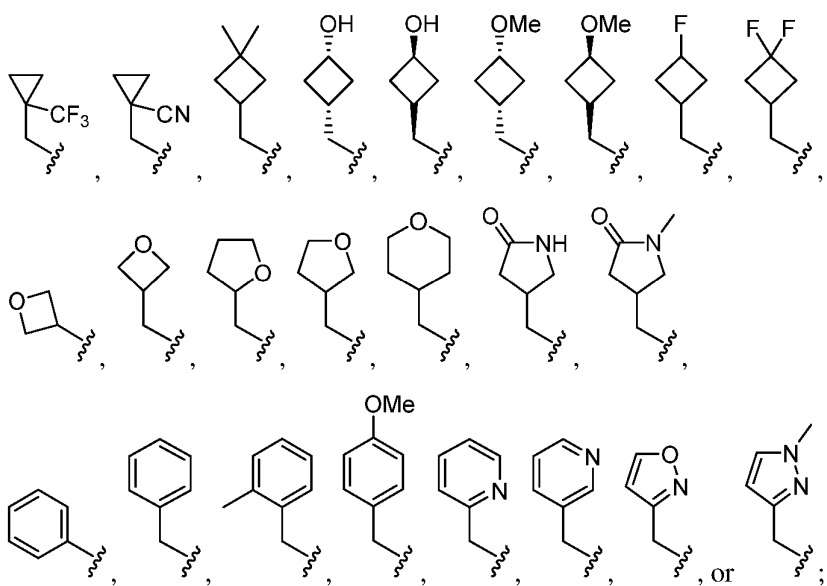
A³ is =C(Me)-, =C(OMe)-, =C(F)-, =C(Cl)-, or =C(CF₃)-;

L² is -C(O)-, -S(O)₂- or -S(O)₂N(Me)-;

R⁴ is methyl, n-propyl, iso-butyl, -CH(OH)CH₃, methoxyethyl, isopropoxyethyl, CH₂CF₃,



15

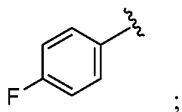


R^6 is hydrogen, methyl, or oxo; and

5 subscript m is 0, 1 or 2.

[0125] In some emodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic or Id, or the pharmaceutically acceptable salt thereof, is the compound wherein

R^1 is

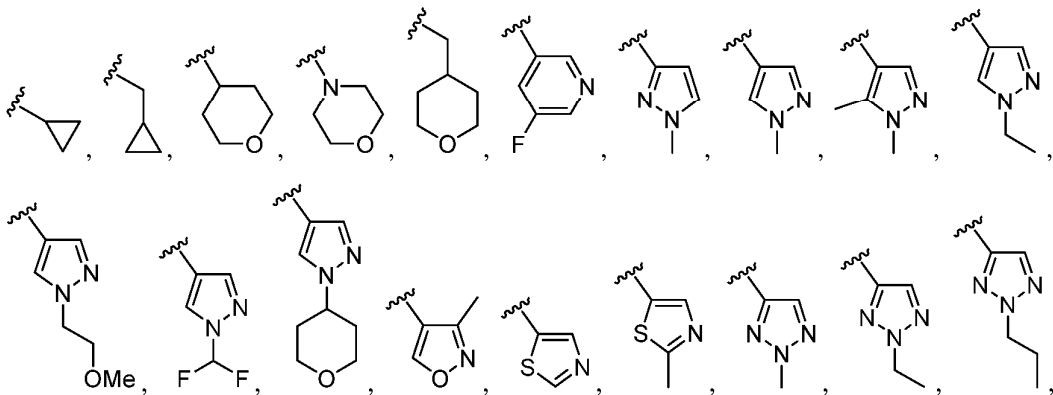


10 A^1 , A^2 and A^4 are each $=CH-$;

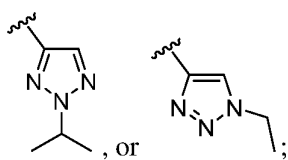
A^3 is $=C(Me)-$, $=C(OMe)-$ or $=C(Cl)-$;

L^2 is $-C(O)-$, $-S(O)_2-$ or $-S(O)_2N(Me)-$;

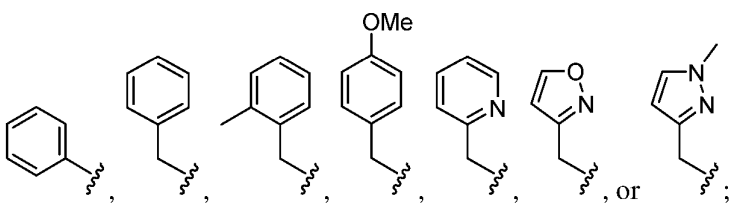
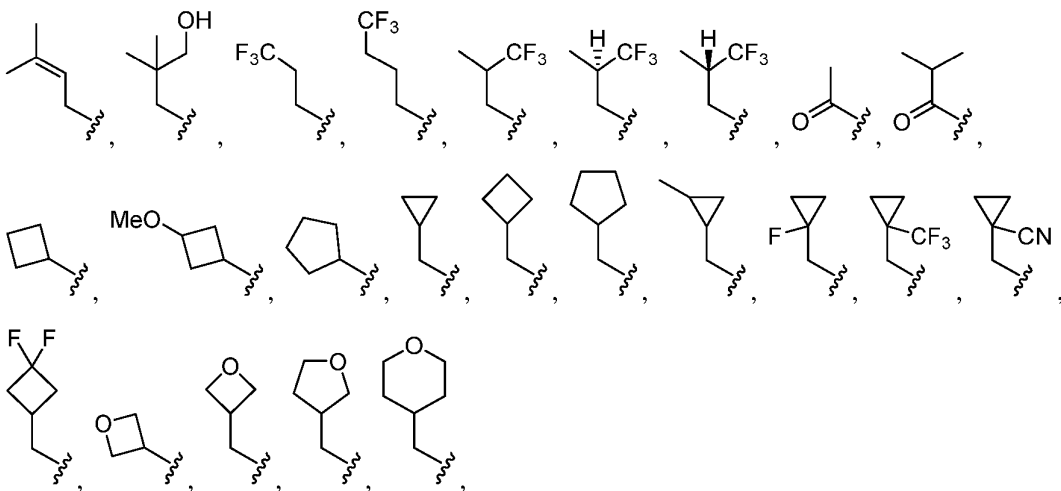
R^4 is methyl, n-propyl, iso-butyl, $-CH(OH)CH_3$, methoxyethyl,



15



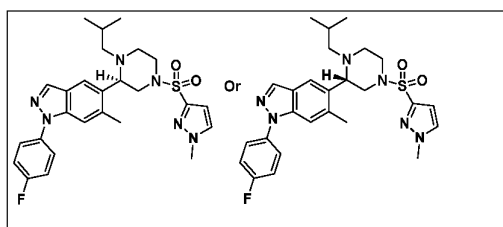
R⁵ is ethyl, iso-propyl, iso-butyl,

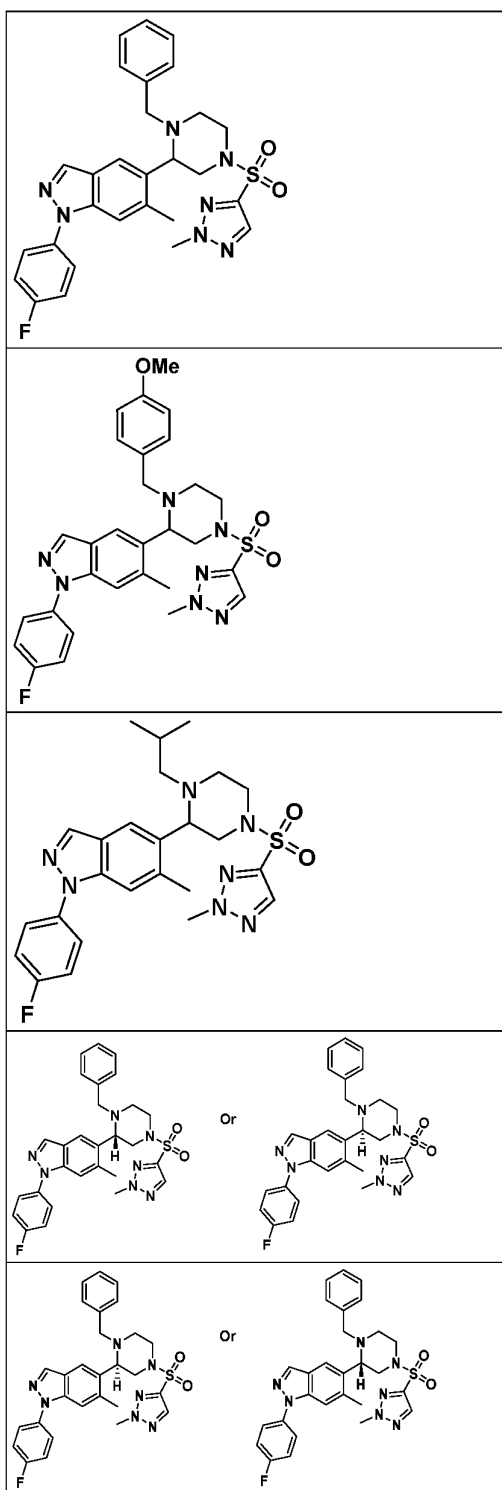


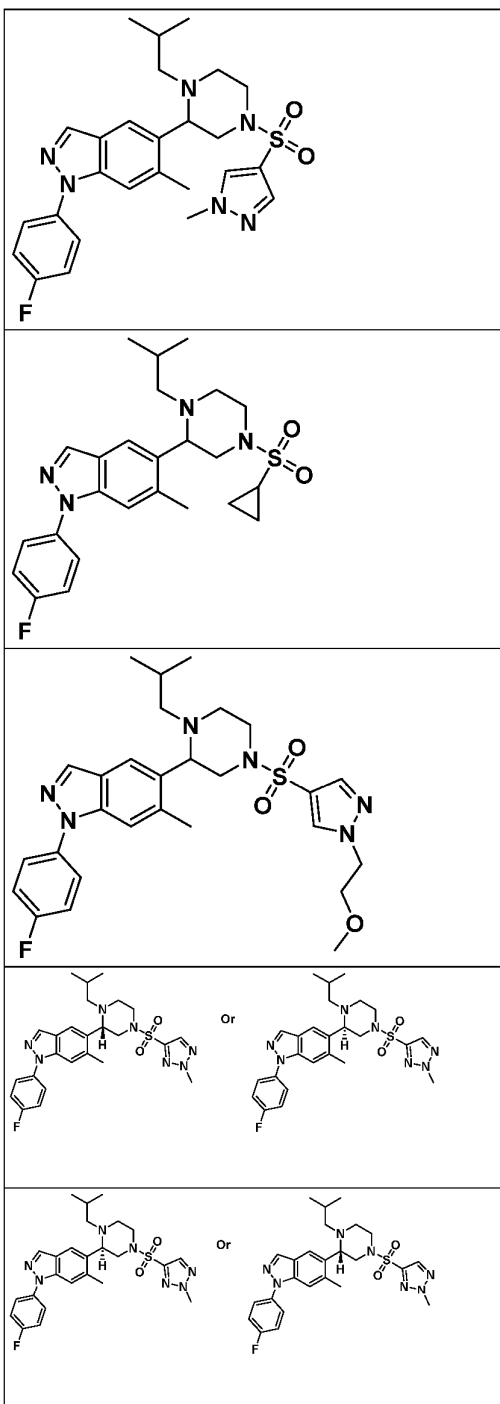
R⁶ is hydrogen or methyl; and
subscript m is 0 or 1.

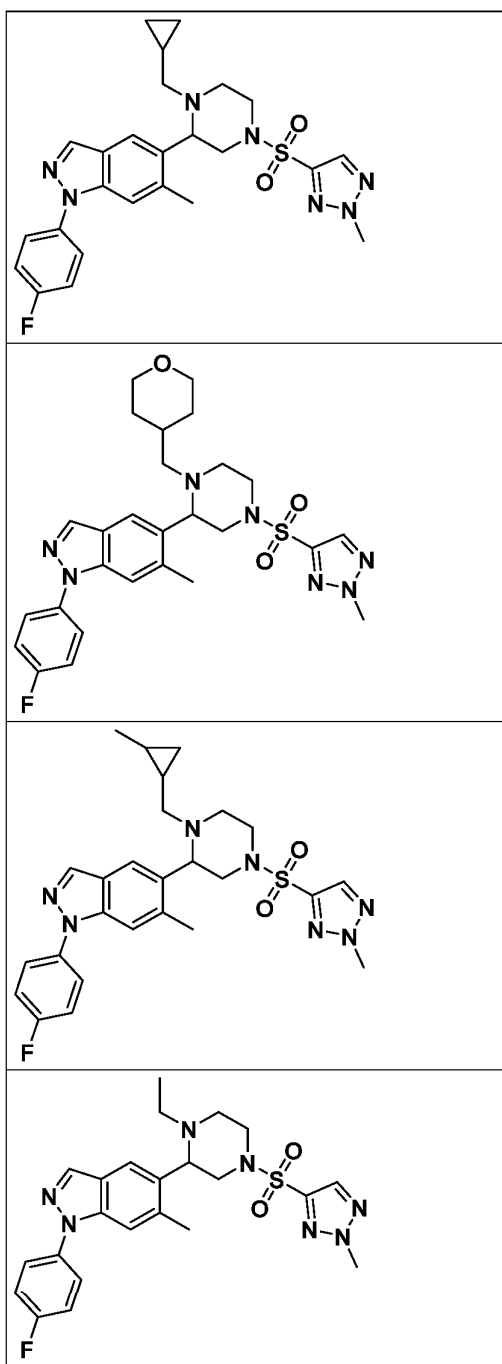
[0126] In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic or Id, or
10 the pharmaceutically acceptable salt thereof, is a compound of Table 1A.

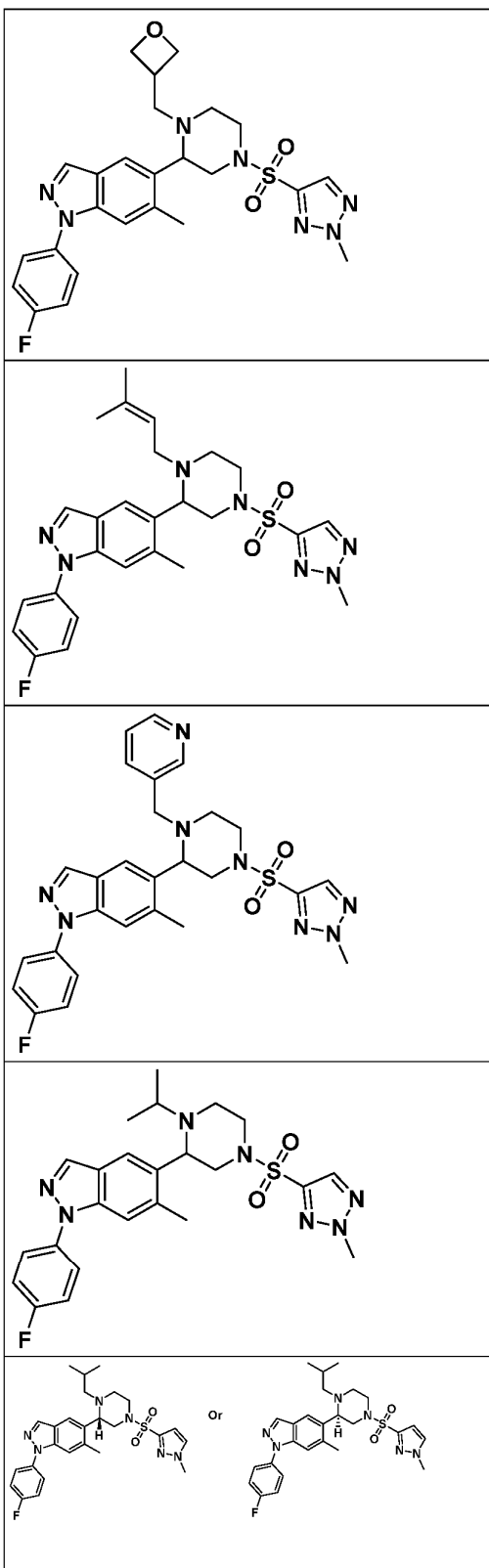
Table 1A.





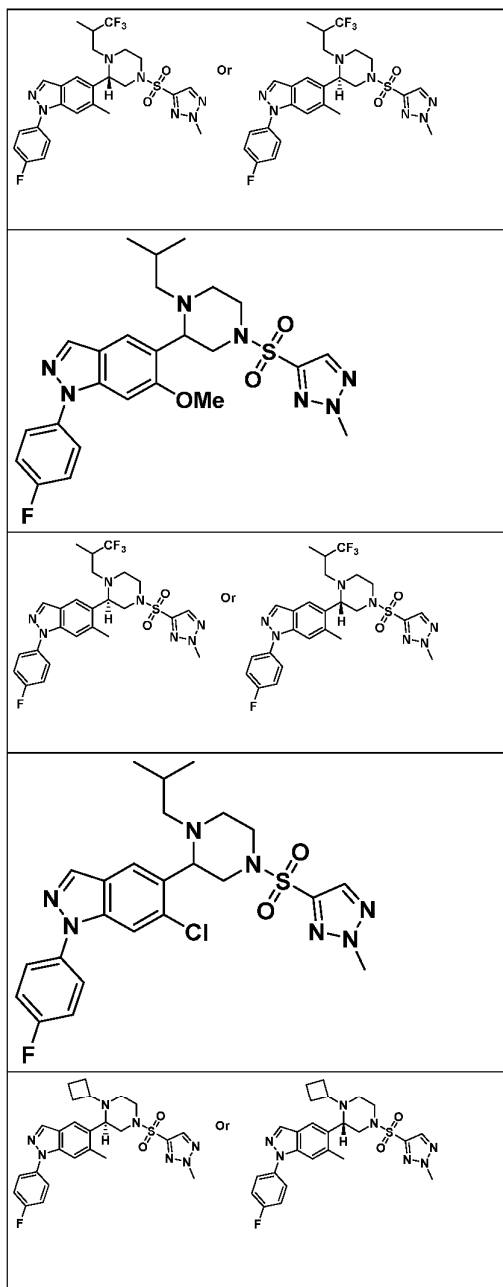


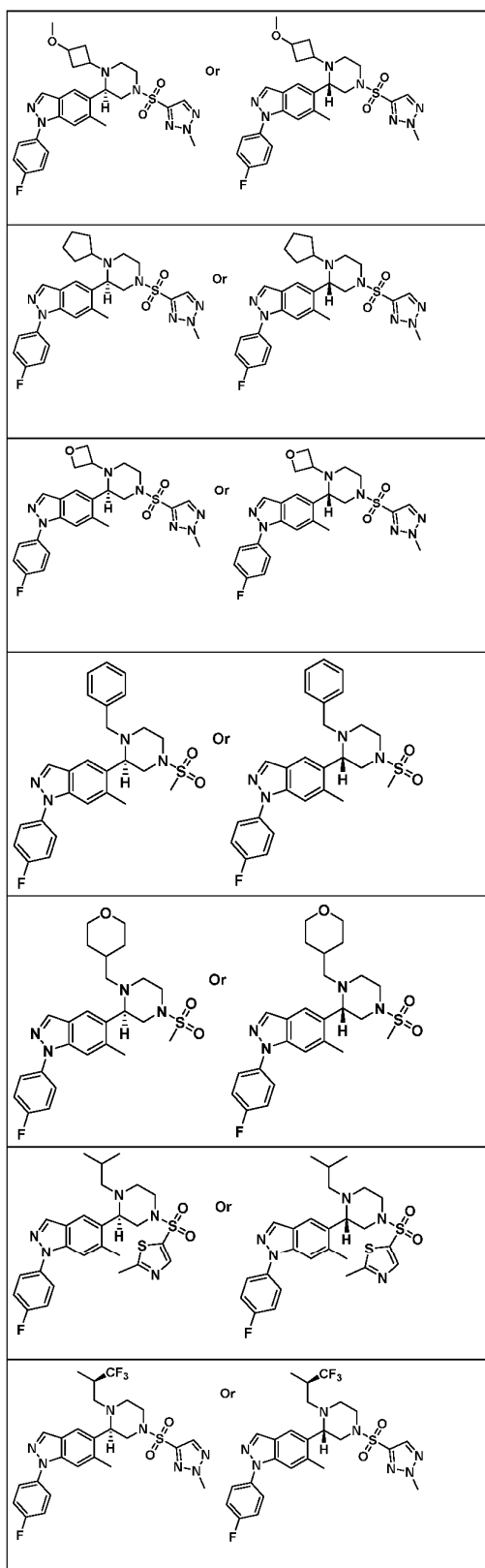


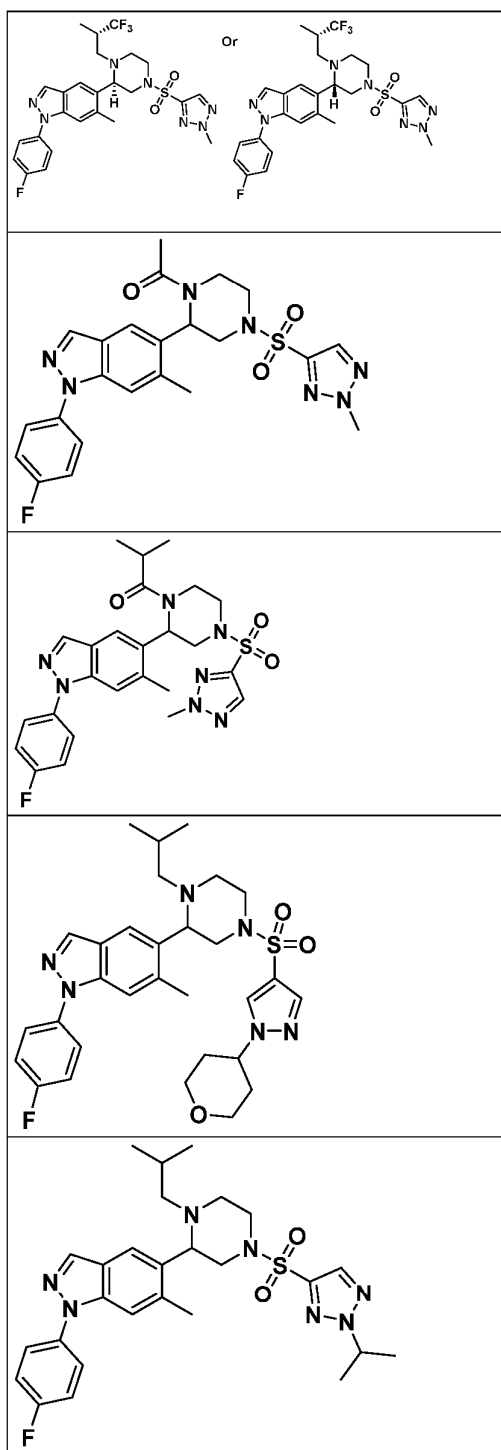


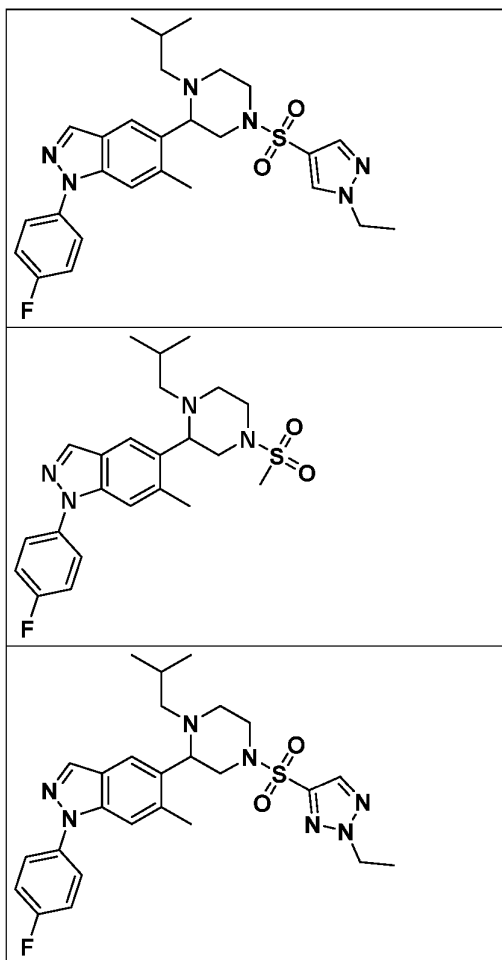
[0127] In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic or Id, or the pharmaceutically acceptable salt thereof, is a compound of Table 1B.

Table 1B.



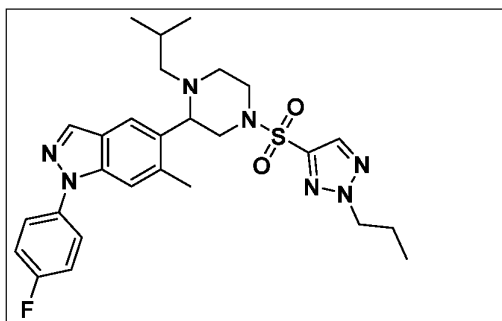


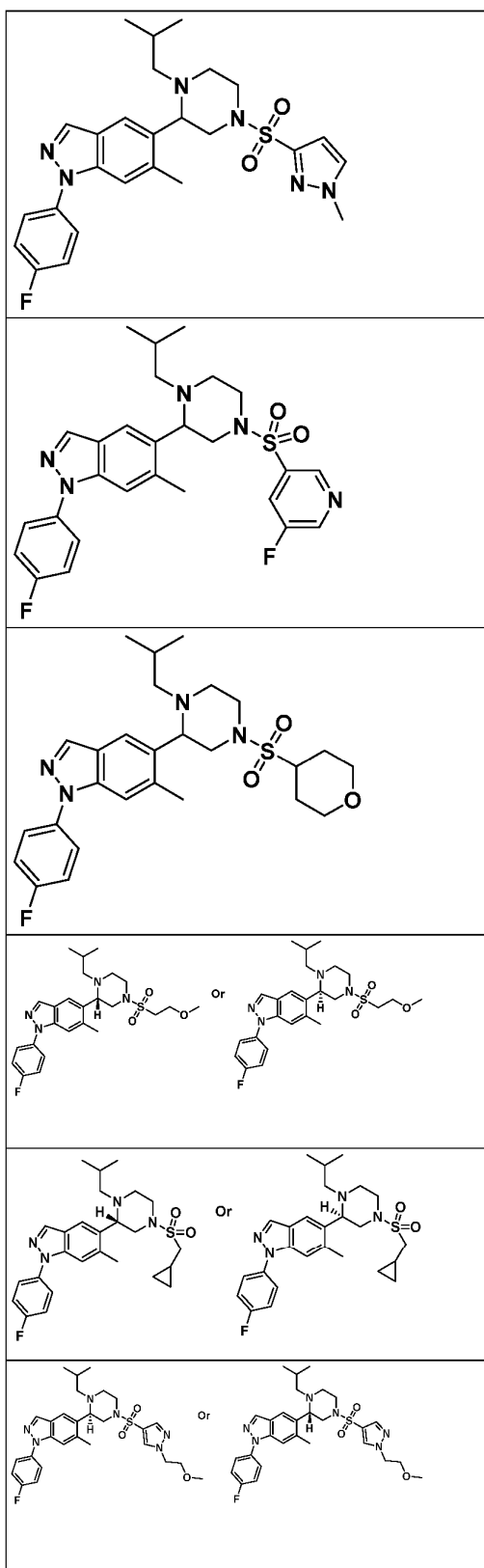


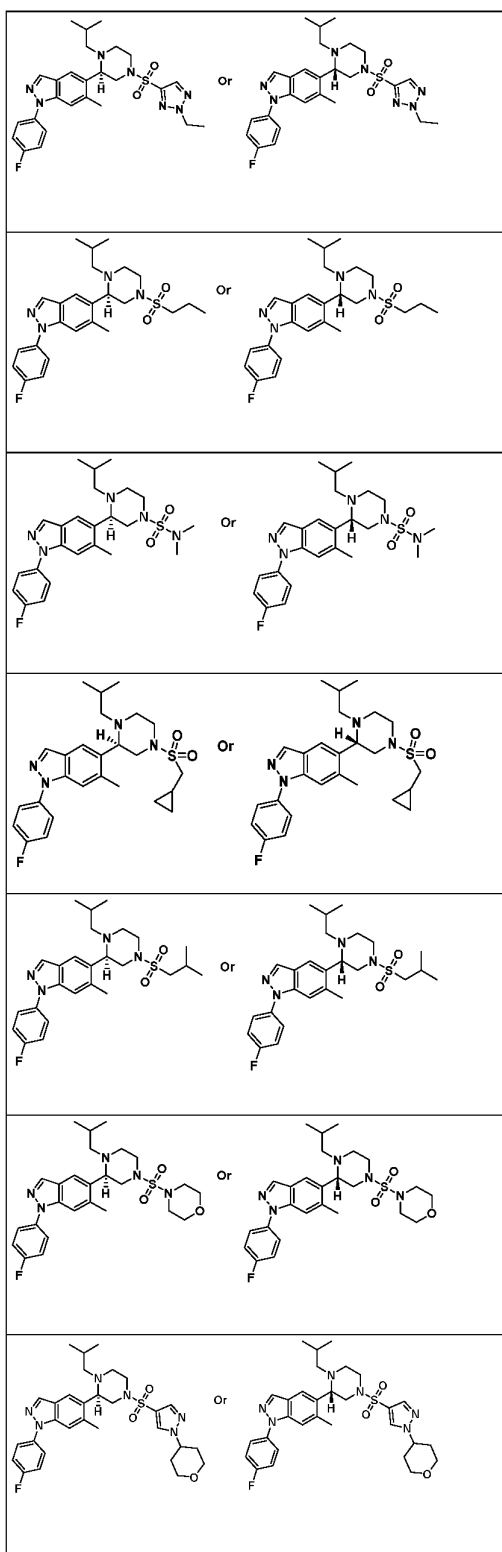


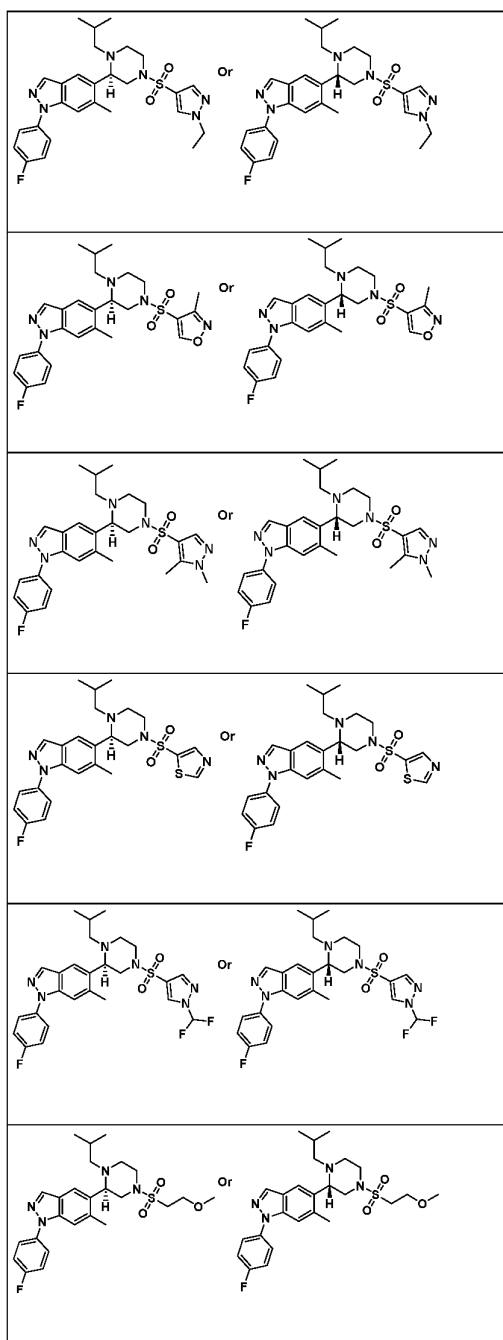
[0128] In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic or Id, or the pharmaceutically acceptable salt thereof, is a compound of Table 1C.

Table 1C.



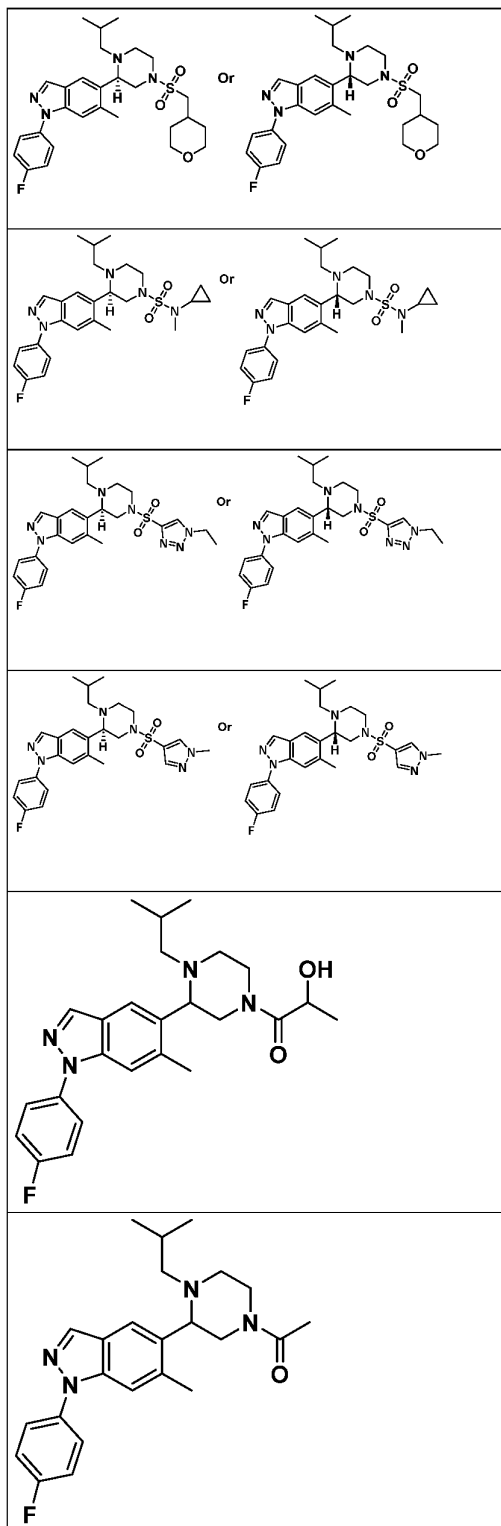


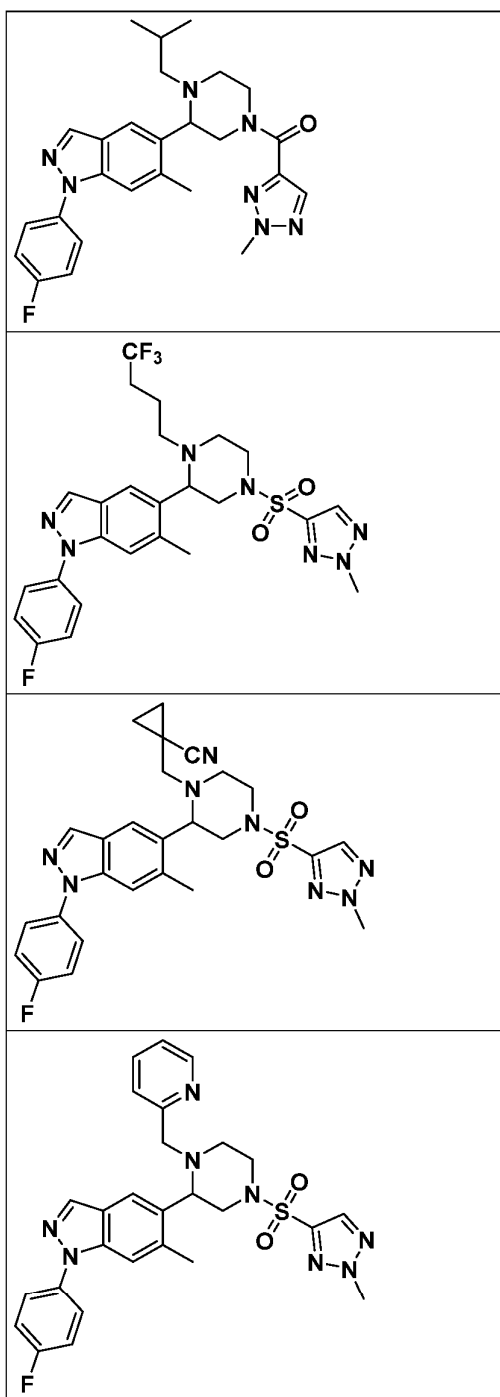


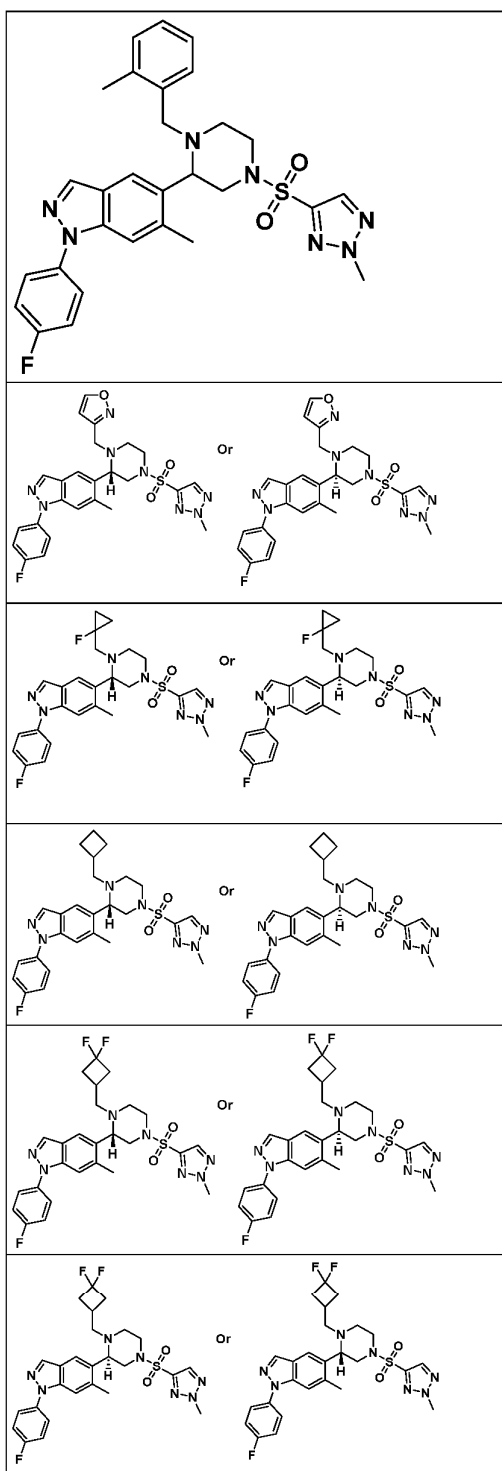


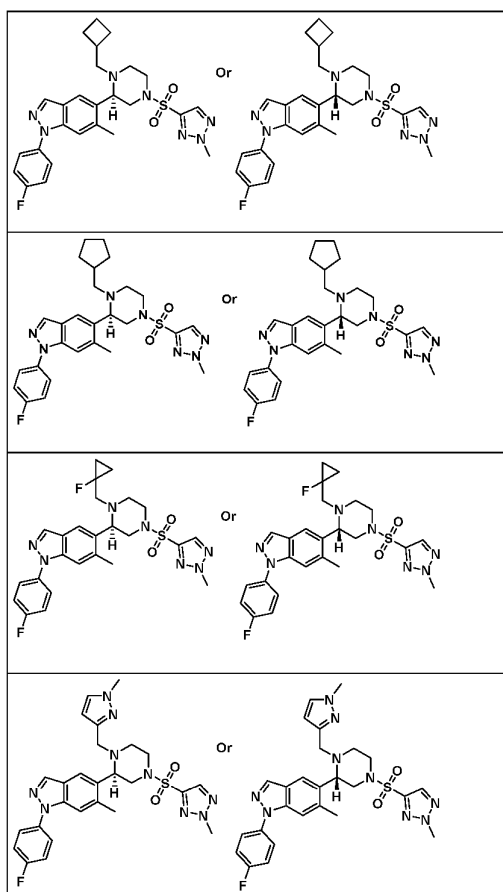
[0129] In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic or Id, or the pharmaceutically acceptable salt thereof, is a compound of Table 1D.

Table 1D.



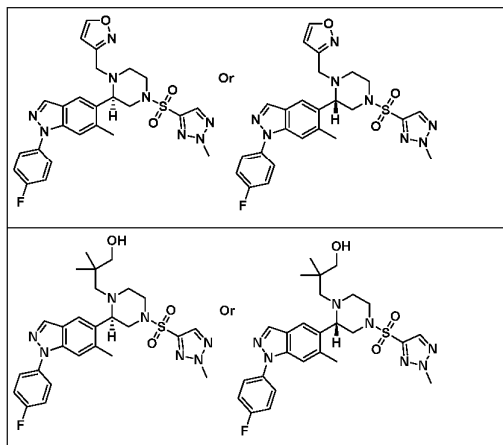


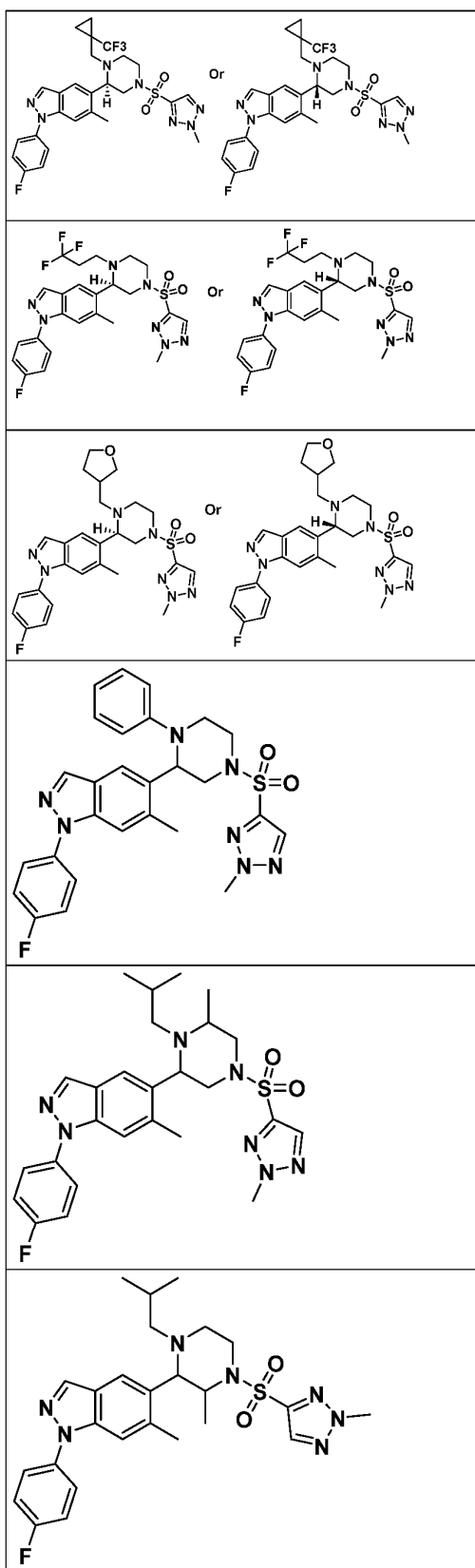


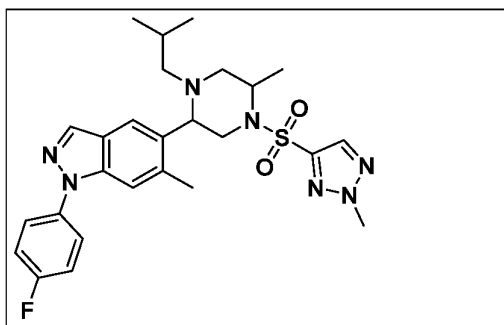


[0130] In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic or Id, or the pharmaceutically acceptable salt thereof, is a compound of Table 1E.

Table 1E.

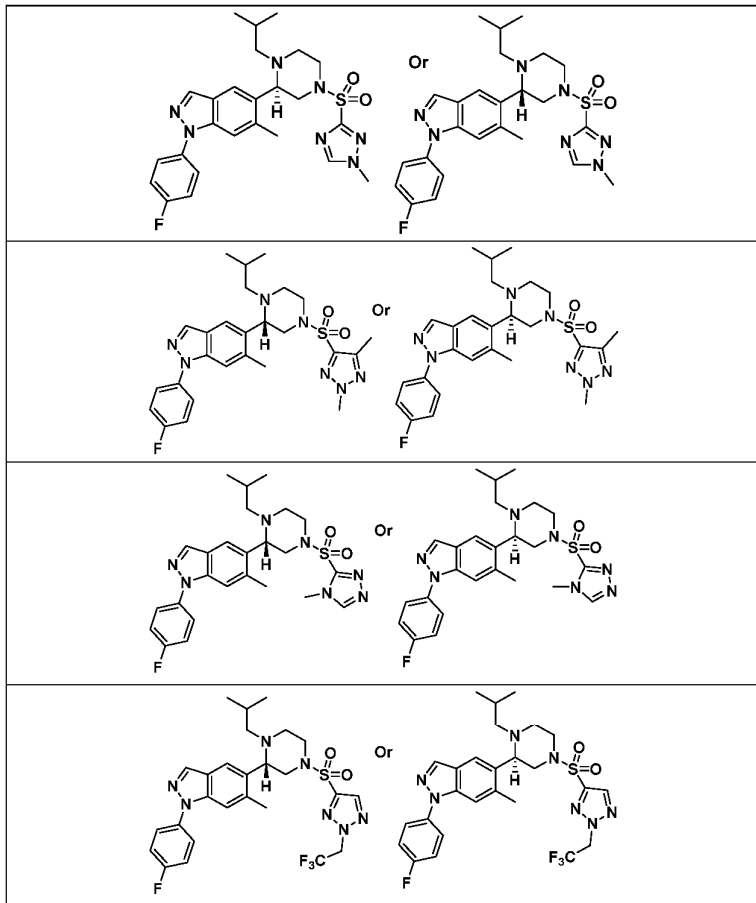


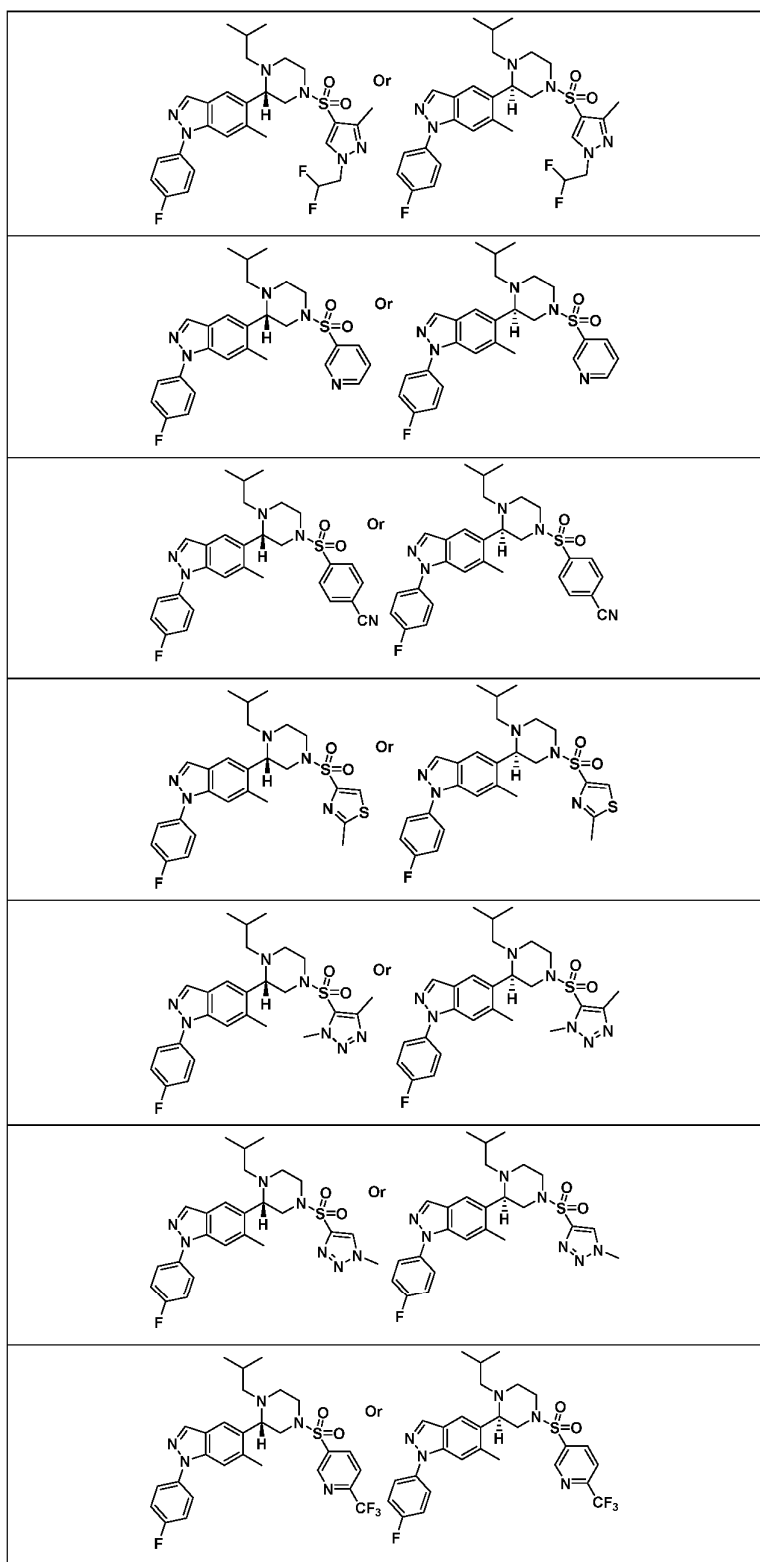


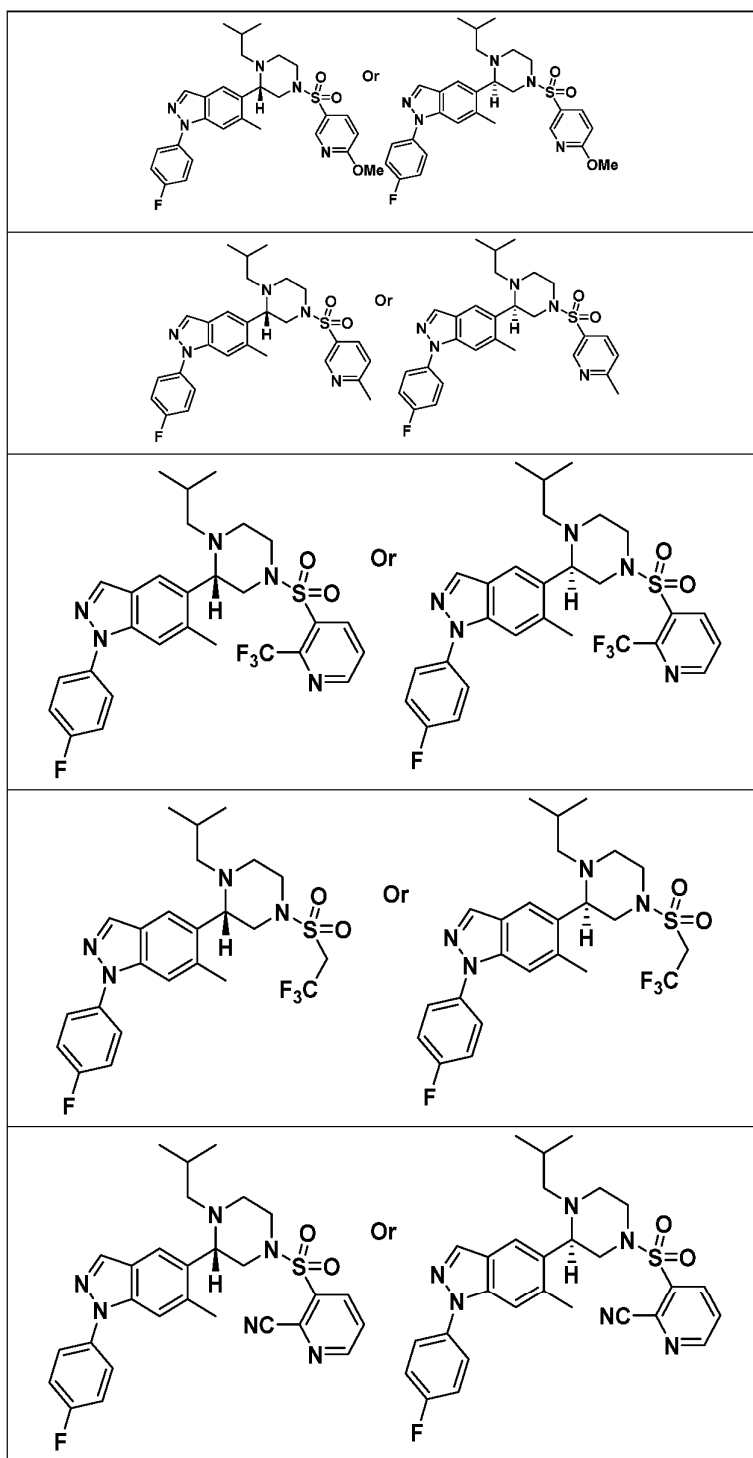


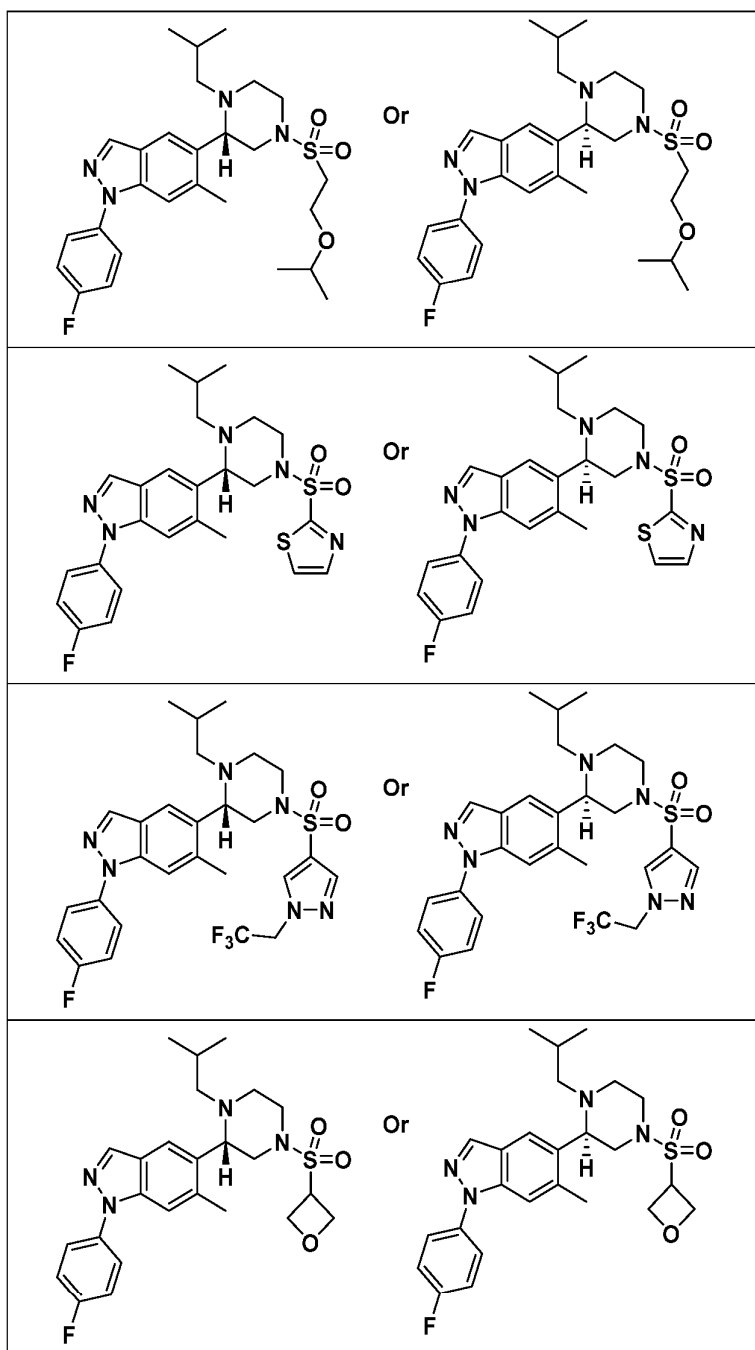
[0131] In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic or Id, or the pharmaceutically acceptable salt thereof, is a compound of Table 1F.

Table 1F.



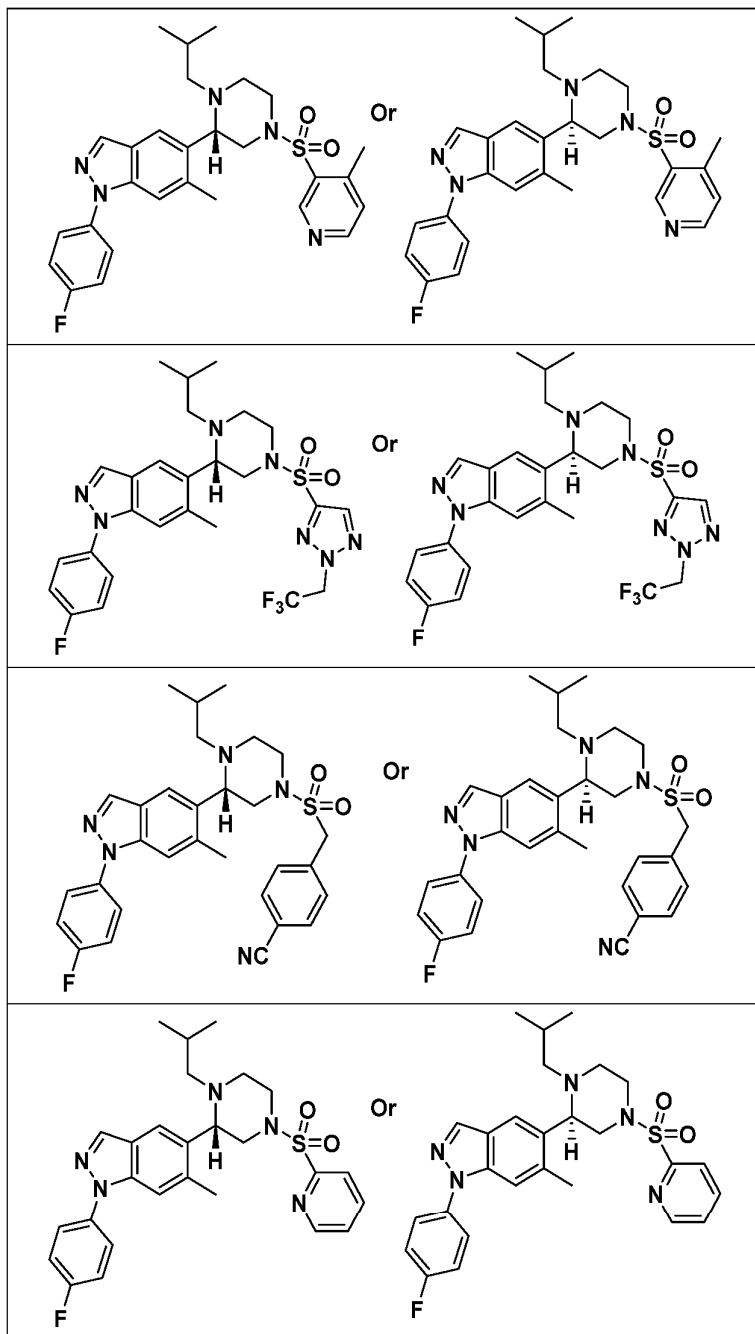


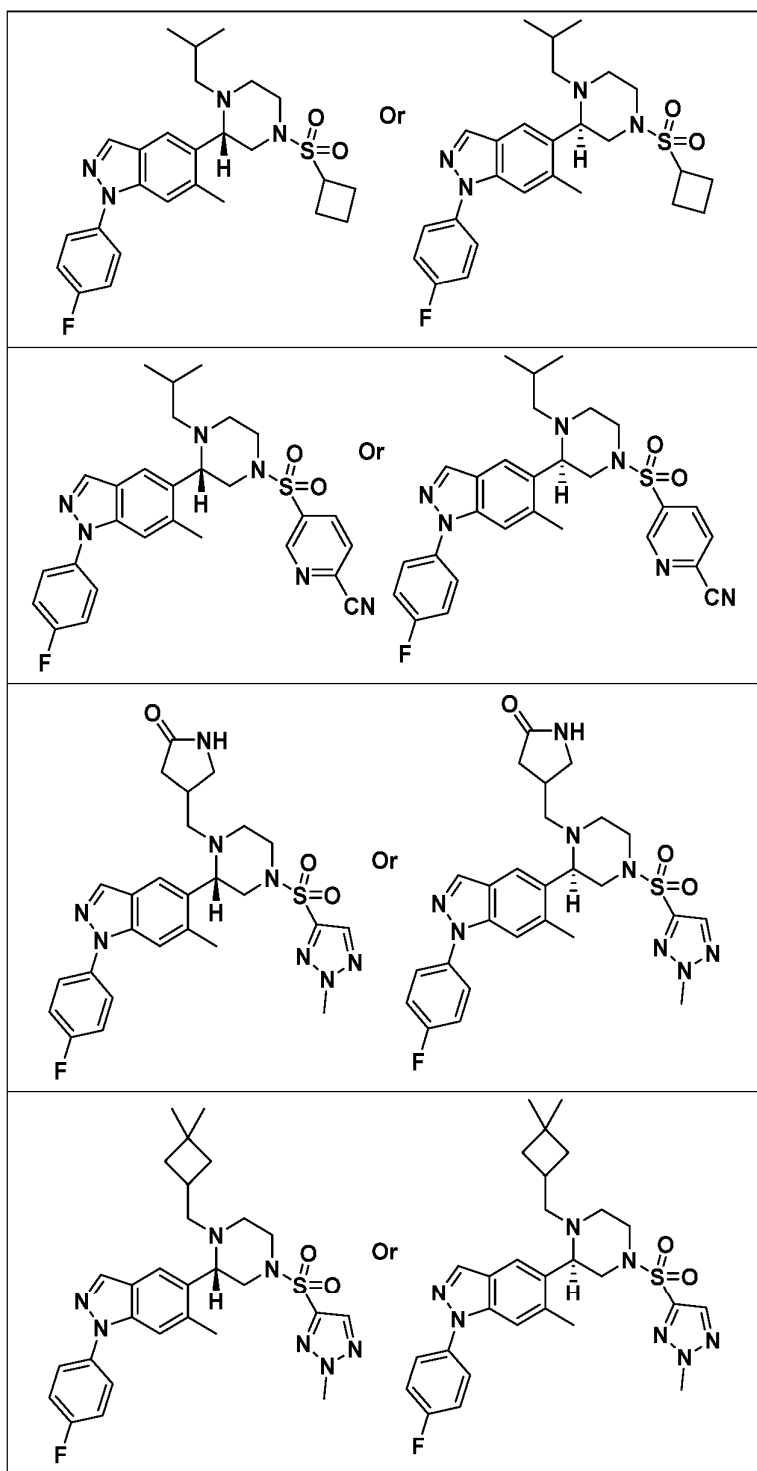


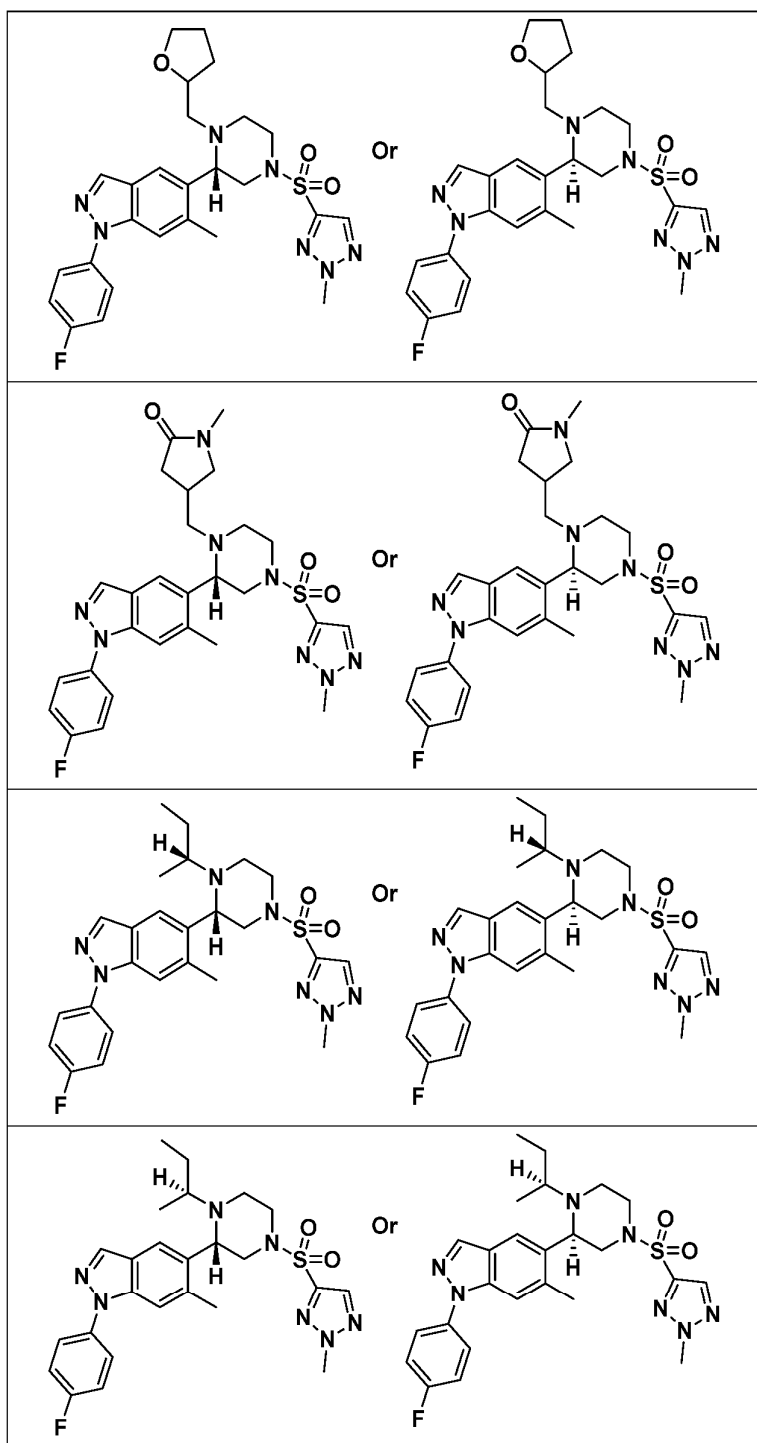


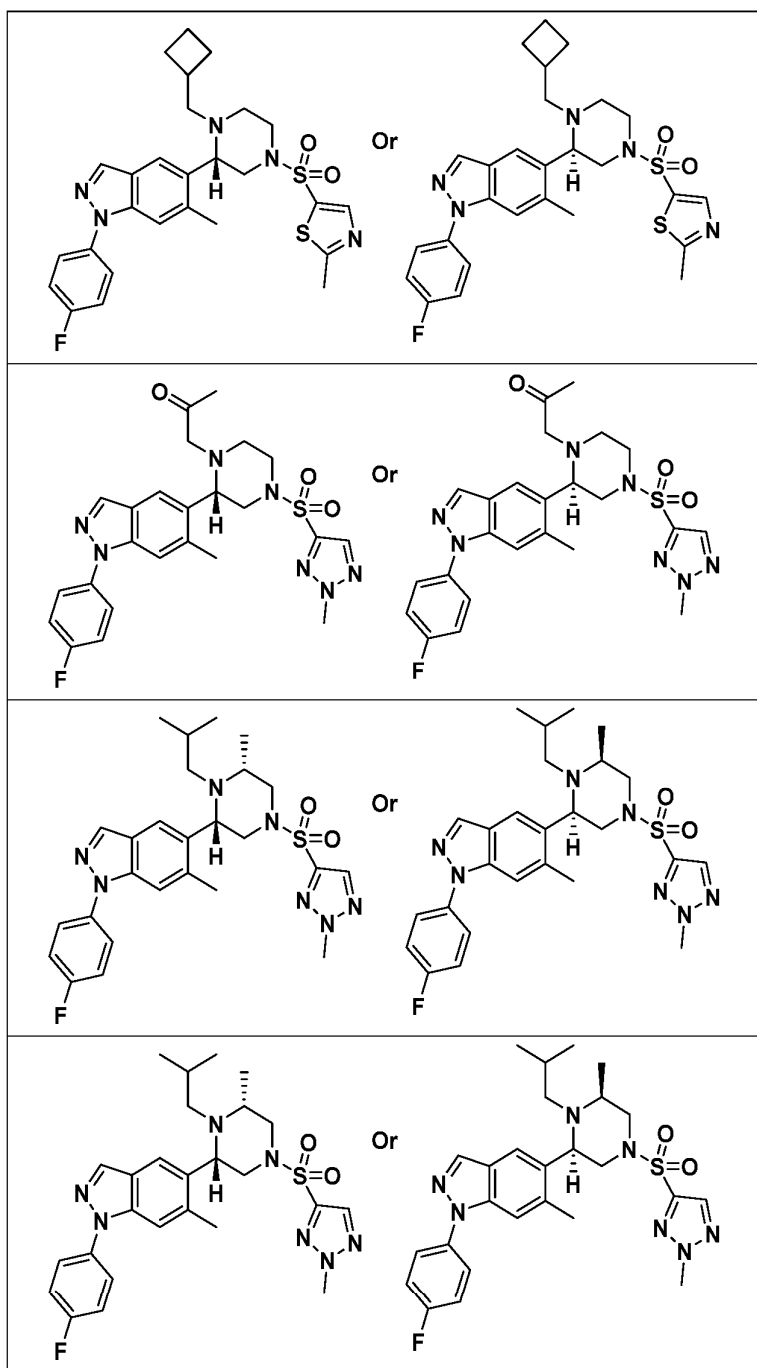
[0132] In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic or Id, or the pharmaceutically acceptable salt thereof, is a compound of Table 1G.

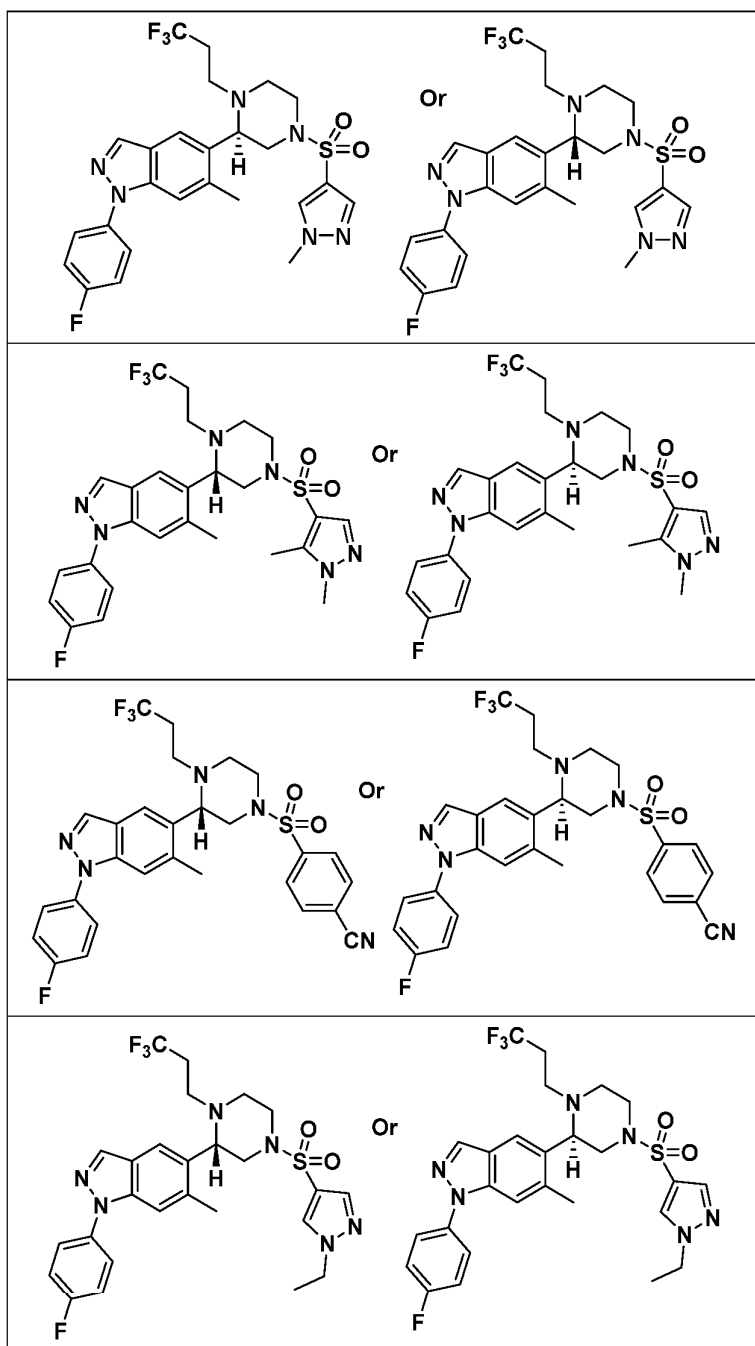
Table 1G.





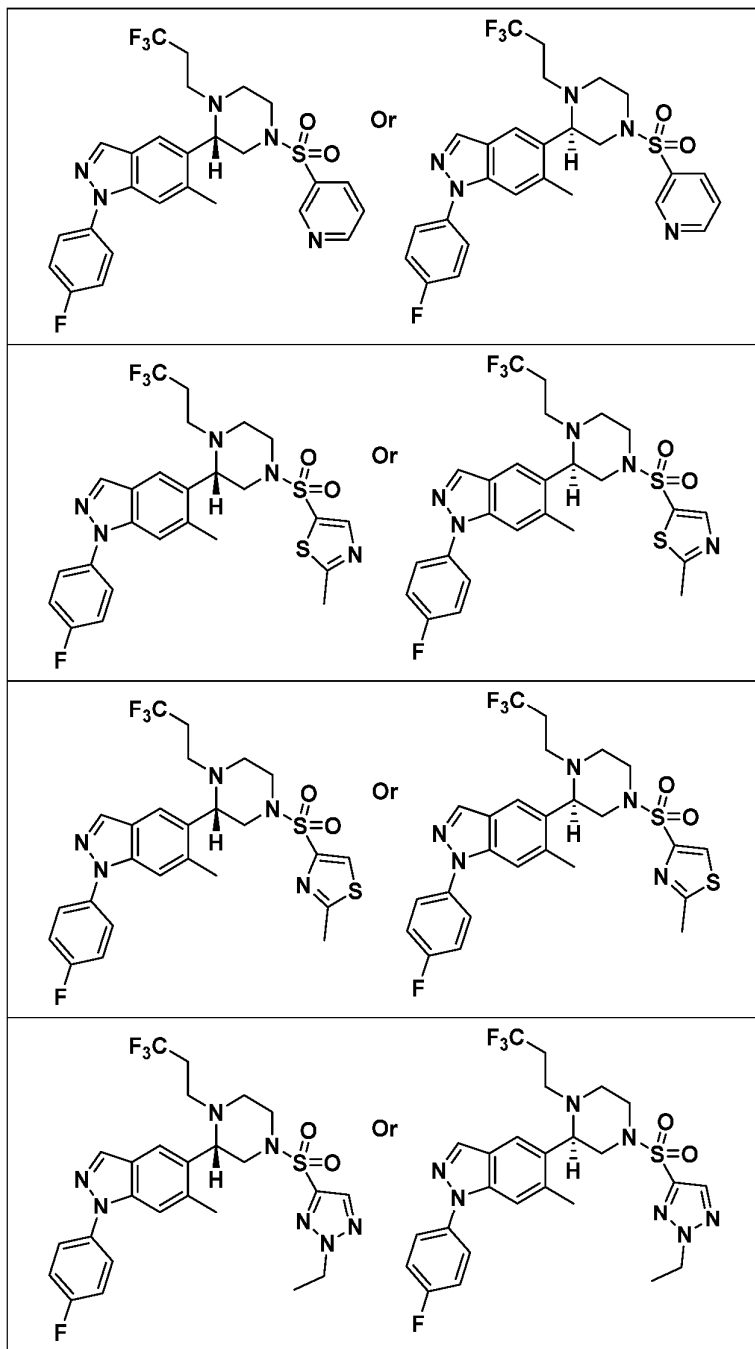


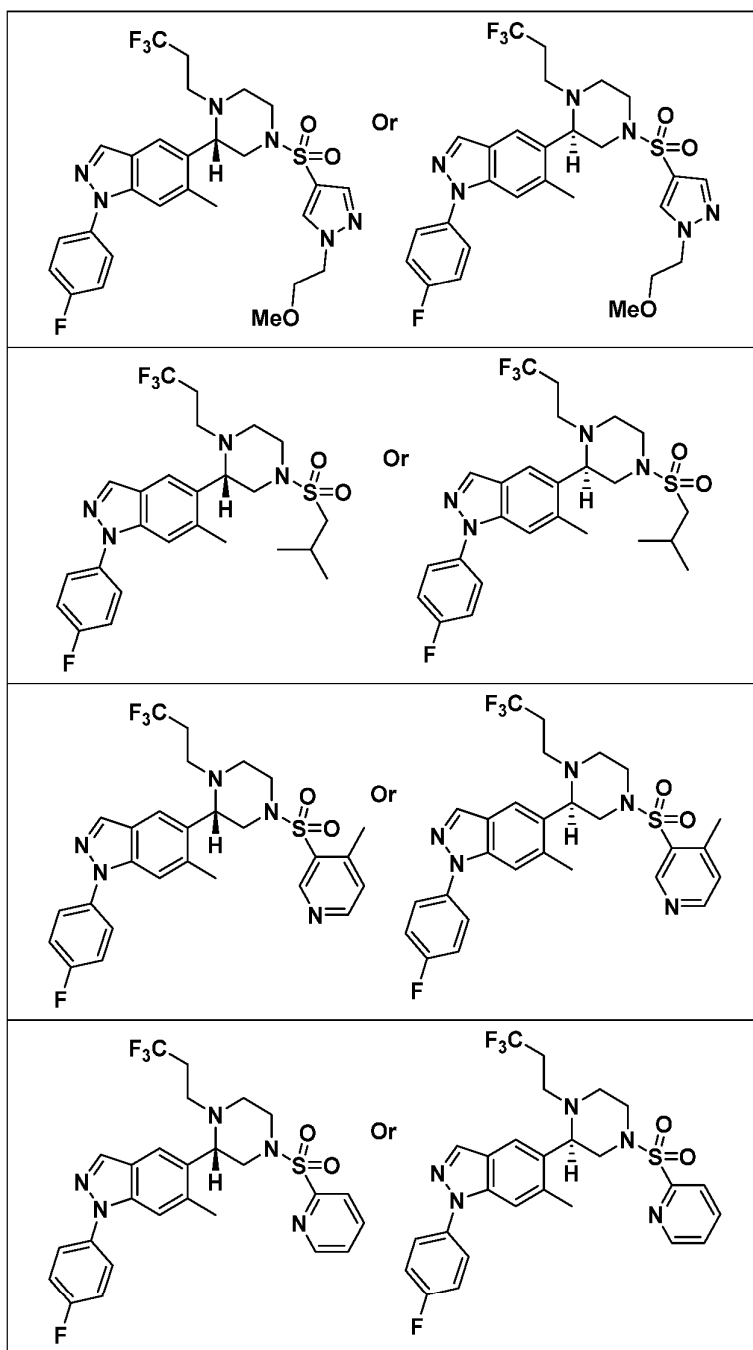


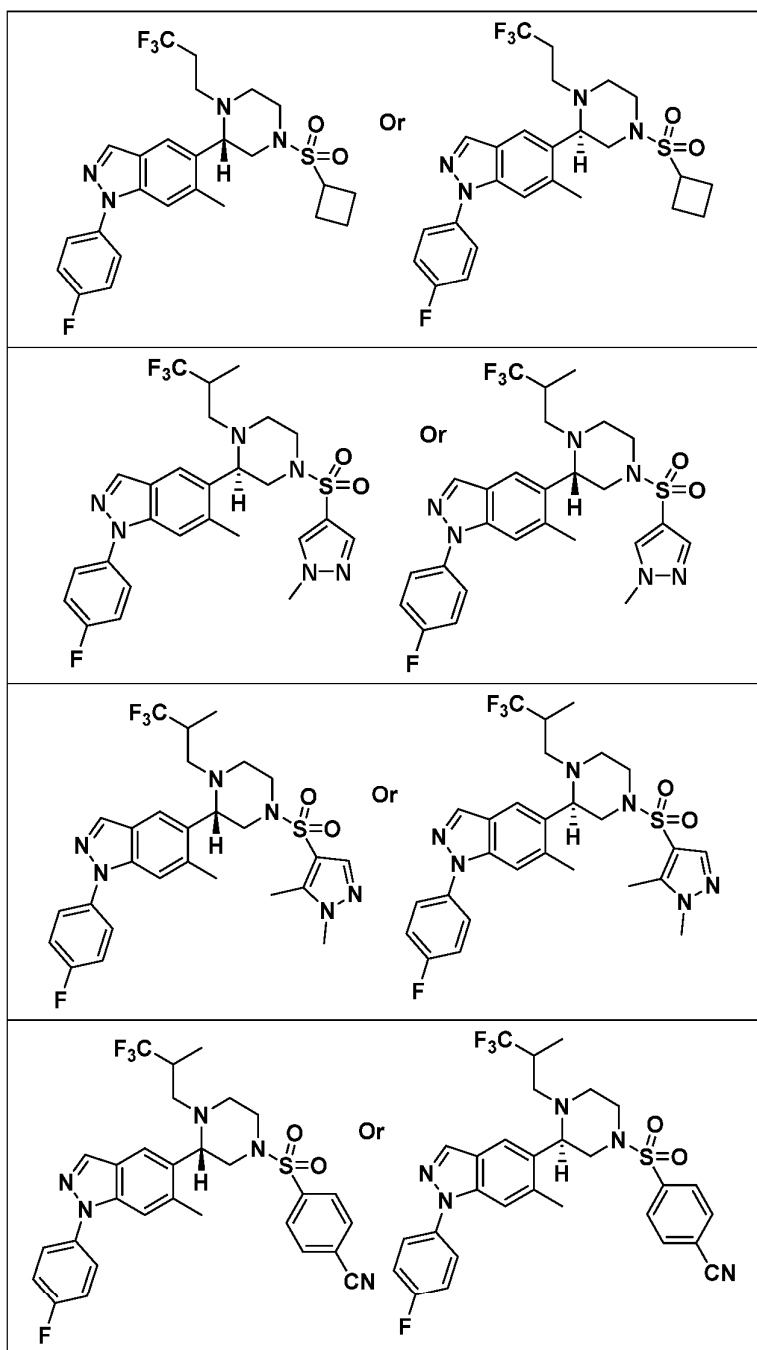


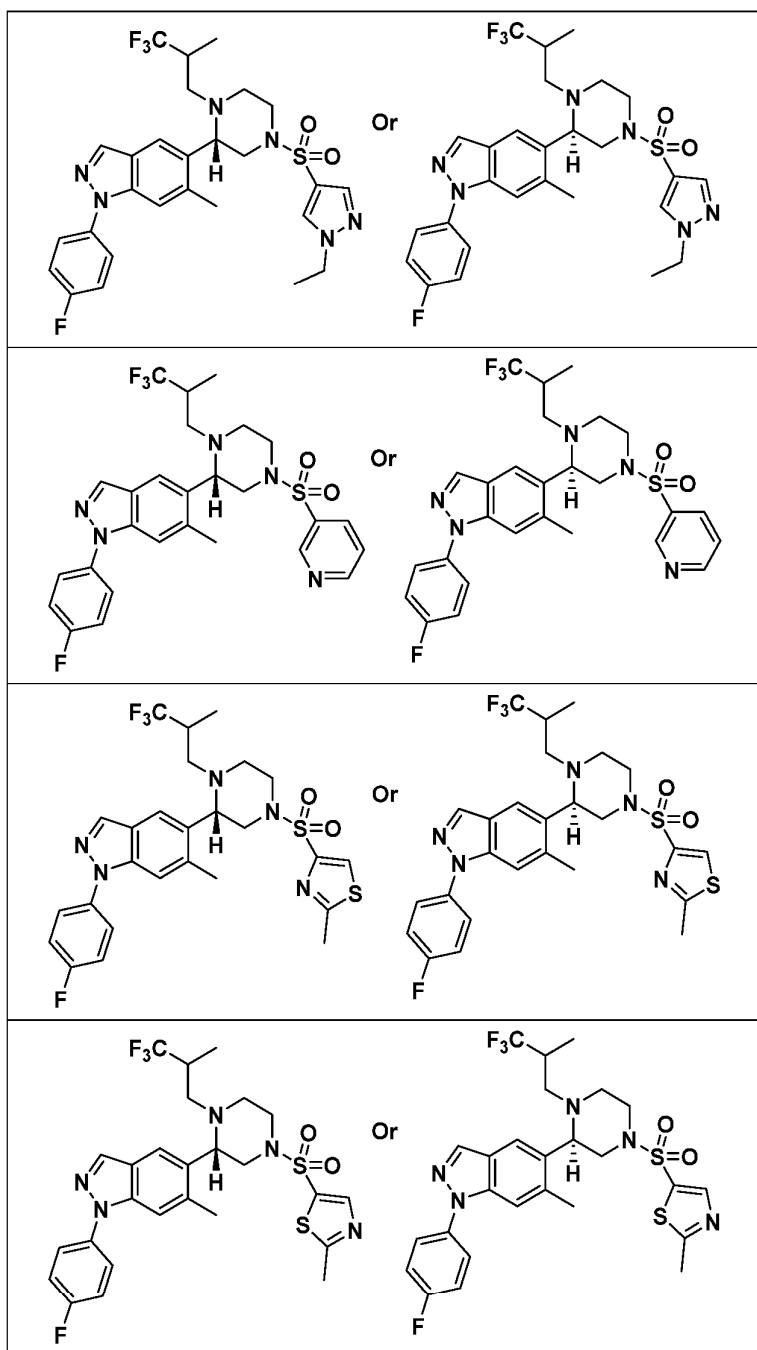
[0133] In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic or Id, or the pharmaceutically acceptable salt thereof, is a compound of Table 1H.

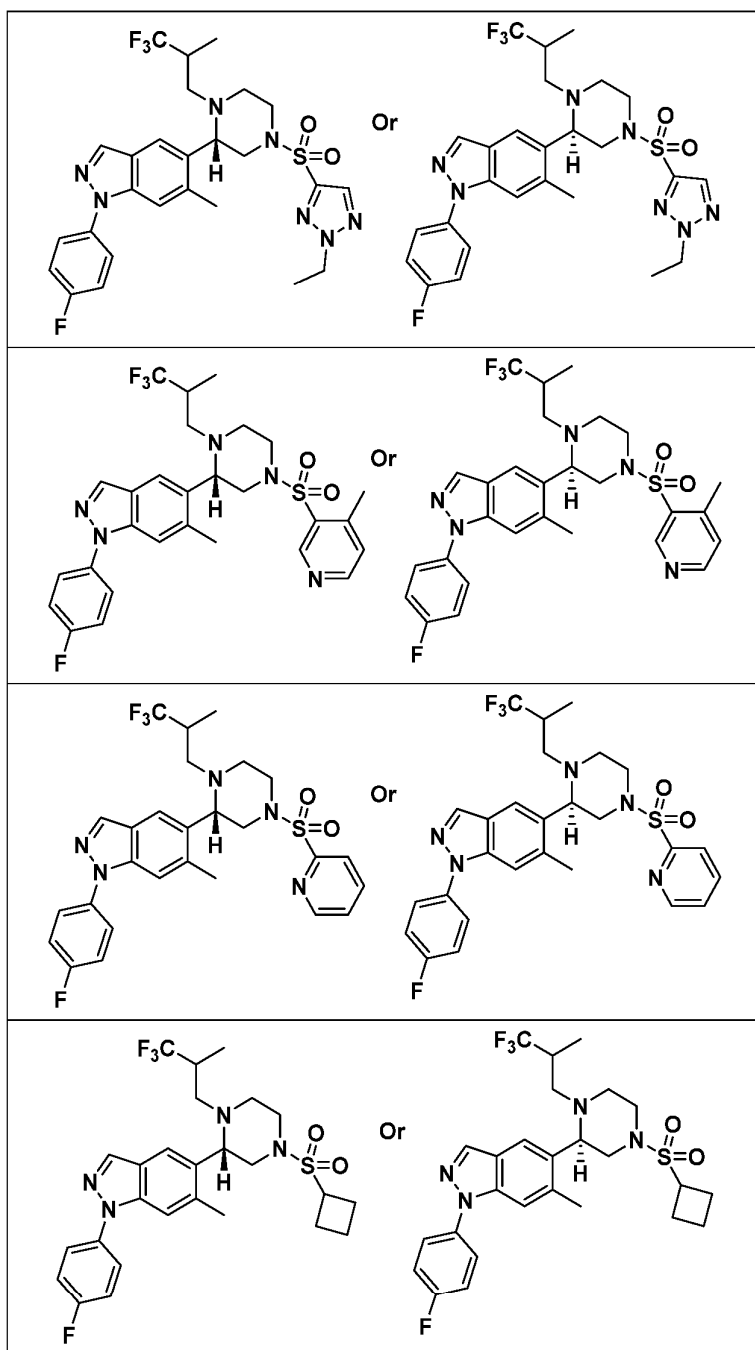
Table 1H.





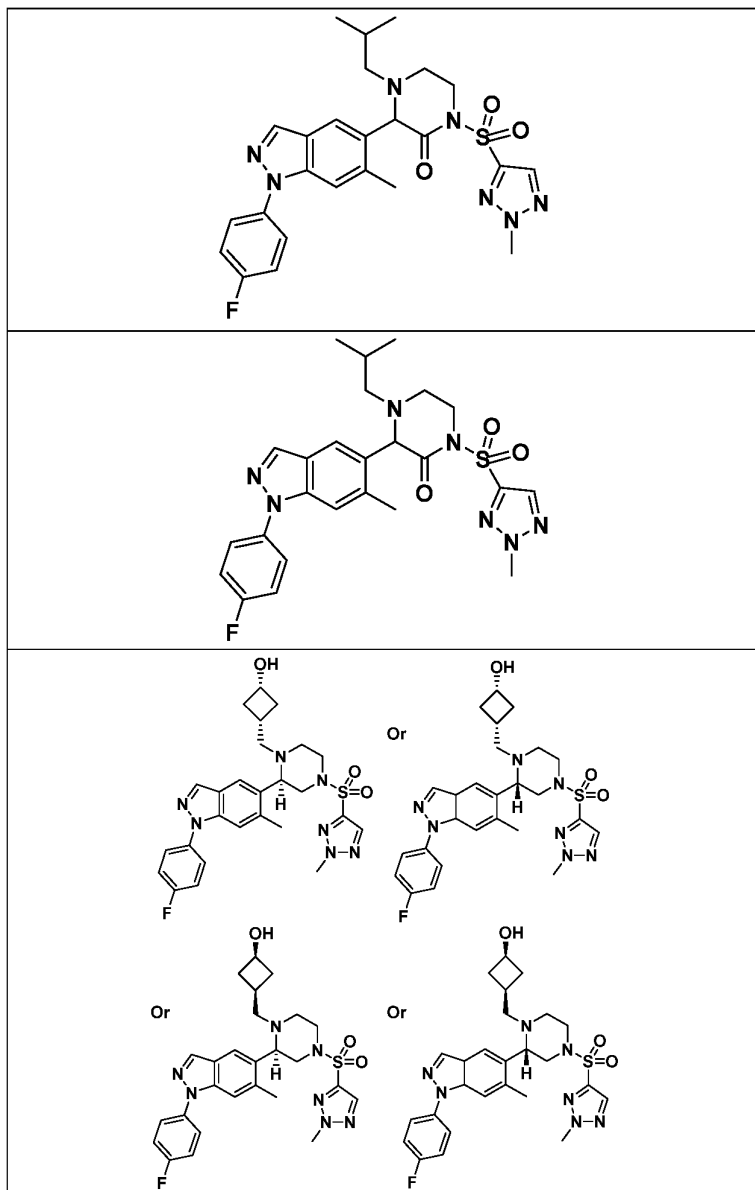


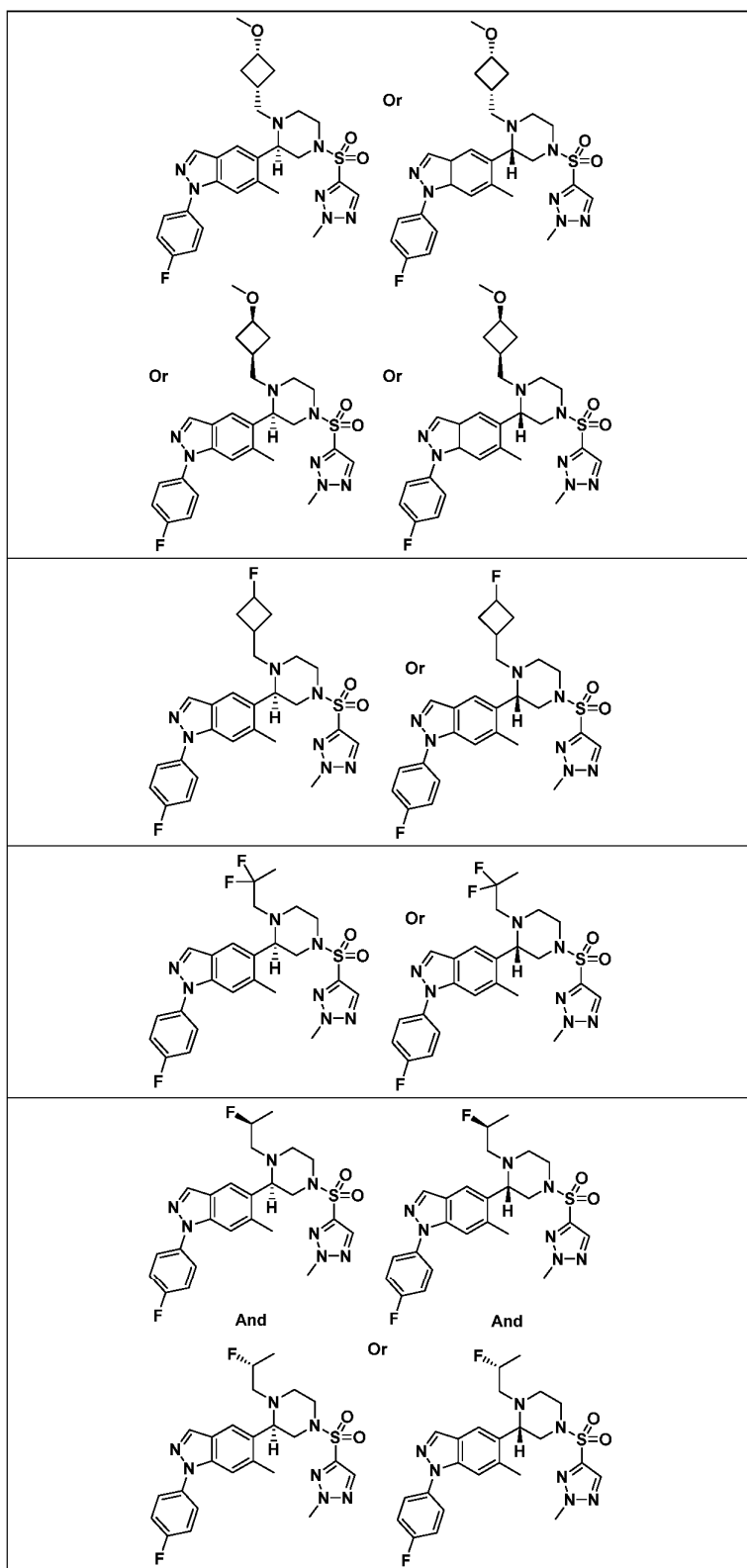


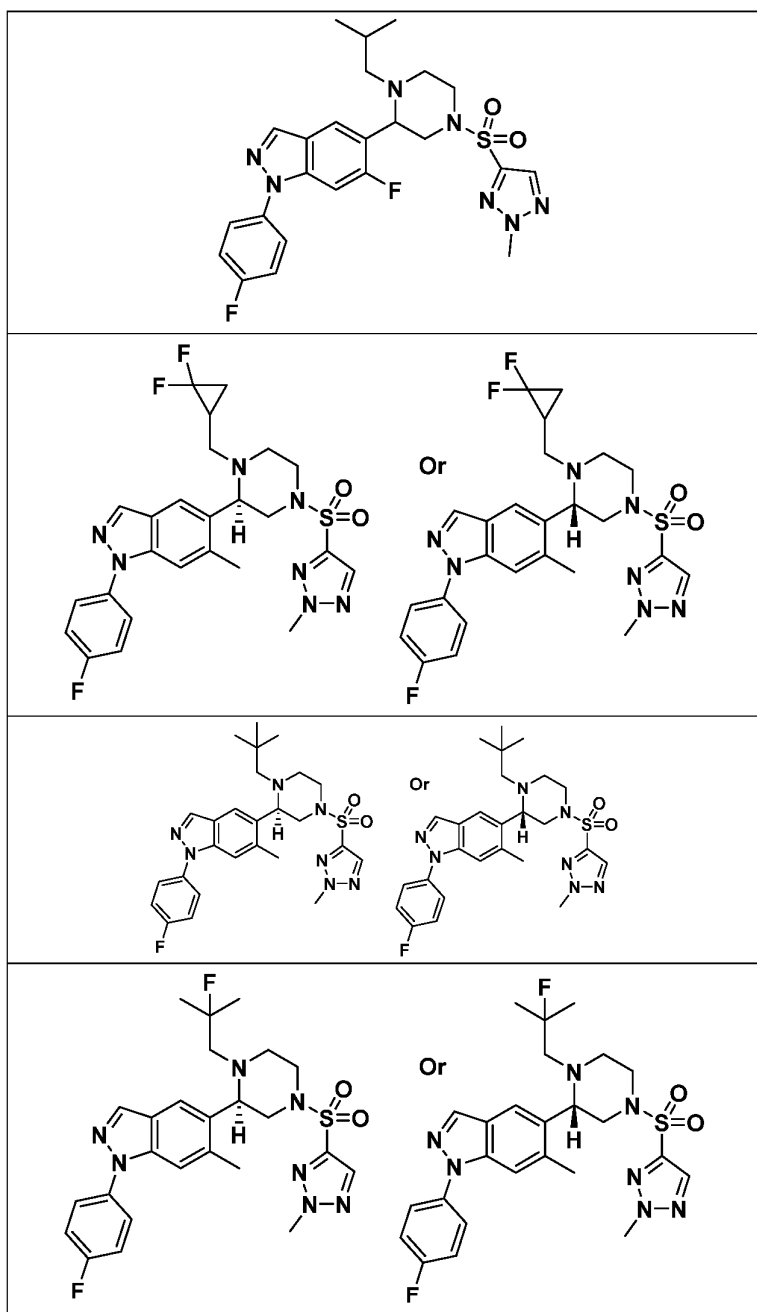


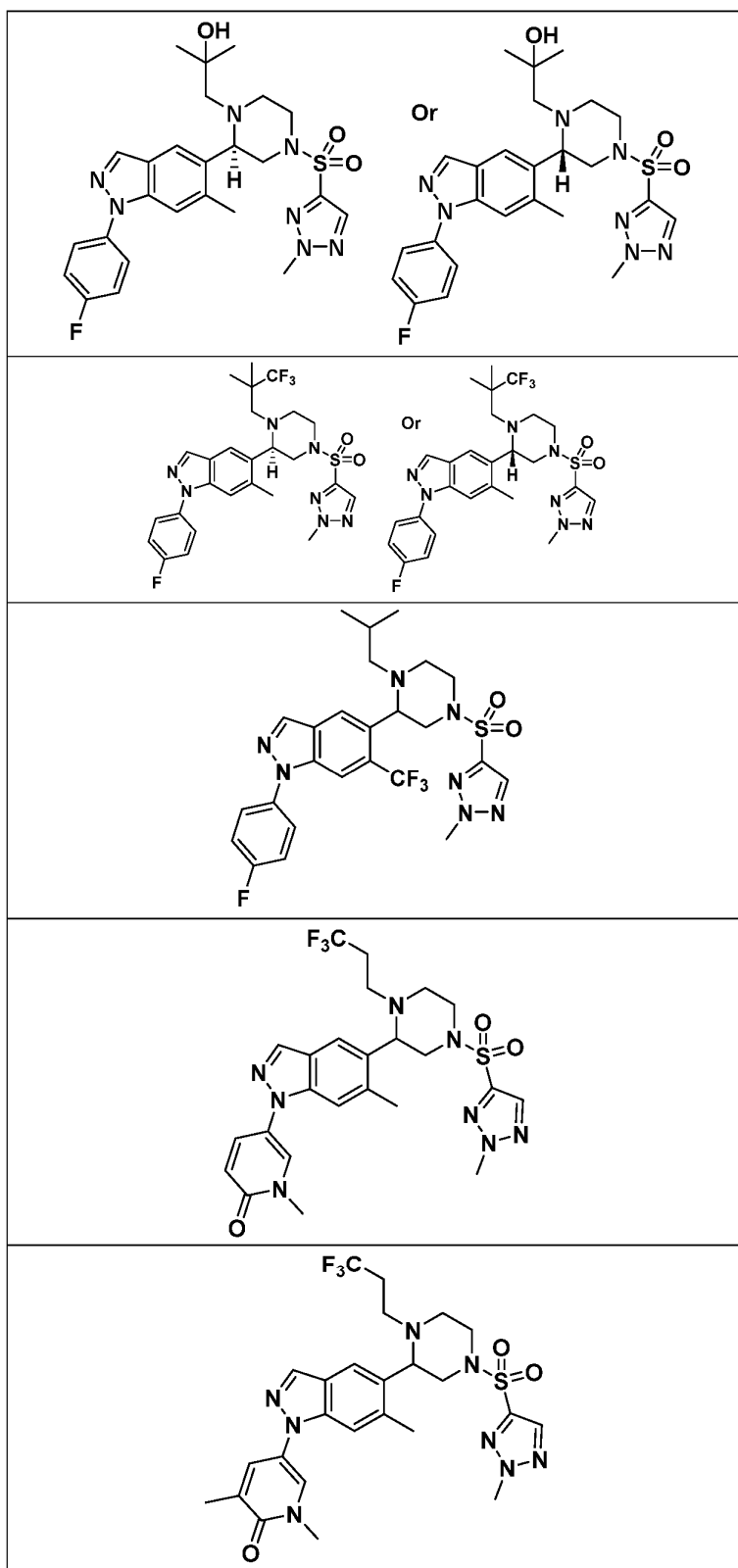
[0134] In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic or Id, or the pharmaceutically acceptable salt thereof, is a compound of Table 1I.

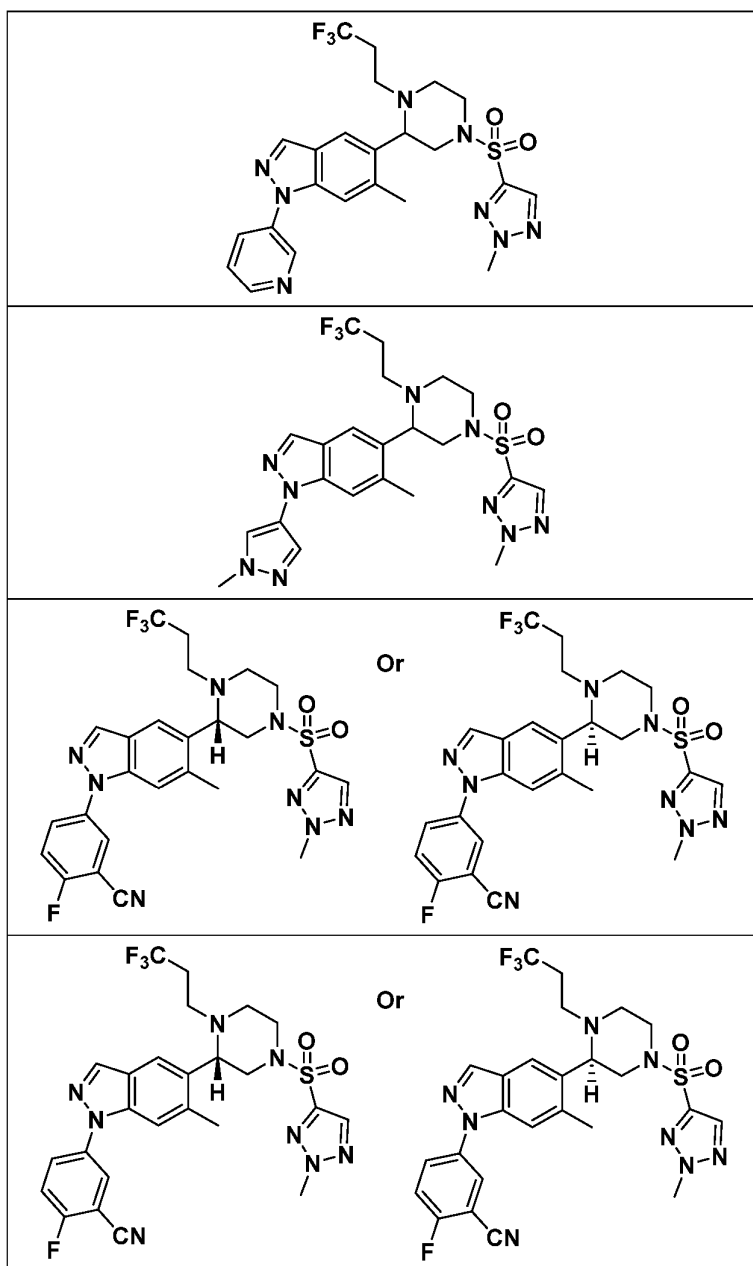
Table II.

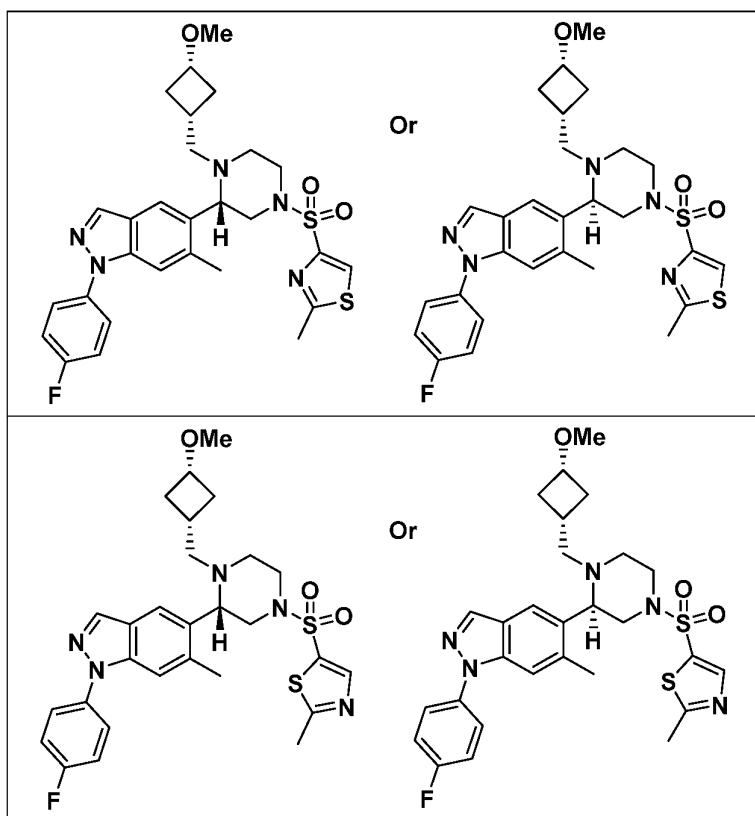






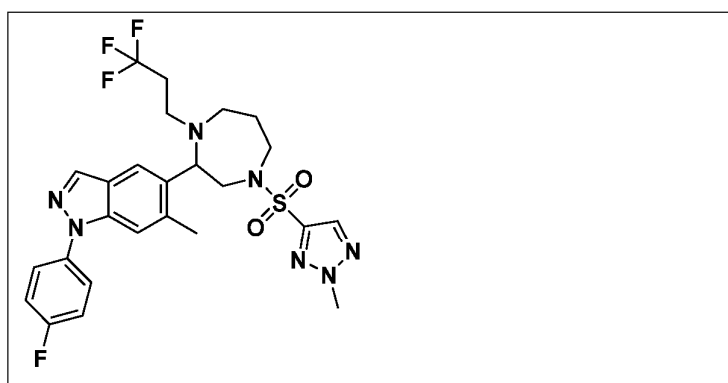


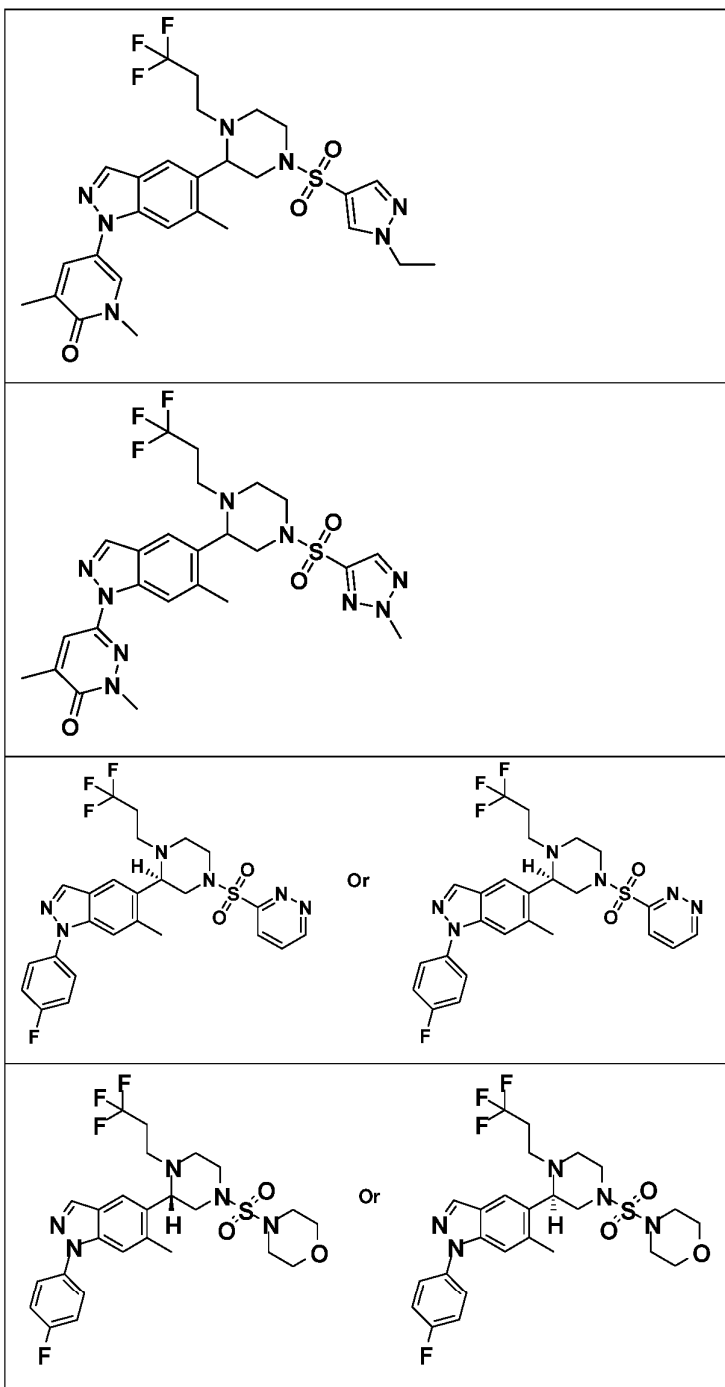


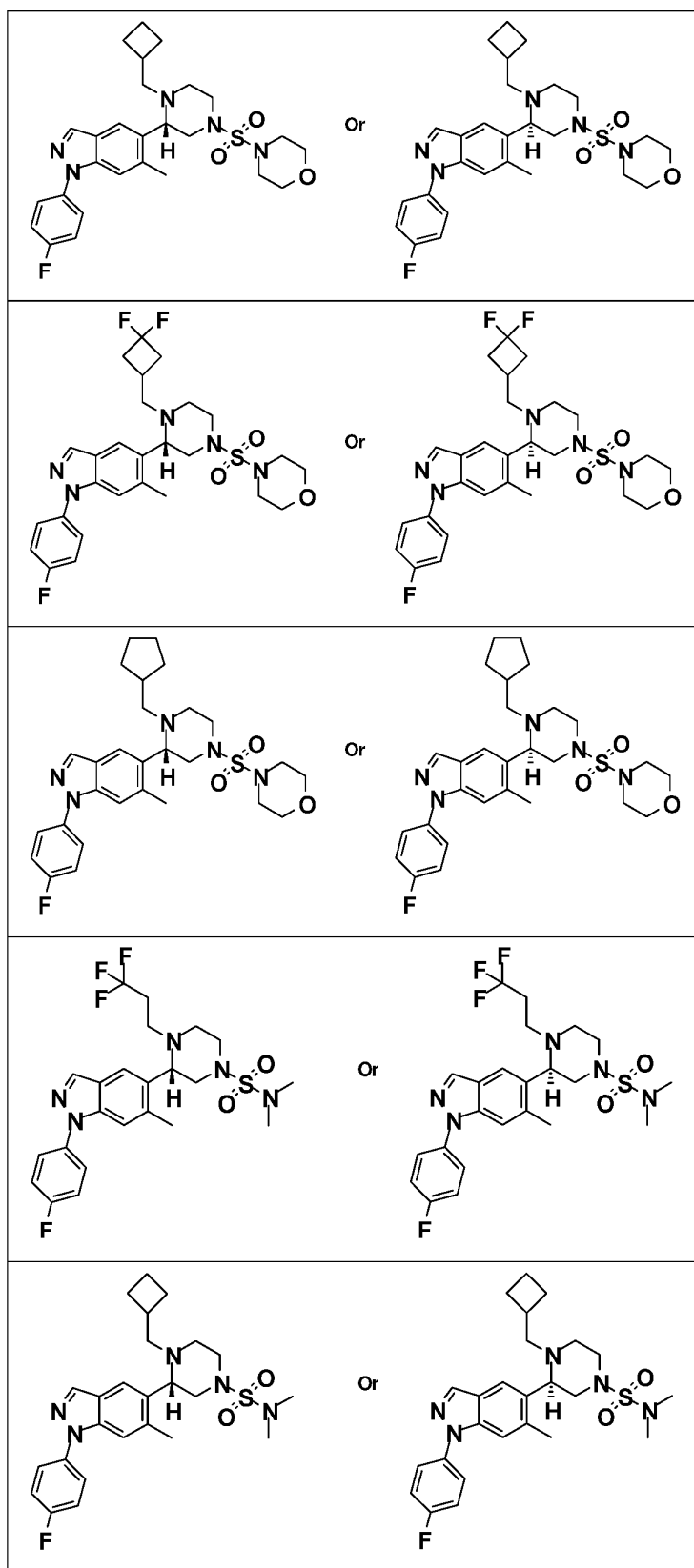


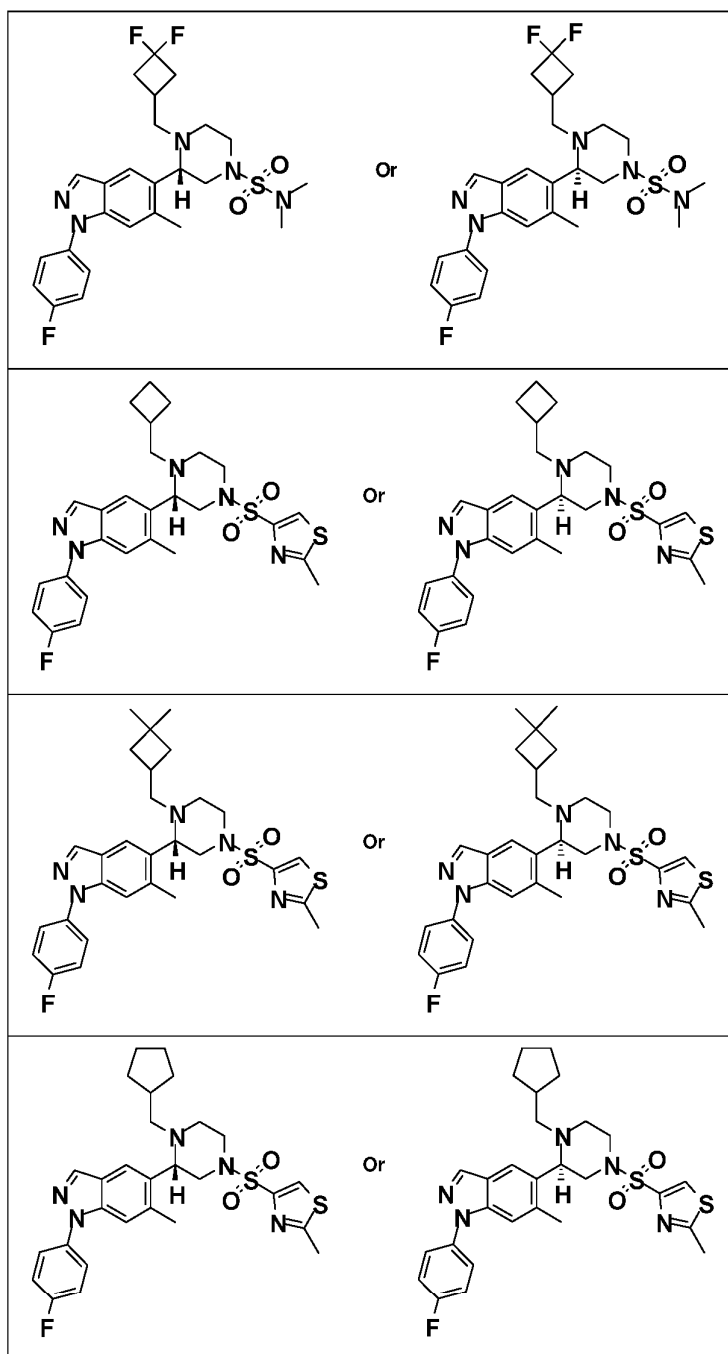
[0135] In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic or Id, or the pharmaceutically acceptable salt thereof, is a compound of Table 1J.

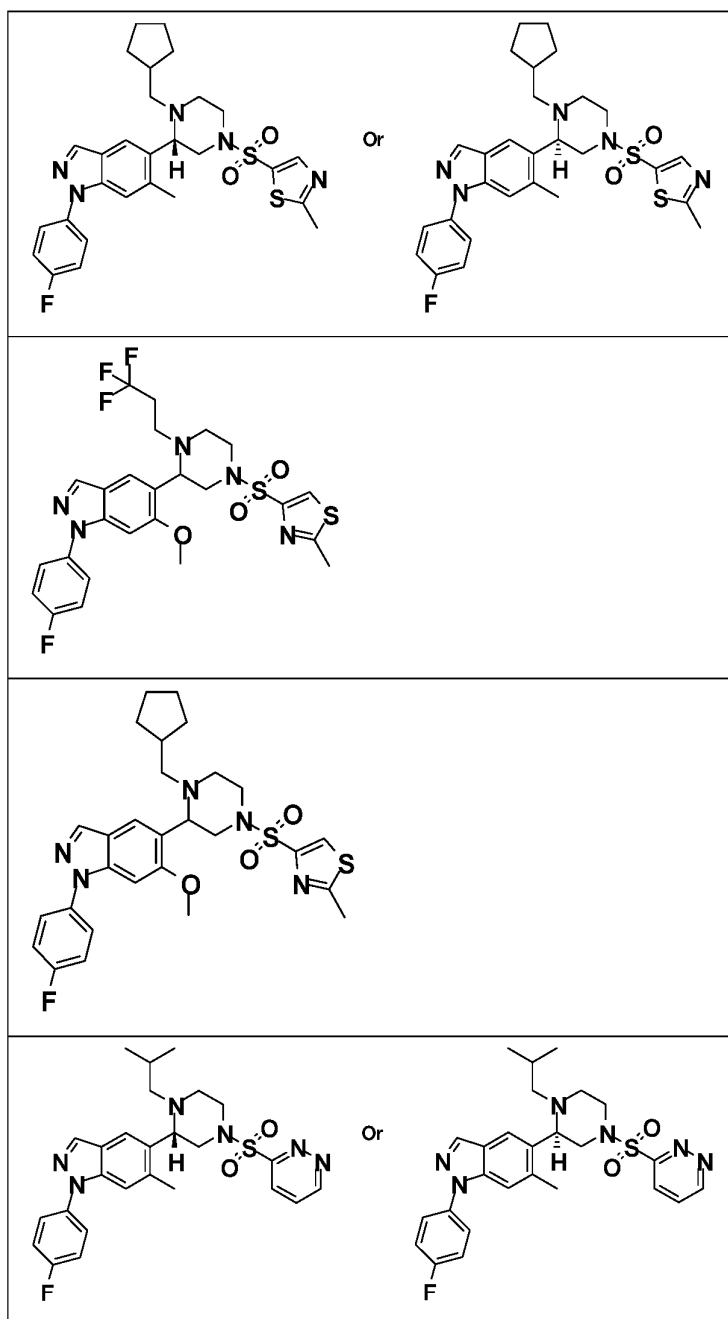
Table 1J.

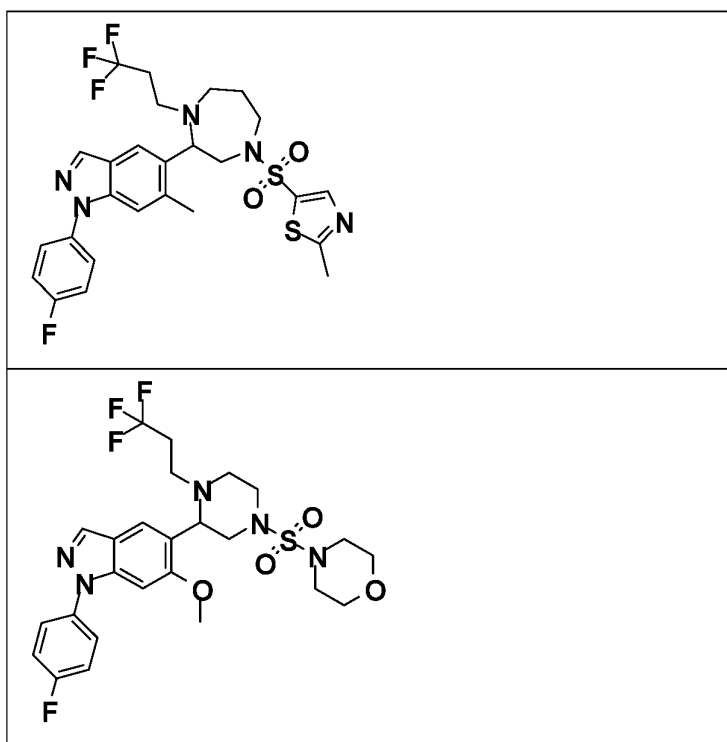






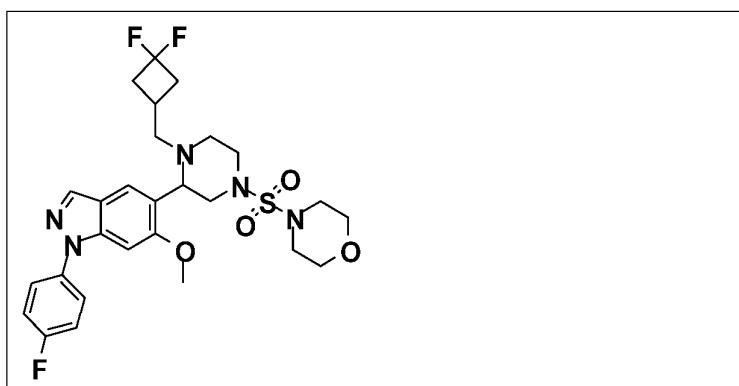


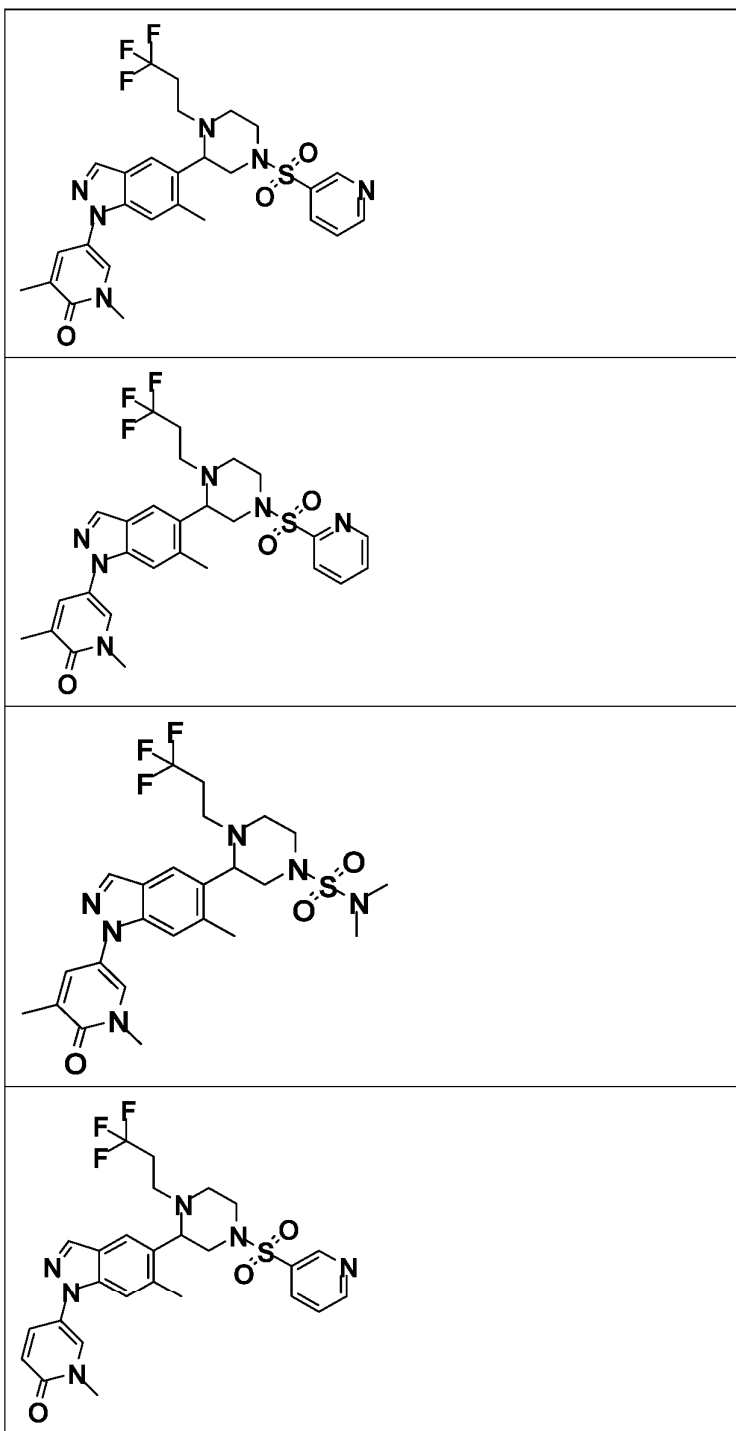


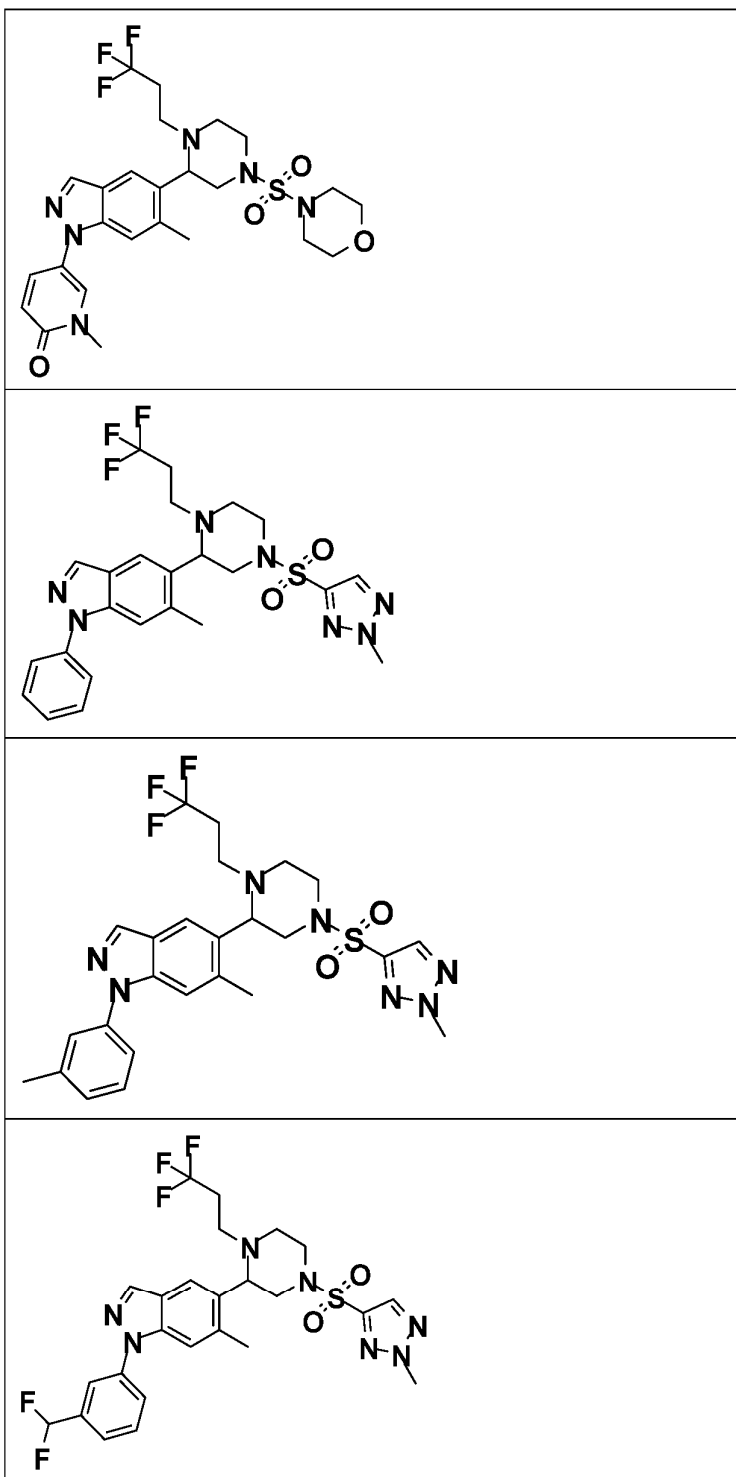


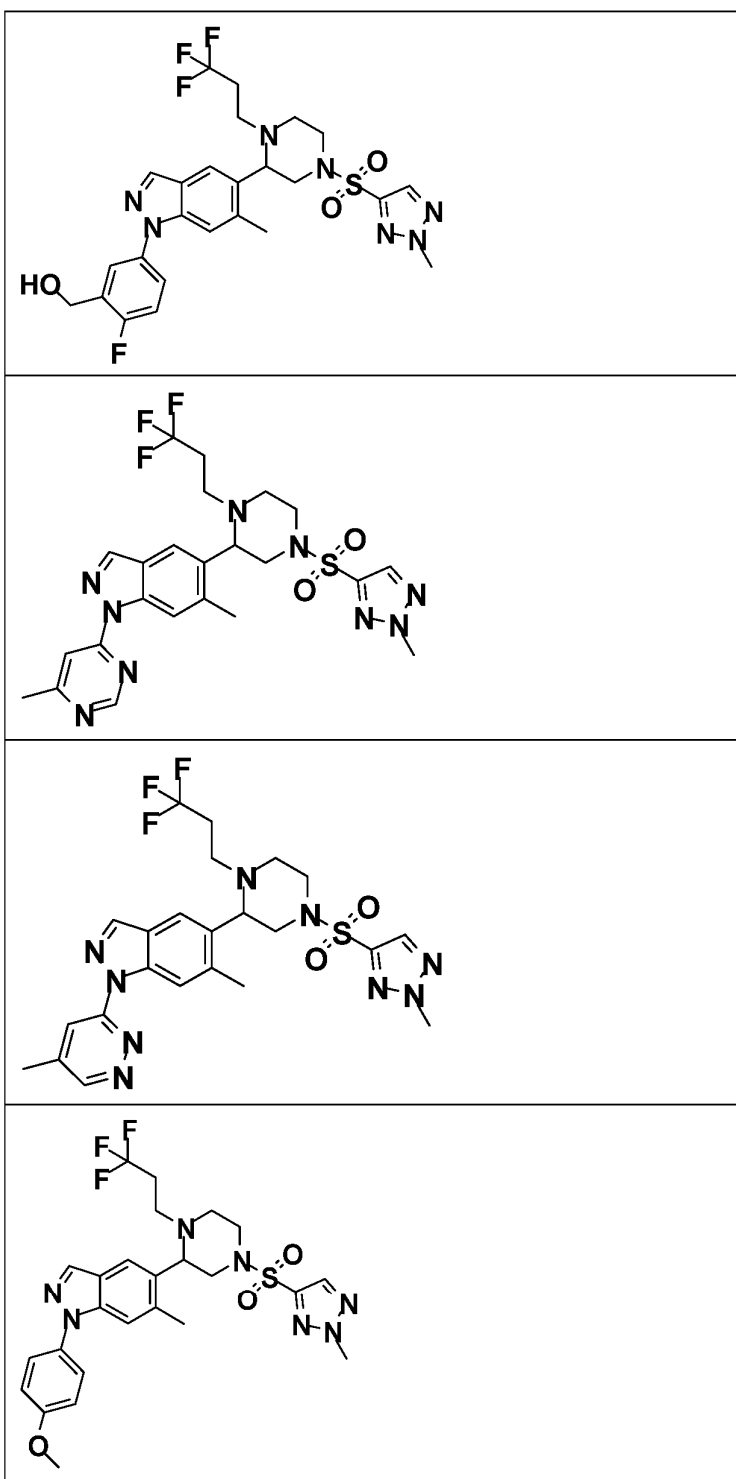
[0136] In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic or Id, or the pharmaceutically acceptable salt thereof, is a compound of Table 1K.

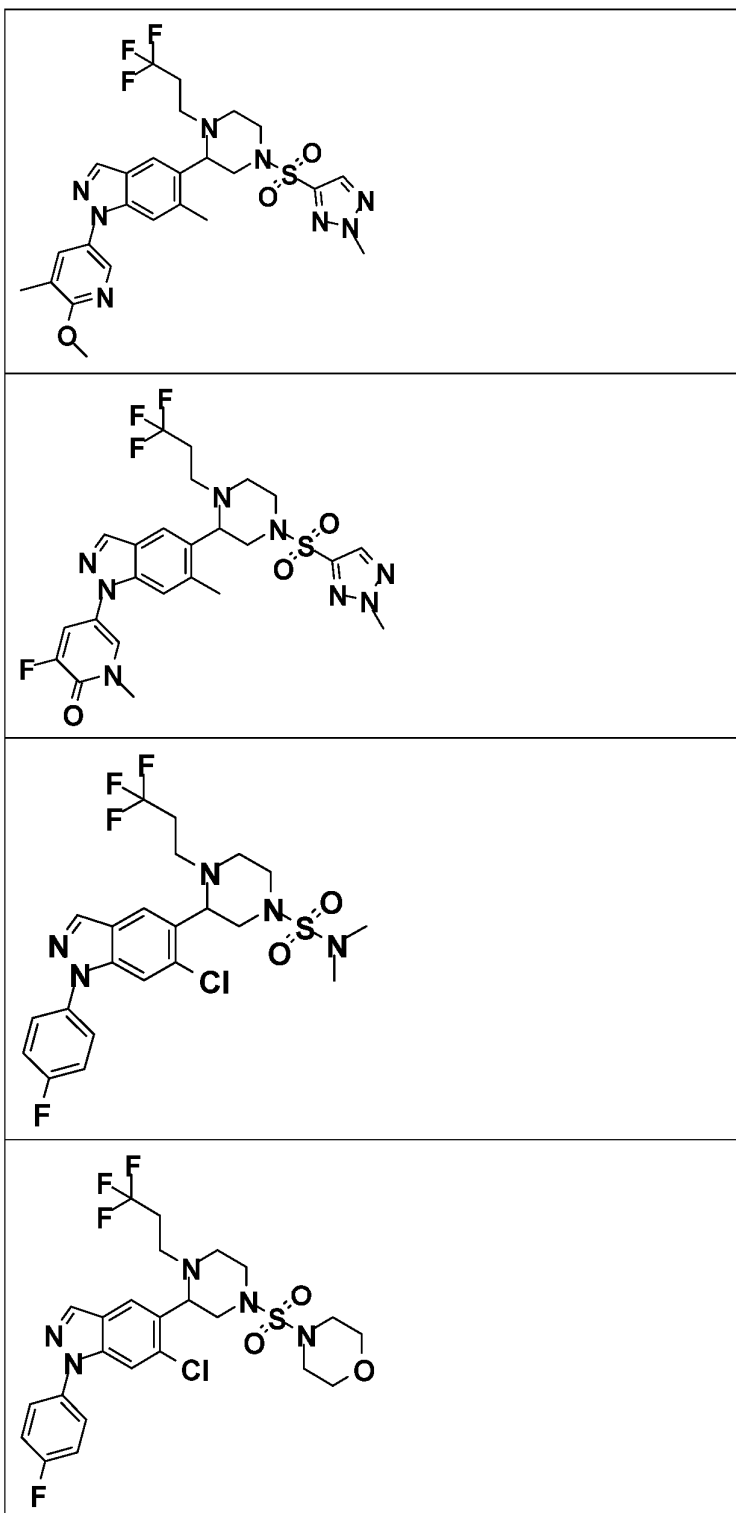
Table 1K.

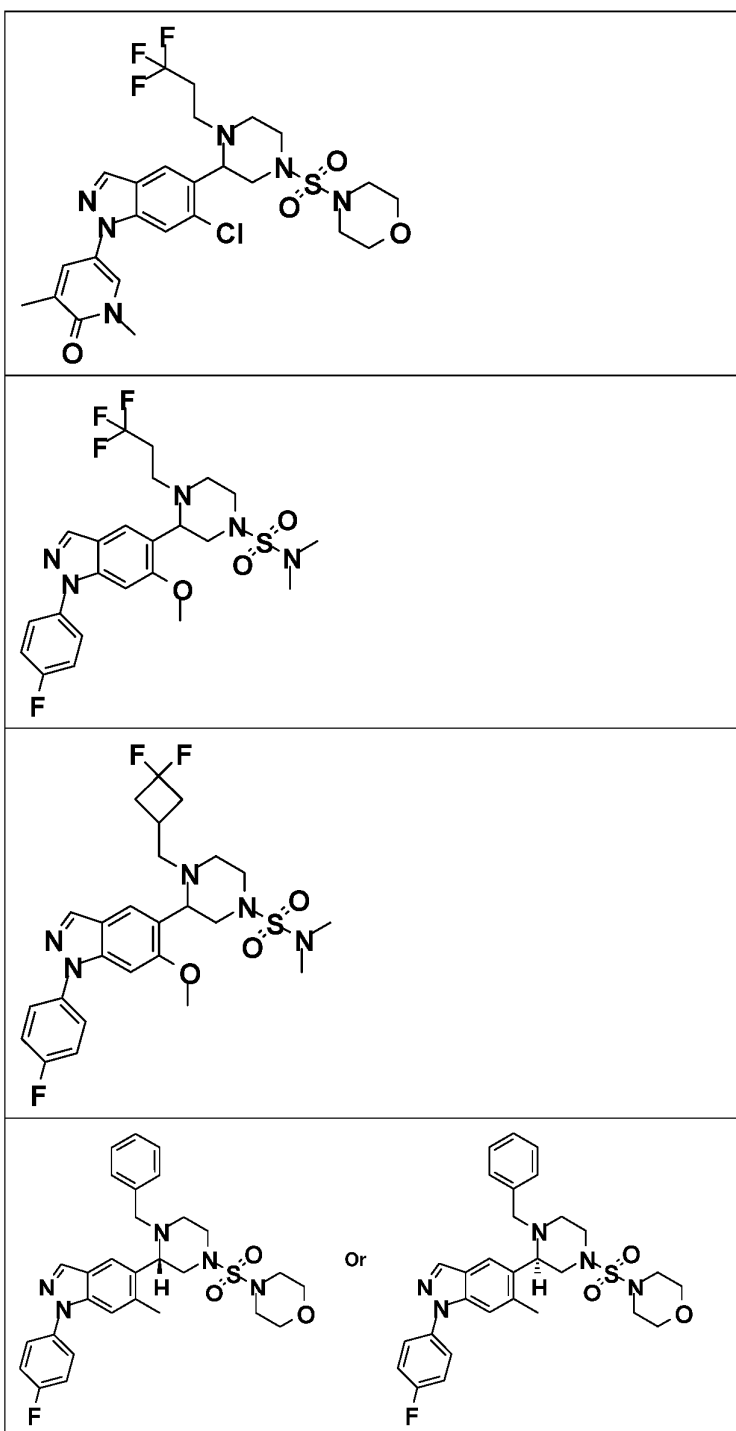


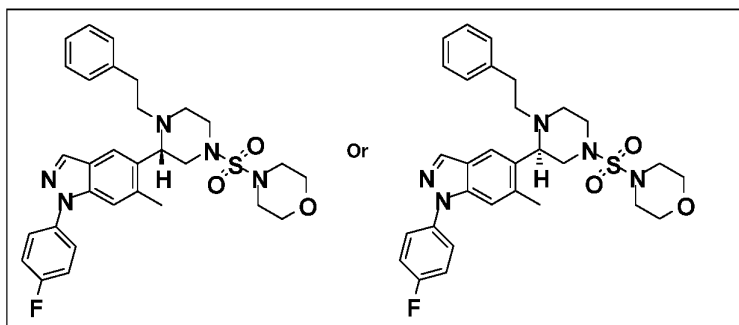












[0137] In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic or Id, or the pharmaceutically acceptable salt thereof, is a compound of Table 1A, Table 1B, Table 1C, Table 1D, Table 1E, Table 1F, Table 1G, Table 1H, Table 1I, Table 1J, or Table 1K. In some

5 embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic or Id, or the pharmaceutically acceptable salt thereof, is a compound of Table 1A, Table 1B, Table 1C, Table 1D, Table 1E, Table 1F, Table 1G, Table 1H, or Table 1I. In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic or Id, or the pharmaceutically acceptable salt thereof, is a compound of Table 1A, Table 1B, Table 1C, Table 1D or Table 1E. In some

10 embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic or Id, or the pharmaceutically acceptable salt thereof, is a compound of Table 1F, Table 1G, Table 1H, or Table 1I. In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic or Id, or the pharmaceutically acceptable salt thereof, is a compound of Table 1J, or Table 1K. In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic or Id, or the

15 pharmaceutically acceptable salt thereof, is a compound of Table 1A. In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic or Id, or the pharmaceutically acceptable salt thereof, is a compound of Table 1B. In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic or Id, or the pharmaceutically acceptable salt thereof, is a compound of Table 1C. In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic or Id, or the pharmaceutically acceptable salt thereof, is a compound of Table 1D. In some

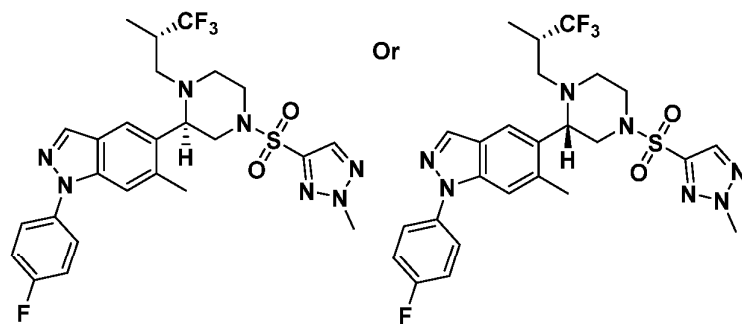
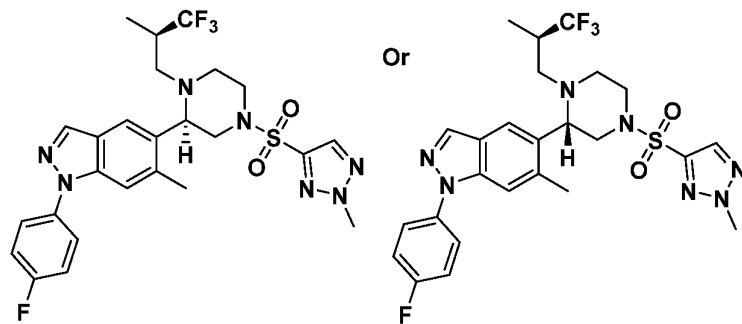
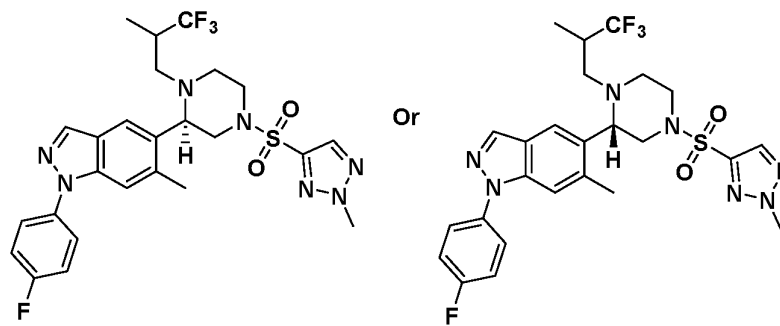
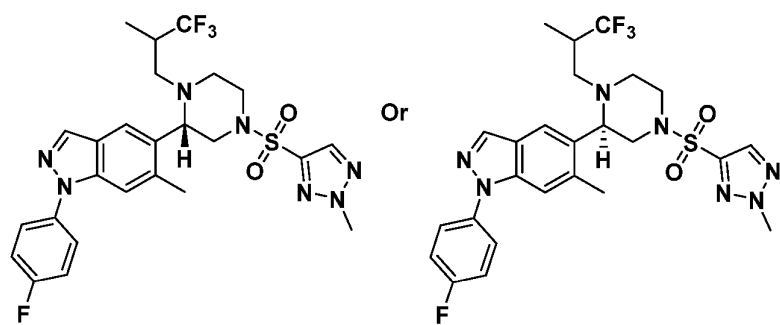
20 embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic or Id, or the pharmaceutically acceptable salt thereof, is a compound of Table 1E. In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic or Id, or the pharmaceutically acceptable salt thereof, is a compound of Table 1F. In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic or Id, or the pharmaceutically acceptable salt thereof, is a compound of Table 1G. In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic or Id, or the pharmaceutically acceptable salt thereof, is a compound of Table 1H. In some

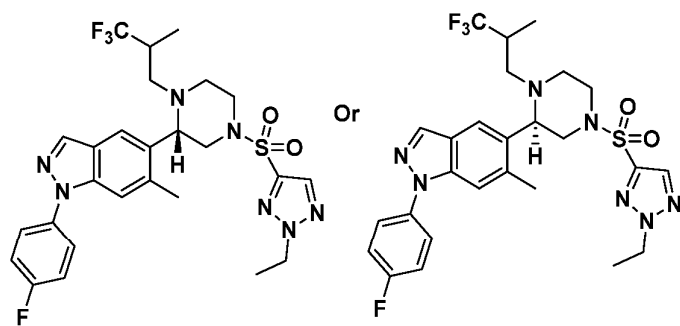
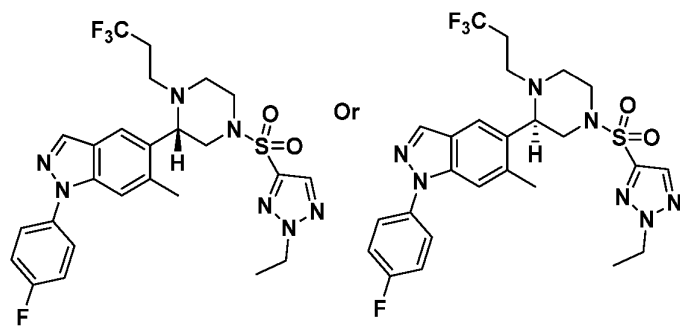
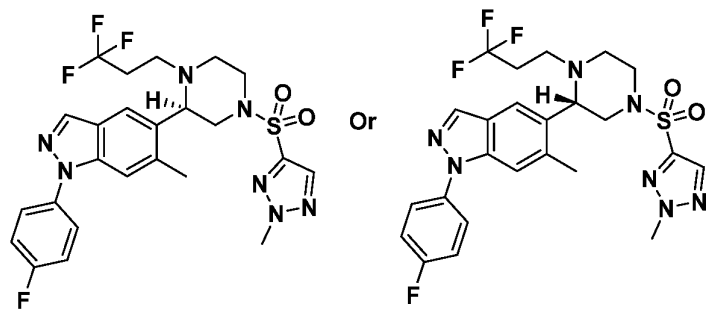
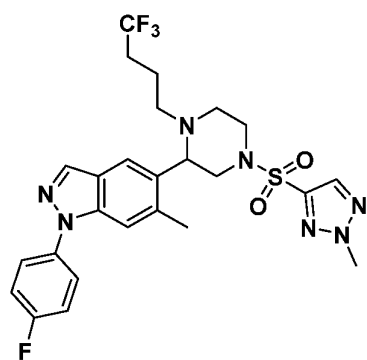
25 embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic or Id, or the pharmaceutically acceptable salt thereof, is a compound of Table 1I. In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic or Id, or the pharmaceutically acceptable salt thereof, is a compound of Table 1J. In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic or Id, or the pharmaceutically acceptable salt thereof, is a compound of Table 1K.

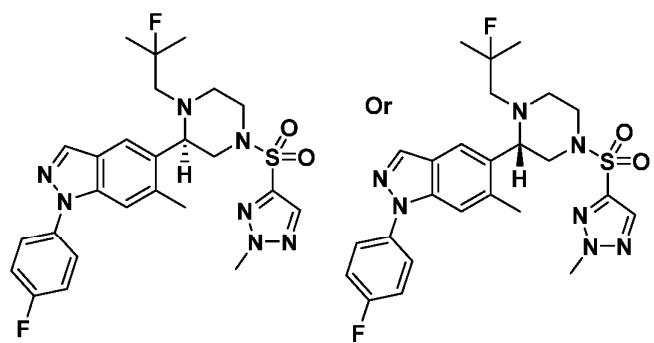
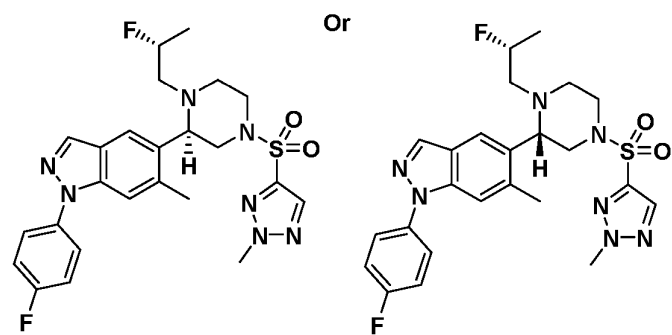
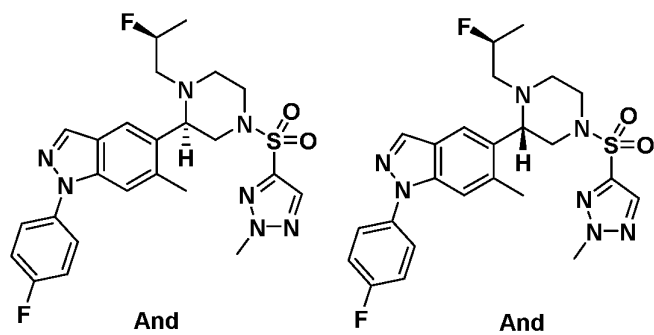
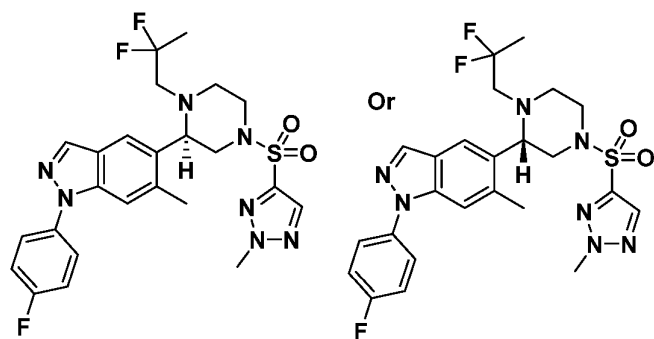
embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic or Id, or the pharmaceutically acceptable salt thereof, is a compound of Table 1I. In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic or Id, or the pharmaceutically acceptable salt thereof, is a compound of Table 1J. In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic or Id, or the pharmaceutically acceptable salt thereof, is a compound of Table 1K.

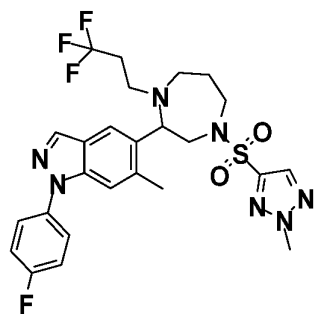
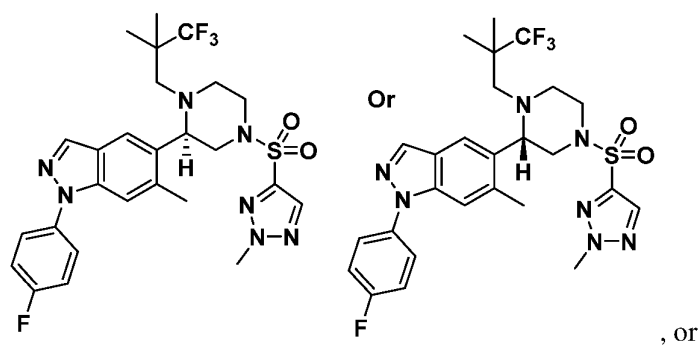
[0138] In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic or Id, is a compound of Table 1A, Table 1B, Table 1C, Table 1D, Table 1E, Table 1F, Table 1G, Table 1H, Table 1I, Table 1J, or Table 1K. In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic or Id is a compound of Table 1A, Table 1B, Table 1C, Table 1D, Table 1E, Table 1F, Table 1G, Table 1H, or Table 1I. In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic or Id is a compound of Table 1A, Table 1B, Table 1C, Table 1D or Table 1E. In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic or Id is a compound of Table 1F, Table 1G, Table 1H, or Table 1I. In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic or Id, is a compound of Table 1J, or Table 1K. In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic or Id is a compound of Table 1A. In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic or Id is a compound of Table 1B. In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic or Id is a compound of Table 1C. In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic or Id is a compound of Table 1D. In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic or Id is a compound of Table 1E. In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic or Id is a compound of Table 1F. In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic or Id is a compound of Table 1G. In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic or Id is a compound of Table 1H. In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic or Id is a compound of Table 1I. In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic or Id, is a compound of Table 1J. In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic or Id, is a compound of Table 1K.

[0139] In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic or Id, or the pharmaceutically acceptable salt thereof, is the compound having the structure:

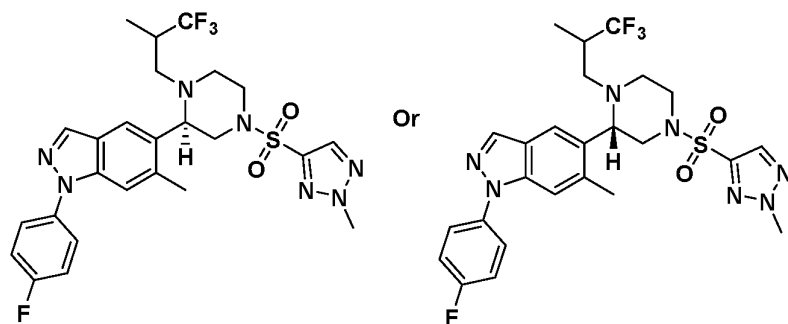






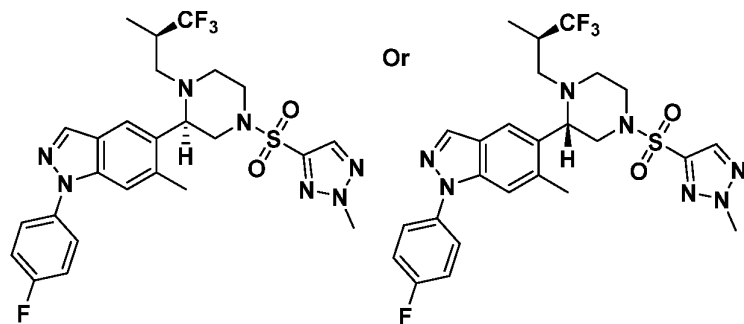


[0140] In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic or Id, or the pharmaceutically acceptable salt thereof, is the compound having the structure

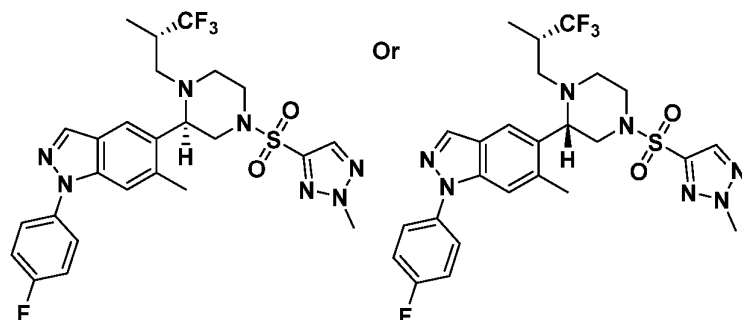


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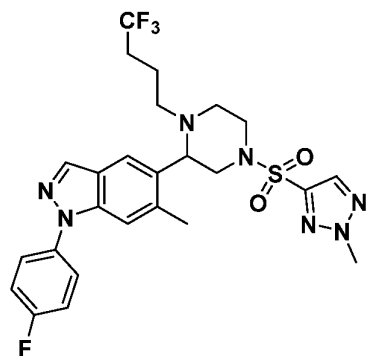
[0141] In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic or Id, or the pharmaceutically acceptable salt thereof, is the compound having the structure



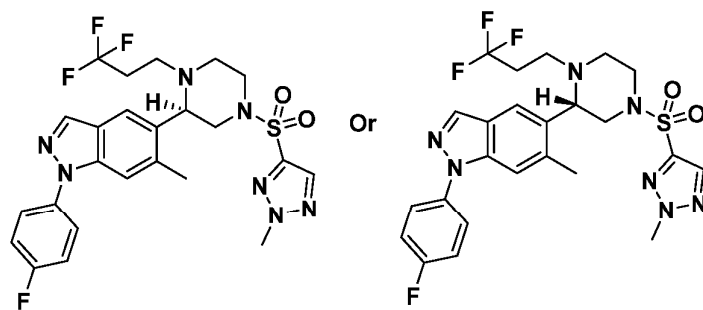
[0142] In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic or Id, or the pharmaceutically acceptable salt thereof, is the compound having the structure



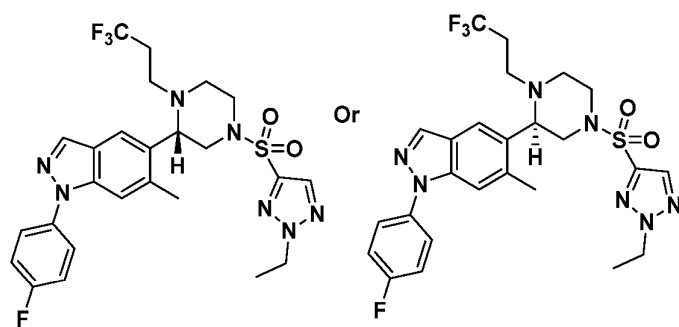
[0143] In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic or Id, or the pharmaceutically acceptable salt thereof, is the compound having the structure



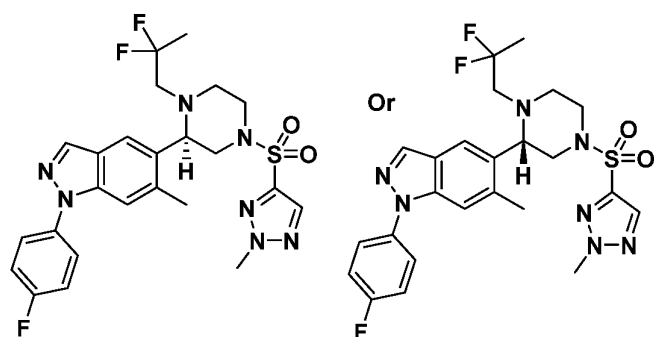
[0144] In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic or Id, or the pharmaceutically acceptable salt thereof, is the compound having the structure



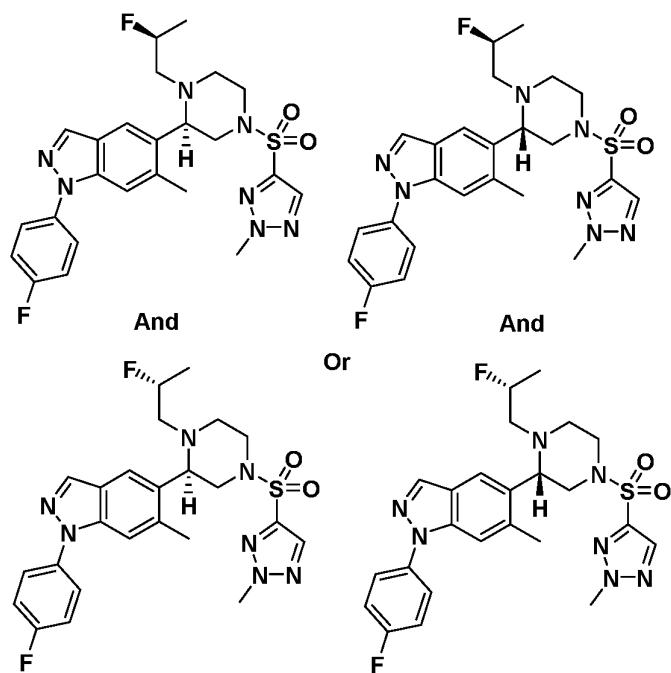
[0145] In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic or Id, or the pharmaceutically acceptable salt thereof, is the compound having the structure



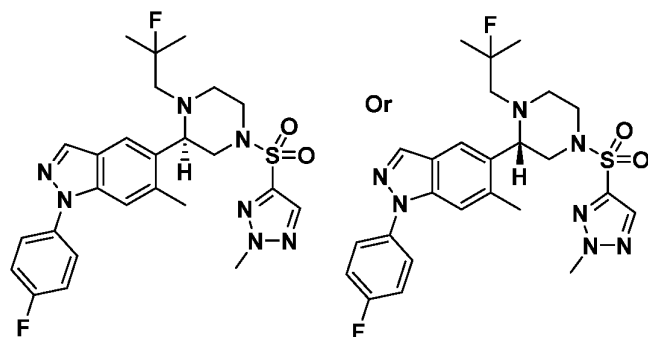
[0146] In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic or Id, or the pharmaceutically acceptable salt thereof, is the compound having the structure



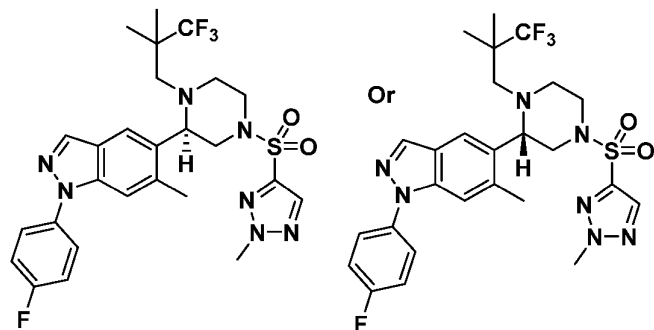
- 5 [0147] In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic or Id, or the pharmaceutically acceptable salt thereof, is the compound having the structure



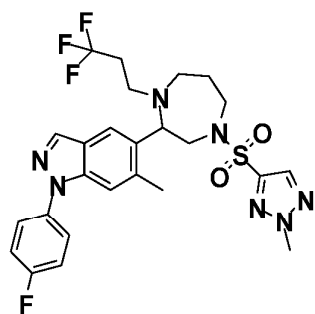
[0148] In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic or Id, or the pharmaceutically acceptable salt thereof, is the compound having the structure



[0149] In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic or Id, or the pharmaceutically acceptable salt thereof, is the compound having the structure



[0150] In some embodiments, the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic or Id, or the pharmaceutically acceptable salt thereof, is the compound having the structure



[0151] The compounds of the present invention may exist as salts. The present invention includes such salts, which can be pharmaceutically acceptable salts. Examples of applicable salt forms include hydrochlorides, hydrobromides, sulfates, methanesulfonates, nitrates, maleates, acetates, citrates, fumarates, tartrates (eg (+)-tartrates, (-)-tartrates or mixtures thereof including racemic mixtures, succinates, benzoates and salts with amino acids such as

glutamic acid. These salts may be prepared by methods known to those skilled in art. Also included are base addition salts such as sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When compounds of the present invention contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived organic acids like acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, lactic, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like. Certain specific compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

[0152] Other salts include acid or base salts of the compounds used in the methods of the present invention. Illustrative examples of pharmaceutically acceptable salts are mineral acid (hydrochloric acid, hydrobromic acid, phosphoric acid, and the like) salts, organic acid (acetic acid, propionic acid, glutamic acid, citric acid and the like) salts, and quaternary ammonium (methyl iodide, ethyl iodide, and the like) salts. It is understood that the pharmaceutically acceptable salts are non-toxic. Additional information on suitable pharmaceutically acceptable salts can be found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, Pa., 1985, which is incorporated herein by reference.

[0153] Pharmaceutically acceptable salts includes salts of the active compounds which are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. When compounds of the present invention contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When compounds of the present invention contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a

sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, lactic, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (*see*, for example, Berge *et al.*, "Pharmaceutical Salts", *Journal of Pharmaceutical Science*, **1977**, 66, 1-19). Certain specific compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

[0154] The neutral forms of the compounds are preferably regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents.

[0155] Certain compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are encompassed within the scope of the present invention. Certain compounds of the present invention may exist in multiple crystalline or amorphous forms.

[0156] Certain compounds of the present invention possess asymmetric carbon atoms (optical centers) or double bonds; the enantiomers, racemates, diastereomers, tautomers, geometric isomers, stereoisometric forms that may be defined, in terms of absolute stereochemistry, as (R)- or (S)- or, as (D)- or (L)- for amino acids, and individual isomers are encompassed within the scope of the present invention. The compounds of the present invention do not include those which are known in art to be too unstable to synthesize and/or isolate. The present invention is meant to include compounds in racemic and optically pure forms. Optically active (R)- and (S)-, or (D)- and (L)-isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques.

[0157] Isomers include compounds having the same number and kind of atoms, and hence the same molecular weight, but differing in respect to the structural arrangement or configuration of the atoms.

5 [0158] Unless otherwise stated, structures depicted herein are also meant to include all stereochemical forms of the structure; i.e., the R and S configurations for each asymmetric center. Therefore, single stereochemical isomers as well as enantiomeric and diastereomeric mixtures of the present compounds are within the scope of the invention.

[0159] Unless otherwise stated, the compounds of the present invention may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such
10 compounds. For example, the compounds of the present invention may be labeled with radioactive or stable isotopes, such as for example deuterium (^2H), tritium (^3H), iodine-125 (^{125}I), fluorine-18 (^{18}F), nitrogen-15 (^{15}N), oxygen-17 (^{17}O), oxygen-18 (^{18}O), carbon-13 (^{13}C), or carbon-14 (^{14}C). All isotopic variations of the compounds of the present invention, whether radioactive or not, are encompassed within the scope of the present invention.

15 [0160] In addition to salt forms, the present invention provides compounds, which are in a prodrug form. Prodrugs of the compounds described herein are those compounds that readily undergo chemical changes under physiological conditions to provide the compounds of the present invention. Additionally, prodrugs can be converted to the compounds of the present invention by chemical or biochemical methods in an *ex vivo* environment. For example,
20 prodrugs can be slowly converted to the compounds of the present invention when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent.

IV. COMPOSITIONS

[0161] In some embodiments, the present invention provides a pharmaceutical composition comprising a compound of any one of the compounds of the present invention and a
25 pharmaceutically acceptable excipient.

[0162] The compounds of the present invention can be prepared and administered in a wide variety of oral, parenteral and topical dosage forms. Oral preparations include tablets, pills, powder, dragees, capsules, liquids, lozenges, gels, syrups, slurries, suspensions, etc., suitable for ingestion by the patient. The compounds of the present invention can also be
30 administered by injection, that is, intravenously, intramuscularly, intracutaneously, subcutaneously, intraduodenally, or intraperitoneally. Also, the compounds described herein

can be administered by inhalation, for example, intranasally. Additionally, the compounds of the present invention can be administered transdermally. The compounds of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic and Id of this invention can also be administered by in intraocular, intravaginal, and intrarectal routes including suppositories, insufflation, powders and aerosol formulations (for examples of steroid inhalants, see Rohatagi, *J. Clin. Pharmacol.* 35:1187-1193, 1995; Tjwa, *Ann. Allergy Asthma Immunol.* 75:107-111, 1995). Accordingly, the present invention also provides pharmaceutical compositions including one or more pharmaceutically acceptable carriers and/or excipients and either a compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic and Id, or a pharmaceutically acceptable salt thereof.

10 [0163] For preparing pharmaceutical compositions from the compounds of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances, which may also act as diluents, flavoring agents, surfactants, binders, preservatives, tablet disintegrating agents, or an
15 encapsulating material. Details on techniques for formulation and administration are well described in the scientific and patent literature, see, e.g., the latest edition of Remington's Pharmaceutical Sciences, Maack Publishing Co, Easton PA ("Remington's").

[0164] In powders, the carrier is a finely divided solid, which is in a mixture with the finely divided active component. In tablets, the active component is mixed with the carrier having
20 the necessary binding properties and additional excipients as required in suitable proportions and compacted in the shape and size desired.

[0165] The powders, capsules and tablets preferably contain from 5% or 10% to 70% of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium
25 carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component with or without other excipients, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and
30 lozenges can be used as solid dosage forms suitable for oral administration.

[0166] Suitable solid excipients are carbohydrate or protein fillers including, but not limited to sugars, including lactose, sucrose, mannitol, or sorbitol; starch from corn, wheat,

rice, potato, or other plants; cellulose such as methyl cellulose, hydroxypropylmethyl-cellulose, or sodium carboxymethylcellulose; and gums including arabic and tragacanth; as well as proteins such as gelatin and collagen. If desired, disintegrating or solubilizing agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, alginic acid, or a salt thereof, such as sodium alginate.

[0167] Dragee cores are provided with suitable coatings such as concentrated sugar solutions, which may also contain gum arabic, talc, polyvinylpyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for product identification or to characterize the quantity of active compound (i.e., dosage). Pharmaceutical preparations of the invention can also be used orally using, for example, push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a coating such as glycerol or sorbitol. Push-fit capsules can contain the compounds of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic and Id mixed with a filler or binders such as lactose or starches, lubricants such as talc or magnesium stearate, and, optionally, stabilizers. In soft capsules, the compounds of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic and Id may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycol with or without stabilizers.

[0168] For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

[0169] Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water/propylene glycol solutions. For parenteral injection, liquid preparations can be formulated in solution in aqueous polyethylene glycol solution.

[0170] Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizers, and thickening agents as desired. Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia, and dispersing or wetting agents such as a naturally occurring phosphatide (e.g., lecithin), a condensation

- product of an alkylene oxide with a fatty acid (e.g., polyoxyethylene stearate), a condensation product of ethylene oxide with a long chain aliphatic alcohol (e.g., heptadecaethylene oxycetanol), a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol (e.g., polyoxyethylene sorbitol mono-oleate), or a condensation product of ethylene oxide with a partial ester derived from fatty acid and a hexitol anhydride (e.g., polyoxyethylene sorbitan mono-oleate). The aqueous suspension can also contain one or more preservatives such as ethyl or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents and one or more sweetening agents, such as sucrose, aspartame or saccharin. Formulations can be adjusted for osmolarity.
- 10 **[0171]** Also included are solid form preparations, which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.
- 15 **[0172]** Oil suspensions can be formulated by suspending the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic and Id in a vegetable oil, such as arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin; or a mixture of these. The oil suspensions can contain a thickening agent, such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents can be added to provide a palatable oral preparation, such as glycerol, sorbitol or sucrose. These formulations can be preserved by the addition of an antioxidant such as ascorbic acid. As an example of an injectable oil vehicle, see Minto, *J. Pharmacol. Exp. Ther.* 281:93-102, 1997. The pharmaceutical formulations of the invention can also be in the form of oil-in-water emulsions. The oily phase can be a vegetable oil or a mineral oil, described above, or a mixture of these. Suitable emulsifying agents include naturally-
- 25 occurring gums, such as gum acacia and gum tragacanth, naturally occurring phosphatides, such as soybean lecithin, esters or partial esters derived from fatty acids and hexitol anhydrides, such as sorbitan mono-oleate, and condensation products of these partial esters with ethylene oxide, such as polyoxyethylene sorbitan mono-oleate. The emulsion can also contain sweetening agents and flavoring agents, as in the formulation of syrups and elixirs.
- 30 Such formulations can also contain a demulcent, a preservative, or a coloring agent.

- [0173] The compounds of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic and Id of the invention can be delivered by transdermally, by a topical route, formulated as applicator sticks, solutions, suspensions, emulsions, gels, creams, ointments, pastes, jellies, paints, powders, and aerosols.
- [0174] The compounds of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic and Id and compositions of the invention can also be delivered as microspheres for slow release in the body. For example, microspheres can be administered via intradermal injection of drug -containing microspheres, which slowly release subcutaneously (see Rao, *J. Biomater Sci. Polym. Ed.* 7:623-645, 1995; as biodegradable and injectable gel formulations (see, e.g., Gao *Pharm. Res.* 12:857-863, 1995); or, as microspheres for oral administration (see, e.g., Eyles, *J. Pharm. Pharmacol.* 49:669-674, 1997). Both transdermal and intradermal routes afford constant delivery for weeks or months.
- [0175] The pharmaceutical formulations of the compounds of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic and Id of the invention can be provided as a salt and can be formed with many acids, including but not limited to hydrochloric, sulfuric, acetic, lactic, tartaric, malic, succinic, etc. Salts tend to be more soluble in aqueous or other protonic solvents that are the corresponding free base forms. In other cases, the preparation may be a lyophilized powder in 1 mM-50 mM histidine, 0.1%-2% sucrose, 2%-7% mannitol at a pH range of 4.5 to 5.5, that is combined with buffer prior to use.
- [0176] The pharmaceutical formulations of the compounds of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic and Id of the invention can be provided as a salt and can be formed with bases, namely cationic salts such as alkali and alkaline earth metal salts, such as sodium, lithium, potassium, calcium, magnesium, as well as ammonium salts, such as ammonium, trimethyl-ammonium, diethylammonium, and tris-(hydroxymethyl)-methyl-ammonium salts.
- [0177] In some embodiments, the formulations of the compounds of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic and Id of the invention can be delivered by the use of liposomes which fuse with the cellular membrane or are endocytosed, i.e., by employing ligands attached to the liposome, or attached directly to the oligonucleotide, that bind to surface membrane protein receptors of the cell resulting in endocytosis. By using liposomes, particularly where the liposome surface carries ligands specific for target cells, or are otherwise preferentially directed to a specific organ, one can focus the delivery of the GR modulator into the target cells in vivo. (See, e.g., Al-Muhammed, *J. Microencapsul.* 13:293-306, 1996; Chonn, *Curr. Opin. Biotechnol.* 6:698-708, 1995; Ostro, *Am. J. Hosp. Pharm.* 46:1576-1587, 1989).

[0178] The pharmaceutical preparation is preferably in unit dosage form. In such form the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

[0179] The quantity of active component in a unit dose preparation may be varied or adjusted from 0.1 mg to 10000 mg, more typically 1.0 mg to 1000 mg, most typically 10 mg to 500 mg, according to the particular application and the potency of the active component.

10 The composition can, if desired, also contain other compatible therapeutic agents.

[0180] The dosage regimen also takes into consideration pharmacokinetics parameters well known in the art, i.e., the rate of absorption, bioavailability, metabolism, clearance, and the like (see, e.g., Hidalgo-Aragones (1996) *J. Steroid Biochem. Mol. Biol.* 58:611-617; Groning (1996) *Pharmazie* 51:337-341; Fotherby (1996) *Contraception* 54:59-69; Johnson (1995) *J. Pharm. Sci.* 84:1144-1146; Rohatagi (1995) *Pharmazie* 50:610-613; Brophy (1983) *Eur. J. Clin. Pharmacol.* 24:103-108; the latest Remington's, *supra*). The state of the art allows the clinician to determine the dosage regimen for each individual patient, GR and/or MR modulator and disease or condition treated.

[0181] Single or multiple administrations of the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic and Id formulations can be administered depending on the dosage and frequency as required and tolerated by the patient. The formulations should provide a sufficient quantity of active agent to effectively treat the disease state. Thus, in one embodiment, the pharmaceutical formulations for oral administration of the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic and Id is in a daily amount of between about 0.5 to about 30 mg per kilogram of body weight per day. In an alternative embodiment, dosages are from about 1 mg to about 20 mg per kg of body weight per patient per day are used. Lower dosages can be used, particularly when the drug is administered to an anatomically secluded site, such as the cerebral spinal fluid (CSF) space, in contrast to administration orally, into the blood stream, into a body cavity or into a lumen of an organ. Substantially higher dosages can be used in topical administration. Actual methods for preparing formulations including the compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic and Id for parenteral administration are known or apparent to those skilled in the art and are described in more detail in such publications as

Remington's, *supra*. See also Nieman, In "Receptor Mediated Antisteroid Action," Agarwal, et al., eds., De Gruyter, New York (1987).

[0182] The compounds described herein can be used in combination with one another, with other active agents known to be useful in modulating a glucocorticoid receptor, or with
5 adjunctive agents that may not be effective alone, but may contribute to the efficacy of the active agent.

[0183] In some embodiments, co-administration includes administering one active agent within 0.5, 1, 2, 4, 6, 8, 10, 12, 16, 20, or 24 hours of a second active agent. Co-administration includes administering two active agents simultaneously, approximately
10 simultaneously (e.g., within about 1, 5, 10, 15, 20, or 30 minutes of each other), or sequentially in any order. In some embodiments, co-administration can be accomplished by co-formulation, i.e., preparing a single pharmaceutical composition including both active agents. In some embodiments, the active agents can be formulated separately. In some
15 embodiments, the active and/or adjunctive agents may be linked or conjugated to one another.

[0184] After a pharmaceutical composition including a compound of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic and Id of the invention has been formulated in one or more acceptable carriers, it can be placed in an appropriate container and labeled for treatment of an indicated condition. For administration of the compounds of Formula J, I, Ia, Ib, Ib-1, Ib-2, Ic and Id,
20 such labeling would include, e.g., instructions concerning the amount, frequency and method of administration.

[0185] In some embodiments, the compositions of the present invention are useful for parenteral administration, such as intravenous (IV) administration or administration into a body cavity or lumen of an organ. The formulations for administration will commonly
25 comprise a solution of the compositions of the present invention dissolved in one or more pharmaceutically acceptable carriers. Among the acceptable vehicles and solvents that can be employed are water and Ringer's solution, an isotonic sodium chloride. In addition, sterile fixed oils can conventionally be employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In
30 addition, fatty acids such as oleic acid can likewise be used in the preparation of injectables. These solutions are sterile and generally free of undesirable matter. These formulations may be sterilized by conventional, well known sterilization techniques. The formulations may

contain pharmaceutically acceptable auxiliary substances as required to approximate physiological conditions such as pH adjusting and buffering agents, tonicity adjusting agents, e.g., sodium acetate, sodium chloride, potassium chloride, calcium chloride, sodium lactate and the like. The concentration of the compositions of the present invention in these
5 formulations can vary widely, and will be selected primarily based on fluid volumes, viscosities, body weight, and the like, in accordance with the particular mode of administration selected and the patient's needs. For IV administration, the formulation can be a sterile injectable preparation, such as a sterile injectable aqueous or oleaginous suspension. This suspension can be formulated according to the known art using those suitable dispersing
10 or wetting agents and suspending agents. The sterile injectable preparation can also be a sterile injectable solution or suspension in a nontoxic parenterally-acceptable diluent or solvent, such as a solution of 1,3-butanediol.

V. METHODS & USE

[0186] In some embodiments, the present invention provides a method of treating a
15 disorder or condition through modulating a glucocorticoid receptor, the method comprising administering to a subject in need of such treatment, a therapeutically effective amount of any one of the compounds of the present invention, or a pharmaceutical composition of the present invention, thereby treating the disorder or condition.

[0187] In an exemplary embodiment, the GR modulator is an antagonist of GR activity
20 (also referred to herein as "a glucocorticoid receptor antagonist"). A glucocorticoid receptor antagonist, as used herein, refers to any composition or compound which partially or completely inhibits (antagonizes) the binding of a glucocorticoid receptor (GR) agonist (e.g. cortisol and synthetic or natural cortisol analog) to a GR thereby inhibiting any biological response associated with the binding of a GR to the agonist.

[0188] In some embodiments, the GR modulator is a specific glucocorticoid receptor
25 antagonist. As used herein, a specific glucocorticoid receptor antagonist refers to a composition or compound which inhibits any biological response associated with the binding of a GR to an agonist by preferentially binding to the GR rather than another nuclear receptor (NR). In some embodiments, the specific glucocorticoid receptor antagonist binds
30 preferentially to GR rather than the mineralocorticoid receptor (MR), aldosterone receptor (AR) or progesterone receptor (PR). In an exemplary embodiment, the specific glucocorticoid receptor antagonist binds preferentially to GR rather than the

mineralocorticoid receptor (MR). In another exemplary embodiment, the specific glucocorticoid receptor antagonist binds preferentially to GR rather than the progesterone receptor (PR). In another exemplary embodiment, the specific glucocorticoid antagonist binds preferentially to GR rather than to the aldosterone receptor (AR).

5 **[0189]** In some embodiments, the specific glucocorticoid receptor antagonist binds to the GR with an association constant (K_d) that is at least 10-fold less than the K_d for any other NR. In some embodiments, the specific glucocorticoid receptor antagonist binds to the GR with an association constant (K_d) that is at least 100-fold less than the K_d for any other NR. In some embodiments, the specific glucocorticoid receptor antagonist binds to the GR with an
10 association constant (K_d) that is at least 1000-fold less than the K_d for any other NR.

[0190] In some embodiments, the present invention provides a method of treating a disorder or condition through antagonizing a glucocorticoid receptor, the method comprising administering to a subject in need of such treatment, an effective amount of any one of the compounds of the present invention, or a pharmaceutical composition of the present
15 invention.

[0191] In some embodiments, the disorder or condition is selected from the group consisting of Alzheimer's disease, amyotrophic lateral sclerosis (ALS), antipsychotic induced weight gain, cancer, Cushing Disease, Cushing's Syndrome, major psychotic depression, Nonalcoholic steatohepatitis, and obesity. In some embodiments, the disorder or condition
20 can be ovarian cancer, breast cancer, non-small cell lung cancer or prostate cancer.

[0192] In some embodiments, the method includes administering one or more second agents (e.g. therapeutic agents). In some embodiments, the method includes administering one or more second agents (e.g. therapeutic agents) in a therapeutically effective amount. In some embodiments, the second agent is an agent known to be useful in modulating a
25 glucocorticoid receptor. In some embodiments, the second agent is an agent for treating Alzheimer's disease, amyotrophic lateral sclerosis (ALS), antipsychotic induced weight gain, cancer, Cushing Disease, Cushing's Syndrome, major psychotic depression, Nonalcoholic steatohepatitis, and obesity. In some embodiments, the second agent is an agent for treating major psychotic depression, stress disorders or antipsychotic induced weight gain. In some
30 embodiments, the second agent is an agent for treating nonalcoholic fatty liver disease and/or nonalcoholic steatohepatitis. In some embodiments, the second agent is an agent for treating

cancer. In some embodiments, the second agent is an anti-cancer agent. In some embodiments, the second agent is a chemotherapeutic.

[0193] In some embodiments, any one of the compounds of the present invention, or a pharmaceutical composition of the present invention can be used for a method of treating a disorder or condition through modulating a glucocorticoid receptor.

[0194] In some embodiments, any one of the compounds of the present invention, or a pharmaceutical composition of the present invention can be used for a method of treating a disorder or condition through antagonizing a glucocorticoid receptor.

[0195] In some embodiments, any one of the compounds of the present invention, or a pharmaceutical composition of the present invention, can be used in the manufacture of a medicament for treating a disorder or condition through modulating a glucocorticoid receptor.

[0196] In some embodiments, any one of the compounds of the present invention, or a pharmaceutical composition of the present invention, can be used in the manufacture of a medicament for treating a disorder or condition through antagonizing a glucocorticoid receptor.

VI. COMPOUND EXAMPLES

General Procedures

[0197] All starting materials and solvents were obtained either from commercial sources or prepared according to the literature citation. Unless otherwise stated all reactions were stirred. Organic solutions were routinely dried over anhydrous magnesium sulfate. Hydrogenations were performed on a Thales H-cube flow reactor under the conditions stated or under pressure in a gas autoclave (bomb).

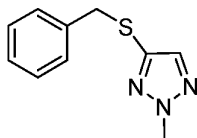
[0198] Column chromatography was performed on pre-packed silica (230-400 mesh, 40-63 μm) cartridges using the amount indicated. SCX was purchased from Supelco and treated with 1 M hydrochloric acid prior to use. Flash column chromatography was performed using prepacked Biotage SFär silica columns or RediSep Silver normal-phase silica flash columns using either a Biotage Isolera (Uppsala, Sweden) or CombiFlash NextGen 300+ (Thousand Oaks, California) purification system. SCX was purchased from Supelco and treated with 1M hydrochloric acid prior to use. Unless stated otherwise the reaction mixture to be purified was first diluted with MeOH and made acidic with a few drops of AcOH. This solution was

loaded directly onto the SCX and washed with MeOH. The desired material was then eluted by washing with 1% NH₃ in MeOH or 0.7 M NH₃ in MeOH.

[0199] *Preparative Reverse Phase High Performance Liquid Chromatography.* Prep HPLC was performed using UV detection at 215 and 254 nm with either a Waters X-Select Prep-C18, 5 µm, 19x50 mm column eluting with a H₂O-MeCN gradient containing 0.1% v/v formic acid over 10 min (**Method A**), or a Waters X-Bridge Prep-C18, 5 µm, 19x50 mm column eluting with a H₂O-MeCN gradient containing 0.1% ammonium bicarbonate over 10 min (**Method B**).

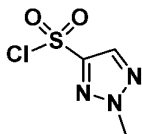
[0200] *Preparative Reverse phase High Performance Liquid Chromatography.* Preparative HPLC was carried out on a Teledyne ACCQPrep HP150 Prep HPLC System with 200-400nm UV variable wavelength detector, ACCQPrep HP150 AS 2x2 – AutoSampler using a Waters XBridge BEH C18 OBD Prep column, 5 µM 19 mm x 50 mm i.d. column and a flow rate of 24 mL/minute eluting with H₂O / MeCN containing 0.1% NH₄OH (**Method AA**) or 0.1% formic acid (**Method BB**) over 10 minutes using UV detection at 254 nm. Gradient information: 0.0–1.0 min, 10% MeCN; 1.0–9.0 min, ramped from 10% MeCN to 100% MeCN; 9.0–10.0 min, held at 100% MeCN.

4-(benzylthio)-2-methyl-2H-1,2,3-triazole



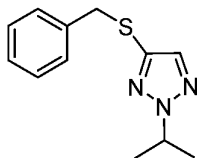
[0201] Preparation of 4-(benzylthio)-2-methyl-2H-1,2,3-triazole was performed according to the procedure described for Example 1 in USPN 10,494,349, which is incorporated herein in its entirety for all purposes.

2-methyl-2H-1,2,3-triazole-4-sulfonyl chloride



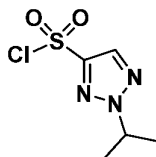
[0202] Preparation of 2-methyl-2H-1,2,3-triazole-4-sulfonyl chloride was performed according to the procedure described for Intermediate 5A in USPN 10,047,082, which is incorporated herein in its entirety for all purposes.

4-(benzylthio)-2-isopropyl-2H-1,2,3-triazole



[0203] Preparation of 4-(benzylthio)-2-isopropyl-2H-1,2,3-triazole was performed according to the procedure described for Example 2 in USPN 10,494,349, which is
5 incorporated herein in its entirety for all purposes.

2-isopropyl-2H-1,2,3-triazol-4-yl)sulfonyl



[0204] Preparation of 2-isopropyl-2H-1,2,3-triazole-4-sulfonyl chloride was performed according to the procedure described for Intermediate 5D in USPN 10,494,349, which is
10 incorporated herein in its entirety for all purposes.

Analytical Methods

[0205] *Reverse Phase High Performance Liquid Chromatography. Method 1:* Waters XSelect CSH UPLC C18 1.7 μ m (2.1 x 30 mm) at 40°C; flow rate 0.77 mL.min⁻¹ eluted with a H₂O-MeCN gradient containing 0.1% v/v formic acid over 3 min employing UV detection
15 between 210 and 400 nm. Gradient information: 0-0.11 min, held at 95% H₂O-5% MeCN, 0.11-2.15 min ramped from 95% H₂O-5% MeCN to 5% H₂O-95% MeCN; 2.15-2.49 min, held at 5% H₂O-95% MeCN, 2.49-2.56 min, ramped from 5% H₂O-95% MeCN to 95% H₂O-5% MeCN; 2.56-3.00 min, held at 95% H₂O-5% MeCN.

[0206] **Method 2:** Apparatus: Agilent 1260; Quaternary Pump, HiP Sampler, Column
20 Compartment, DAD:260+/- 90nm, G6150 MSD: ESI; Column: Waters Cortecs C18, 30 x 2.1 mm, 2.7 μ m, Temp: 40°C, Flow: 1.35 mL/min, Gradient: t₀ = 5% B, t_{2.5min} = 100% B, t_{3.0min} = 100% B, Eluent A: 0.1% Formic in water, Eluent B: acetonitrile.

[0207] **Method 3:** Apparatus: Agilent 1260; Quaternary Pump, HiP Sampler, Column Compartment, DAD:260+/- 90nm, G6150 MSD: ESI; Column: Waters XBridge C18, 30 x

- 2.1 mm, 2.5 μ m, Temp: 40°C, Flow: 1.35 mL/min, Gradient: t₀ = 5% B, t_{2.5min} = 100% B, t_{3.0min} = 100% B, Eluent A: 0.1% NH₃ in water, Eluent B: acetonitrile.
- [0208] Method 4:** Apparatus: Agilent 1260; Quaternary Pump, HiP Sampler, Column Compartment, DAD:260+/- 90nm, G6150 MSD: ESI; Column: Waters Cortecs C18, 30 x 2.1 mm, 2.7 μ m, Temp: 40°C, Flow: 1.35 mL/min, Gradient: t₀ = 5% B, t_{2.5min} = 100% B, t_{3.0min} = 100% B, Eluent A: 0.1% Formic in water, Eluent B: Acetonitrile.
- [0209] Method 5:** Apparatus: Waters HClass; Binary Solvent Pump, SM-FTN, CMA, PDA:210-400 nm, QDa: ACQ-QDa ESI; Column: Waters BEH C18, 30 x 2.1 mm, 1.7 μ m, Temp: 40°C, Flow: 0.77 mL/min, Gradient: t₀ = 2% B, t_{2.5min} = 100% B, t_{3.0min} = 100% B, Eluent A: 0.1% NH₃ in water, Eluent B: Acetonitrile.
- [0210] Method 6:** Apparatus: Waters HClass; Quaternary Solvent Pump, SM-FTN, CMA, PDA:210-400 nm, QDa: ACQ-QDa ESI; Column: Waters CSH C18, 30 x 2.1 mm, 1.7 μ m, Temp: 40°C, Flow: 0.77 mL/min, Gradient: t₀ = 2% B, t_{2.5min} = 100% B, t_{3.0min} = 100% B, Eluent A: 0.1% Formic acid in water, Eluent B: acetonitrile.
- [0211] Method 7:** Waters HClass; Quaternary Solvent Pump, SM-FTN, CMA, PDA:210-400 nm, QDa: ACQ-QDa ESI; Column: Waters CSH C18, 30 x 2.1 mm, 1.7 μ m, Temp: 40°C, Flow: 0.77 mL/min, Gradient: t₀ = 2% B, t_{2.5min} = 100% B, t_{3.0min} = 100% B, Eluent A: 0.1% Formic acid in water, Eluent B: acetonitrile.
- [0212] Method 8:** UPLC_Basic, Apparatus: Waters HClass; Binary Solvent Pump, SM-FTN, CMA, PDA:210-400 nm, QDa: ACQ-QDa ESI; Column: Waters BEH C18, 30 x 2.1 mm, 1.7 μ m, Temp: 40°C, Flow: 0.77 mL/min, Gradient: t₀ = 2% B, t_{2.5min} = 100% B, t_{3.0min} = 100% B, Eluent A: 0.1% NH₃ in water, Eluent B: Acetonitrile.
- [0213] Method 9:** LCMS_Acidic, Apparatus: Agilent 1260; Binary Pump, HiP Sampler, Column Compartment, DAD:260+/- 90nm, G6150 MSD: ESI; Column: Waters Cortecs C18, 30 x 2.1 mm, 2.7 μ m, Temp: 40°C, Flow: 1.35 mL/min, Gradient: t₀ = 5% B, t_{2.5min} = 100% B, t_{3.0min} = 100% B, Eluent A: 0.1% Formic in water, Eluent B: acetonitrile.
- [0214] Method 11:** Phenomenex Luna® C18 2.5 μ m (2.0 x 50 mm) at 45 °C; flow rate 1.0 mL.min⁻¹ eluted with a H₂O-MeCN gradient containing 0.1% v/v formic acid over 5.50 min employing UV detection at 254 nm. Gradient information: 0-0.50 min, held at 99% H₂O-1% MeCN; 0.50-3.50 min ramped from 99% H₂O-1% MeCN to 0% H₂O-100% MeCN; 3.50-

4.25 min, held at 0% H₂O-100% MeCN; 4.25-5.00 min, ramped from 0% H₂O-100% MeCN to 99% H₂O-1% MeCN; 5.00-5.50 min, held at 99% H₂O-1% MeCN.

- [0215] Method 12:** Phenomenex Luna® C18 2.5 µm (2.0 x 50 mm) at 45 °C; flow rate 1.0 mL.min⁻¹ eluted with a H₂O-MeCN gradient containing 0.1% v/v formic acid over 3.75 min
5 employing UV detection at 254 nm. Gradient information: 0-0.50 min, held at 99% H₂O-1% MeCN; 0.50-2.00 min ramped from 99% H₂O-1% MeCN to 0% H₂O-100% MeCN; 2.00-3.25 min, held at 0% H₂O-100% MeCN; 3.25-3.26 min, ramped from 0% H₂O-100% MeCN to 99% H₂O-1% MeCN; 3.26-3.75 min, held at 99% H₂O-1% MeCN.

- [0216] NMR spectra** were recorded using either a Bruker Avance III HD 500 MHz
10 instrument or a Bruker Avance Neo 400 MHz, using either residual non-deuterated solvent, or tetra-methylsilane as reference or Varian Y 400 MHz instrument, using tetra-methylsilane as reference, or a QOne AS400 400 MHz spectrometer using either residual non-deuterated solvent, or tetra-methylsilane as reference.

[0217] All chemical names have been generated using ChemDraw.

- 15 Abbreviations

DCM = dichloromethane

DIBAL-H – diisobutylaluminium hydride

DIPEA = diisopropylethylamine

DMF = dimethylformamide

- 20 DMSO = dimethyl sulfoxide

EtOAc = ethyl acetate

EtOH = ethanol

H, hr, HR, Hr = hours

MeCN = acetonitrile

- 25 MeOH = methanol

min = minutes

MgSO₄ = magnesium sulfate

NaHCO₃ = sodium hydrogen carbonate

NaOH = sodium hydroxide

Na₂SO₄ = sodium sulfate

NH₄Cl = ammonium chloride

5 RT, rt = room temperature

sat. = saturated

SFC = supercritical fluid chromatography

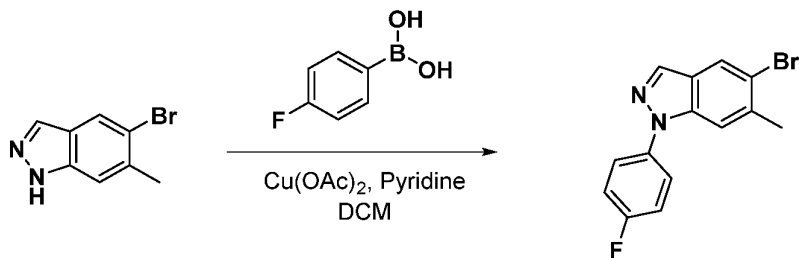
TBME = t-butylmethylether

THF = tetrahydrofuran

10 Wt = weight

Example 1: 1-(4-fluorophenyl)-5-(1-isobutyl-4-((1-methyl-1H-pyrazol-3-yl)sulfonyl)piperazin-2-yl)-6-methyl-1H-indazole

Intermediate ZA: 5-bromo-1-(4-fluorophenyl)-6-methyl-1H-indazole

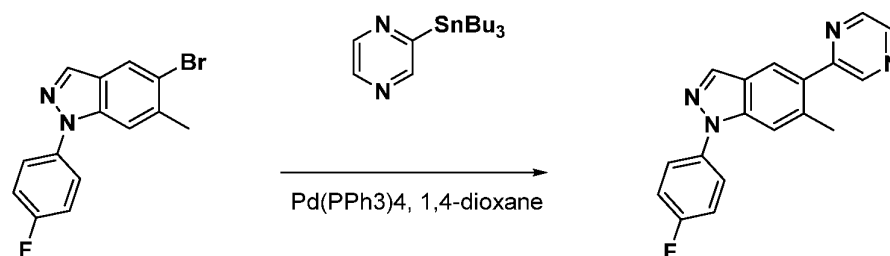


- 15 **[0218]** Pyridine (18.7 g, 19.1 mL, 237 mmol) was added to a solution of 5-bromo-6-methyl-1H-indazole (25.0 g, 118 mmol), (4-fluorophenyl)boronic acid (33.1 g, 237 mmol) and copper (II) acetate (21.5 g, 118 mmol) in DCM (500 mL). The reaction mixture was stirred at 20 °C for 21 hours. The reaction mixture was concentrated under reduced pressure, redissolved in EtOAc (500 mL) and washed with water (200 mL), 1N HCl (200 mL),
- 20 saturated sodium hydrogen carbonate (2 x 200 mL) and brine (100 mL). The organic layer was concentrated, dried using MgSO₄, filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by chromatography on silica gel (330 g cartridge, 0-10% EtOAc/isohehexane) to afford 5-bromo-1-(4-fluorophenyl)-6-methyl-1H-indazole (**Intermediate ZA**) (34.2 g, 0.11 mol, 81% yield) as a yellow solid; R_t 2.33 min

(Method 7); m/z 305.3 and 307.5 ($M+H$)⁺ (ES^+); δ_H (DMSO- d_6 , 400 MHz) δ 8.30 (d, J = 0.9 Hz, 1H), 8.16 (s, 1H), 7.81 (s, 1H), 7.80 – 7.76 (m, 2H), 7.50 – 7.38 (m, 2H), 2.50 (s, 3H).

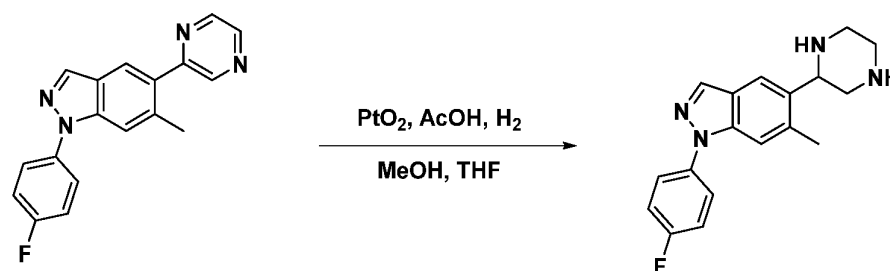
[0219] Alternatively, 5-bromo-1-(4-fluorophenyl)-6-methyl-1H-indazole can be prepared according to the method for Intermediate C in PCT Publication No. WO2021/262587.

5 Intermediate A: 1-(4-fluorophenyl)-6-methyl-5-(pyrazin-2-yl)-1H-indazole



- [0220] A solution of 5-bromo-1-(4-fluorophenyl)-6-methyl-1H-indazole (7.98 g, 26.2 mmol) and 2-(tributylstannyl)pyrazine (10.0 g, 8.55 mL, 27.1 mmol) in 1,4-dioxane (200 mL) was degassed (bubbling nitrogen) for 20 mins. Tetrakis(triphenylphosphine palladium(0)) (1.51 g, 1.31 mmol) was then added and the reaction mixture stirred at 90 °C for 18 hours. Tetrakis(triphenylphosphine palladium(0)) (604 mg, 523 μ mol) was added and the reaction mixture stirred at 90 °C for 4 days. The reaction mixture was cooled to rt and concentrated *in vacuo*. The crude product was purified by chromatography on silica gel (220g cartridge, 0-100% EtOAc/isohexane) to afford the product as a pale yellow solid.
- 15 The solid triturated with EtOAc (3 x 50 mL) to afford 1-(4-fluorophenyl)-6-methyl-5-(pyrazin-2-yl)-1H-indazole (5.20 g, 17.1 mmol, 65.3 %) as an off white solid; R^t 0.19 min (Method 4); m/z 305.0 ($M+H$)⁺ (ES^+).

Intermediate B: 1-(4-fluorophenyl)-6-methyl-5-(piperazin-2-yl)-1H-indazole

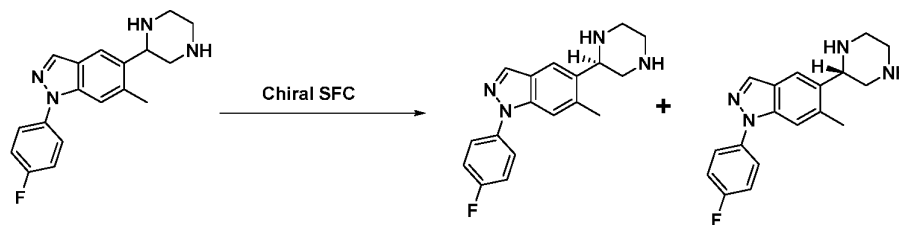


- 20 [0221] 1-(4-Fluorophenyl)-6-methyl-5-(pyrazin-2-yl)-1H-indazole (4.00 g, 13.1 mmol) was partially dissolved in MeOH (150 mL) and THF (150 mL) and then treated with acetic acid

(7.89 g, 7.81 mL, 131 mmol) and platinum (IV) oxide (149 mg, 657 μ mol). The reaction mixture was then stirred at 60 °C for 40 hours under an atmosphere of hydrogen (5 bar). After cooling to rt, the reaction mixture was filtered through a glass microfibre pad, washing with MeOH (20 mL). The filtrate was concentrated *in vacuo* to a yellow oil, before being taken up in DCM (100 mL) and washed with sat. aqueous NaHCO₃ (2 x 80 mL). The organics were dried over MgSO₄ and concentrated *in vacuo*. The crude product was purified by chromatography on silica gel (80 g cartridge, 0-10% (0.7 M Ammonia/MeOH)/DCM, then isocratic 10% (0.7 M Ammonia/MeOH)/DCM) to afford 1-(4-fluorophenyl)-6-methyl-5-(piperazin-2-yl)-1H-indazole (2.63 g, 8.3 mmol, 63 %) as a white solid; R^t 0.25 min (Method 4); m/z 311.2 (M+H)⁺ (ES⁺). ¹H NMR (400 MHz, DMSO) δ 8.26 (d, J = 0.9 Hz, 1H), 8.00 (s, 1H), 7.91 – 7.69 (m, 2H), 7.57 (s, 1H), 7.41 (t, J = 8.8 Hz, 2H), 3.87 (dd, J = 9.8, 2.6 Hz, 1H), 2.98 – 2.87 (m, 2H), 2.86 – 2.76 (m, 2H), 2.65 (td, J = 12.2, 3.2 Hz, 1H), 2.48 (s, 3H), 2.34 (dd, J = 12.0, 9.8 Hz, 1H).

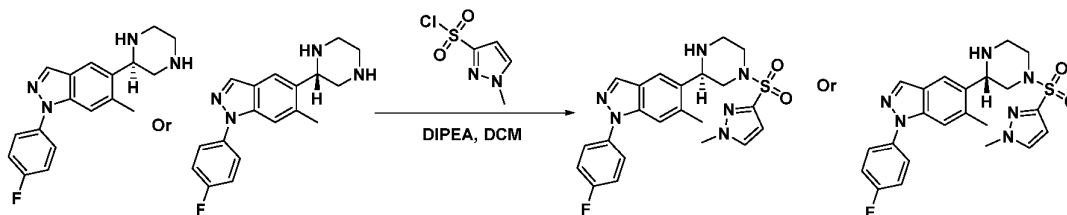
Intermediate C: 1-(4-fluorophenyl)-6-methyl-5-(piperazin-2-yl)-1H-indazole isomer 1

Intermediate D: 1-(4-fluorophenyl)-6-methyl-5-(piperazin-2-yl)-1H-indazole isomer 2



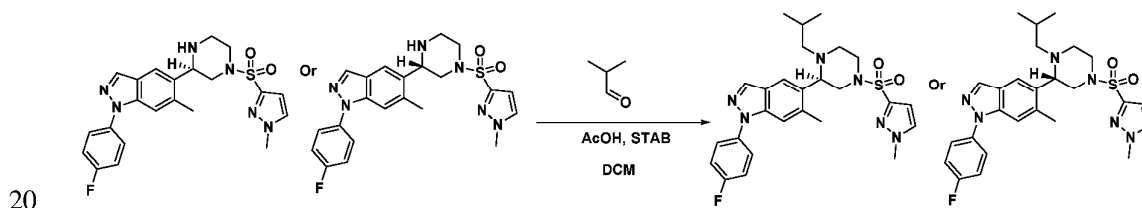
[0222] 1-(4-Fluorophenyl)-6-methyl-5-(piperazin-2-yl)-1H-indazole (2.63 g, 8.3 mmol) was dissolved to 100 mg/mL in MeOH, filtered and was then separated by chiral SFC on a Waters prep 100 with UV detection across all wavelengths with PDA as well as a QDA, 40 °C, 120 bar. The column was a Phenomenex Lux® 5 μ M Cellulose-4, LC Column 250 x 21 mm, AXIA™ packed} flow rate 65 mL/ min of 45 %, 55 % CO₂. to give the separated stereoisomers 1-(4-fluorophenyl)-6-methyl-5-(piperazin-2-yl)-1H-indazole (1.45g, isomer 1) (**Intermediate C**), and 1-(4-fluorophenyl)-6-methyl-5-(piperazin-2-yl)-1H-indazole (1.48g isomer 2) (**Intermediate D**). Data identical to **Intermediate B**.

Intermediate E: 1-(4-fluorophenyl)-6-methyl-5-(4-((1-methyl-1H-pyrazol-3-yl)sulfonyl)piperazin-2-yl)-1H-indazole



[0223] To a solution of 1-(4-fluorophenyl)-6-methyl-5-(piperazin-2-yl)-1H-indazole (250 mg, 556 μmol) in DCM (6 mL) were added N-ethyl-N-isopropylpropan-2-amine (215 mg, 290 μL , 1.67 mmol) and 1-methyl-1H-pyrazole-3-sulfonyl chloride (110 mg, 611 μmol). The reaction mixture was stirred at rt for 90 mins before being quenched with NaHCO_3 (5 mL). The layers were separated, and the aqueous layer extracted with DCM (3 x 5 mL). Combined organic extracts were dried over MgSO_4 and concentrated *in vacuo*. The crude product was purified by chromatography on silica gel (12 g cartridge, 0-10% (0.7 M Ammonia/MeOH)/DCM) to afford 1-(4-fluorophenyl)-6-methyl-5-(4-((1-methyl-1H-pyrazol-3-yl)sulfonyl)piperazin-2-yl)-1H-indazole (153 mg, 0.32 mmol, 58 %) as a flocculent white solid; R^t 1.31 min (Method 4); m/z 455.0 ($\text{M}+\text{H}^+$) (ES^+). δH NMR (400 MHz, DMSO) δ 8.26 (d, $J = 0.9$ Hz, 1H), 7.95 – 7.90 (m, 2H), 7.83 – 7.73 (m, 2H), 7.63 (s, 1H), 7.48 – 7.36 (m, 2H), 6.66 (d, $J = 2.3$ Hz, 1H), 3.99 (d, $J = 10.0$ Hz, 1H), 3.93 (s, 3H), 3.64 – 3.49 (m, 2H), 3.09 (d, $J = 11.9$ Hz, 1H), 2.86 (m, 2H), 2.58 – 2.52 (m, 1H), 2.18 (t, $J = 10.9$ Hz, 1H).

Example 1: 1-(4-fluorophenyl)-5-(1-isobutyl-4-((1-methyl-1H-pyrazol-3-yl)sulfonyl)piperazin-2-yl)-6-methyl-1H-indazole

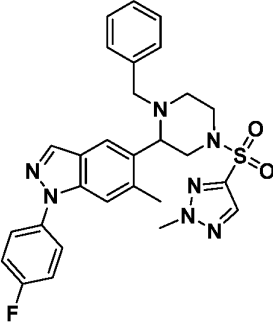


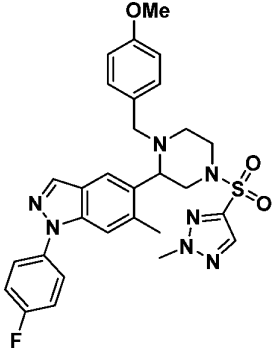
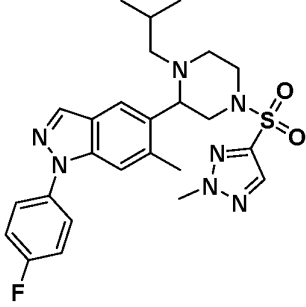
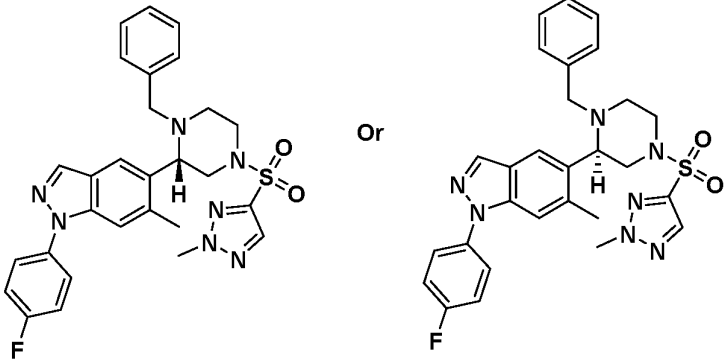
[0224] To a solution of 1-(4-fluorophenyl)-6-methyl-5-(4-((1-methyl-1H-pyrazol-3-yl)sulfonyl)piperazin-2-yl)-1H-indazole (153 mg, 337 μmol) in DCM (4.00 mL) were added isobutyraldehyde (36.4 mg, 46 μL , 505 μmol) and acetic acid. The reaction mixture was stirred at rt for 45 mins before the addition of sodium triacetoxyborohydride (214 mg, 1.01

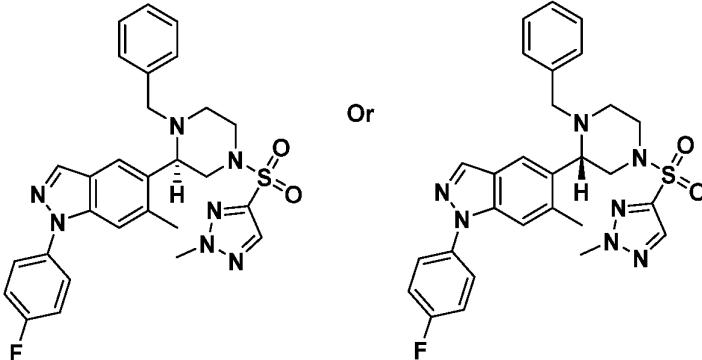
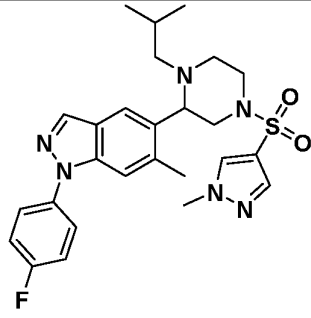
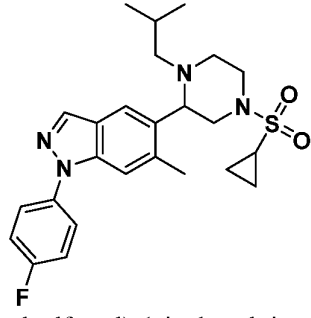
mmol). The reaction mixture was then stirred for a further 3 days at rt before being quenched with sat. aqueous NaHCO₃ (6 mL). The layers were separated, and the aqueous layer extracted with DCM (3 x 5 mL). The combined organic extracts were dried over MgSO₄ and concentrated *in vacuo*. The crude product was purified by chromatography on silica gel (12 g cartridge, 0-60% EtOAc/isohehexane) to afford 1-(4-fluorophenyl)-5-(1-isobutyl-4-((1-methyl-1H-pyrazol-3-yl)sulfonyl)piperazin-2-yl)-6-methyl-1H-indazole (122 mg, 0.23 mmol, 67 %) as a white solid; R_t 1.84 min (Method 4); m/z 511.2 (M+H)⁺ (ES⁺). ¹H NMR (400 MHz, DMSO) δ 8.28 (d, J = 0.9 Hz, 1H), 7.94 (d, J = 2.3 Hz, 1H), 7.85 – 7.75 (m, 3H), 7.63 (s, 1H), 7.50 – 7.37 (m, 2H), 6.65 (d, J = 2.3 Hz, 1H), 3.93 (s, 3H), 3.68 (d, J = 11.6 Hz, 1H), 3.56 (dd, J = 10.5, 3.2 Hz, 1H), 3.47 – 3.39 (m, 1H), 3.21 (d, J = 11.8 Hz, 1H), 2.73 – 2.63 (m, 1H), 2.48 (s, 3H), 2.33 (m, 1H), 2.19 (t, J = 11.7 Hz, 1H), 2.02 (t, J = 12.2 Hz, 1H), 1.77 (d, J = 10.2 Hz, 2H), 0.80 (d, J = 6.3 Hz, 3H), 0.64 (d, J = 6.3 Hz, 3H).

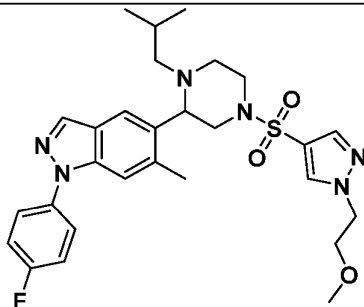
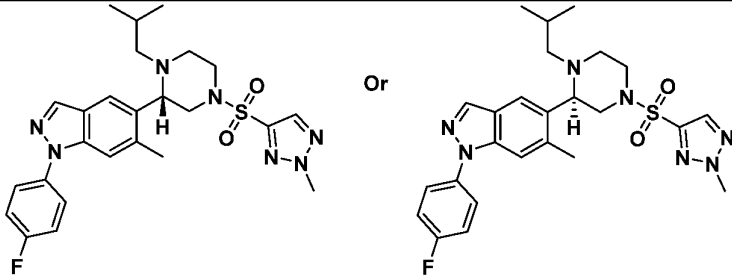
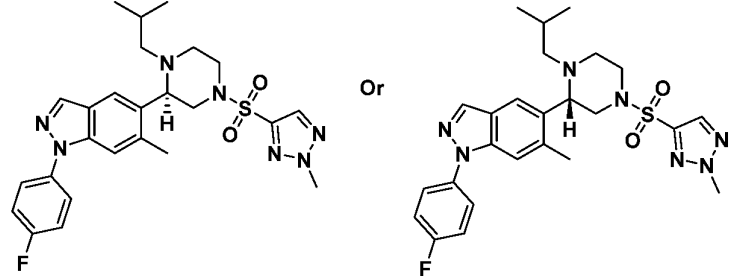
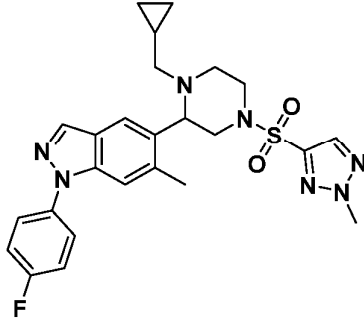
Examples 2 -22

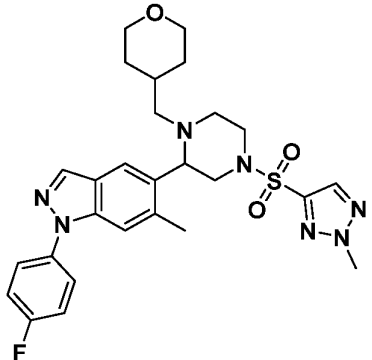
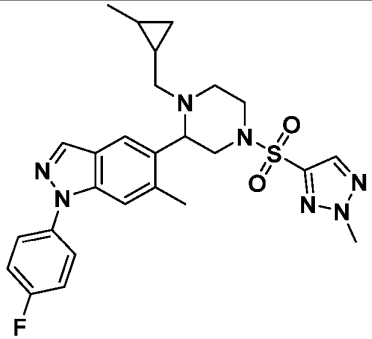
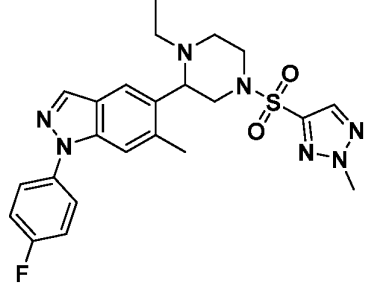
Table 2: The examples shown in the table below were prepared by similar methods to those described for Example 1

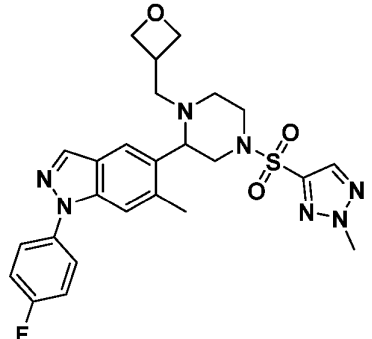
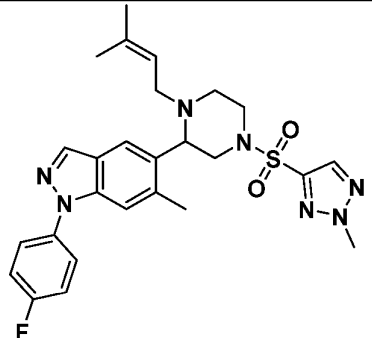
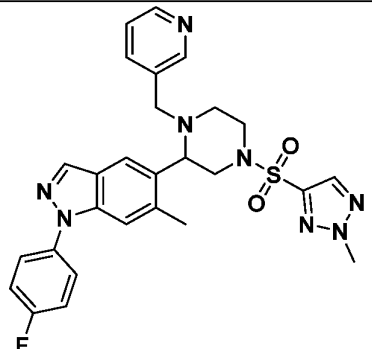
Example	Structure	LC-MS analysis
2	 5-(1-benzyl-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-2-yl)-1-(4-fluorophenyl)-6-methyl-1H-indazole	R_t 2.31 min (Method 9); m/z 546.2 (M+H)⁺ (ES⁺)

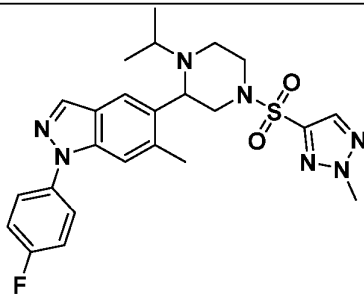
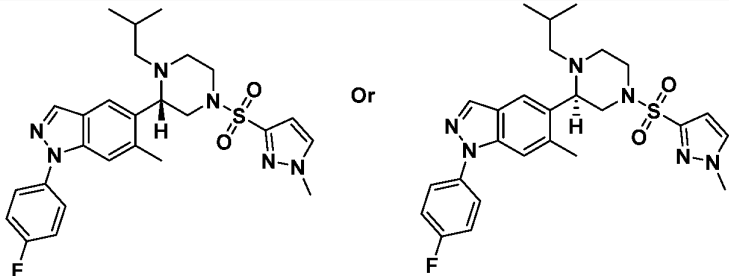
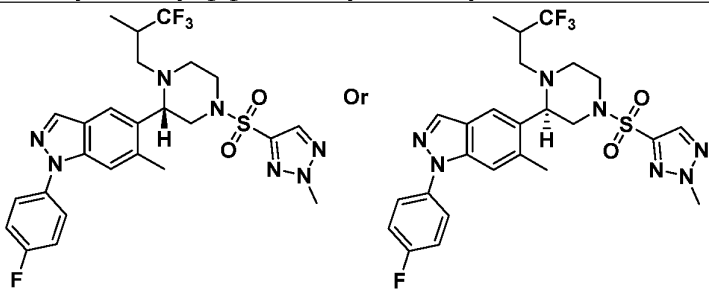
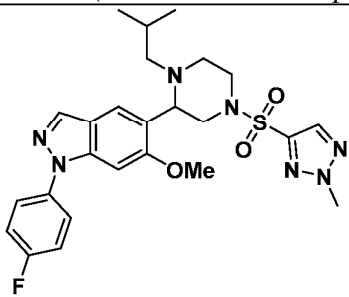
Example	Structure	LC-MS analysis
3	 1-(4-fluorophenyl)-5-(1-(4-methoxybenzyl)-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-2-yl)-6-methyl-1H-indazole	R^t 2.15 min (Method 9); m/z 576.2 (M+H)⁺ (ES⁺)
4	 1-(4-fluorophenyl)-5-(1-isobutyl-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-2-yl)-6-methyl-1H-indazole	R^t 2.02 min (Method 9); m/z 512.2 (M+H)⁺ (ES⁺)
5	 5-(1-benzyl-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-2-yl)-1-(4-fluorophenyl)-6-methyl-1H-indazole	R^t 2.28 min (Method 9); m/z 546.2 (M+H)⁺ (ES⁺)

Example	Structure	LC-MS analysis
6	 5-(1-benzyl-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-2-yl)-1-(4-fluorophenyl)-6-methyl-1H-indazole	R^t 2.28 min (Method 7); m/z 546.2 (M+H)⁺ (ES⁺)
7	 1-(4-fluorophenyl)-5-(1-isobutyl-4-((1-methyl-1H-pyrazol-4-yl)sulfonyl)piperazin-2-yl)-6-methyl-1H-indazole	R^t 1.85 min (Method 9); m/z 511.4 (M+H)⁺ (ES⁺)
8	 5-(4-(cyclopropylsulfonyl)-1-isobutylpiperazin-2-yl)-1-(4-fluorophenyl)-6-methyl-1H-indazole	R^t 1.80 min (Method 6); m/z 471.3 (M+H)⁺ (ES⁺)

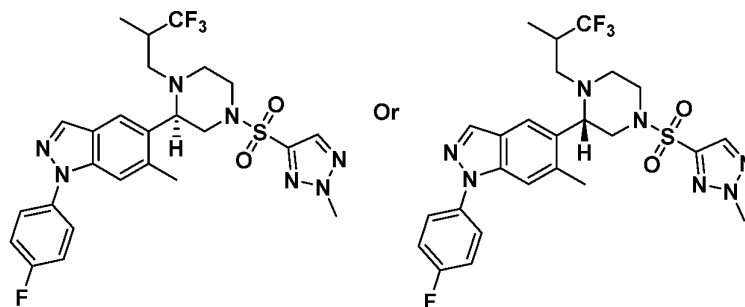
Example	Structure	LC-MS analysis
9	 1-(4-fluorophenyl)-5-(1-isobutyl-4-((1-(2-methoxyethyl)-1H-pyrazol-4-yl)sulfonyl)piperazin-2-yl)-6-methyl-1H-indazole	R^t 1.84 min (Method 9); m/z 555.2 (M+H)⁺ (ES⁺)
10	 1-(4-fluorophenyl)-5-(1-isobutyl-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-2-yl)-6-methyl-1H-indazole	R^t 1.65 min (Method 9); m/z 512.1 (M+H)⁺ (ES⁺)
11	 1-(4-fluorophenyl)-5-(1-isobutyl-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-2-yl)-6-methyl-1H-indazole	R^t 1.64 min (Method 9); m/z 511.2 (M+H)⁺ (ES⁺)
12	 5-(1-(cyclopropylmethyl)-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-2-yl)-1-(4-fluorophenyl)-6-methyl-1H-indazole	R^t 1.61 min (Method 9); m/z 510.2 (M+H)⁺ (ES⁺)

Example	Structure	LC-MS analysis
13	 1-(4-fluorophenyl)-6-methyl-5-(4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)-1-((tetrahydro-2H-pyran-4-yl)methyl)piperazin-2-yl)-1H-indazole	R^t 1.85 min (Method 9); m/z 554.2 (M+H)⁺ (ES⁺)
14	 1-(4-fluorophenyl)-6-methyl-5-(4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)-1-(2-methylcyclopropyl)methyl)piperazin-2-yl)-1H-indazole	R^t 1.72 min (Method 9); m/z 524.2 (M+H)⁺ (ES⁺)
15	 5-(1-ethyl-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-2-yl)-1-(4-fluorophenyl)-6-methyl-1H-indazole	R^t 1.50 min (Method 7); m/z 484.2 (M+H)⁺ (ES⁺)

Example	Structure	LC-MS analysis
16	 1-(4-fluorophenyl)-6-methyl-5-(4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)-1-(oxetan-3-ylmethyl)piperazin-2-yl)-1H-indazole	R^t 1.74 min (Method 9); m/z 526.2 (M+H)⁺ (ES⁺)
17	 1-(4-fluorophenyl)-6-methyl-5-(4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)-1-(3-methylbut-2-en-1-yl)piperazin-2-yl)-1H-indazole	R^t 1.75 min (Method 7); m/z 524.3 (M+H)⁺ (ES⁺)
18	 1-(4-fluorophenyl)-6-methyl-5-(4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)-1-(pyridin-3-ylmethyl)piperazin-2-yl)-1H-indazole	R^t 1.69 min (Method 9); m/z 547.2 (M+H)⁺ (ES⁺)

Example	Structure	LC-MS analysis
19	 1-(4-fluorophenyl)-5-(1-isopropyl-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-2-yl)-6-methyl-1H-indazole	R^t 1.56 min (Method 9); m/z 498.2 (M+H)⁺ (ES⁺)
20	 1-(4-fluorophenyl)-5-(1-isobutyl-4-((1-methyl-1H-pyrazol-3-yl)sulfonyl)piperazin-2-yl)-6-methyl-1H-indazole	R^t 1.85 min (Method 9); m/z 511.2 (M+H)⁺ (ES⁺)
21	 1-(4-fluorophenyl)-6-methyl-5-(4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)-1-(3,3,3-trifluoro-2-methylpropyl)piperazin-2-yl)-1H-indazole (enantiomer of Example 23)	R^t 2.31 and 2.34 min (Method 9); m/z 566.2 (M+H)⁺ (ES⁺)
22	 1-(4-fluorophenyl)-5-(1-isobutyl-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-2-yl)-6-methoxy-1H-indazole	R^t 1.64 min (Method 9); m/z 528.2 (M+H)⁺ (ES⁺)

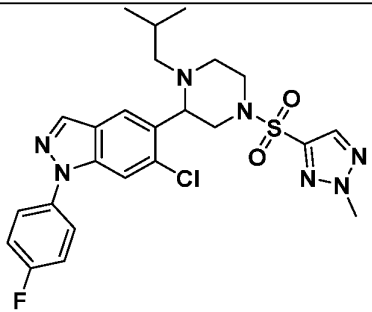
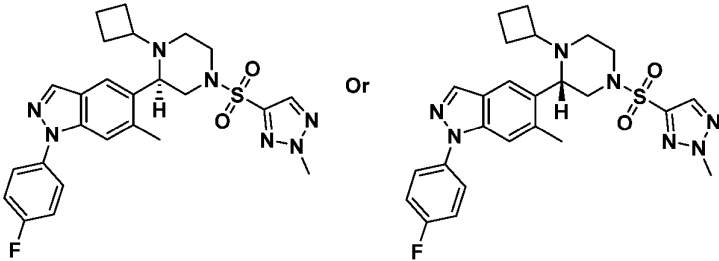
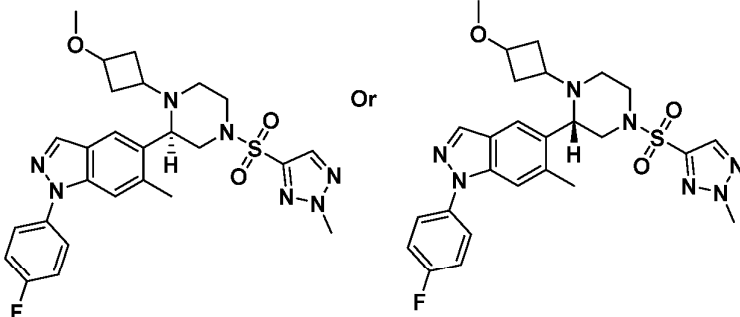
Example 23: 1-(4-fluorophenyl)-6-methyl-5-((2R)-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)-1-(3,3,3-trifluoro-2-methylpropyl)piperazin-2-yl)-1H-indazole (Enantiomer of Example 21)

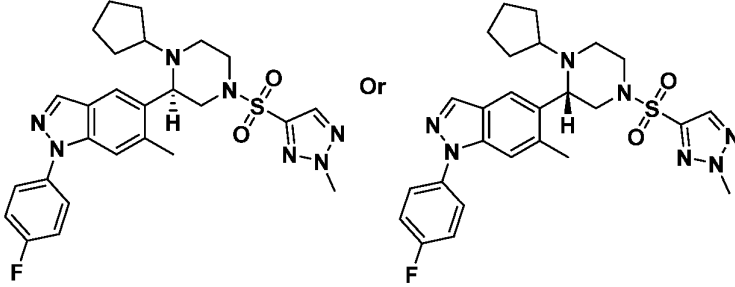
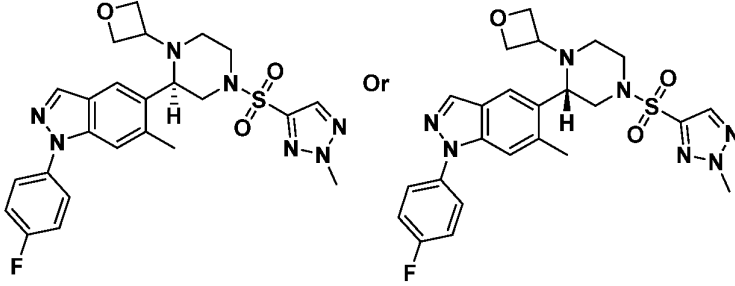
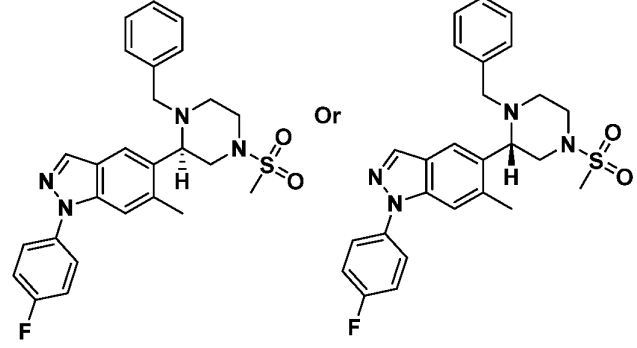


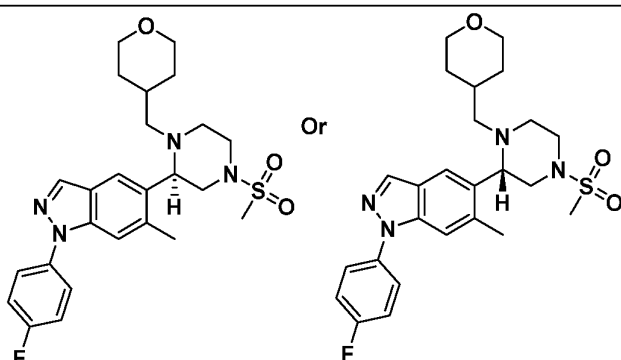
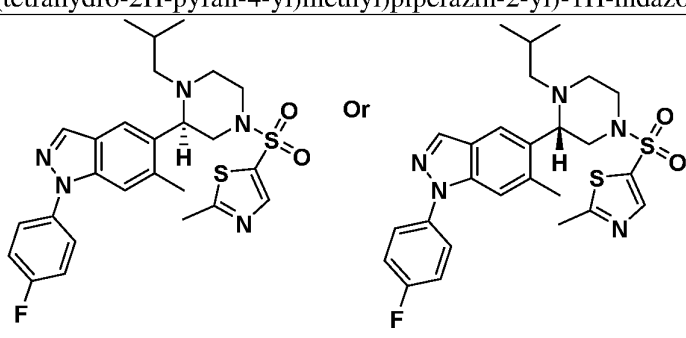
- 5 **[0225]** To a solution of 3,3,3-trifluoro-2-methylpropanal (2.81 g, 2.03 Eq, 22.3 mmol) in DCM (120 mL) were added 4 Å MS (activated with heat gun under vacuum for 10 mins) and the mixture stirred for 15 mins at rt. Acetic acid (1.32 g, 1.31 mL, 2 Eq, 22.0 mmol) was then added and the mixture stirred for a further 30 mins. (R)-1-(4-fluorophenyl)-6-methyl-5-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-2-yl)-1H-indazole (5.00 g, 1 Eq, 11.0
- 10 mmol) was then added and the reaction mixture stirred at rt for 15 hours. Sodium triacetoxhydroborate (6.98 g, 3 Eq, 32.9 mmol) was then added and the reaction mixture stirred for a further 5 hours. The reaction mixture was quenched with MeOH (30 mL) and sat. aq. NaHCO₃ (200 mL). The molecular sieves were filtered off and the layers separated. The aqueous layer was extracted with DCM (3 x 100 mL). Combined organic extracts were dried
- 15 over MgSO₄ and concentrated in vacuo. The crude product was purified by chromatography on silica gel (120 g cartridge, 0-60% EtOAc/isohehexane) to afford 1-(4-fluorophenyl)-6-methyl-5-((2R)-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)-1-(3,3,3-trifluoro-2-methylpropyl)piperazin-2-yl)-1H-indazole (4.02 g, 7.11 mmol, 64.8 %) as a flocculent white solid. The product was analysed by UPLC (CSH C18 Column, 130Å, 1.7 µm, 2.1 mm x 30
- 20 mm, 3 min method, 0.1% Formic acid, 2-100% MeCN/water): 3289-390-col, m/z 566.4 (M+H)⁺ (ES⁺); no ion (M-H)⁻ (ES⁻), at 2.313 and 2.342 min, 98.71% purity 210-400nm. ¹H NMR in DMSO-d₆ 3289-390-rd was consistent with product structure at 98% purity.
- Indazole CH₃ obscured under DMSO. ¹H NMR (400 MHz, DMSO) δ 8.32 – 8.24 (m, 2H), 7.87 – 7.75 (m, 3H), 7.66 (t, J = 1.6 Hz, 1H), 7.49 – 7.38 (m, 2H), 4.27 (d, J = 1.6 Hz, 3H),
- 25 3.68 (m, 2H), 3.48 (dd, J = 12.4, 9.7 Hz, 1H), 3.35 - 3.26 (obscured m, 1 H), 2.81 – 2.58 (m, 3H), 2.47 – 1.90 (m, 3H), 0.99 - 0.87 (m 3H). R^t 2.31 and 2.34 min (Method 9).

Examples 24-31

Table 3: The examples shown in the table below were prepared by similar methods to those described for Example 1

Example	Structure	LC-MS analysis
24	 6-chloro-1-(4-fluorophenyl)-5-(1-isobutyl-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-2-yl)-1H-indazole	R^t 2.38 min (Method 9); m/z 532.2/534.0 (M+H)⁺ (ES⁺)
25	 5-(1-cyclobutyl-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-2-yl)-1-(4-fluorophenyl)-6-methyl-1H-indazole	R^t 1.50 min (Method 7); m/z 510.4 (M+H)⁺ (ES⁺)
26	 1-(4-fluorophenyl)-5-(1-(3-methoxycyclobutyl)-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-2-yl)-6-methyl-1H-indazole	R^t 1.73 min (Method 8); m/z 540.3 (M+H)⁺ (ES⁺)

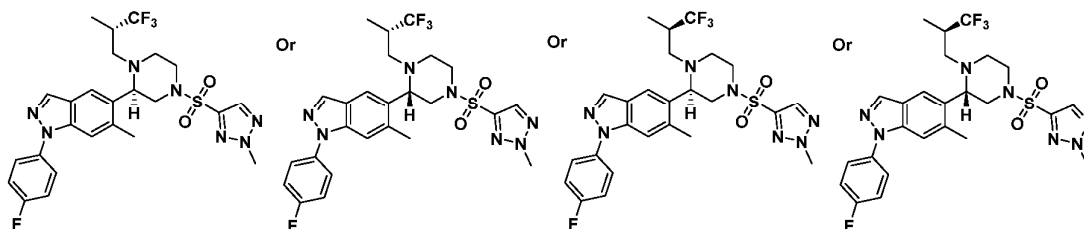
Example	Structure	LC-MS analysis
27	 5-(1-cyclopentyl-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-2-yl)-1-(4-fluorophenyl)-6-methyl-1H-indazole	R^t 1.62 min (Method 7); m/z 524.4 (M+H)⁺ (ES⁺)
28	 1-(4-fluorophenyl)-6-methyl-5-(4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)-1-(oxetan-3-yl)piperazin-2-yl)-1H-indazole	R^t 1.83 min (Method 7); m/z 512.4 (M+H)⁺ (ES⁺)
29	 5-(1-benzyl-4-(methylsulfonyl)piperazin-2-yl)-1-(4-fluorophenyl)-6-methyl-1H-indazole	R^t 2.03 min (Method 9); m/z 479.2 (M+H)⁺ (ES⁺)

Example	Structure	LC-MS analysis
30	 1-(4-fluorophenyl)-6-methyl-5-(4-(methylsulfonyl)-1-((tetrahydro-2H-pyran-4-yl)methyl)piperazin-2-yl)-1H-indazole	R^t 1.56 min (Method 9); m/z 487.2 (M+H)⁺ (ES⁺)
31	 5-((3-((1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)-4-isobutylpiperazin-1-yl)sulfonyl)-2-methylthiazole	R^t 2.20 min (Method 9); m/z 528.2 (M+H)⁺ (ES⁺)

Example 32: 1-(4-fluorophenyl)-6-methyl-5-(4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)-1-(3,3,3-trifluoro-2-methylpropyl)piperazin-2-yl)-1H-indazole

Example 33: 1-(4-fluorophenyl)-6-methyl-5-(4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)-1-(3,3,3-trifluoro-2-methylpropyl)piperazin-2-yl)-1H-indazole

5

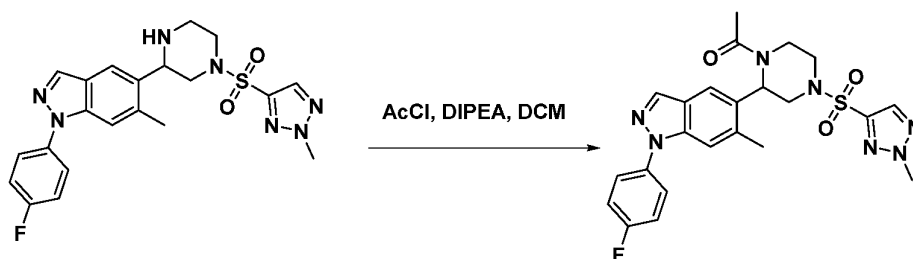


[0226] 1-(4-Fluorophenyl)-6-methyl-5-(4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)-1-(3,3,3-trifluoro-2-methylpropyl)piperazin-2-yl)-1H-indazole (48.8mg, 0.083mmol) was dissolved in 1 mL DMSO, filtered and purified by reversed phase preparative HPLC (Waters

10 2767 Sample Manager, Waters 2545 Binary Gradient Module, Waters Systems Fluidics

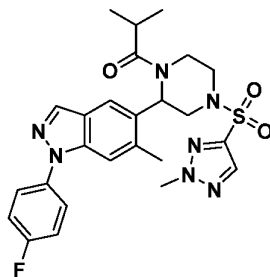
Organiser, Waters 515 ACD pump, Waters 515 Makeup pump, Waters 2998 Photodiode Array Detector, Waters QDa) on a Waters X-Select CSH C18 ODB prep column, 130Å, 5 µm, 30 mm X 100 mm, flow rate 40 mL min⁻¹ eluting with a 0.1% Formic acid in water-MeCN gradient over 17.5 mins using UV across all wavelengths with PDA as well as a QDA and ELS detector. At-column dilution pump gives 2 mL min⁻¹ Methanol over the entire method, which is included in the following MeCN percentages. Gradient information: 0.0-0.5 min, 55% MeCN; 0.5-21.0 min, ramped from 55% MeCN to 85% MeCN; 21.0-21.2 min, ramped from 85% MeCN to 100% MeCN; 21.2-24.0 min, held at 100% MeCN. The clean fractions were evaporated in a Genevac affording 1-(4-fluorophenyl)-6-methyl-5-((R)-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)-1-((R)-3,3,3-trifluoro-2-methylpropyl)piperazin-2-yl)-1H-indazole (14.2 mg, 24 µmol, 57 %, 95% Purity) (**Example 32**) as a clear colourless solid; R^t 2.18 min (Method 9); m/z 566.4 (M+H)⁺ (ES⁺); δH NMR (400 MHz, MeOD) δ 8.16 (d, J = 0.9 Hz, 1H), 8.05 (s, 1H), 7.92 (s, 1H), 7.84 – 7.71 (m, 2H), 7.59 (s, 1H), 7.36 (t, J = 8.7 Hz, 2H), 4.31 (s, 3H), 3.93 – 3.81 (m, 1H), 3.73 (dd, J = 10.3, 3.2 Hz, 1H), 3.66 (dd, J = 12.0, 2.8 Hz, 1H), 2.90 (td, J = 11.8, 2.8 Hz, 1H), 2.79 (dd, J = 13.4, 8.8 Hz, 1H), 2.70 – 2.35 (m, 7H), 1.99 (dd, J = 13.3, 4.7 Hz, 1H), 0.98 (d, J = 7.0 Hz, 3H), and 1-(4-fluorophenyl)-6-methyl-5-((R)-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)-1-((S)-3,3,3-trifluoro-2-methylpropyl)piperazin-2-yl)-1H-indazole (13.8 mg, 23 µmol, 56 %, 95% Purity) (**Example 33**) as a clear colourless solid; R^t 2.35 min (Method 9); m/z 566.4 (M+H)⁺ (ES⁺); δH NMR (400 MHz, MeOD) δ 8.19 (d, J = 0.9 Hz, 1H), 8.05 (s, 1H), 7.93 (s, 1H), 7.82 – 7.72 (m, 2H), 7.64 – 7.57 (m, 1H), 7.36 (dd, J = 9.5, 7.8 Hz, 2H), 4.31 (s, 3H), 3.89 (dd, J = 11.8, 2.7 Hz, 1H), 3.78 (dd, J = 10.5, 3.2 Hz, 1H), 3.71 – 3.64 (m, 1H), 3.28 (d, J = 11.8 Hz, 1H), 2.91 (td, J = 11.9, 2.8 Hz, 1H), 2.74 – 2.51 (m, 5H), 2.50 – 2.29 (m, 2H), 2.22 (dd, J = 12.1, 3.1 Hz, 1H), 1.08 (d, J = 6.8 Hz, 3H).

Example 34: 1-(2-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-1-yl)ethan-1-one



[0227] To a solution of 1-(4-fluorophenyl)-6-methyl-5-(4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-2-yl)-1H-indazole (25 mg, 55 μ mol) in DCM (1.00 mL) were added N-ethyl-N-isopropylpropan-2-amine (35 mg, 48 μ L, 0.27 mmol) and acetyl chloride (8.6 mg, 7.8 μ L, 0.11 mmol). The reaction mixture was stirred for 45 mins at rt before being quenched with sat. aqueous NaHCO₃ (3 mL). The organics were extracted with DCM (3 x 3 mL), with the aid of a phase separator and then concentrated onto silica gel. The crude product was purified by chromatography on silica gel (4 g cartridge, 0-100% 3:1 EtOAc-EtOH/isohexane) to afford 1-(2-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-1-yl)ethan-1-one (24 mg, 46 μ mol, 83 %) as a pale yellow solid; R^t 1.84 min (Method 4); m/z 511.2 (M+H)⁺ (ES⁺); δ H NMR (400 MHz, DMSO) δ 8.25 (d, J = 0.9 Hz, 1H), 8.16 (s, 1H), 7.90 (s, 1H), 7.83 – 7.72 (m, 2H), 7.59 (q, J = 1.0 Hz, 1H), 7.44 – 7.35 (m, 2H), 5.57 (t, J = 5.1 Hz, 1H), 4.22 (s, 3H), 4.11 (d, J = 14.0 Hz, 1H), 3.83 (ddd, J = 13.3, 5.1, 1.1 Hz, 1H), 3.78 – 3.57 (m, 2H), 3.42 (dd, J = 13.3, 5.1 Hz, 1H), 3.16 (td, J = 10.9, 4.5 Hz, 1H), 2.47 (d, J = 0.9 Hz, 3H), 1.96 (d, J = 3.3 Hz, 3H).

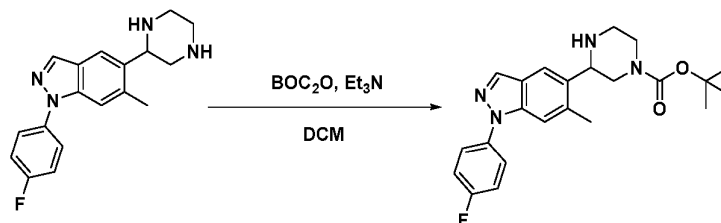
Example 35: 1-(2-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-1-yl)-2-methylpropan-1-one



[0228] The compound was prepared by similar methods to those described for **Example 34**; R_t 1.97 min (Method 1); m/z 526.4 (M+H)⁺ (ES⁺). δ H 8.24 (d, J = 0.9 Hz, 1H), 8.16 (s, 1H), 7.87 (s, 1H), 7.83 – 7.74 (m, 2H), 7.59 (d, J = 1.3 Hz, 1H), 7.44 – 7.34 (m, 2H), 5.60 (t, J = 5.3 Hz, 1H), 4.21 (s, 3H), 4.17 (d, J = 4.9 Hz, 1H), 3.82 (dd, J = 13.3, 5.5 Hz, 1H), 3.76 – 3.65 (m, 2H), 3.43 (obsc m, 1H), 3.14 (m, 1H), 2.79 (p, J = 6.7 Hz, 1H), 2.46 (d, J = 0.8 Hz, 3H), 0.99 (d, J = 6.7 Hz, 3H), 0.91 (d, J = 6.6 Hz, 3H).

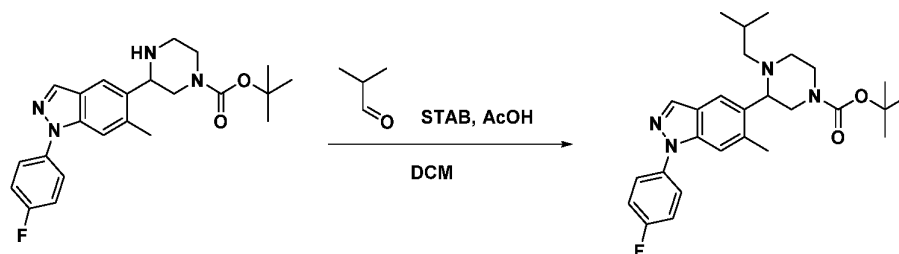
Example 36: 1-(4-fluorophenyl)-5-(1-isobutyl-4-((1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-4-yl)sulfonyl)piperazin-2-yl)-6-methyl-1H-indazole

Intermediate F: tert-butyl 3-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)piperazine-1-carboxylate



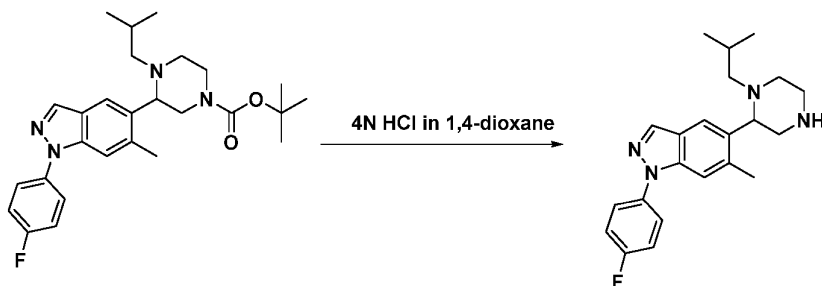
[0229] To a solution of 1-(4-fluorophenyl)-6-methyl-5-(piperazin-2-yl)-1H-indazole (3.30 g, 10.6 mmol) [**Intermediate B**] in DCM (100 mL) were added triethylamine (1.29 g, 1.77 mL, 12.8 mmol) and di-tert-butyl dicarbonate (2.32 g, 10.6 mmol) and the reaction mixture stirred at rt overnight. The reaction mixture was quenched with water (40 mL) and the layers separated. The aqueous layer was extracted with DCM (2 x 20 mL). Combined organic extracts were dried over MgSO₄ and concentrated in vacuo. The crude product was purified by chromatography on silica gel (80 g cartridge, 0-10% (0.7 M Ammonia/MeOH)/DCM) to afford tert-butyl 3-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)piperazine-1-carboxylate (3.83 g, 8.9 mmol, 83 %) as a pale yellow solid; Rt 1.41 min (Method 4); m/z 355.2 (M+H)⁺ (ES⁺).

Intermediate G: tert-butyl 3-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)-4-isobutylpiperazine-1-carboxylate.



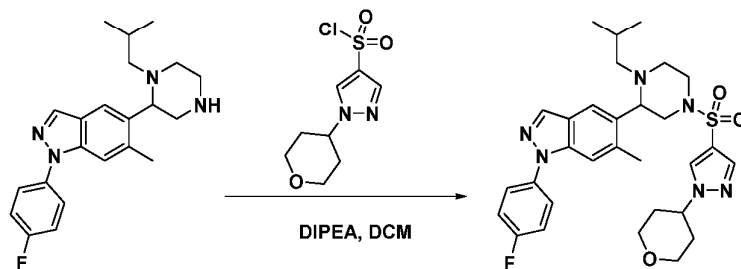
[0230] The compound was prepared by similar methods to those described for **Example 1** to give tert-butyl 3-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)-4-isobutylpiperazine-1-carboxylate (2.4g, 63 %); Rt 1.82 min (Method 1); m/z 467.2 (M+H)⁺ (ES⁺); ¹H NMR (400 MHz, DMSO) δ 8.30 (d, J = 0.9 Hz, 1H), 7.93 (s, 1H), 7.86 – 7.74 (m, 2H), 7.63 (s, 1H), 7.46 – 7.38 (m, 2H), 3.96 (d, J = 13.0 Hz, 1H), 3.77 (s, 1H), 3.13 (d, J = 11.8 Hz, 1H), 3.01 (s, 1H), 2.69 (d, J = 19.9 Hz, 1H), 2.13 – 1.91 (m, 2H), 1.77 (ddd, J = 22.8, 12.0, 5.6 Hz, 2H), 1.40 (s, 9H), 1.24 (s, 2H), 0.94 – 0.79 (m, 4H), 0.65 (d, J = 6.5 Hz, 3H)

Intermediate H: 1-(4-fluorophenyl)-5-(1-isobutylpiperazin-2-yl)-6-methyl-1H-indazole



[0231] To a solution of tert-butyl 3-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)-4-isobutylpiperazine-1-carboxylate (350 mg, 750 μ mol) in 1,4-dioxane (3.50 mL) was added HCl (4M in dioxane) (547 mg, 3.75 mL, 4 molar, 15.0 mmol) and the reaction mixture stirred at rt for 5 hours. Additional 1,4-dioxane (3.50 mL) and HCl (4M in dioxane) (547 mg, 3.75 mL, 15.0 mmol) were added and the reaction mixture stirred for a further 18 hours. The reaction mixture was then concentrated to a white solid and the residue redissolved in DCM (10 mL). Sat. aqueous NaHCO_3 (10 mL) was added, and the layers separated. The aqueous was extracted with DCM (2 x 5 mL). Combined organic extracts were dried over MgSO_4 and concentrated *in vacuo* to afford 1-(4-fluorophenyl)-5-(1-isobutylpiperazin-2-yl)-6-methyl-1H-indazole (268 mg, 0.69 mmol, 93 %) as a pale tan solid, which was used without further purification; Rt 1.48 min (Method 4); m/z 367.2 (M+H)⁺ (ES⁺); δ H NMR (400 MHz, DMSO) δ 8.31 – 8.23 (m, 1H), 7.91 (s, 1H), 7.79 (m, 2H), 7.58 (d, J = 3.9 Hz, 1H), 7.42 (m, 2H), 3.57 (dd, J = 3.6, 1.6 Hz, 1H), 3.06 (d, J = 11.4 Hz, 1H), 2.93 (d, J = 12.5 Hz, 1H), 2.80 (d, J = 12.4 Hz, 2H), 2.47 (obs s, 4H), 2.00 (t, J = 10.6 Hz, 2H), 1.80 (s, 1H), 1.72 (d, J = 12.1 Hz, 1H), 0.92 – 0.74 (m, 3H), 0.72 – 0.50 (m, 3H).

Example 36: 1-(4-fluorophenyl)-5-(1-isobutyl-4-((1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-4-yl)sulfonyl)piperazin-2-yl)-6-methyl-1H-indazole

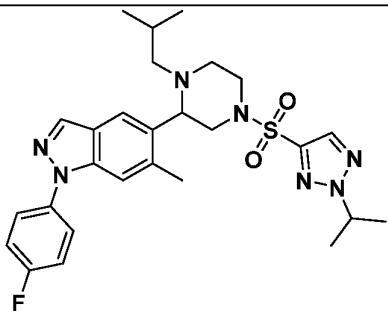
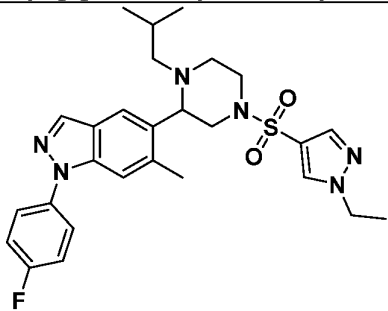
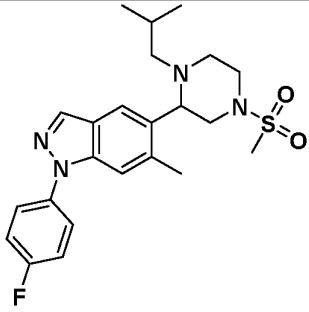


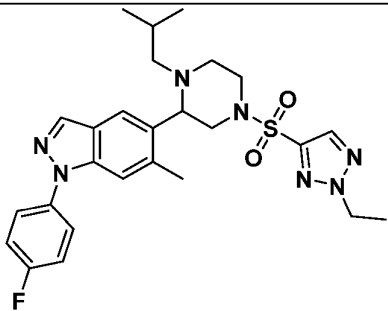
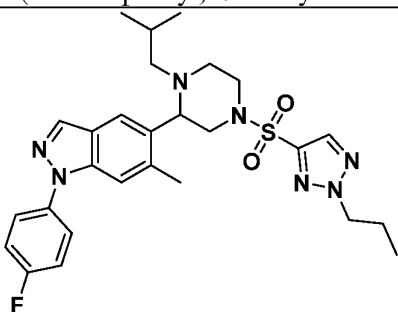
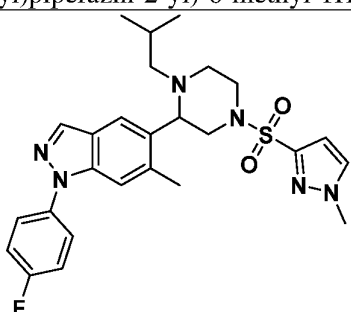
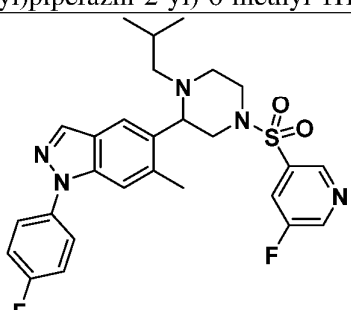
[0232] The compound was prepared by similar methods to those described for **Example 1**; Rt 1.94 min (Method 4); m/z 581.2 (M+H)⁺ (ES⁺); δ H NMR (400 MHz, DMSO) δ 8.41 (s,

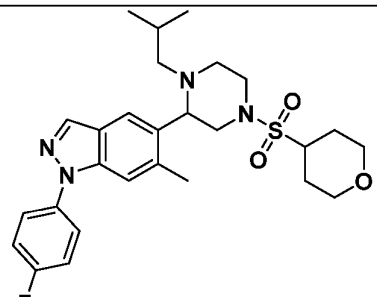
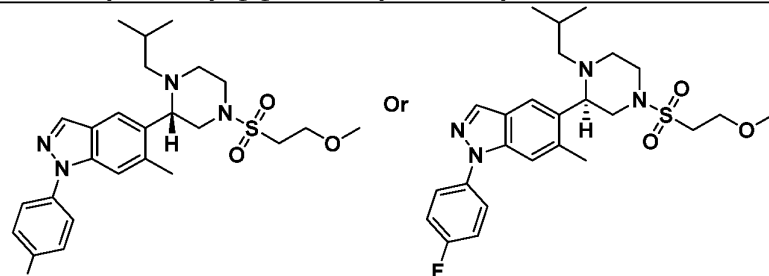
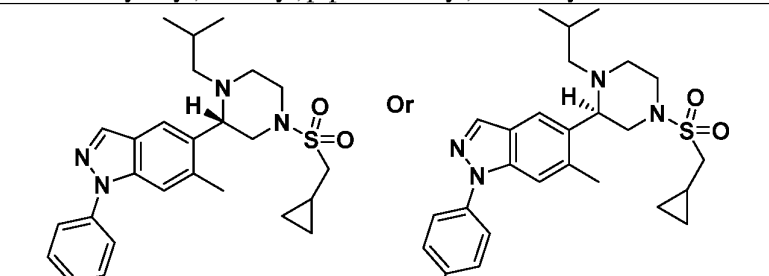
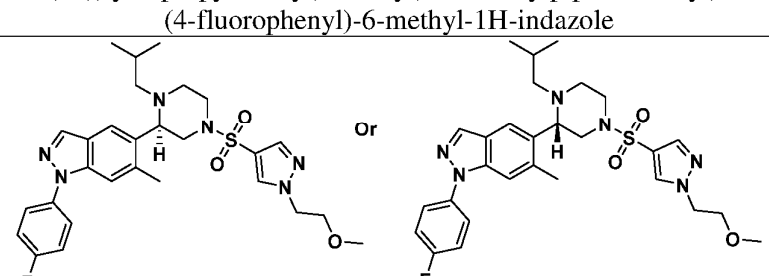
1H), 8.27 (d, J = 0.9 Hz, 1H), 7.89 – 7.73 (m, 4H), 7.64 (s, 1H), 7.50 – 7.35 (m, 2H), 4.48 (tt, J = 10.4, 5.1 Hz, 1H), 3.94 (d, J = 12.2 Hz, 2H), 3.69 – 3.52 (m, 2H), 3.42 (ddd, J = 14.9, 9.2, 3.1 Hz, 3H), 3.23 (d, J = 11.8 Hz, 1H), 2.47 (m, 4H), 2.22 (dd, J = 29.0, 17.1 Hz, 2H), 2.04 – 1.85 (m, 5H), 1.84 – 1.70 (m, 2H), 0.78 (d, J = 6.2 Hz, 3H), 0.64 (d, J = 6.3 Hz, 3H).

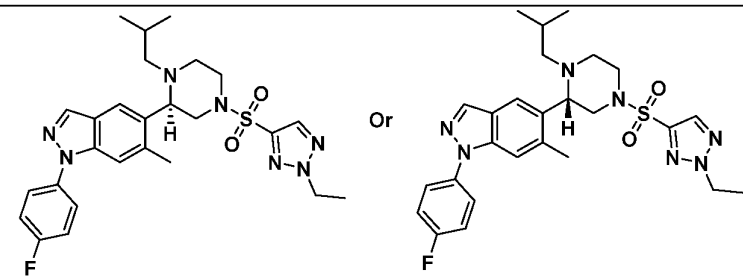
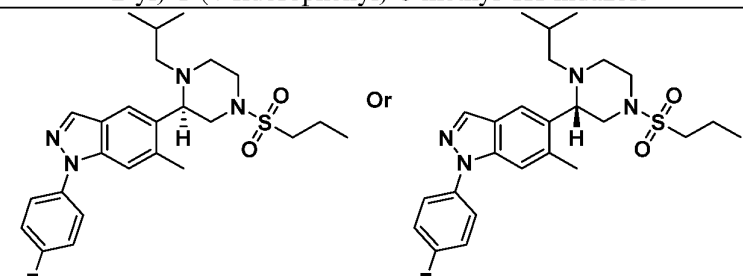
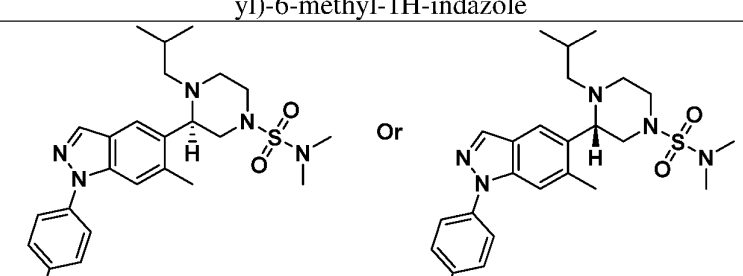
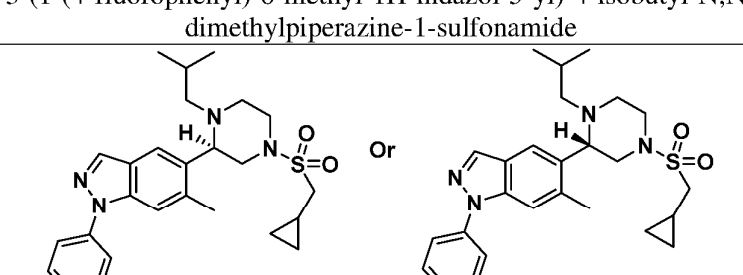
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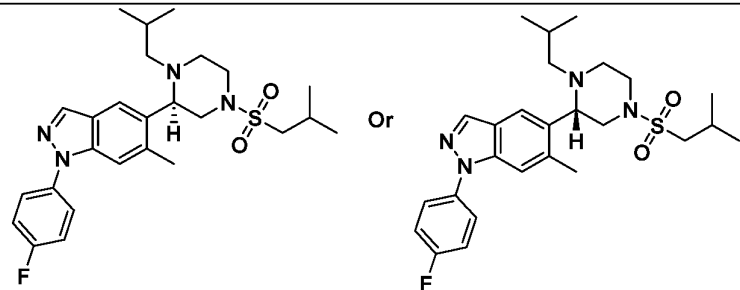
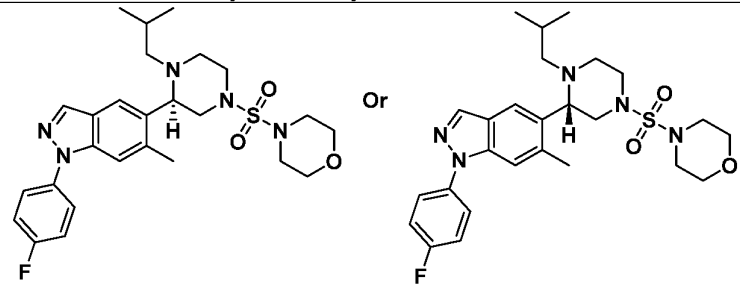
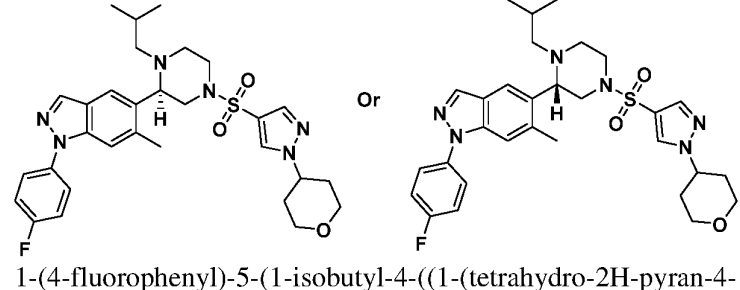
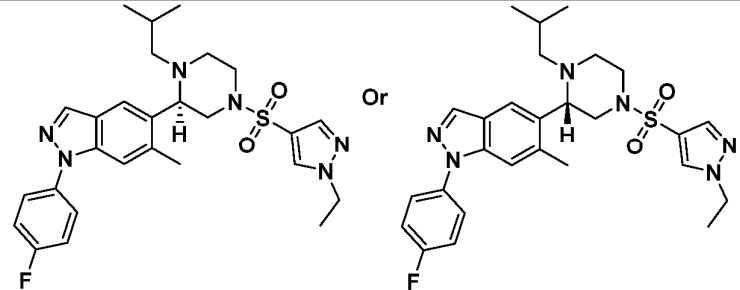
Table 4: The examples shown in the table below were prepared by similar methods to those described for Example 36

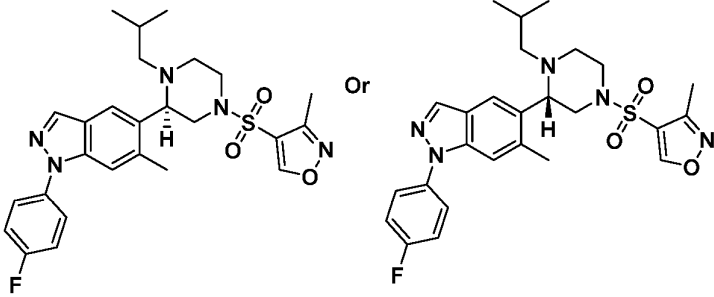
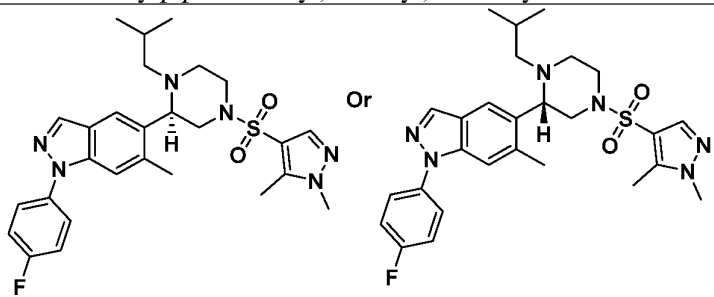
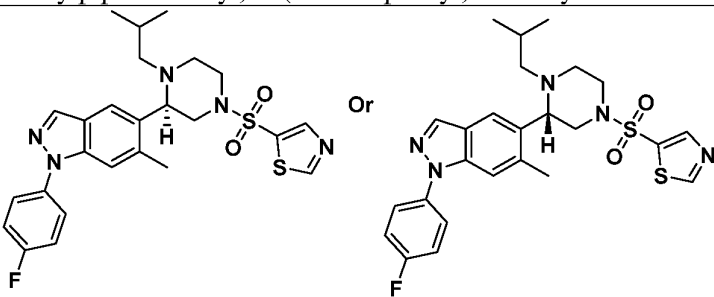
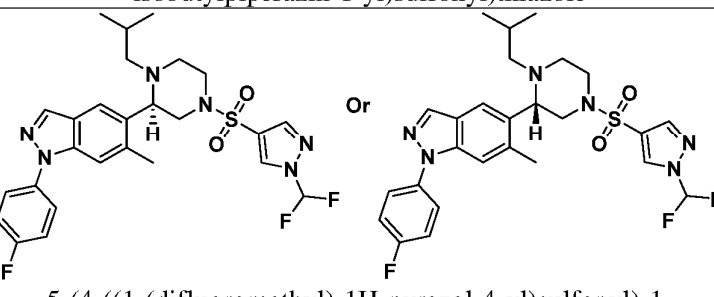
Example	Structure	LC-MS analysis
37	 1-(4-fluorophenyl)-5-(1-isobutyl-4-((2-isopropyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-2-yl)-6-methyl-1H-indazole	R^t 2.38 min (Method 7); m/z 540.0 (M+H)⁺ (ES⁺)
38	 5-(4-((1-ethyl-1H-pyrazol-4-yl)sulfonyl)-1-isobutylpiperazin-2-yl)-1-(4-fluorophenyl)-6-methyl-1H-indazole	R^t 1.98 min (Method 7); m/z 525.4 (M+H)⁺ (ES⁺)
39	 1-(4-fluorophenyl)-5-(1-isobutyl-4-(methylsulfonyl)piperazin-2-yl)-6-methyl-1H-indazole	R^t 1.67 min (Method 7); m/z 445.4 (M+H)⁺ (ES⁺)

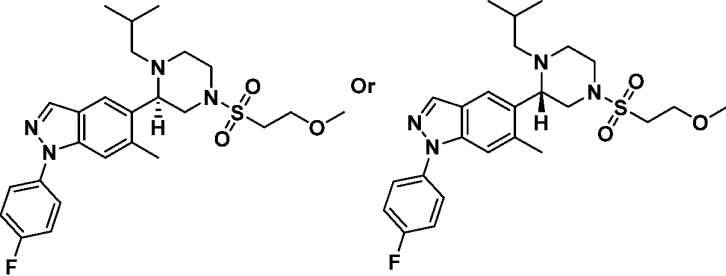
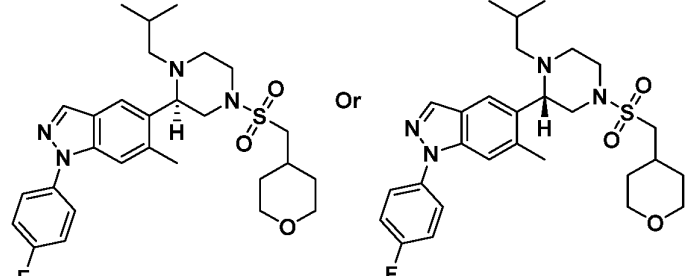
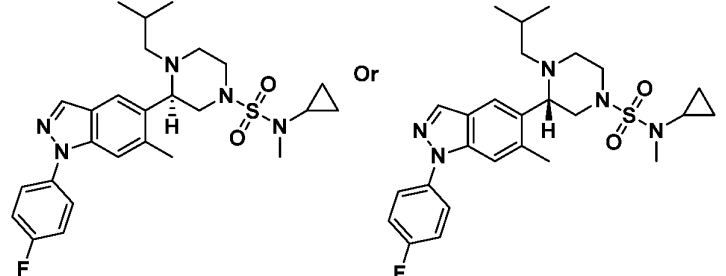
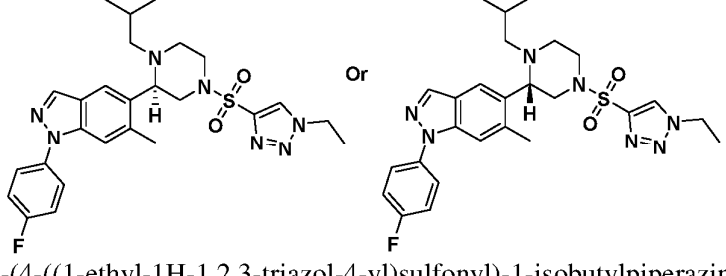
Example	Structure	LC-MS analysis
40	 5-(4-((2-ethyl-2H-1,2,3-triazol-4-yl)sulfonyl)-1-isobutylpiperazin-2-yl)-1-(4-fluorophenyl)-6-methyl-1H-indazole	R^t 2.21 min (Method 7); m/z 526.5 (M+H)⁺ (ES⁺)
41	 1-(4-fluorophenyl)-5-(1-isobutyl-4-((2-propyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-2-yl)-6-methyl-1H-indazole	R^t 2.39 min (Method 7); m/z 540.2 (M+H)⁺ (ES⁺)
42	 1-(4-fluorophenyl)-5-(1-isobutyl-4-((1-methyl-1H-pyrazol-3-yl)sulfonyl)piperazin-2-yl)-6-methyl-1H-indazole	R^t 1.86 min (Method 9); m/z 511.4 (M+H)⁺ (ES⁺)
43	 1-(4-fluorophenyl)-5-(4-((5-fluoropyridin-3-yl)sulfonyl)-1-isobutylpiperazin-2-yl)-6-methyl-1H-indazole	R^t 2.18 min (Method 9); m/z 526.2 (M+H)⁺ (ES⁺)

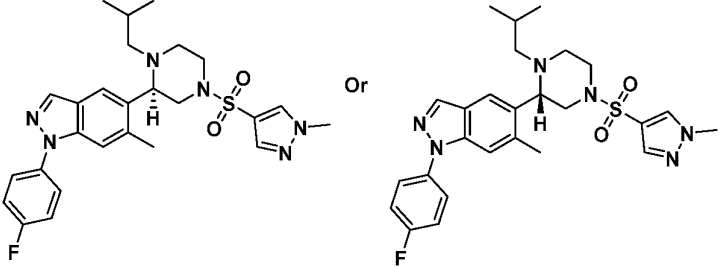
Example	Structure	LC-MS analysis
44	 1-(4-fluorophenyl)-5-(1-isobutyl-4-((tetrahydro-2H-pyran-4-yl)sulfonyl)piperazin-2-yl)-6-methyl-1H-indazole	R^t 1.74 min (Method 9); m/z 515.2 (M+H)⁺ (ES⁺)
45	 1-(4-fluorophenyl)-5-(1-isobutyl-4-((2-methoxyethyl)sulfonyl)piperazin-2-yl)-6-methyl-1H-indazole	R^t 1.68 min (Method 7); m/z 489.5 (M+H)⁺ (ES⁺)
46	 5-(4-((cyclopropylmethyl)sulfonyl)-1-isobutylpiperazin-2-yl)-1-(4-fluorophenyl)-6-methyl-1H-indazole	R^t 1.84 min (Method 7); m/z 485.4 (M+H)⁺ (ES⁺)
47	 1-(4-fluorophenyl)-5-(1-isobutyl-4-((1-(2-methoxyethyl)-1H-pyrazol-4-yl)sulfonyl)piperazin-2-yl)-6-methyl-1H-indazole	R^t 1.89 min (Method 9); m/z 555.2 (M+H)⁺ (ES⁺)

Example	Structure	LC-MS analysis
48	 5-(4-((2-ethyl-2H-1,2,3-triazol-4-yl)sulfonyl)-1-isobutylpiperazin-2-yl)-1-(4-fluorophenyl)-6-methyl-1H-indazole	R^t 2.15 min (Method 9); m/z 526.2 (M+H)⁺ (ES⁺)
49	 1-(4-fluorophenyl)-5-(1-isobutyl-4-(propylsulfonyl)piperazin-2-yl)-6-methyl-1H-indazole	R^t 1.72 min (Method 9); m/z 473.2 (M+H)⁺ (ES⁺)
50	 3-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)-4-isobutyl-N,N-dimethylpiperazine-1-sulfonamide	R^t 1.62 min (Method 9); m/z 474.2 (M+H)⁺ (ES⁺)
51	 5-(4-((cyclopropylmethyl)sulfonyl)-1-isobutylpiperazin-2-yl)-1-(4-fluorophenyl)-6-methyl-1H-indazole	R^t 1.73 min (Method 9); m/z 485.2 (M+H)⁺ (ES⁺)

Example	Structure	LC-MS analysis
52	 1-(4-fluorophenyl)-5-(1-isobutyl-4-(isobutylsulfonyl)piperazin-2-yl)-6-methyl-1H-indazole	R^t 2.02 min (Method 9); m/z 487.2 (M+H)⁺ (ES⁺)
53	 4-((3-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)-4-isobutylpiperazin-1-yl)sulfonyl)morpholine	R^t 1.78 min (Method 9); m/z 516.2 (M+H)⁺ (ES⁺)
54	 1-(4-fluorophenyl)-5-(1-isobutyl-4-((1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-4-yl)sulfonyl)piperazin-2-yl)-6-methyl-1H-indazole	R^t 1.93 min (Method 9); m/z 581.2 (M+H)⁺ (ES⁺)
55	 5-(4-((1-ethyl-1H-pyrazol-4-yl)sulfonyl)-1-isobutylpiperazin-2-yl)-1-(4-fluorophenyl)-6-methyl-1H-indazole	R^t 1.94 min (Method 9); m/z 525.2 (M+H)⁺ (ES⁺)

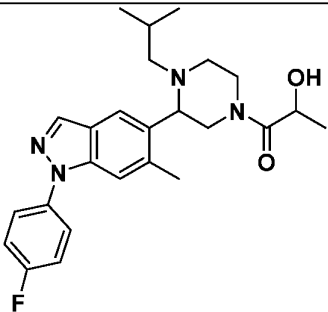
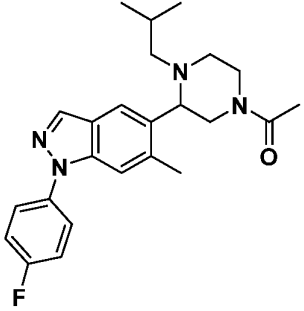
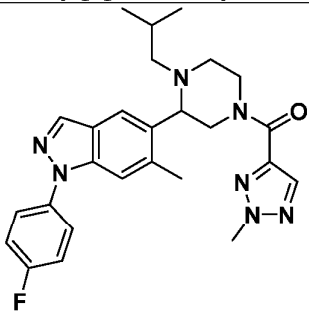
Example	Structure	LC-MS analysis
56	 4-((3-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)-4-isobutylpiperazin-1-yl)sulfonyl)-3-methylisoxazole	R^t 2.15 min (Method 9); m/z 512.2 (M+H)⁺ (ES⁺)
57	 5-(4-((1,5-dimethyl-1H-pyrazol-4-yl)sulfonyl)-1-isobutylpiperazin-2-yl)-1-(4-fluorophenyl)-6-methyl-1H-indazole	R^t 1.86 min (Method 9); m/z 525.2 (M+H)⁺ (ES⁺)
58	 5-(3-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)-4-isobutylpiperazin-1-yl)sulfonylthiazole	R^t 2.11 min (Method 9); m/z 514.2 (M+H)⁺ (ES⁺)
59	 5-(4-((1-(difluoromethyl)-1H-pyrazol-4-yl)sulfonyl)-1-isobutylpiperazin-2-yl)-1-(4-fluorophenyl)-6-methyl-1H-indazole	R^t 2.09 min (Method 9); m/z 547.2 (M+H)⁺ (ES⁺)

Example	Structure	LC-MS analysis
60	 1-(4-fluorophenyl)-5-(1-isobutyl-4-((2-methoxyethyl)sulfonyl)piperazin-2-yl)-6-methyl-1H-indazole	R^t 1.80 min (Method 9); m/z 488.6 (M+H)⁺ (ES⁺)
61	 1-(4-fluorophenyl)-5-(1-isobutyl-4-(((tetrahydro-2H-pyran-4-yl)methyl)sulfonyl)piperazin-2-yl)-6-methyl-1H-indazole	R^t 1.90 min (Method 9); m/z 529.2 (M+H)⁺ (ES⁺)
62	 N-cyclopropyl-3-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)-4-isobutyl-N-methylpiperazine-1-sulfonamide	R^t 1.94 min (Method 9); m/z 500.2 (M+H)⁺ (ES⁺)
63	 5-(4-(((1-ethyl-1H-1,2,3-triazol-4-yl)sulfonyl)-1-isobutylpiperazin-2-yl)-1-(4-fluorophenyl)-6-methyl-1H-indazole	R^t 1.95 min (Method 9); m/z 526.2 (M+H)⁺ (ES⁺)

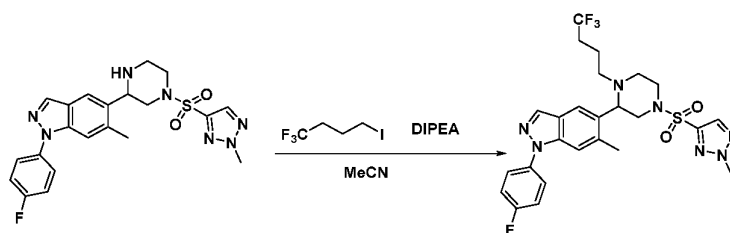
Example	Structure	LC-MS analysis
64	 1-(4-fluorophenyl)-5-(1-isobutyl-4-((1-methyl-1H-pyrazol-4-yl)sulfonyl)piperazin-2-yl)-6-methyl-1H-indazole	R^t 1.82 min (Method 9); m/z 511.5 ($M+H$)⁺ (ES^+)

Examples 65 - 67

Table 5: The examples shown in the table below were prepared by similar methods to those described in Example 34 using Intermediate H.

Example	Structure	LC-MS analysis
65	 1-(3-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)-4-isobutylpiperazin-1-yl)-2-hydroxypropan-1-one	R^t 1.41 min (Method 9); m/z 439.2 (M+H)⁺ (ES⁺)
66	 1-(3-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)-4-isobutylpiperazin-1-yl)ethan-1-one	R^t 1.42 min (Method 9); m/z 409.2 (M+H)⁺ (ES⁺)
67	 (3-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)-4-isobutylpiperazin-1-yl)(2-methyl-2H-1,2,3-triazol-4-yl)methanone	R^t 1.60 min (Method 9); m/z 476.2 (M+H)⁺ (ES⁺)

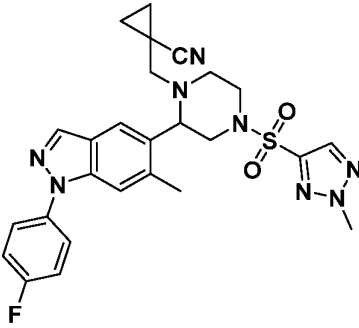
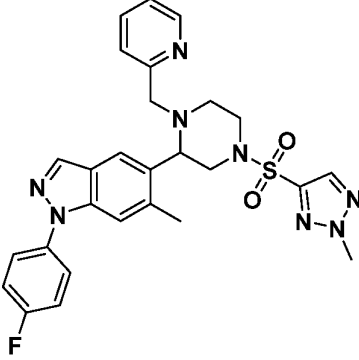
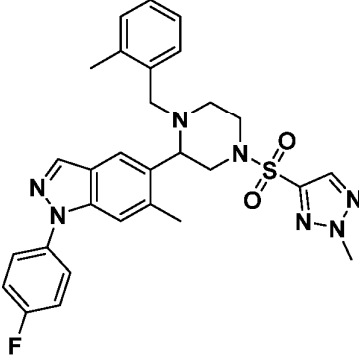
- 5 **Example 68: 1-(4-fluorophenyl)-6-methyl-5-(4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)-1-(4,4,4-trifluorobutyl)piperazin-2-yl)-1H-indazole**

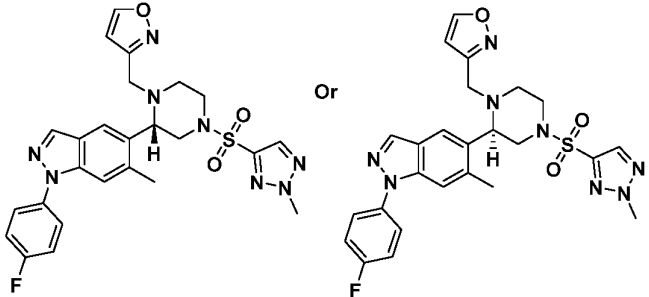
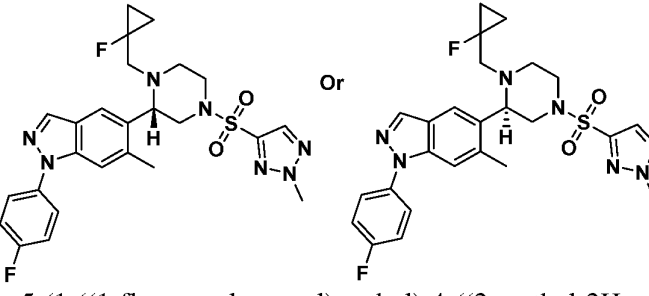
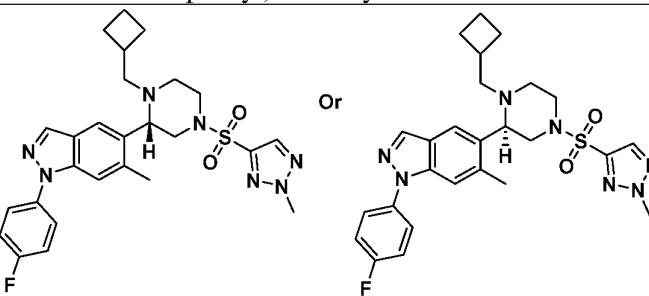


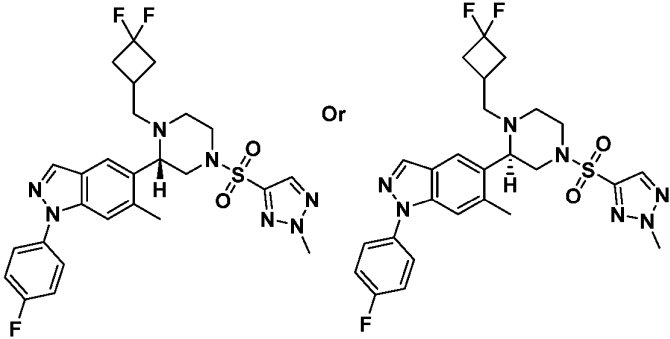
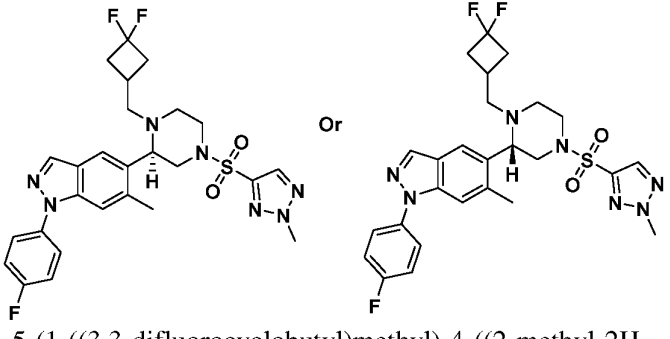
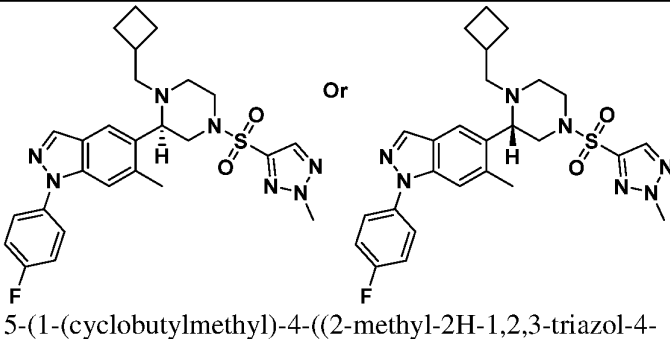
[0233] To a solution of 1,1,1-trifluoro-4-iodobutane (77.5 mg, 0.33 mmol) in MeCN (0.50 mL) were added N-ethyl-N-isopropylpropan-2-amine (85 mg, 0.11 mL, 0.66 mmol) and 1-(4-fluorophenyl)-6-methyl-5-(4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-2-yl)-1H-indazole (30 mg, 66 μ mol). The reaction mixture was stirred at 130°C for 3hr (if alkyl bromide or chloride, sodium iodide was used as an additive. Reaction temperature and time ranged from 80°C to 140°C and 2 – 24 hrs respectively). After cooling to rt, the reaction mixture was partitioned between water (3 mL) and DCM (3 mL) and the layers separated. The aqueous layer was extracted with DCM (3 x 3 mL). Combined organic extracts were dried over MgSO₄ and concentrated in vacuo. The crude product was purified by chromatography on silica gel (4 g cartridge, 0-80% EtOAc/isohexane) to afford 1-(4-fluorophenyl)-6-methyl-5-(4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)-1-(4,4,4-trifluorobutyl)piperazin-2-yl)-1H-indazole (13 mg, 22 μ mol, 33 %) as a white solid; Rt 2.21 min (Method 4); m/z 566.4 (M+H)⁺ (ES⁺); δ H NMR (400 MHz, DMSO) δ 8.28 (d, J = 0.7 Hz, 2H), 7.83 (s, 1H), 7.82 – 7.75 (m, 2H), 7.65 (s, 1H), 7.47 – 7.39 (m, 2H), 4.27 (s, 3H), 3.72 (d, J = 11.7 Hz, 1H), 3.66 (dd, J = 10.5, 3.1 Hz, 1H), 3.47 (d, J = 11.8 Hz, 1H), 3.22 (d, J = 11.8 Hz, 1H), 2.82 – 2.70 (m, 1H), 2.43 (m, 1H), 2.38 – 2.10 (m, 2H), 2.10 – 1.87 (m, 2H), 1.67 – 1.43 (m, 2H).

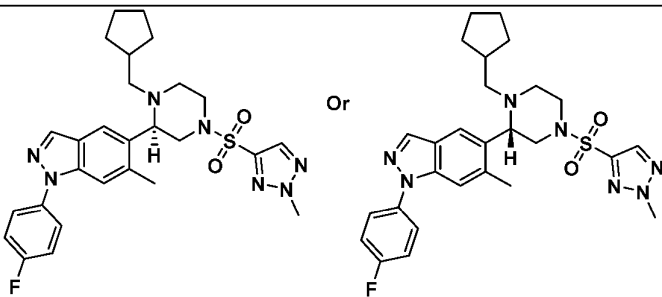
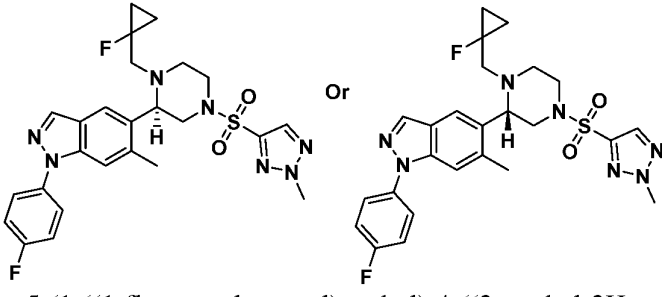
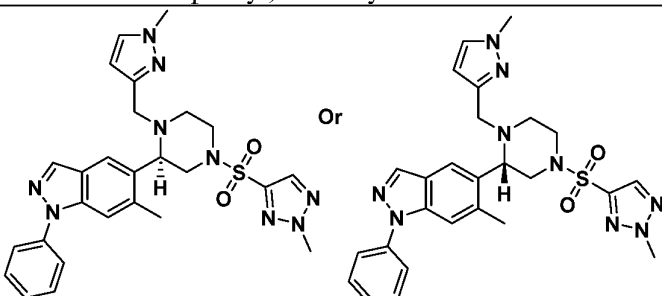
Examples 69- 83

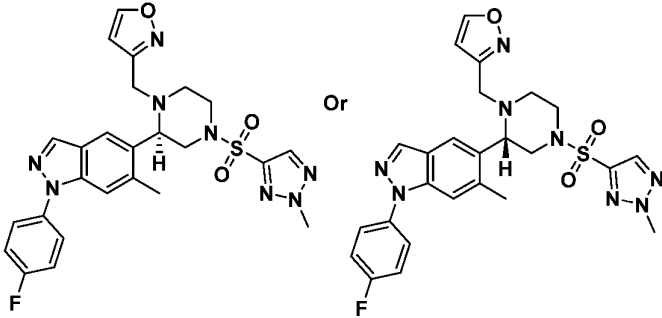
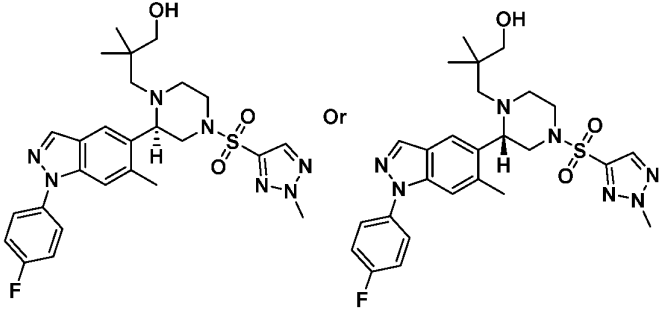
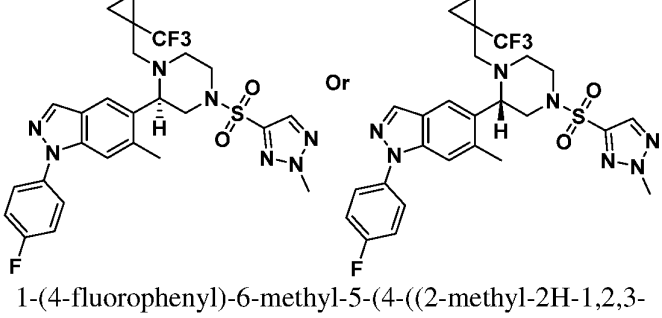
Table 6: The examples shown in the table below were prepared by similar methods to those described in Example 68.

Example	Structure	LC-MS analysis
69	 1-((2-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-1-yl)methyl)cyclopropane-1-carbonitrile	R^t 2.09 min (Method 7); m/z 535.2 (M+H)⁺ (ES⁺)
70	 1-(4-fluorophenyl)-6-methyl-5-(4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)-1-(pyridin-2-ylmethyl)piperazin-2-yl)-1H-indazole	R^t 1.64 min (Method 9); m/z 547.2 (M+H)⁺ (ES⁺)
71	 1-(4-fluorophenyl)-6-methyl-5-(4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)-1-(2-methylbenzyl)piperazin-2-yl)-1H-indazole	R^t 2.40 min (Method 9); m/z 560.2 (M+H)⁺ (ES⁺)

Example	Structure	LC-MS analysis
72	 3-((2-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-1-yl)methyl)isoxazole	R^t 2.06 min (Method 7); m/z 537.4 (M+H)⁺ (ES⁺)
73	 5-(1-((1-fluorocyclopropyl)methyl)-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-2-yl)-1-(4-fluorophenyl)-6-methyl-1H-indazole	R^t 2.13 min (Method 9); m/z 528.2 (M+H)⁺ (ES⁺)
74	 5-(1-(cyclobutylmethyl)-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-2-yl)-1-(4-fluorophenyl)-6-methyl-1H-indazole	R^t 1.82 min (Method 9); m/z 524.2 (M+H)⁺ (ES⁺)

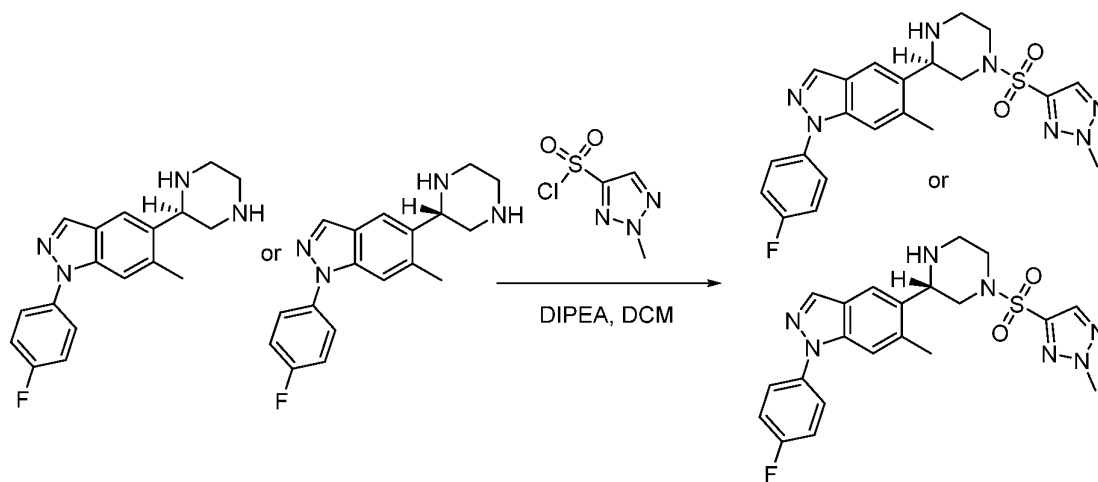
Example	Structure	LC-MS analysis
75	 5-(1-((3,3-difluorocyclobutyl)methyl)-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-2-yl)-1-(4-fluorophenyl)-6-methyl-1H-indazole	R^t 2.11 min (Method 9); m/z 560.2 (M+H)⁺ (ES⁺)
76	 5-(1-((3,3-difluorocyclobutyl)methyl)-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-2-yl)-1-(4-fluorophenyl)-6-methyl-1H-indazole	R^t 2.12 min (Method 7); m/z 560.4 (M+H)⁺ (ES⁺)
77	 5-(1-(cyclobutylmethyl)-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-2-yl)-1-(4-fluorophenyl)-6-methyl-1H-indazole	R^t 1.80 min (Method 7); m/z 524.5 (M+H)⁺ (ES⁺)

Example	Structure	LC-MS analysis
78	 5-(1-(cyclopentylmethyl)-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-2-yl)-1-(4-fluorophenyl)-6-methyl-1H-indazole	R^t 2.05 min (Method 7); m/z 538.4 (M+H)⁺ (ES⁺)
79	 5-(1-((1-fluorocyclopropyl)methyl)-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-2-yl)-1-(4-fluorophenyl)-6-methyl-1H-indazole	R^t 2.14 min (Method 9); m/z 528.2 (M+H)⁺ (ES⁺)
80	 1-(4-fluorophenyl)-6-methyl-5-(1-((1-methyl-1H-pyrazol-3-yl)methyl)-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-2-yl)-1H-indazole	R^t 1.76 min (Method 7); m/z 550.6 (M+H)⁺ (ES⁺)

Example	Structure	LC-MS analysis
81	 3-((2-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-1-yl)methyl)isoxazole	R^t 2.06 min (Method 7); m/z 537.4 (M+H)⁺ (ES⁺)
82	 3-(2-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-1-yl)-2,2-dimethylpropan-1-ol	R^t 1.57 min (Method 7); m/z 542.4 (M+H)⁺ (ES⁺)
83	 1-(4-fluorophenyl)-6-methyl-5-(4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)-1-((1-(trifluoromethyl)cyclopropyl)methyl)piperazin-2-yl)-1H-indazole	R^t 2.38 min (Method 7); m/z 578.4 (M+H)⁺ (ES⁺)

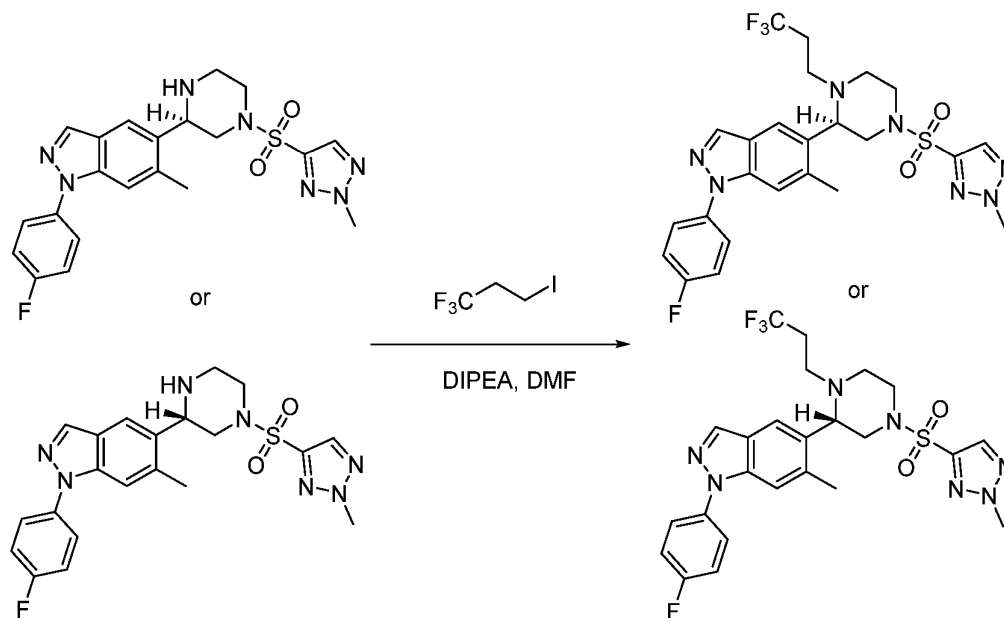
Example 84: 1-(4-fluorophenyl)-6-methyl-5-(4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)-1-(3,3,3-trifluoropropyl)piperazin-2-yl)-1H-indazole

Intermediate AZ: 1-(4-fluorophenyl)-6-methyl-5-(4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-2-yl)-1H-indazole



- [0234]** DCM (3.6 L) was charged to an agitated reactor under nitrogen at room temperature
- 5 followed by the addition of 1-(4-fluorophenyl)-6-methyl-5-(piperazin-2-yl)-1H-indazole (120 g, 0.39 mol) and N-ethyl-N-isopropylpropan-2-amine (151 g, 1.17 mol). The reaction mixture was cooled to 0°C and a solution of 2-methyl-2H-1,2,3-triazole-4-sulfonyl chloride (212 g, 1.17 mol) in DCM (750 ml) was added at a controlled rate and following complete addition the resultant mixture was stirred for at least 2 h at 0°C. The reaction mixture was then
- 10 quenched by the addition of sat. aq. NaHCO₃ (1500 ml). The phases were separated and the aqueous phase extracted with DCM (2 x 750 ml). The combined organic phases were concentrated *in vacuo* and the residue purified by silica chromatography to provide 1-(4-fluorophenyl)-6-methyl-5-(4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-2-yl)-1H-indazole as an off-white solid in 70% yield and a purity of >98% by HPLC. m/z 456.2
- 15 (M+H)⁺ (ES⁺).

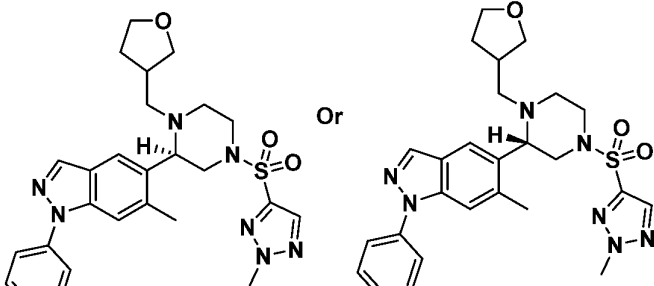
Example 84: 1-(4-fluorophenyl)-6-methyl-5-(4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)-1-(3,3,3-trifluoropropyl)piperazin-2-yl)-1H-indazole



[0235] To a solution of (R)-1-(4-fluorophenyl)-6-methyl-5-(4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-2-yl)-1H-indazole (2.50 g, 1 Eq, 5.49 mmol) in MeCN (10.0 mL) were added 1,1,1-trifluoro-3-iodopropane (9.83 g, 8 Eq, 43.9 mmol) and N-ethyl-N-isopropylpropan-2-amine (7.09 g, 10 Eq, 54.9 mmol). The reaction mixture was heated in the microwave at 150°C for 3 hrs. Power 150; Pressure 125. The reaction was concentrated under vacuum and partitioned between water (40 mL) and DCM (2 x 100 mL) the combined organic layers were dried using sodium sulfate and concentrated under vacuum to give a tan gum. The crude product was purified by chromatography on silica gel (80 g cartridge, 0-50% EtOAc/isohexane) to afford (R)-1-(4-fluorophenyl)-6-methyl-5-(4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)-1-(3,3,3-trifluoropropyl)piperazin-2-yl)-1H-indazole (1.98 g, 3.54 mmol, 64.5 %, 98.6% Purity) as a colourless glass. m/z 552.2 ($M+H$)⁺ (ES⁺). δ H NMR (300 MHz, DMSO) δ 8.31 – 8.28 (m, 2H), 7.87 (s, 1H), 7.84 – 7.78 (m, 2H), 7.68 (s, 1H), 7.48 – 7.39 (m, 2H), 4.29 (s, 3H), 3.77 – 3.74 (m, 2H), 3.54 – 3.50 (m, 1H), 3.35 – 3.28 (m, 1H), 2.79 – 2.65 (m, 2H), 2.51 – 2.34 (m, 4H), 2.27 – 2.12 (m, 1H) - Indazole CH₃ obscured by DMSO. R^t 2.35 min (Method 7).

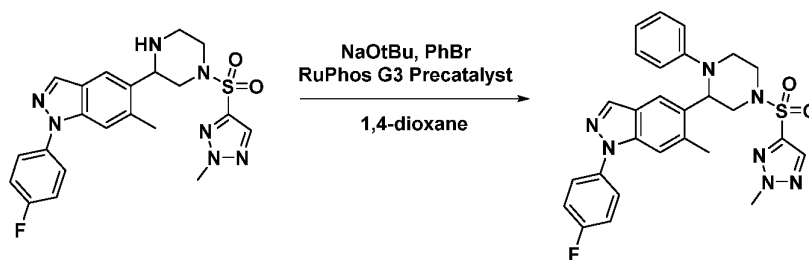
Example 85: 1-(4-fluorophenyl)-6-methyl-5-(4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)-1-((tetrahydrofuran-3-yl)methyl)piperazin-2-yl)-1H-indazole

Table 7: The example shown in the table below were prepared by similar methods to those described in Example 68.

Example	Structure	LC-MS analysis
85	 1-(4-fluorophenyl)-6-methyl-5-(4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)-1-((tetrahydrofuran-3-yl)methyl)piperazin-2-yl)-1H-indazole	R^t 1.83 and 1.89 min (Method 7); m/z 540.4 (M+H)⁺ (ES⁺)

5

Example 86: 1-(4-fluorophenyl)-6-methyl-5-(4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)-1-phenylpiperazin-2-yl)-1H-indazole

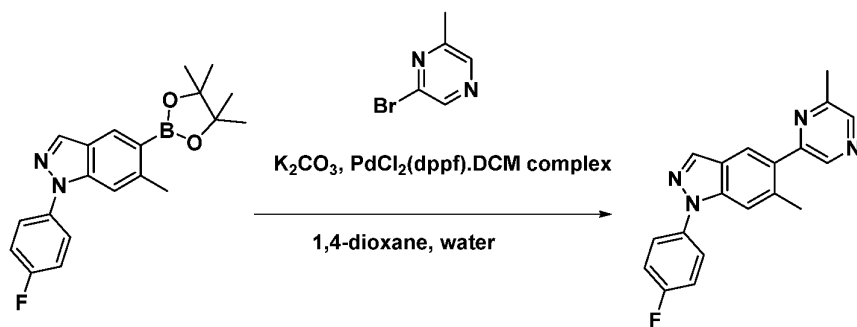


- [0236]** A solution of 1-(4-fluorophenyl)-6-methyl-5-(4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-2-yl)-1H-indazole (50 mg, 0.11 mmol) (prepared using similar methods to **Example 1**) and bromobenzene (34 mg, 23 μ L, 0.22 mmol) in 1,4-dioxane (1.50 mL) was degassed with bubbling nitrogen for 10 mins. RuPhos G3 Precatalyst (9.2 mg, 11 μ mol) and sodium tert-butoxide (2M in THF) (63 mg, 0.33 mL, 2 molar, 0.66 mmol) were then added and the reaction mixture stirred at 90 °C for 3 hours before being left to stand at rt overnight.
- After cooling to rt, the reaction mixture was quenched with MeOH (1 mL) and filtered through celite, washing with DCM (10 mL). The filtrate was then concentrated in vacuo. The

crude product was purified by chromatography on silica gel (4 g cartridge, 0-100% EtOAc/isohehexane) to afford 1-(4-fluorophenyl)-6-methyl-5-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)-1-phenylpiperazin-2-yl)-1H-indazole (27 mg, 48 μ mol, 44 %) as a white solid; Rt 2.23 min (Method 4); m/z 532.2 (M+H)⁺ (ES⁺); δ H NMR (400 MHz, DMSO) δ 8.28 (s, 1H), 8.15 (d, J = 0.9 Hz, 1H), 7.78 – 7.69 (m, 3H), 7.59 (s, 1H), 7.45 – 7.35 (m, 2H), 7.16 – 7.06 (m, 2H), 6.93 – 6.84 (m, 2H), 6.82 – 6.73 (m, 1H), 4.69 (dd, J = 8.8, 3.5 Hz, 1H), 4.21 (s, 3H), 3.66 (d, J = 9.7 Hz, 3H), 3.25 (t, J = 9.8 Hz, 1H), 3.15 (t, J = 9.4 Hz, 1H), 2.81 (dd, J = 12.3, 8.8 Hz, 1H), 2.58 (s, 3H).

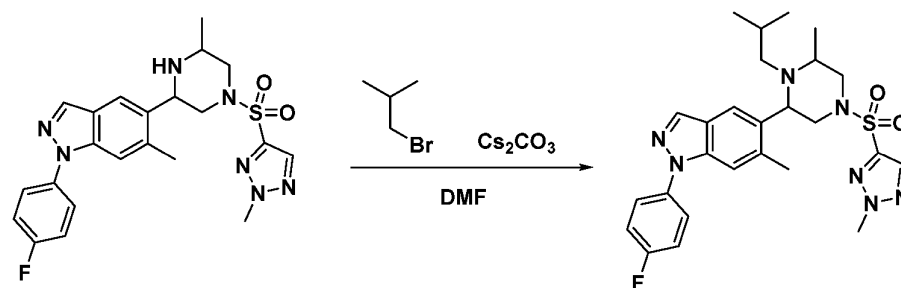
Example 87: 1-(4-fluorophenyl)-5-(1-isobutyl-6-methyl-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-2-yl)-6-methyl-1H-indazole

Intermediate I: 1-(4-fluorophenyl)-6-methyl-5-(6-methylpyrazin-2-yl)-1H-indazole



[0237] A solution of 1-(4-fluorophenyl)-6-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole (1.00 g, 2.84 mmol), 2-bromo-6-methylpyrazine (589 mg, 3.41 mmol) and potassium carbonate (589 mg, 4.26 mmol) in 1,4-dioxane (24.0 mL) and water (6.00 mL) was degassed (bubbling nitrogen) for 20 mins. PdCl₂(dppf).DCM complex (232 mg, 284 μ mol) was then added and the reaction mixture stirred at 90 °C for 4 hours. After cooling to rt, the reaction mixture was partitioned between water (10 mL), brine (10 mL) and EtOAc (20 mL). The layers were separated, and the aqueous layer extracted with EtOAc (3 x 10 mL). Combined organic extracts were dried over MgSO₄ and concentrated in vacuo. The crude product was purified by chromatography on silica gel (24 g cartridge, 0-50% EtOAc/isohehexane) to afford 1-(4-fluorophenyl)-6-methyl-5-(6-methylpyrazin-2-yl)-1H-indazole (850 mg, 2.3 mmol, 82 %) as a white solid; Rt 1.96 min (Method 4); m/z 319.2 (M+H)⁺ (ES⁺). δ H NMR (400 MHz, DMSO) δ 8.66 (s, 1H), 8.55 (s, 1H), 8.39 (d, J = 0.9 Hz, 1H), 7.96 (s, 1H), 7.89 – 7.80 (m, 2H), 7.76 (m, 1H), 7.51 – 7.40 (m, 2H), 2.57 (s, 3H), 2.47 (d, J = 0.9 Hz, 3H).

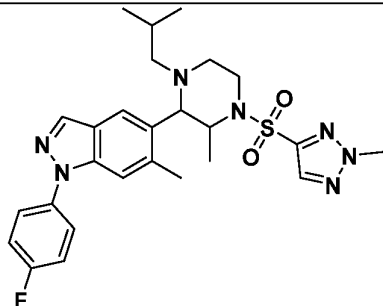
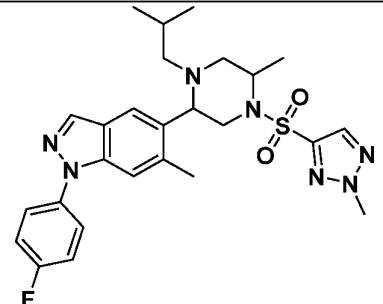
Example 87: 1-(4-fluorophenyl)-5-(1-isobutyl-6-methyl-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-2-yl)-6-methyl-1H-indazole



- [0238] To a solution of 1-(4-fluorophenyl)-6-methyl-5-(6-methyl-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-2-yl)-1H-indazole (50 mg, 0.11 mmol) (prepared using a similar method to those described for **Example 1**) in DMF (1 mL) were added cesium carbonate (0.28 g, 0.85 mmol) and 1-bromo-2-methylpropane (567 mg, 450 μ L, 4.14 mmol). The reaction mixture was stirred at 90 $^{\circ}$ C for 6 days. After cooling to rt, the reaction mixture was quenched with water (3 mL) and DCM (3 mL) and the layers separated. The aqueous
- 10 was extracted with further DCM (3 x 3 mL). Combined organic extracts were washed with half-saturated brine (2 x 5 mL), dried over MgSO_4 , and concentrated in vacuo. The crude product was purified by chromatography on silica gel (4 g cartridge, 0-100% EtOAc/isohexane) to afford 1-(4-fluorophenyl)-5-(1-isobutyl-6-methyl-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-2-yl)-6-methyl-1H-indazole (10 mg, 18 μ mol, 17 %) as
- 15 a white solid; Rt 1.79 min (Method 4); m/z 526.2 ($\text{M}+\text{H}$) $^{+}$ (ES $^{+}$). δ H NMR (400 MHz, DMSO) δ 8.30 (s, 1H), 8.28 (d, J = 0.9 Hz, 1H), 7.84 (s, 1H), 7.81 – 7.75 (m, 2H), 7.64 (s, 1H), 7.46 – 7.38 (m, 2H), 4.29 (s, 3H), 3.97 (dd, J = 10.7, 3.2 Hz, 1H), 3.59 (d, J = 11.6 Hz, 1H), 3.42 (d, J = 12.2 Hz, 1H), 2.82 (m, 1H), 2.62 (t, J = 11.3 Hz, 1H), 2.44 (d, J = 11.1 Hz, 1H), 1.30 (dt, J = 13.4, 6.6 Hz, 1H), 1.13 (d, J = 6.2 Hz, 3H), 0.54 (dd, J = 6.7, 4.6 Hz, 6H).

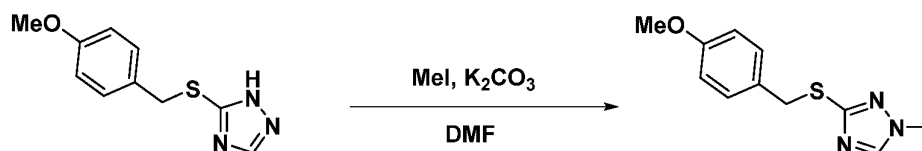
Examples 88 - 89

Table 8: The examples shown in the table below were prepared by similar methods to those described in Example 87 and Example 1.

Example	Structure	LC-MS analysis
88	 1-(4-fluorophenyl)-5-(1-isobutyl-3-methyl-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-2-yl)-6-methyl-1H-indazole	R^t 2.23 min and 2.25 min (Method 9); m/z 526.2 (M+H)⁺ (ES⁺)
89	 1-(4-fluorophenyl)-5-(1-isobutyl-5-methyl-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-2-yl)-6-methyl-1H-indazole	R^t 2.55 min (Method 9); m/z 526.2 (M+H)⁺ (ES⁺)

5 Example 92: 1-(4-fluorophenyl)-5-(1-isobutyl-4-((1-methyl-1H-1,2,4-triazol-3-yl)sulfonyl)piperazin-2-yl)-6-methyl-1H-indazole

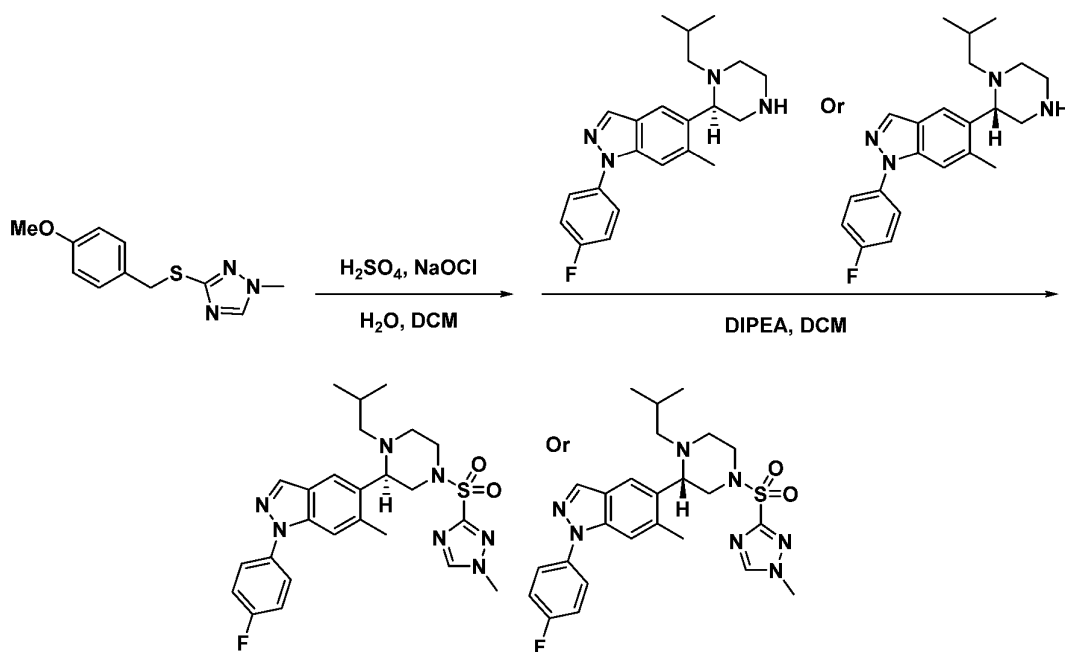
Intermediate J: 3-((4-methoxybenzyl)thio)-1-methyl-1H-1,2,4-triazole



[0239] To a stirred solution of 3-((4-methoxybenzyl)thio)-1H-1,2,4-triazole (2.46 g, 11.1 mmol) and potassium carbonate (4.61 g, 33.4 mmol) in dry DMF (11.1 mL) under a nitrogen

atmosphere at 0 °C was added iodomethane (1.97 g, 869 µL, 13.9 mmol) dropwise. The reaction mixture was stirred 20 °C for 48 hours. The reaction mixture was diluted with EtOAc (50 mL) and transferred into a separating funnel. The organic layer was extracted. The aqueous layer was washed with EtOAc (1 x 100 mL). The combined organic layers were collected, washed with brine (100mL), dried over magnesium sulfate, filtered and adsorbed onto silica *in vacuo*. The crude product was purified by chromatography on silica gel (40 g cartridge, 0-100% EtOAc/isohexane) to afford 3-((4-methoxybenzyl)thio)-1-methyl-1H-1,2,4-triazole (0.80 g, 3.4 mmol, 31 %) as a clear yellow oil; Rt 1.38 min (Method 7); m/z 236.2 (M+H)⁺ (ES⁺). δH (CDCl₃, 400 MHz) δ 7.96 (s, 1H), 7.54 – 7.25 (m, 2H), 6.86 – 6.65 (m, 2H), 4.31 (s, 2H), 3.86 (d, J = 1.0 Hz, 3H), 3.78 (d, J = 0.8 Hz, 3H).

Example 92: 1-(4-fluorophenyl)-5-(1-isobutyl-4-((1-methyl-1H-1,2,4-triazol-3-yl)sulfonyl)piperazin-2-yl)-6-methyl-1H-indazole



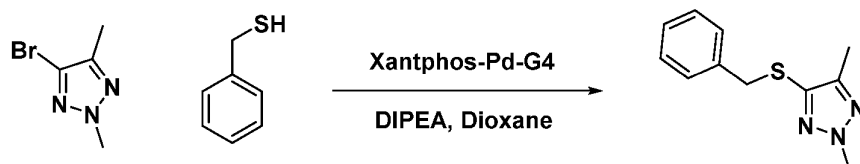
[0240] To a stirred solution of 3-((4-methoxybenzyl)thio)-1-methyl-1H-1,2,4-triazole **Intermediate J** (0.28 g, 1.2 mmol) in DCM (4.00 mL) and water (1.00 mL) was added Cl₂ gas, generated by the dropwise addition of 2M H₂SO₄ (2.3 g, 1.3 mL, 24 mmol) into sodium hypochlorite (15 g, 12 mL, 12% Wt, 24 mmol). The solution of 3-((4-methoxybenzyl)thio)-1-methyl-1H-1,2,4-triazole (0.28 g, 1.2 mmol) was contacted with Cl₂ for 2 min at 20 °C, until the reaction mixture took on a green colour. The reaction mixture was then stirred for an additional 5 min prior to a further charge of distilled water (5 mL) being added and the was

reaction transferred to a phase separator. The organic layer was used without further purification or analysis.

[0241] To a stirred solution of 1-(4-fluorophenyl)-5-(1-isobutylpiperazin-2-yl)-6-methyl-1H-indazole (20.0 mg, 54.6 μ mol) and DIPEA (742 mg, 1.00 mL, 5.74 mmol) in dry DCM (1.00 mL) under a nitrogen atmosphere at 20 °C was added 1-methyl-1H-1,2,4-triazole-3-sulfonyl chloride as a solution in DCM (39.6 mg, 6.00 mL, 218 μ mol). The reaction mixture was stirred at 20 °C for 3 hours. The reaction mixture was diluted with sat. NH_4Cl (3 mL) and transferred into a phase separator. The organic layer was washed with NaHCO_3 (1 x 2 mL). The organic layers were collected and concentrated *in vacuo*. The material was dissolved in 2 mL DMSO, filtered and purified by reversed phase preparative HPLC (Waters 2767 Sample Manager, Waters 2545 Binary Gradient Module, Waters Systems Fluidics Organiser, Waters 515 ACD pump, Waters 515 Makeup pump, Waters 2998 Photodiode Array Detector, Waters QDa) on a Waters X-Select CSH C18 ODB prep column, 130Å, 5 μ m, 30 mm X 100 mm, flow rate 40 mL min⁻¹ eluting with a 0.1% formic acid in water-MeCN gradient over 8.5 mins using UV across all wavelengths with PDA as well as a QDA and ELS detector. At-column dilution pump gives 2 mL min⁻¹ methanol over the entire method, which is included in the following MeCN percentages. Gradient information: 0.0-0.5 min, 42.5% MeCN; 0.5-5.5 min, ramped from 42.5% MeCN to 72.5% MeCN; 5.5-5.6 min, ramped from 72.5% MeCN to 100% MeCN; 5.6-8.5 min, held at 100% MeCN. The clean fractions were evaporated in a Genevac and azeotropically dried with acetonitrile. to afford 1-(4-fluorophenyl)-5-(1-isobutyl-4-((1-methyl-1H-1,2,4-triazol-3-yl)sulfonyl)piperazin-2-yl)-6-methyl-1H-indazole **Example 92** (1.80 mg, 3.3 μ mol, 6.1%); Rt 1.80 min (Method 7); m/z 512.4 (M+H)⁺ (ES⁺). δ H (MeOD, 400 MHz) δ 8.59 (s, 1H), 8.17 (s, 1H), 7.94 (s, 1H), 7.82 – 7.69 (m, 2H), 7.57 (s, 1H), 7.36 (t, J = 8.7 Hz, 2H), 4.04 (s, 3H), 3.90 (d, J = 12.1 Hz, 1H), 3.73 – 3.57 (m, 2H), 3.30 (d, J = 11.9 Hz, 1H), 3.08 (td, J = 12.1, 2.8 Hz, 1H), 2.79 (t, J = 11.1 Hz, 1H), 2.56 (s, 3H), 2.35 – 2.22 (m, 1H), 2.13 (t, J = 12.2 Hz, 1H), 1.92 – 1.80 (m, 2H), 0.88 (d, J = 6.3 Hz, 3H), 0.72 (d, J = 6.3 Hz, 3H).

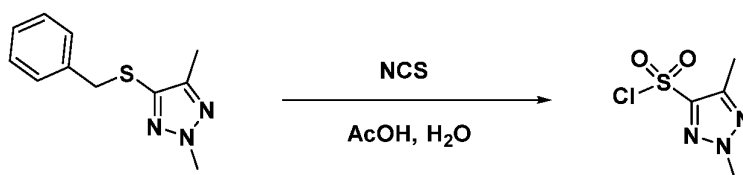
Example 93: 5-(4-((2,5-dimethyl-2H-1,2,3-triazol-4-yl)sulfonyl)-1-isobutylpiperazin-2-yl)-1-(4-fluorophenyl)-6-methyl-1H-indazole

Intermediate K: 4-(benzylthio)-2,5-dimethyl-2H-1,2,3-triazole



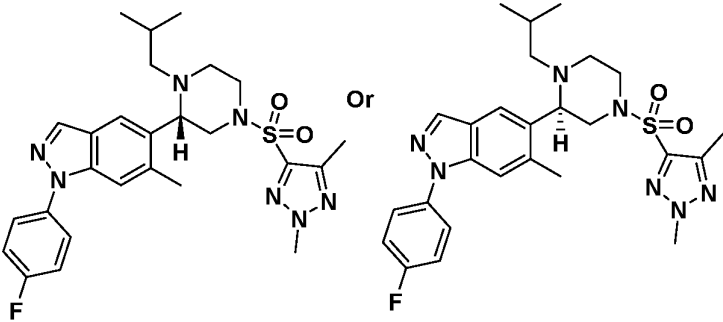
- 5 [0242] A solution of 4-bromo-2,5-dimethyl-2H-1,2,3-triazole (0.20 g, 1.1 mmol), phenylmethanethiol (0.28 g, 0.27 mL, 2.3 mmol) and DIPEA (0.29 g, 0.40 mL, 2.3 mmol) in 1,4-dioxane (2.3 mL) was prepared and added to xantphos-Pd-G4 (0.10 g, 0.11 mmol) in a vial that was sealed and sparged for 5 min prior to being heated to 90 °C and stirred for 16 hours. The reaction mixture was then adsorbed onto silica gel. The crude product was
- 10 purified by chromatography on silica gel (12 g cartridge, 0-100% EtOAc/isohexane) to afford 4-(benzylthio)-2,5-dimethyl-2H-1,2,3-triazole **Intermediate K** (43.0 mg, 196 μmol, 17 %) as a clear orange oil; Rt 1.76 min (Method 7); m/z 220.1 (M+H)⁺ (ES⁺).

Intermediate L: 2,5-dimethyl-2H-1,2,3-triazole-4-sulfonyl chloride



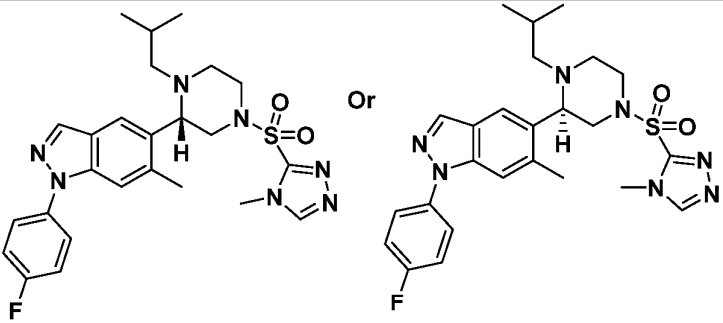
- 15 [0243] To a stirred solution of 4-(benzylthio)-2,5-dimethyl-2H-1,2,3-triazole (43.0 mg, 196 μmol) in AcOH (1.00 mL) and water (500 μL) under a nitrogen atmosphere at 20 °C was added N-chlorosuccinimide (NCS) (105 mg, 784 μmol). The reaction mixture was then stirred for 1 hour at room temperature. The reaction mixture was diluted with distilled water (2 mL) and transferred into a phase separator. The solution was washed with DCM (1 x 2
- 20 mL). The DCM layer was then washed with water (2mL) and then NaHCO₃ (sat aq, 2mL) to afford 2,5-dimethyl-2H-1,2,3-triazole-4-sulfonyl chloride **Intermediate L** as a solution in DCM. A sample of the organic layer was then quenched with a 10 vol% morpholine/methanol solution and analysed by LCMS; Rt 1.14 min (Method 7); m/z 247.1 (M+H)⁺ (ES⁺) (morpholine adduct).

Table 9: The example shown in the table below was prepared by similar methods to those described in Example 36 using Intermediate L.

Example	Structure	LC-MS analysis
93	 5-(4-((2,5-dimethyl-2H-1,2,3-triazol-4-yl)sulfonyl)-1-isobutylpiperazin-2-yl)-1-(4-fluorophenyl)-6-methyl-1H-indazole	R^t 2.11 min (Method 7); m/z 526.4 (M+H)⁺ (ES⁺)

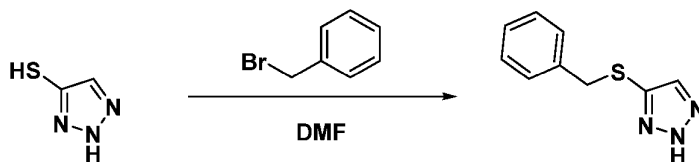
Example 94: 1-(4-fluorophenyl)-5-(1-isobutyl-4-((4-methyl-4H-1,2,4-triazol-3-yl)sulfonyl)piperazin-2-yl)-6-methyl-1H-indazole

Table 10: The example shown in the table below was prepared by similar methods to those described in Example 93

Example	Structure	LC-MS analysis
94	 1-(4-fluorophenyl)-5-(1-isobutyl-4-((4-methyl-4H-1,2,4-triazol-3-yl)sulfonyl)piperazin-2-yl)-6-methyl-1H-indazole	R^t 1.77 min (Method 7); m/z 512.4 (M+H)⁺ (ES⁺)

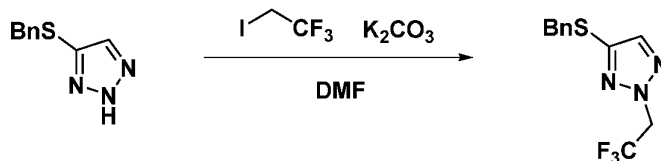
Example 95: 1-(4-fluorophenyl)-5-(1-isobutyl-4-((2-(2,2,2-trifluoroethyl)-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-2-yl)-6-methyl-1H-indazole

Intermediate M: 4-(benzylthio)-2H-1,2,3-triazole



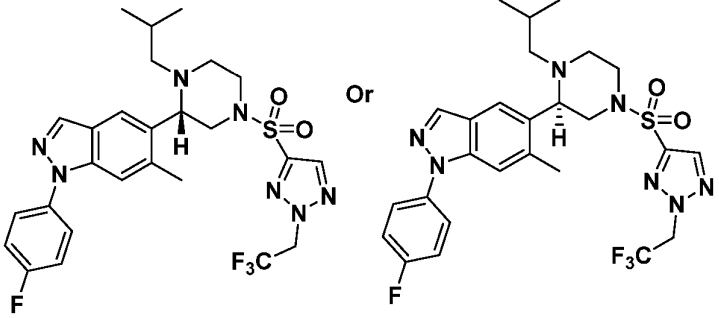
- 5 [0244] To a stirred solution of 2H-1,2,3-triazole-4-thiol, sodium (5.00 g, 40.3 mmol) in dry DMF (30.0 mL) under a nitrogen atmosphere at 20 °C was added benzyl bromide (6.89 g, 4.79 mL, 40.3 mmol). The reaction mixture was stirred for 3 hours. The reaction mixture was quenched into ice water (500mL) producing a slurry that was stirred overnight. Precipitate was collected under vacuum and azeotroped twice with toluene 50 mL to afford 4-
- 10 (benzylthio)-2H-1,2,3-triazole **Intermediate M** (6.43 g, 26 mmol, 65 %) as a yellow solid; Rt 1.39 min (Method 7); m/z 192.2 (M+H)⁺ (ES⁺).

Intermediate N: 4-(benzylthio)-2-(2,2,2-trifluoroethyl)-2H-1,2,3-triazole



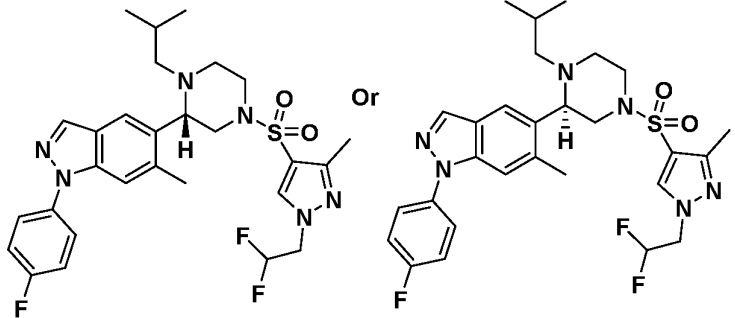
- [0245] To a stirred solution of 4-(benzylthio)-2H-1,2,3-triazole (6.40 g, 33.5 mmol) in dry
- 15 DMF (66.9 mL) under a nitrogen atmosphere at 20 °C was added potassium carbonate (11.6 g, 83.7 mmol) (pulverised) and 1,1,1-trifluoro-2-iodoethane (15.8 g, 7.36 mL, 75.3 mmol). The reaction mixture was stirred for 18 hours, and then at 50 °C for a further 24 hours. The reaction mixture was diluted with EtOAc (100 mL) and transferred into a separating funnel. The organic layer was washed with half saturated brine (100 mL) and the brine layer
- 20 extracted with EtOAc (2 x 100mL) The combined organic layers were collected, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by chromatography on silica gel (120 g cartridge, 10-100% EtOAc/isohexane) to afford 3 main bands. The first band was concentrated *in vacuo* to afford 4-(benzylthio)-2-(2,2,2-trifluoroethyl)-2H-1,2,3-triazole (2.10 g, 6.5 mmol, 20 %) as an off-white solid; Rt 0.94 min
- 25 (Method 9); m/z 274.0 (M+H)⁺ (ES⁺).

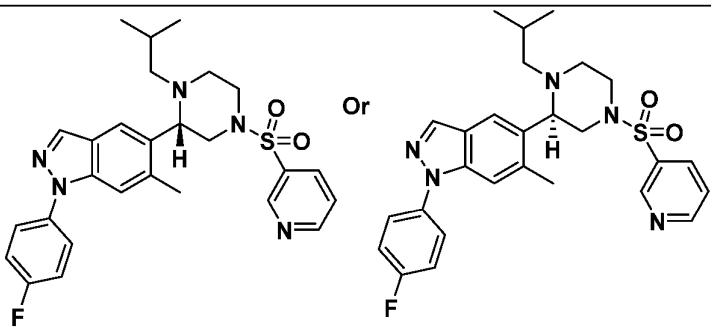
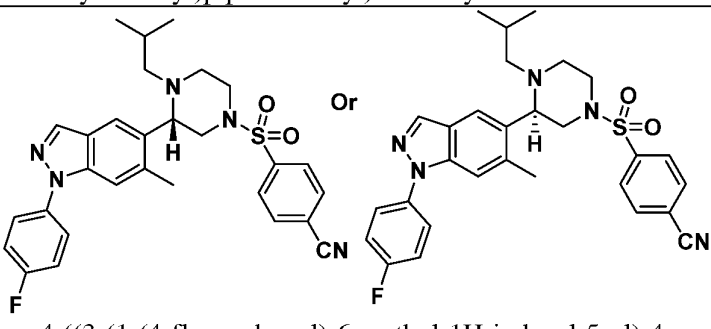
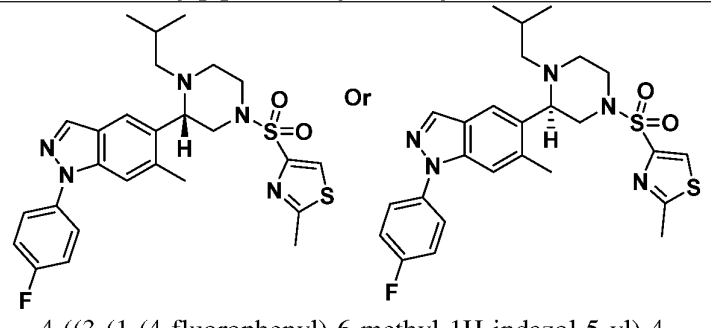
Table 11: The example shown in the table below was prepared by similar methods to those described in Example 93 using Intermediate N

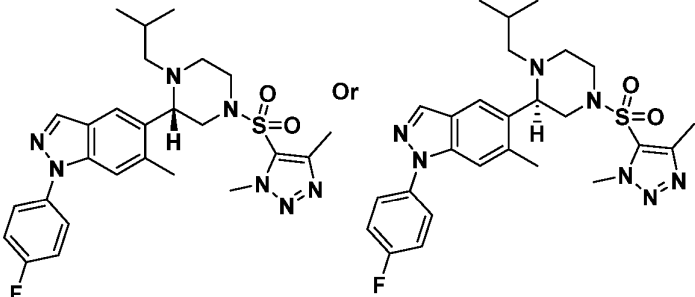
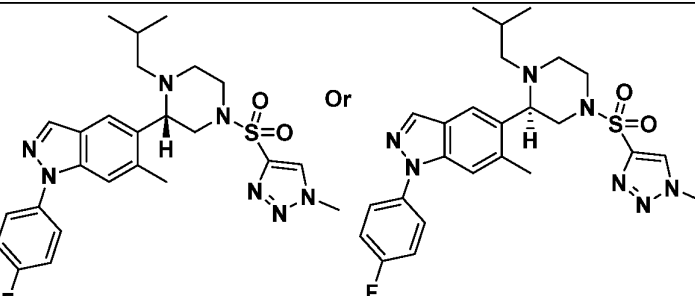
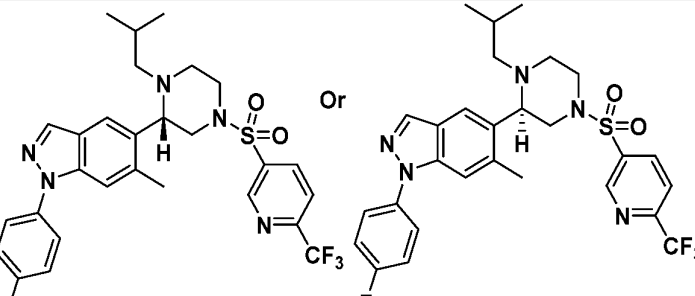
Example	Structure	LC-MS analysis
95	 1-(4-fluorophenyl)-5-(1-isobutyl-4-((2-(2,2,2-trifluoroethyl)-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-2-yl)-6-methyl-1H-indazole	R^t 2.34 min (Method 7); m/z 580.4 (M+H)⁺ (ES⁺)

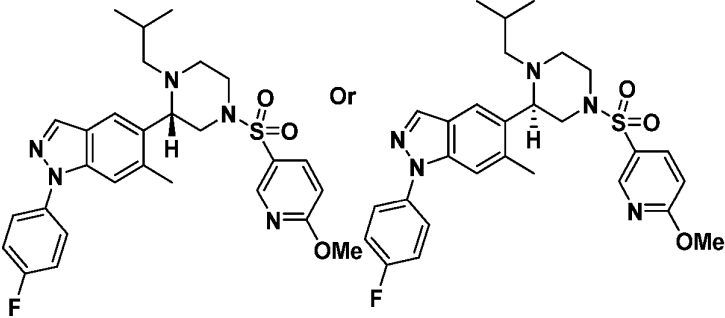
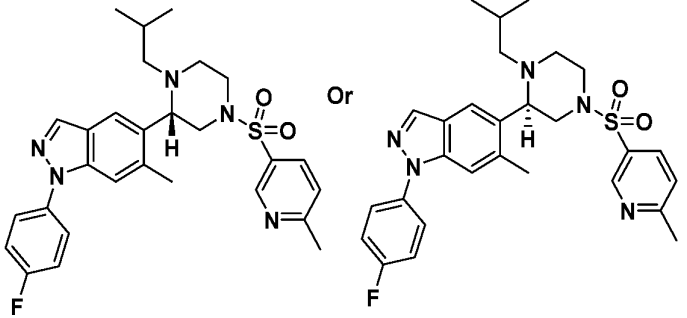
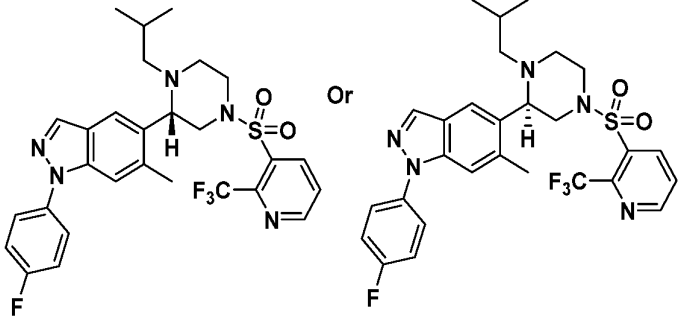
Examples 96 - 117

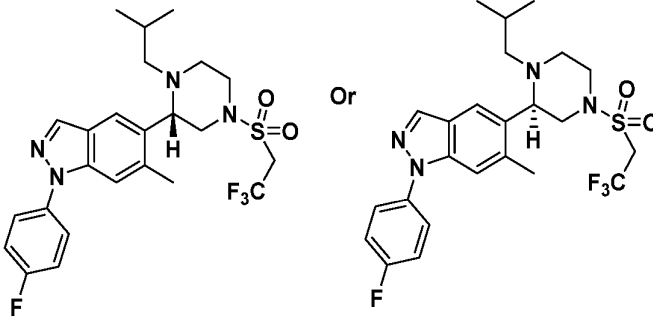
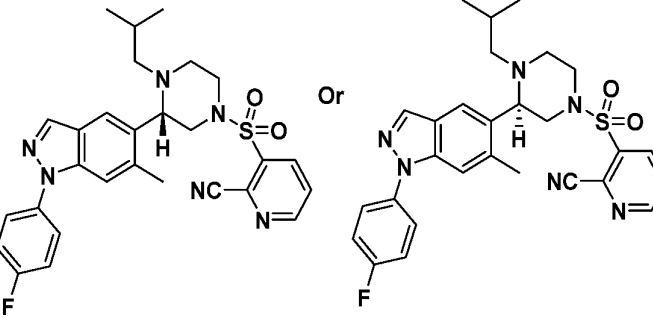
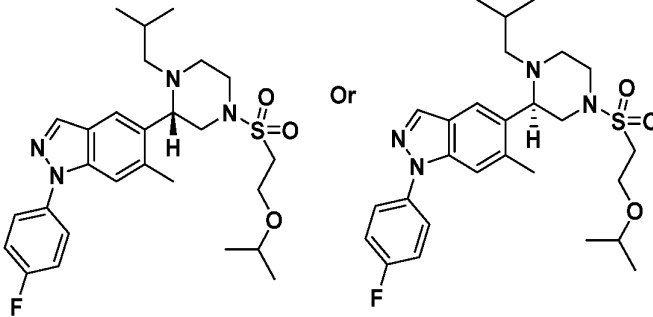
- 5 **Table 12:** The examples shown in the table below were prepared by similar methods to those described in Example 36

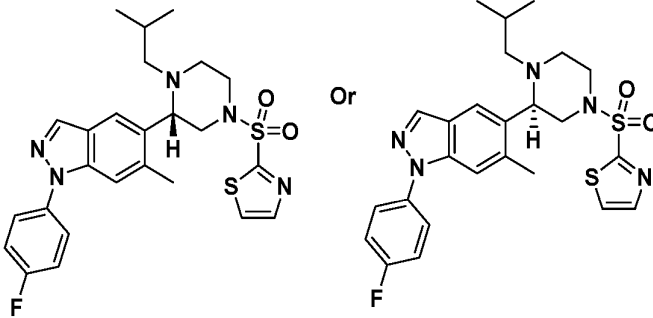
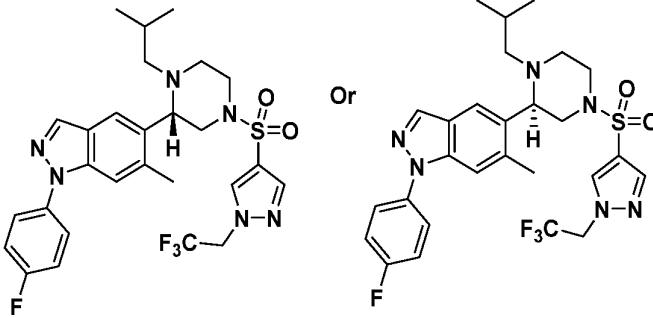
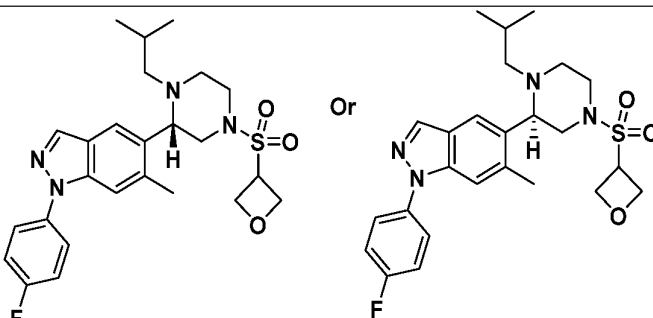
Example	Structure	LC-MS analysis
96	 5-(4-((1-(2,2-difluoroethyl)-3-methyl-1H-pyrazol-4-yl)sulfonyl)-1-isobutylpiperazin-2-yl)-1-(4-fluorophenyl)-6-methyl-1H-indazole	R^t 2.03 min (Method 7); m/z 575.4 (M+H)⁺ (ES⁺)

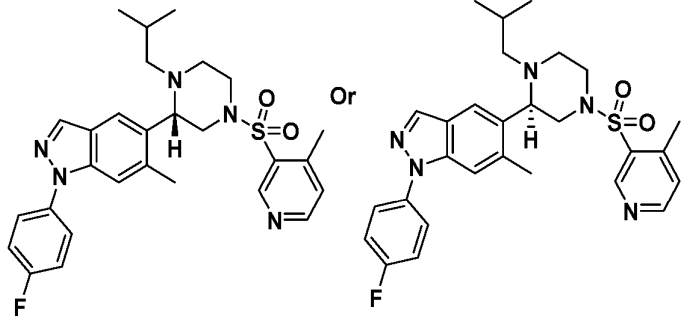
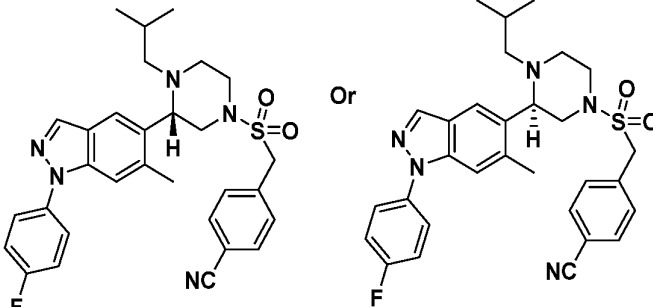
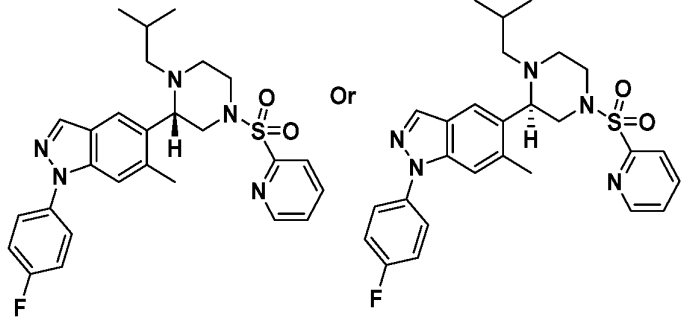
Example	Structure	LC-MS analysis
97	 1-(4-fluorophenyl)-5-(1-isobutyl-4-(pyridin-3-ylsulfonyl)piperazin-2-yl)-6-methyl-1H-indazole	R^t 2.02 min (Method 7); m/z 508.4 (M+H)⁺ (ES⁺)
98	 4-((3-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)-4-isobutylpiperazin-1-yl)sulfonyl)benzonitrile	R^t 2.31 min (Method 7); m/z 532.4 (M+H)⁺ (ES⁺)
99	 4-((3-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)-4-isobutylpiperazin-1-yl)sulfonyl)-2-methylthiazole	R^t 1.98 min (Method 9); m/z 528.2 (M+H)⁺ (ES⁺)

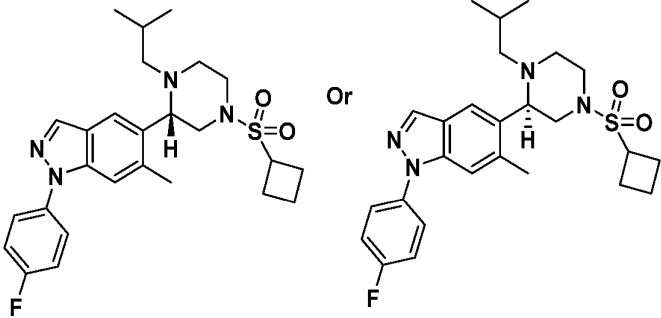
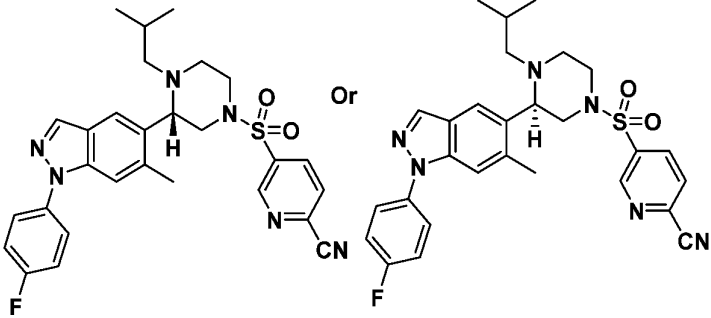
Example	Structure	LC-MS analysis
100	 5-(4-((1,4-dimethyl-1H-1,2,3-triazol-5-yl)sulfonyl)-1-isobutylpiperazin-2-yl)-1-(4-fluorophenyl)-6-methyl-1H-indazole	R^t 2.19 min (Method 7); m/z 526.3 (M+H)⁺ (ES⁺)
101	 1-(4-fluorophenyl)-5-(1-isobutyl-4-((1-methyl-1H-1,2,3-triazol-4-yl)sulfonyl)piperazin-2-yl)-6-methyl-1H-indazole	R^t 1.85 min (Method 9); m/z 512.2 (M+H)⁺ (ES⁺)
102	 1-(4-fluorophenyl)-5-(1-isobutyl-4-((6-(trifluoromethyl)pyridin-3-yl)sulfonyl)piperazin-2-yl)-6-methyl-1H-indazole	R^t 2.45 min (Method 9); m/z 576.2 (M+H)⁺ (ES⁺)

Example	Structure	LC-MS analysis
103	 1-(4-fluorophenyl)-5-(1-isobutyl-4-((6-methoxypyridin-3-yl)sulfonyl)piperazin-2-yl)-6-methyl-1H-indazole	R^t 2.25 min (Method 9); m/z 538.2 (M+H)⁺ (ES⁺)
104	 1-(4-fluorophenyl)-5-(1-isobutyl-4-((6-methylpyridin-3-yl)sulfonyl)piperazin-2-yl)-6-methyl-1H-indazole	R^t 2.07 min (Method 9); m/z 522.2 (M+H)⁺ (ES⁺)
105	 1-(4-fluorophenyl)-5-(1-isobutyl-4-((2-(trifluoromethyl)pyridin-3-yl)sulfonyl)piperazin-2-yl)-6-methyl-1H-indazole	R^t 2.26 min (Method 9); m/z 576.2 (M+H)⁺ (ES⁺)

Example	Structure	LC-MS analysis
106	 1-(4-fluorophenyl)-5-(1-isobutyl-4-((2,2,2-trifluoroethyl)sulfonyl)piperazin-2-yl)-6-methyl-1H-indazole	R^t 2.22 min (Method 9); m/z 513.2 (M+H)⁺ (ES⁺)
107	 3-((3-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)-4-isobutylpiperazin-1-yl)sulfonyl)picolinonitrile	R^t 2.22 min (Method 7); m/z 533.4 (M+H)⁺ (ES⁺)
108	 1-(4-fluorophenyl)-5-(1-isobutyl-4-((2-isopropoxyethyl)sulfonyl)piperazin-2-yl)-6-methyl-1H-indazole	R^t 1.96 min (Method 7); m/z 517.5 (M+H)⁺ (ES⁺)

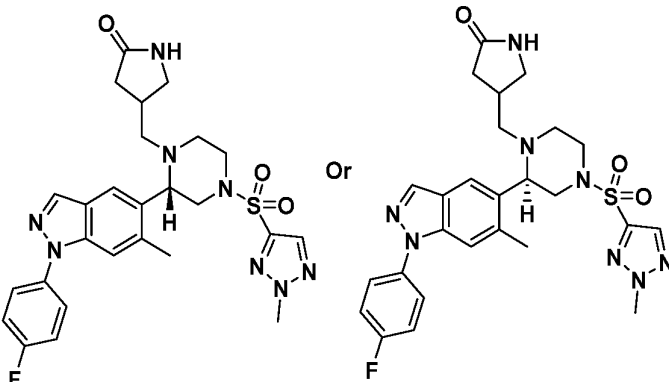
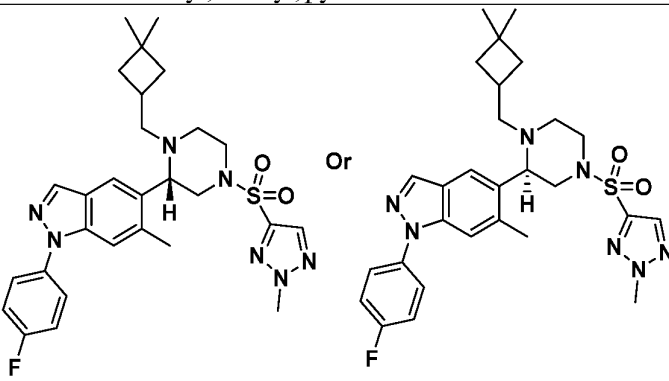
Example	Structure	LC-MS analysis
109	 2-((3-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)-4-isobutylpiperazin-1-yl)sulfonyl)thiazole	R^t 2.30 min (Method 9); m/z 514.1 (M+H)⁺ (ES⁺)
110	 1-(4-fluorophenyl)-5-(1-isobutyl-4-((1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)sulfonyl)piperazin-2-yl)-6-methyl-1H-indazole	R^t 2.12 min (Method 7); m/z 579.4 (M+H)⁺ (ES⁺)
111	 1-(4-fluorophenyl)-5-(1-isobutyl-4-(oxetan-3-ylsulfonyl)piperazin-2-yl)-6-methyl-1H-indazole	R^t 1.74 min (Method 9); m/z 487.2 (M+H)⁺ (ES⁺)

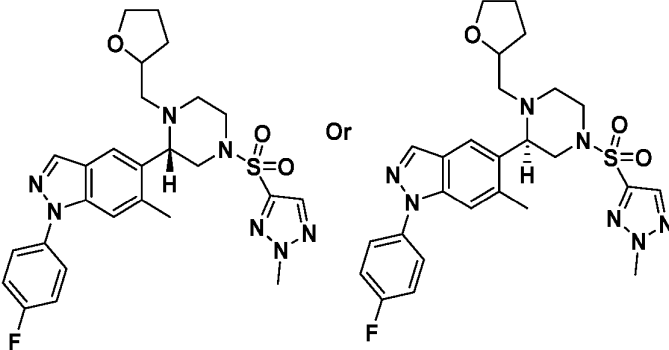
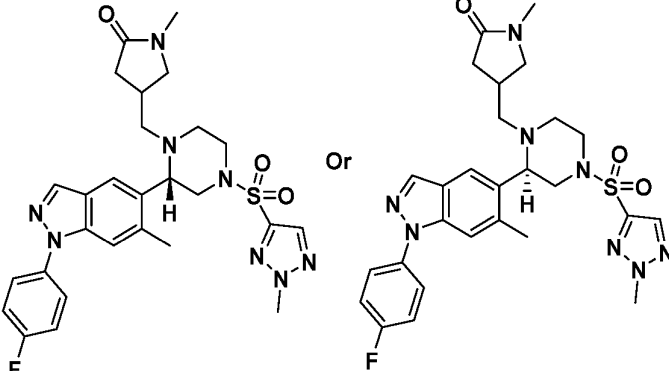
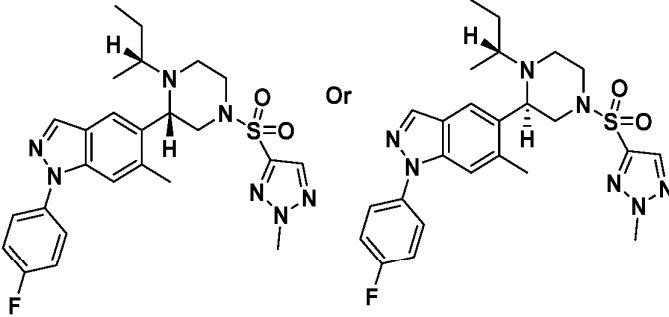
Example	Structure	LC-MS analysis
112	 1-(4-fluorophenyl)-5-(1-isobutyl-4-((4-methylpyridin-3-yl)sulfonyl)piperazin-2-yl)-6-methyl-1H-indazole	R^t 2.01 min (Method 9); m/z 522.2 (M+H)⁺ (ES⁺)
114	 4-(((3-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)-4-isobutylpiperazin-1-yl)sulfonyl)methyl)benzonitrile	R^t 1.99 min (Method 7); m/z 546.4 (M+H)⁺ (ES⁺)
115	 1-(4-fluorophenyl)-5-(1-isobutyl-4-(pyridin-2-ylsulfonyl)piperazin-2-yl)-6-methyl-1H-indazole	R^t 1.89 min (Method 7); m/z 508.4 (M+H)⁺ (ES⁺)

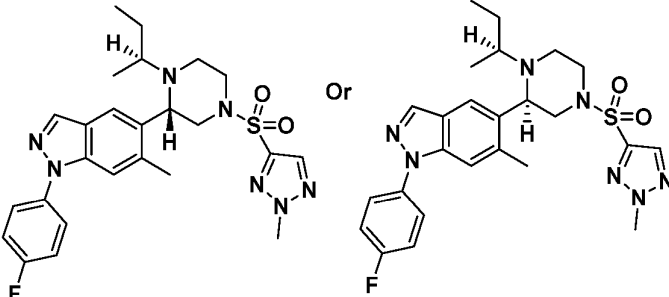
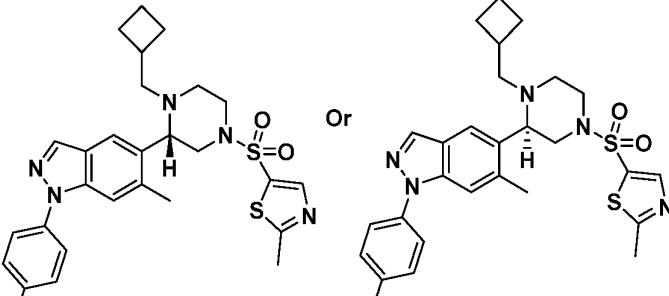
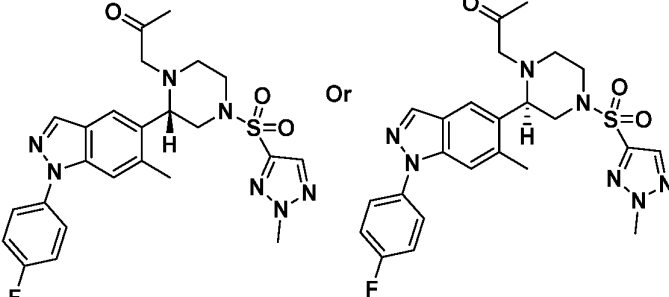
Example	Structure	LC-MS analysis
116	 5-(4-(cyclobutylsulfonyl)-1-isobutylpiperazin-2-yl)-1-(4-fluorophenyl)-6-methyl-1H-indazole	R^t 1.85 min (Method 7); m/z 485.4 (M+H)⁺ (ES⁺)
117	 5-((3-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)-4-isobutylpiperazin-1-yl)sulfonyl)picolinonitrile	R^t 2.24 min (Method 9); m/z 533.2 (M+H)⁺ (ES⁺)

Examples 118 - 125

Table 13: The examples shown in the table below were prepared by similar methods to those described in Example 68

Example	Structure	LC-MS analysis
118	 4-((2-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-1-yl)methyl)pyrrolidin-2-one	R^t 1.69 min (Method 9); m/z 553.2 (M+H)⁺ (ES⁺)
119	 5-(1-((3,3-dimethylcyclobutyl)methyl)-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-2-yl)-1-(4-fluorophenyl)-6-methyl-1H-indazole	R^t 2.03 min (Method 9); m/z 552.2 (M+H)⁺ (ES⁺)

Example	Structure	LC-MS analysis
120	 1-(4-fluorophenyl)-6-methyl-5-(4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)-1-((tetrahydrofuran-2-yl)methyl)piperazin-2-yl)-1H-indazole	R^t 1.76 and 1.86 min (Method 9); m/z 540.2 (M+H)⁺ (ES⁺)
121	 4-((2-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-1-yl)methyl)-1-methylpyrrolidin-2-one	R^t 1.76 min (Method 7); m/z 567.4 (M+H)⁺ (ES⁺)
122	 5-(1-(sec-butyl)-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-2-yl)-1-(4-fluorophenyl)-6-methyl-1H-indazole	R^t 1.66 min (Method 9); m/z 512.2 (M+H)⁺ (ES⁺)

Example	Structure	LC-MS analysis
123	 5-(1-(sec-butyl)-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-2-yl)-1-(4-fluorophenyl)-6-methyl-1H-indazole	R^t 1.81 min (Method 9); m/z 512.2 (M+H)⁺ (ES⁺)
124	 5-((4-(cyclobutylmethyl)-3-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)piperazin-1-yl)sulfonyl)-2-methylthiazole	R^t 2.26 and 2.29 min (Method 7) m/z 579.5 (M+H)⁺ (ES⁺)
125	 1-(2-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-1-yl)propan-2-one	R^t 1.95 min (Method 7); m/z 512.3 (M+H)⁺ (ES⁺)

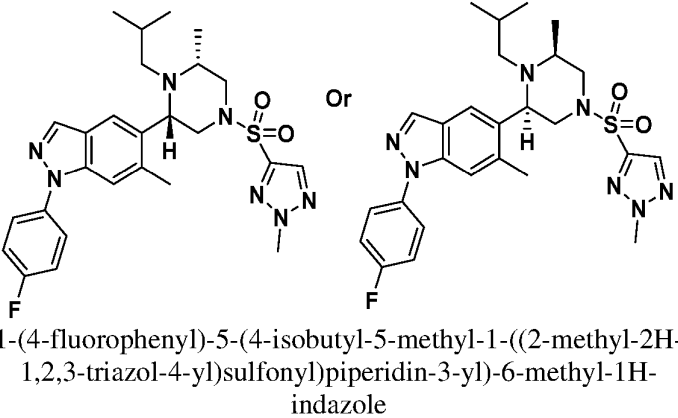
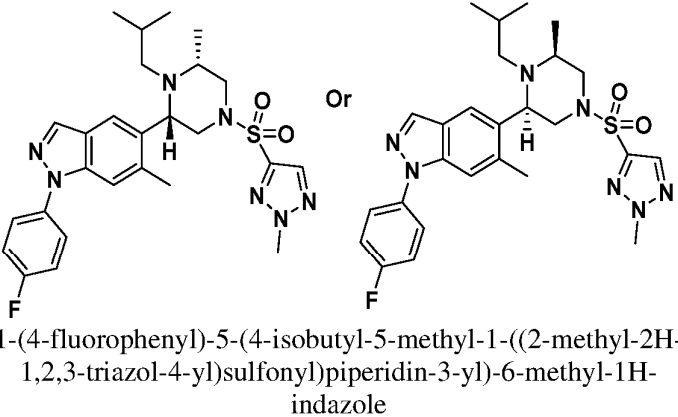
Example 126 and 127: 1-(4-fluorophenyl)-5-(4-isobutyl-5-methyl-1-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperidin-3-yl)-6-methyl-1H-indazole

- [0246] 1-(4-fluorophenyl)-5-(4-isobutyl-5-methyl-1-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperidin-3-yl)-6-methyl-1H-indazole **Example 87** was dissolved in MeOH (1.5 ml), filtered and was then separated by chiral SFC on a Waters prep 100 with a PDA and a

QDA detectors, 40 °C, 120 bar. The column was a Chiralpak IH, 5 µM, 21 mm X 250 mm; flow rate 65 mL/ min of 25 % MeOH (no buffer), 75% CO₂. The clean fractions were pooled, rinsed with methanol and concentrated to dryness using a rotary evaporator. The residues were re-dissolved in methanol transferred into final vials and evaporated on a Biotage V10.

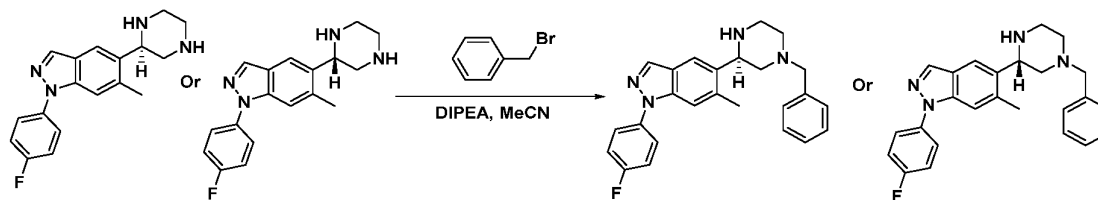
- 5 The samples were then further dried in a vacuum oven at 30 °C/ 5mbar over night to afford 1-(4-fluorophenyl)-5-(4-isobutyl-5-methyl-1-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperidin-3-yl)-6-methyl-1H-indazole **Example 126** and 1-(4-fluorophenyl)-5-(4-isobutyl-5-methyl-1-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperidin-3-yl)-6-methyl-1H-indazole **Example 127** as white solids.

10 **Table 14. Examples 126 and 127**

Example	Structure	LC-MS analysis
126	 1-(4-fluorophenyl)-5-(4-isobutyl-5-methyl-1-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperidin-3-yl)-6-methyl-1H-indazole	R^t 1.82 min (Method 9); m/z 526.2 (M+H)⁺ (ES⁺)
127	 1-(4-fluorophenyl)-5-(4-isobutyl-5-methyl-1-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperidin-3-yl)-6-methyl-1H-indazole	R^t 1.82 min (Method 9); m/z 526.2 (M+H)⁺ (ES⁺)

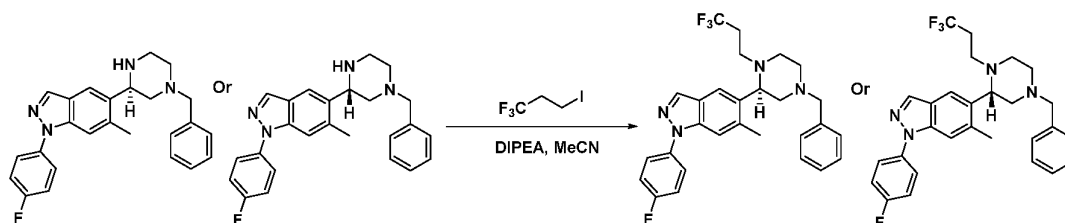
Example 128: 1-(4-fluorophenyl)-6-methyl-5-(4-((1-methyl-1H-pyrazol-4-yl)sulfonyl)-1-(3,3,3-trifluoropropyl)piperazin-2-yl)-1H-indazole

Intermediate O: tert-butyl 3-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)piperazine-1-carboxylate



- [0247] A solution of 1-(4-fluorophenyl)-6-methyl-5-(piperazin-2-yl)-1H-indazole (1.00 g, 3.22 mmol) in MeCN (10.0 mL) was cooled to 0 °C and treated with N-ethyl-N-isopropylpropan-2-amine (833 mg, 1.12 mL, 6.44 mmol) and (bromomethyl)benzene (661 mg, 459 μ L, 3.87 mmol). The reaction was warmed to RT and stirred for 48 hrs. The reaction was quenched with water (10 mL), diluted with EtOAc (2 x 30mL) and the phases separated. The bulked organic extracts were dried using sodium sulfate and concentrated under vacuum.
- 5
- [0248] The crude product was purified by chromatography on silica gel (24 g cartridge, 0-5% (0.7 M Ammonia/MeOH)/DCM) to afford 5-(4-benzylpiperazin-2-yl)-1-(4-fluorophenyl)-6-methyl-1H-indazole **Intermediate O** (850 mg, 2.12 mmol, 65.9 %) as a tan foam; Rt 1.35 min (Method 7); m/z 401.5 (M+H)⁺ (ES⁺).
- 10

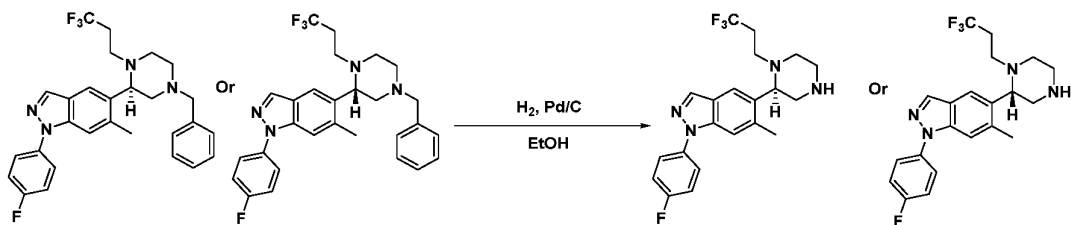
Intermediate P: 5-(4-benzyl-1-(3,3,3-trifluoropropyl)piperazin-2-yl)-1-(4-fluorophenyl)-6-methyl-1H-indazole



- [0249] To a solution of 5-(4-benzylpiperazin-2-yl)-1-(4-fluorophenyl)-6-methyl-1H-indazole (320 mg, 799 μ mol) in MeCN (2.00 mL) were added 1,1,1-trifluoro-3-iodopropane (1.79 g, 937 μ L, 7.99 mmol) and N-ethyl-N-isopropylpropan-2-amine (1.03 g, 1.39 mL, 7.99 mmol). The reaction mixture was heated in the microwave at 150 °C for 2 hrs. The reaction was quenched with water (15 mL) and the organics extracted with DCM (2 x 15 mL) through a phase separator cartridge and concentrated in vacuo. The crude product was purified by chromatography on silica gel (24 g cartridge, 0-5% (0.7 M ammonia/MeOH)/DCM) to afford the product as a brown solid. The crude product was repurified by chromatography on silica
- 20

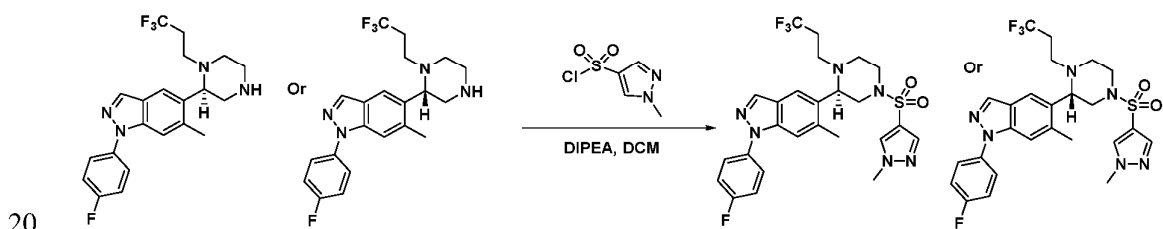
gel (12 g cartridge, 0-50% EtOAc/isohexane containing 1% DIPEA) to afford 5-(4-benzyl-1-(3,3,3-trifluoropropyl)piperazin-2-yl)-1-(4-fluorophenyl)-6-methyl-1H-indazole (**Intermediate P**) as a clear colourless gum; Rt 1.53 min (Method 7); m/z 497.4 (M+H)⁺ (ES⁺).

5 **Intermediate Q: 1-(4-fluorophenyl)-6-methyl-5-(1-(3,3,3-trifluoropropyl)piperazin-2-yl)-1H-indazole**



[0250] 5-(4-benzyl-1-(3,3,3-trifluoropropyl)piperazin-2-yl)-1-(4-fluorophenyl)-6-methyl-1H-indazole **Intermediate P** (300 mg, 604 μ mol) was dissolved in EtOH (5 mL) and treated with 10% palladium on carbon (12.9 mg, 121 μ mol). The mixture was purged with nitrogen (x3) then hydrogen (x3) before being hydrogenated at 5 atm at 40 °C overnight. The catalyst was removed by filtration, washing with MeOH/EtOAc (1:1) (20 mL). The solvent was removed *in vacuo*. The crude product was purified by chromatography on silica gel (12 g cartridge, 0-100% EtOAc/isohexane containing 1% DIPEA) to afford 1-(4-fluorophenyl)-6-methyl-5-(1-(3,3,3-trifluoropropyl)piperazin-2-yl)-1H-indazole **Intermediate Q** (170 mg, 0.41 mmol, 68 %) as a clear colourless gum; Rt 1.36 min (Method 7); m/z 407.4 (M+H)⁺ (ES⁺).

Example 128: 1-(4-fluorophenyl)-6-methyl-5-(4-((1-methyl-1H-pyrazol-4-yl)sulfonyl)-1-(3,3,3-trifluoropropyl)piperazin-2-yl)-1H-indazole

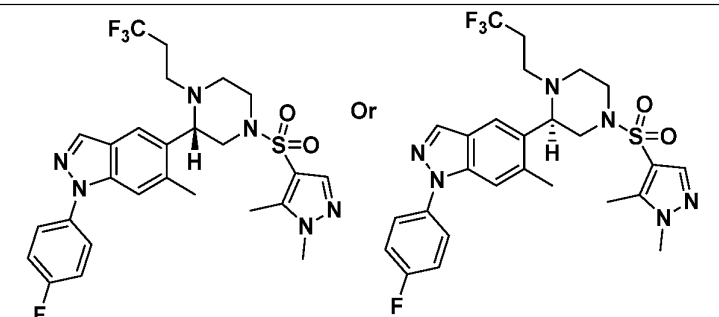
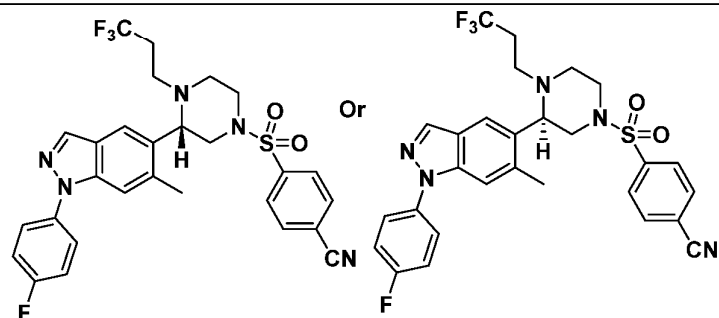


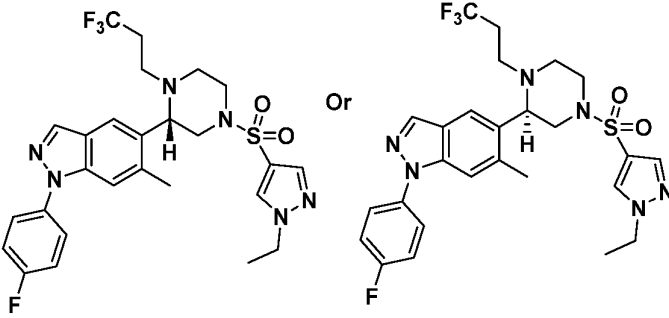
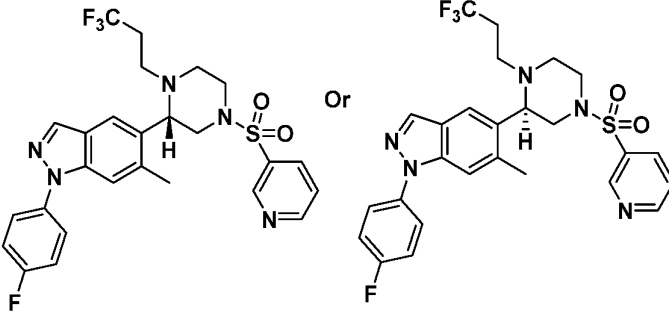
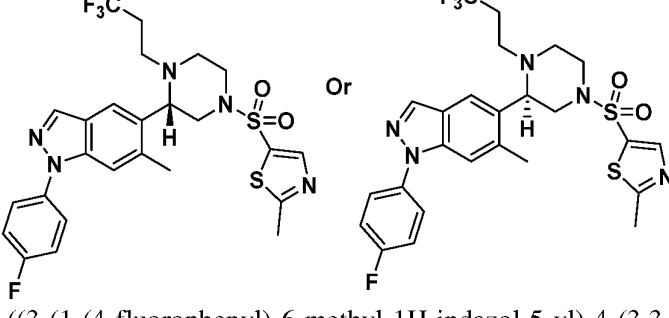
[0251] To a solution of 1-(4-fluorophenyl)-6-methyl-5-(1-(3,3,3-trifluoropropyl)piperazin-2-yl)-1H-indazole **Intermediate Q** (15.0 mg, 36.9 μ mol) in DCM (1.00 mL) were added N-ethyl-N-isopropylpropan-2-amine (14.3 mg, 19.2 μ L, 111 μ mol) and 1-methyl-1H-pyrazole-

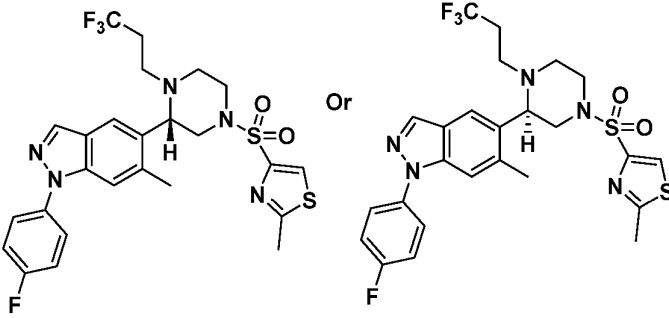
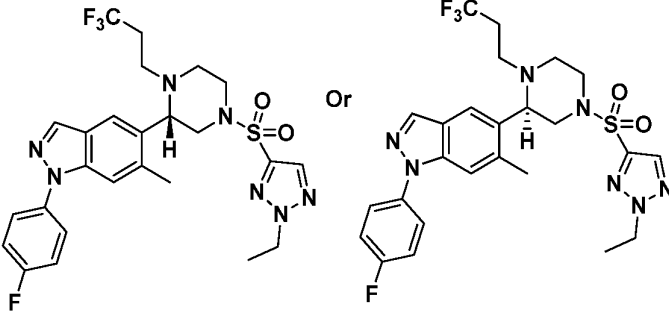
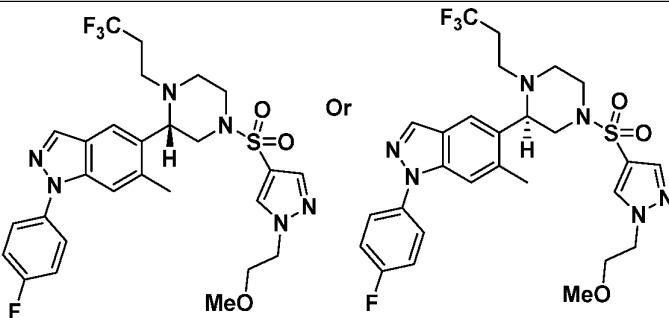
4-sulfonyl chloride (9.33 mg, 51.7 μmol). The reaction mixture was stirred for 2 hours at rt before being quenched with sat. aq. NaHCO_3 (1mL) and passed through a phase separator cartridge. The organics were removed *in vacuo*. The crude product was purified by chromatography on silica gel (4 g cartridge, 0-100% EtOAc/isohexane) to afford 1-(4-fluorophenyl)-6-methyl-5-(4-((1-methyl-1H-pyrazol-4-yl)sulfonyl)-1-(3,3,3-trifluoropropyl)piperazin-2-yl)-1H-indazole (12.5 mg, 21.7 μmol , 58.9 %); Rt 2.14 min (Method 7); m/z 551.4 (M+H)⁺ (ES⁺). δH (DMSO- d_6 , 400 MHz) δ 8.31 (s, 1H), 8.26 (s, 1H), 7.84 – 7.73 (m, 4H), 7.66 (s, 1H), 7.43 (t, J = 8.8 Hz, 2H), 3.88 (s, 3H), 3.80 – 3.70 (m, 1H), 3.62 (d, J = 8.7 Hz, 1H), 3.40 (d, J = 11.6 Hz, 1H), 3.30 – 3.25 (m, 1H), 2.71 – 2.60 (m, 1H), 2.51 (s, 3H), 2.43 (m, 4H), 2.20 (dt, J = 12.8, 6.6 Hz, 1H), 2.08 (s, 1H). Indazole Me obscured by DMSO.

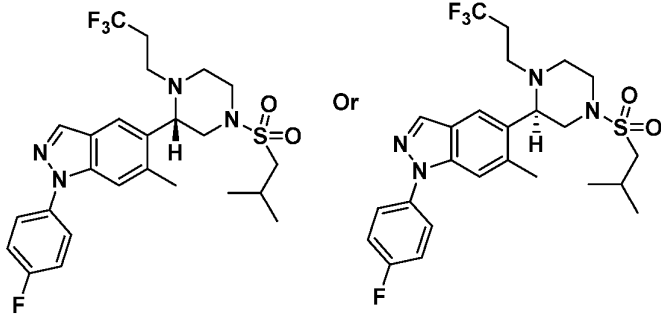
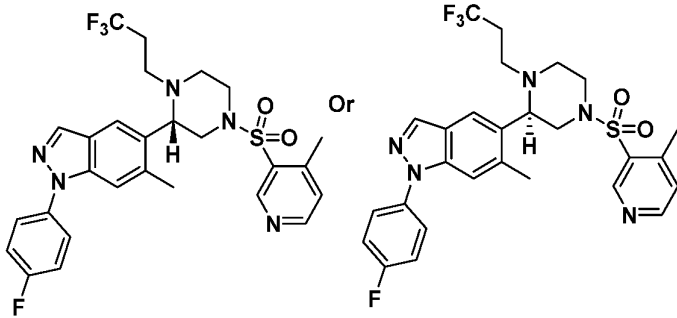
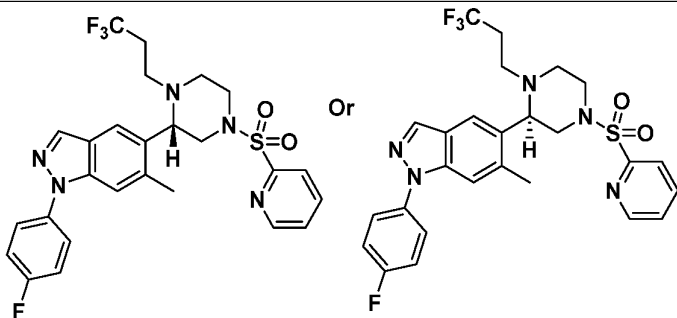
Examples 129 - 140

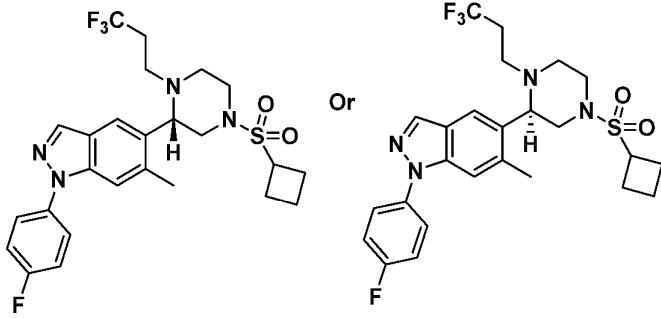
Table 15: The examples shown in the table below were prepared by similar methods to those described for Example 128

Example	Structure	LC-MS analysis
129	 5-(4-((1,5-dimethyl-1H-pyrazol-4-yl)sulfonyl)-1-(3,3,3-trifluoropropyl)piperazin-2-yl)-1-(4-fluorophenyl)-6-methyl-1H-indazole	R_t 2.16 min (Method 7); m/z 565.4 (M+H)⁺ (ES⁺)
130	 4-((3-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)-4-(3,3,3-trifluoropropyl)piperazin-1-yl)sulfonyl)benzonitrile	R_t 2.33 min (Method 9); m/z 572.4 (M+H)⁺ (ES⁺)

Example	Structure	LC-MS analysis
131	 5-(4-((1-ethyl-1H-pyrazol-4-yl)sulfonyl)-1-(3,3,3-trifluoropropyl)piperazin-2-yl)-1-(4-fluorophenyl)-6-methyl-1H-indazole	R^t 2.21 min (Method 7); m/z 565.4 (M+H)⁺ (ES⁺)
132	 1-(4-fluorophenyl)-6-methyl-5-(4-(pyridin-3-ylsulfonyl)-1-(3,3,3-trifluoropropyl)piperazin-2-yl)-1H-indazole	R^t 2.20 min (Method 7); m/z 548.3 (M+H)⁺ (ES⁺)
133	 5-((3-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)-4-(3,3,3-trifluoropropyl)piperazin-1-yl)sulfonyl)-2-methylthiazole	R^t 2.31 min (Method 9); m/z 568.2 (M+H)⁺ (ES⁺)

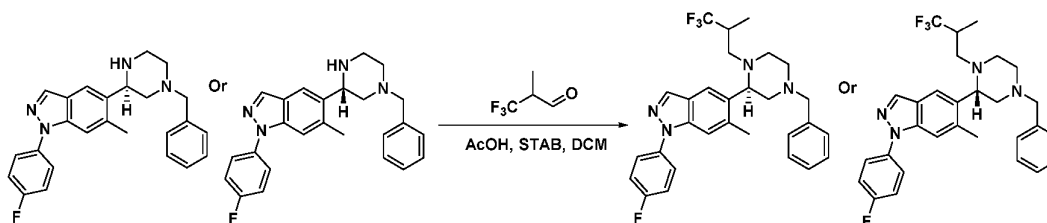
Example	Structure	LC-MS analysis
134	 4-((3-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)-4-(3,3,3-trifluoropropyl)piperazin-1-yl)sulfonyl)-2-methylthiazole	R^t 2.26 min (Method 7); m/z 568.4 (M+H)⁺ (ES⁺)
135	 5-(4-((2-ethyl-2H-1,2,3-triazol-4-yl)sulfonyl)-1-(3,3,3-trifluoropropyl)piperazin-2-yl)-1-(4-fluorophenyl)-6-methyl-1H-indazole	R^t 2.29 min (Method 9); m/z 566.2 (M+H)⁺ (ES⁺)
136	 1-(4-fluorophenyl)-5-(4-((1-(2-methoxyethyl)-1H-pyrazol-4-yl)sulfonyl)-1-(3,3,3-trifluoropropyl)piperazin-2-yl)-6-methyl-1H-indazole	R^t 2.16 min (Method 9); m/z 595.2 (M+H)⁺ (ES⁺)

Example	Structure	LC-MS analysis
137	 1-(4-fluorophenyl)-5-(4-(isobutylsulfonyl)-1-(3,3,3-trifluoropropyl)piperazin-2-yl)-6-methyl-1H-indazole	R^t 2.35 min (Method 9); m/z 527.2 (M+H)⁺ (ES⁺)
138	 1-(4-fluorophenyl)-6-methyl-5-(4-((4-methylpyridin-3-yl)sulfonyl)-1-(3,3,3-trifluoropropyl)piperazin-2-yl)-1H-indazole	R^t 2.25 min (Method 9); m/z 562.2 (M+H)⁺ (ES⁺)
139	 1-(4-fluorophenyl)-6-methyl-5-(4-(pyridin-2-ylsulfonyl)-1-(3,3,3-trifluoropropyl)piperazin-2-yl)-1H-indazole	R^t 2.23 min (Method 7); m/z 548.3 (M+H)⁺ (ES⁺)

Example	Structure	LC-MS analysis
140	 5-(4-(cyclobutylsulfonyl)-1-(3,3,3-trifluoropropyl)piperazin-2-yl)-1-(4-fluorophenyl)-6-methyl-1H-indazole	R _t 2.29 min (Method 7); m/z 525.4 (M+H) ⁺ (ES ⁺)

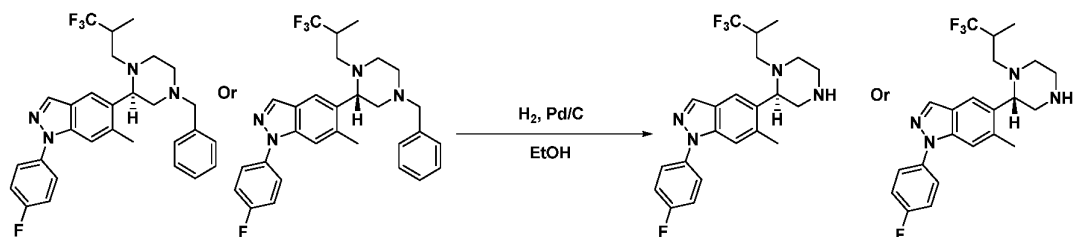
Example 141: 1-(4-fluorophenyl)-6-methyl-5-(4-((1-methyl-1H-pyrazol-4-yl)sulfonyl)-1-(3,3,3-trifluoro-2-methylpropyl)piperazin-2-yl)-1H-indazole

Intermediate R: 5-(4-benzyl-1-(3,3,3-trifluoro-2-methylpropyl)piperazin-2-yl)-1-(4-fluorophenyl)-6-methyl-1H-indazole



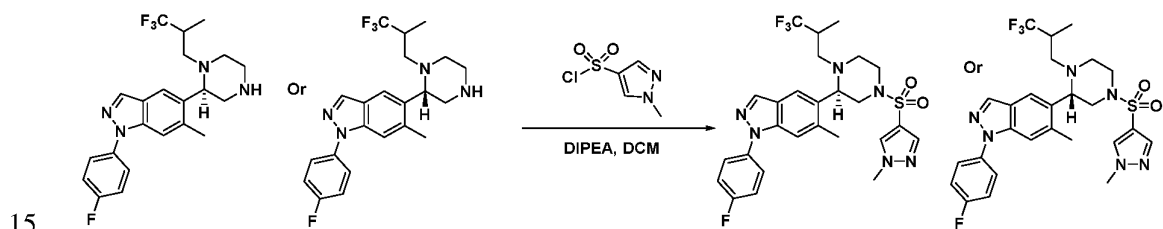
[0252] To a solution of 5-(4-benzylpiperazin-2-yl)-1-(4-fluorophenyl)-6-methyl-1H-indazole (500 mg, 1.25 mmol) in DCM (5.00 mL) were added 3,3,3-trifluoro-2-methylpropanal (236 mg, 1.87 mmol) and acetic acid (90.0 mg, 85.7 μ L, 1.50 mmol). The reaction mixture was stirred at rt for 45 mins before the addition of sodium triacetoxyhydroborate (794 mg, 3.75 mmol). The reaction mixture was then stirred for a further 2 days at rt before being quenched with sat. aq. NaHCO₃ (8 mL). The layers were separated, and the aqueous layer extracted with DCM (3 x 15 mL). Combined organic extracts were dried over MgSO₄ and concentrated in vacuo. The crude product was purified by chromatography on silica gel (12 g cartridge, 0-100% EtOAc/isohexane) to afford 5-(4-benzyl-1-(3,3,3-trifluoro-2-methylpropyl)piperazin-2-yl)-1-(4-fluorophenyl)-6-methyl-1H-indazole **Intermediate R** (350 mg, 685 μ mol, 54.9 %) as a white solid; R_t 1.64 and 1.65 min (Method 7); m/z 511.5 (M+H)⁺ (ES⁺).

Intermediate S: 1-(4-fluorophenyl)-6-methyl-5-(1-(3,3,3-trifluoro-2-methylpropyl)piperazin-2-yl)-1H-indazole



[0253] 5-(4-benzyl-1-(3,3,3-trifluoro-2-methylpropyl)piperazin-2-yl)-1-(4-fluorophenyl)-6-methyl-1H-indazole **Intermediate R** (350 mg, 685 μ mol) was dissolved in EtOH (5 mL) and treated with 10% palladium on carbon (14.6 mg, 137 μ mol). The mixture was purged with nitrogen (x3) then hydrogen (x3) before being hydrogenated at 5 atm overnight 40 $^{\circ}$ C. The catalyst was removed by filtration, washing with MeOH/EtOAc (1:1) (20 mL). The solvent was removed in vacuo to give 1-(4-fluorophenyl)-6-methyl-5-(1-(3,3,3-trifluoro-2-methylpropyl)piperazin-2-yl)-1H-indazole **Intermediate S** (300 mg, 0.66 mmol, 96 %) as a cloudy glass, which was used without further purification; Rt 1.43 and 1.48 min (Method 7); m/z 421.4 (M+H)⁺ (ES⁺).

Example 141: 1-(4-fluorophenyl)-6-methyl-5-(4-((1-methyl-1H-pyrazol-4-yl)sulfonyl)-1-(3,3,3-trifluoro-2-methylpropyl)piperazin-2-yl)-1H-indazole

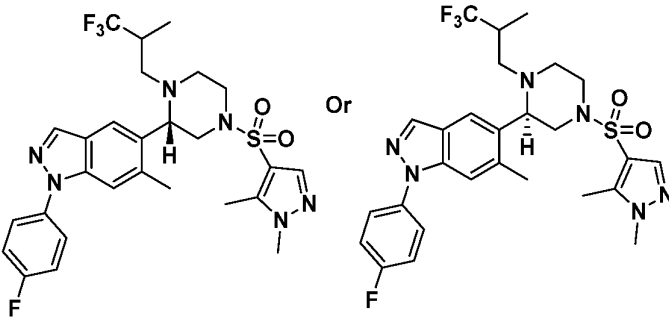
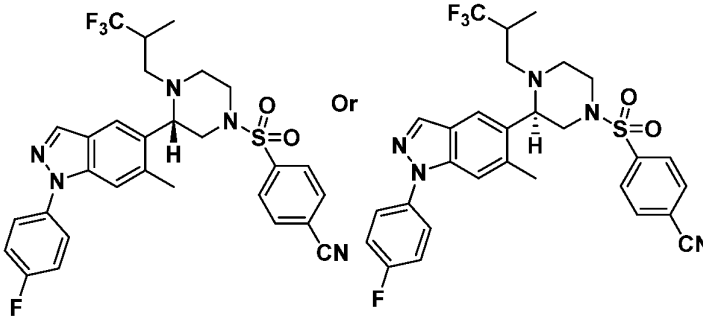
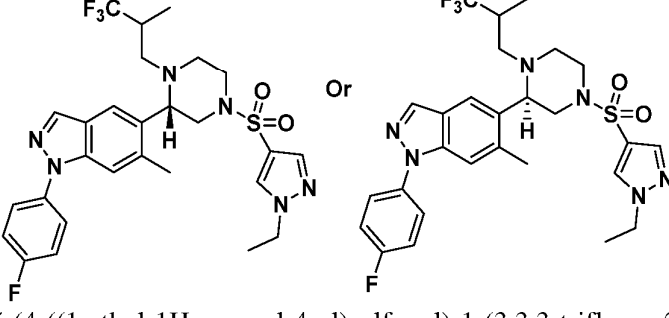


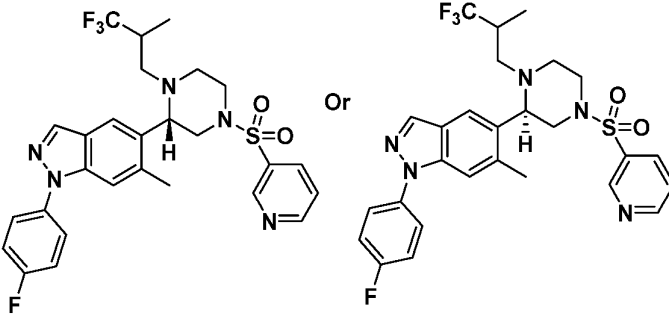
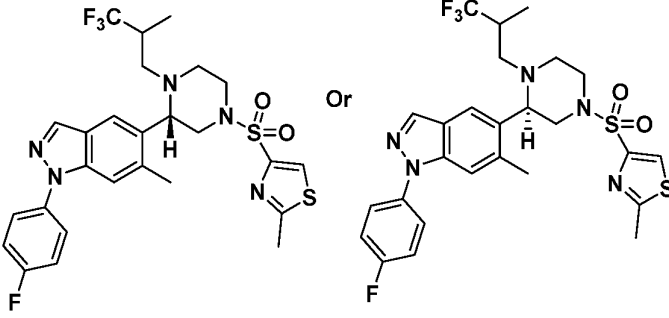
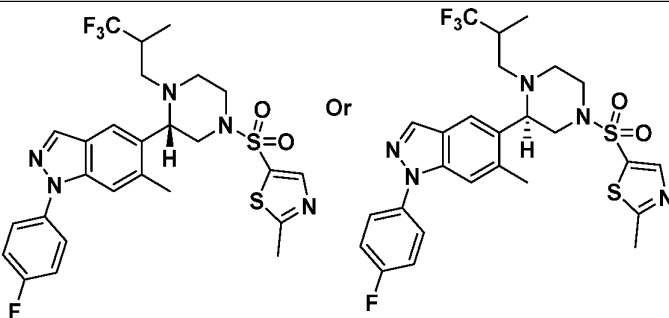
[0254] To a solution of 1-(4-fluorophenyl)-6-methyl-5-(1-(3,3,3-trifluoro-2-methylpropyl)piperazin-2-yl)-1H-indazole **Intermediate S** (15.0 mg, 35.7 μ mol) in DCM (1.00 mL) were added N-ethyl-N-isopropylpropan-2-amine (13.8 mg, 18.6 μ L, 107 μ mol) and 1-methyl-1H-pyrazole-4-sulfonyl chloride (9.02 mg, 49.9 μ mol). The reaction mixture was stirred for 2 hours at rt before being quenched with sat. aq. NaHCO₃ (1 mL) and passed through a phase separator cartridge. The organics were removed *in vacuo*. The crude product was purified by chromatography on silica gel (4 g cartridge, 0-100% EtOAc/isohexane) to afford 1-(4-fluorophenyl)-6-methyl-5-(4-((1-methyl-1H-pyrazol-4-yl)sulfonyl)-1-(3,3,3-

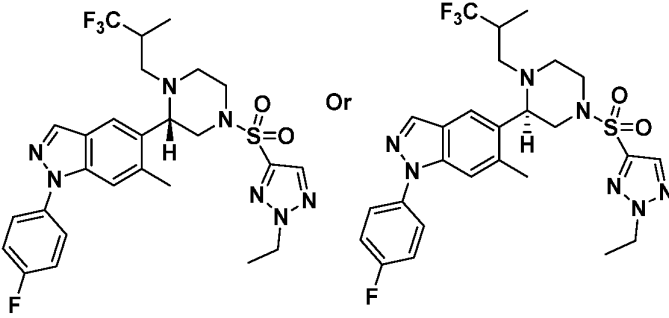
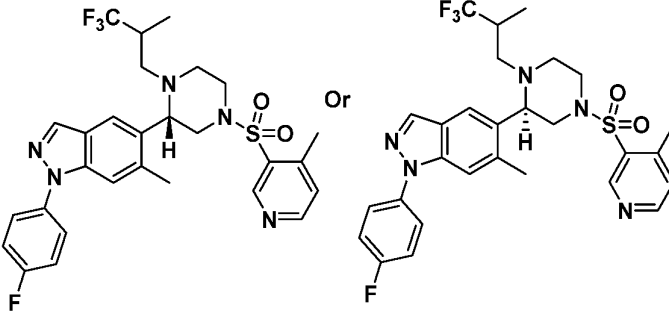
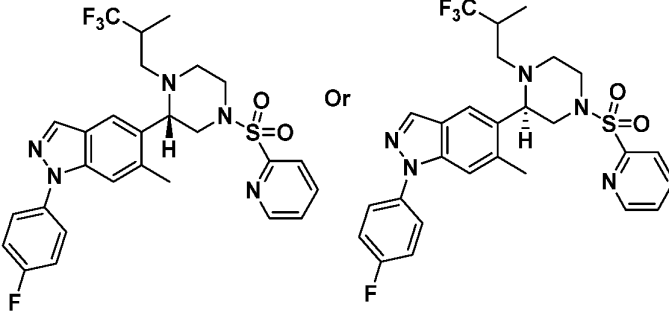
trifluoro-2-methylpropyl)piperazin-2-yl)-1H-indazole **Example 141**; Rt 2.22 and 2.26 min (Method 7); m/z 565.5 (M+H)⁺ (ES⁺).

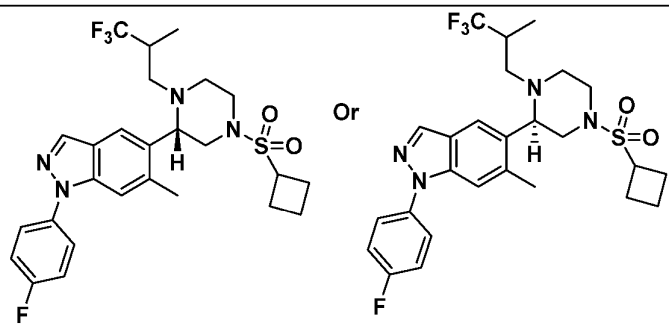
Examples 142 - 151

Table 16: The examples shown in the table below were prepared by similar methods to those described for Example 141

Example	Structure	LC-MS analysis
142	 5-(4-((1,5-dimethyl-1H-pyrazol-4-yl)sulfonyl)-1-(3,3,3-trifluoro-2-methylpropyl)piperazin-2-yl)-1-(4-fluorophenyl)-6-methyl-1H-indazole	R_t 2.26 and 2.29 min (Method 7) m/z 579.5 (M+H)⁺ (ES⁺)
143	 4-((3-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)-4-(3,3,3-trifluoro-2-methylpropyl)piperazin-1-yl)sulfonyl)benzonitrile	R_t 2.41 and 2.43 min (Method 7); m/z 586.3 (M+H)⁺ (ES⁺)
144	 5-(4-((1-ethyl-1H-pyrazol-4-yl)sulfonyl)-1-(3,3,3-trifluoro-2-methylpropyl)piperazin-2-yl)-1-(4-fluorophenyl)-6-methyl-1H-indazole	R_t 2.30 and 2.33 min (Method 7); m/z 579.4 (M+H)⁺ (ES⁺)

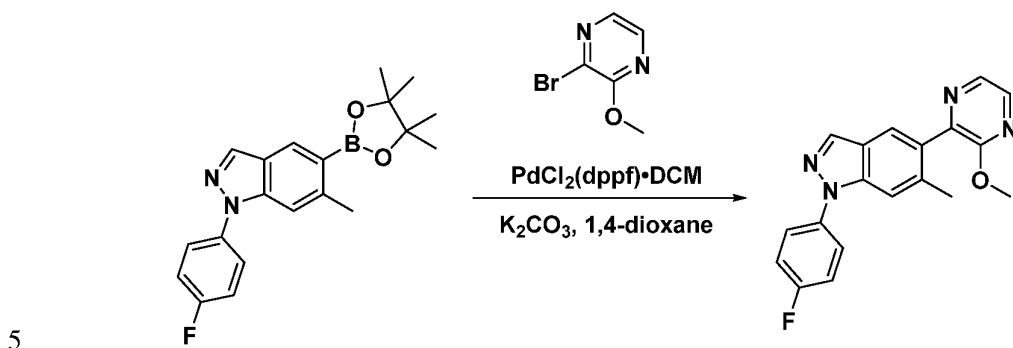
Example	Structure	LC-MS analysis
145	 1-(4-fluorophenyl)-6-methyl-5-(4-(pyridin-3-ylsulfonyl)-1-(3,3,3-trifluoro-2-methylpropyl)piperazin-2-yl)-1H-indazole	R ^t 2.29 and 2.32 min (Method 9); m/z 562.3 (M+H) ⁺ (ES ⁺)
146	 4-((3-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)-4-(3,3,3-trifluoro-2-methylpropyl)piperazin-1-yl)sulfonyl)-2-methylthiazole	R ^t 2.35 and 2.38 min (Method 7); m/z 582.5 (M+H) ⁺ (ES ⁺)
147	 5-((3-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)-4-(3,3,3-trifluoro-2-methylpropyl)piperazin-1-yl)sulfonyl)-2-methylthiazole	R ^t 2.39 and 2.42 min (Method 7); m/z 582.5 (M+H) ⁺ (ES ⁺)

Example	Structure	LC-MS analysis
148	 5-((2-ethyl-2H-1,2,3-triazol-4-yl)sulfonyl)-1-(3,3,3-trifluoro-2-methylpropyl)piperazin-2-yl)-1-(4-fluorophenyl)-6-methyl-1H-indazole	R^t 2.37 and 2.40 min (Method 9); m/z 580.2 (M+H)⁺ (ES⁺)
149	 1-(4-fluorophenyl)-6-methyl-5-(4-((4-methylpyridin-3-yl)sulfonyl)-1-(3,3,3-trifluoro-2-methylpropyl)piperazin-2-yl)-1H-indazole	R^t 2.34 and 2.37 min (Method 9); m/z 576.2 (M+H)⁺ (ES⁺)
150	 1-(4-fluorophenyl)-6-methyl-5-(4-(pyridin-2-ylsulfonyl)-1-(3,3,3-trifluoro-2-methylpropyl)piperazin-2-yl)-1H-indazole	R^t 2.32 and 2.35 min (Method 7); m/z 562.4 (M+H)⁺ (ES⁺)

Example	Structure	LC-MS analysis
151	 5-(4-(cyclobutylsulfonyl)-1-(3,3,3-trifluoro-2-methylpropyl)piperazin-2-yl)-1-(4-fluorophenyl)-6-methyl-1H-indazole	R_t 2.38 and 2.41 min (Method 7); m/z 539.4 (M+H)⁺ (ES⁺)

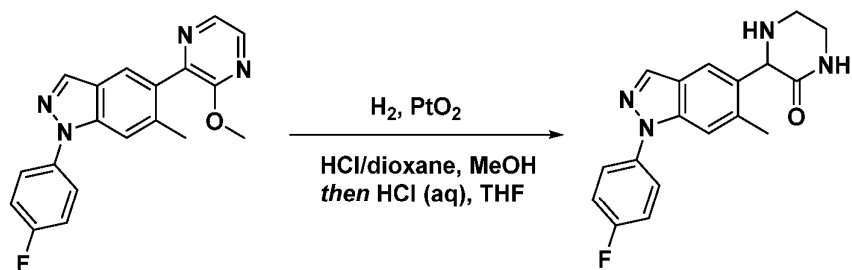
Example 152: 3-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)-4-isobutyl-1-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-2-one

Intermediate T: 1-(4-fluorophenyl)-5-(3-methoxypyrazin-2-yl)-6-methyl-1H-indazole



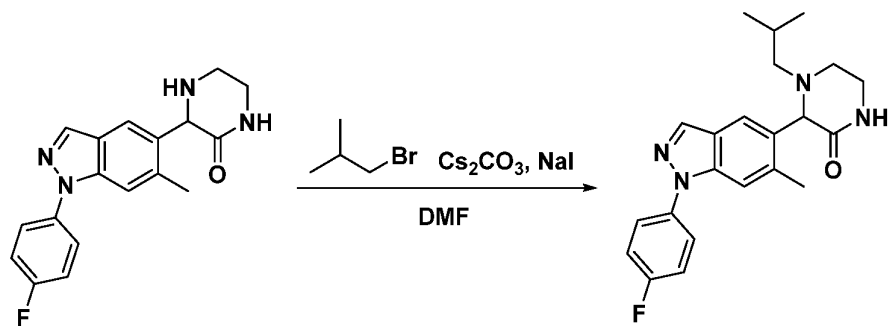
[0255] A solution of 1-(4-fluorophenyl)-6-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole (0.80 g, 2.3 mmol), 2-bromo-3-methoxypyrazine (0.52 g, 2.7 mmol) and potassium carbonate (0.47 g, 3.4 mmol) in 1,4-dioxane (20 mL) and water (5 mL) was degassed (bubbling N₂) for 2 mins. PdCl₂(dppf).DCM complex (0.19 g, 0.23 mmol) was then added and the reaction mixture stirred at 90 °C for 2 hours. The reaction mixture was diluted with DCM (50 mL) and transferred into a separating funnel. The organic layer was washed with half saturated brine (1 x 50 mL). The combined organic layers were collected, dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified by chromatography on silica gel (12 g cartridge, 5-100 EtOAc/isohexane) to afford 1-(4-fluorophenyl)-5-(3-methoxypyrazin-2-yl)-6-methyl-1H-indazole **Intermediate T** (0.38 g, 1.1 mmol, 50 %) as a flocculent white solid; R_t 1.98 min (Method 9); m/z 335.0 (M+H)⁺ (ES⁺).

Intermediate U: 3-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)piperazin-2-one



[0256] To a solution of 1-(4-fluorophenyl)-5-(3-methoxypyrazin-2-yl)-6-methyl-1H-indazole **Intermediate T** (150 mg, 449 μ mol) in MeOH (10.0 mL) were added HCl (4 M in 1,4-dioxane) (327 mg, 2.24 mL, 4 molar, 8.97 mmol) and platinum(IV) oxide (10.2 mg, 44.9 μ mol). The reaction mixture was subjected to hydrogenation at 5 bar at 50 $^{\circ}$ C for 20 hours. The reaction mixture was then concentrated *in vacuo* before being redissolved in THF (5 mL) and 1 M HCl (aq., 5 mL) added. The mixture was stirred overnight and then quenched with sat. aq. NaHCO_3 (15 mL). DCM (10 mL) was added, and the layers separated. The aqueous was extracted with DCM (3 x 5 mL). Combined organic extracts were dried over MgSO_4 and concentrated *in vacuo*. The crude product was purified by chromatography on silica gel (12 g cartridge, 0-10% (0.7 M ammonia/MeOH)/DCM) to afford 3-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)piperazin-2-one **Intermediate U** (52.0 mg, 0.10 mmol, 23 %) as a flocculent white solid; Rt 0.74 min (Method 9); m/z 325.2 ($M+H$) $^{+}$ (ES $^{+}$). δ H (DMSO- d_6 , 400 MHz) δ 8.28 (d, J = 0.9 Hz, 1H), 7.85 – 7.75 (m, 3H), 7.71 (s, 1H), 7.58 (s, 1H), 7.42 (t, J = 8.8 Hz, 2H), 4.57 (s, 1H), 3.36 (d, J = 7.8 Hz, 1H), 3.18 (dd, J = 12.7, 7.7 Hz, 1H), 2.98 (s, 1H), 2.88 (s, 2H), 2.52 (s, 3H).

Intermediate V: 3-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)-4-isobutylpiperazin-2-one

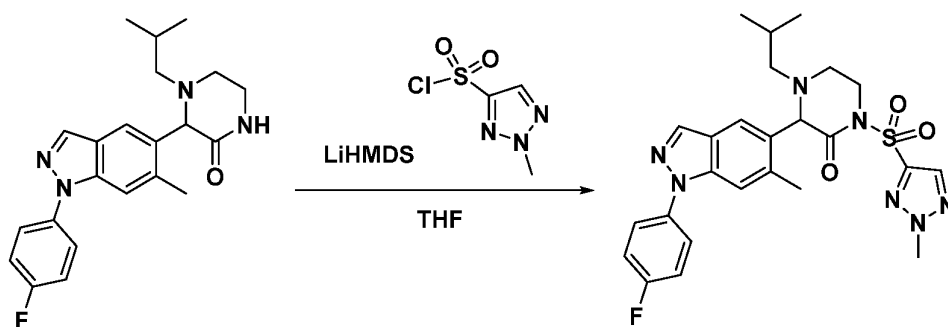


[0257] To a solution of 3-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)piperazin-2-one **Intermediate U** (42.0 mg, 129 μ mol) in DMF (2.00 mL) were added 1-bromo-2-methylpropane (710 mg, 563 μ L, 5.18 mmol), cesium carbonate (338 mg, 1.04 mmol) and sodium iodide (77.6 mg, 518 μ mol). The reaction mixture was stirred at 100 °C for 2 hours.

5 After cooling to rt, the reaction mixture was quenched with water (10 mL) and brine (10 mL) and the organics extracted with EtOAc (3 x 8 mL). Combined organics were dried over MgSO₄ and concentrated in vacuo. The crude product was purified by chromatography on silica gel (4 g cartridge, 0-100% EtOAc/isohehexane) to afford 3-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)-4-isobutylpiperazin-2-one **Intermediate V** (28.0 mg, 34 μ mol, 26 %) as an

10 off-white solid; Rt 1.90 min (Method 9); m/z 381.2 (M+H)⁺ (ES⁺).

Example 152: 3-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)-4-isobutyl-1-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-2-one



[0258] To a solution of 3-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)-4-isobutylpiperazin-2-one **Intermediate V** (28.0 mg, 46% Wt, 33.9 μ mol) in THF (1.00 mL) at -78 °C was added LiHMDS (1 M in THF) (17.0 mg, 102 μ L, 1.00 molar, 102 μ mol) and the reaction mixture stirred for 30 mins at -78 °C. 2-Methyl-2H-1,2,3-triazole-4-sulfonyl chloride (18.4 mg, 102 μ mol) (as a solution in THF (0.30 mL)) was then added and the reaction mixture stirred for 90 mins, warming to rt. The reaction mixture was quenched with sat. aq.

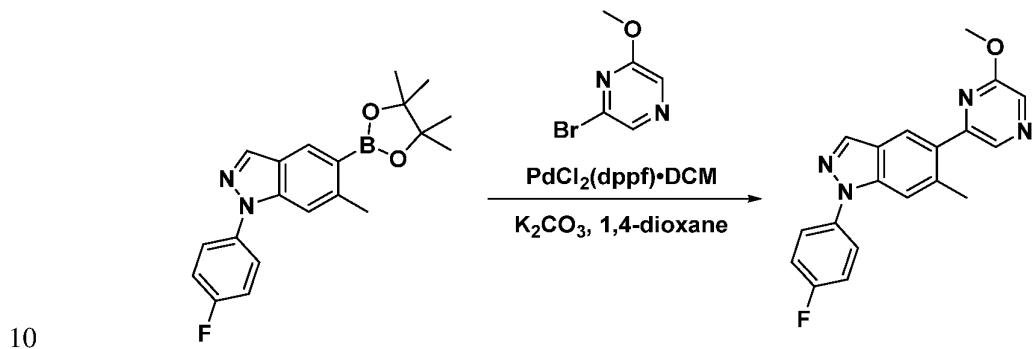
20 NaHCO₃ (3 mL) and EtOAc (5 mL). The layers were separated, and the aqueous layer extracted with EtOAc (3 x 5 mL). Combined organic extracts were dried over MgSO₄ and concentrated *in vacuo*. The crude product was purified by chromatography on silica gel (4 g cartridge, 0-100% EtOAc/isohehexane) to afford the product at ~88%. This material was then submitted for reverse phase purification to afford 3-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)-4-isobutyl-1-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-2-one

25 **Example 152** (6.00 mg, 11 μ mol, 32 %, 95% Purity) as a white solid; Rt 2.27 min (Method

9); m/z 526.2 (M+H)⁺ (ES⁺). δ H (DMSO-d₆, 400 MHz) δ 8.37 (s, 1H), 8.30 (d, J = 0.9 Hz, 1H), 7.84 – 7.75 (m, 2H), 7.74 (s, 1H), 7.55 (s, 1H), 7.45 – 7.37 (m, 2H), 4.32 (s, 1H), 4.27 (s, 3H), 4.15 (d, J = 11.7 Hz, 1H), 3.91 (td, J = 11.6, 3.7 Hz, 1H), 3.37 (d, J = 12.7 Hz, 1H), 2.61 (t, J = 10.6 Hz, 1H), 2.07 (dd, J = 12.2, 4.0 Hz, 1H), 1.84 (t, J = 11.4 Hz, 1H), 1.68 (d, J = 6.2 Hz, 1H), 0.65 (d, J = 6.5 Hz, 3H), 0.62 (d, J = 6.4 Hz, 3H). 3H obscured by DMSO peak.

Example 153: 3-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)-4-isobutyl-1-((2-methyl-2H-1,2,3-triazol-4-yl)sulfinyl)piperazin-2-one

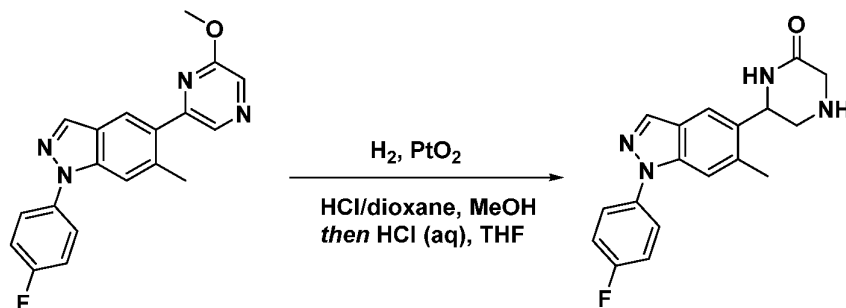
Intermediate W: 1-(4-fluorophenyl)-5-(6-methoxypyrazin-2-yl)-6-methyl-1H-indazole



15 **[0259]** A solution of 1-(4-fluorophenyl)-6-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole (0.80 g, 2.3 mmol), 2-bromo-6-methoxypyrazine (0.52 g, 2.7 mmol) and potassium carbonate (0.47 g, 3.4 mmol) in 1,4-dioxane (20 mL) and water (5 mL) was degassed (bubbling N₂) for 20 mins. PdCl₂(dppf).DCM complex (0.19 g, 0.23 mmol) was then added and the reaction mixture stirred at 90 °C for 2 hours. The reaction mixture was diluted with EtOAc (50 mL) and transferred into a separating funnel. The organic layer was washed with half saturated brine (1 x 50 mL). The combined organic layers were collected, dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified by chromatography on silica gel (12 g cartridge, 5-100 EtOAc/isohexane) to afford

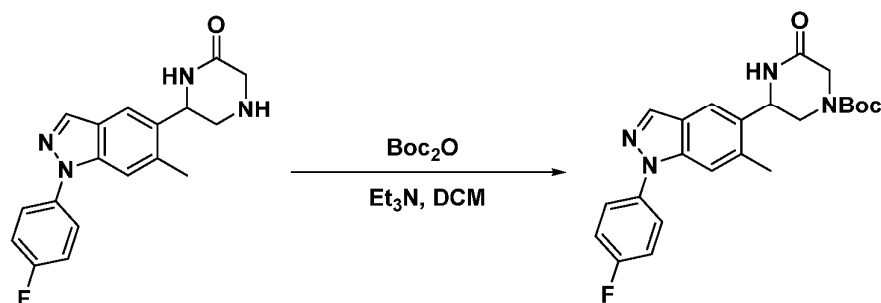
20 1-(4-fluorophenyl)-5-(6-methoxypyrazin-2-yl)-6-methyl-1H-indazole **Intermediate W** (0.46 g, 1.3 mmol, 59 %) as a flocculent white solid; Rt 2.24 min (Method 9); m/z 335.1 (M+H)⁺ (ES⁺).

Intermediate X: 6-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)piperazin-2-one



To a suspension of 1-(4-fluorophenyl)-5-(6-methoxypyrazin-2-yl)-6-methyl-1H-indazole **Intermediate W** (410 mg, 1.23 mmol) in MeOH (40 mL) were added HCl (4 M in dioxane) (894 mg, 6.13 mL, 4 molar, 24.5 mmol) and platinum(IV) oxide (27.8 mg, 123 μmol). The reaction mixture was stirred at 50 $^\circ\text{C}$ for 16 hours under an atmosphere of H_2 (5 bar). After cooling to rt, the reaction mixture was filtered through a glass microfibre pad, washing with EtOAc (50 mL). The filtrate was concentrated *in vacuo* and redissolved in EtOAc (50 mL). NaHCO_3 (100 mL) was added, and the layers separated. The aqueous was extracted with EtOAc (3 x 30 mL). Combined organic extracts were dried over MgSO_4 and concentrated *in vacuo*. The crude product was purified by chromatography on silica gel (12 g cartridge, 0–10% (0.7 M ammonia/MeOH)/DCM) to afford 6-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)piperazin-2-one **Intermediate X** (220 mg, 0.58 mmol, 47 %, 85%) as a white solid; R_t 0.90 min (Method 9); m/z 325.2 ($\text{M}+\text{H}$)⁺ (ES^+). δH (DMSO- d_6 , 400 MHz) δ 8.33 (d, $J = 0.9$ Hz, 1H), 7.91 (s, 1H), 7.83 – 7.75 (m, 3H), 7.62 (s, 1H), 7.46 – 7.38 (m, 2H), 4.83 (s, 1H), 3.30 (obscured m, 3H), 3.21 – 3.11 (m, 1H), 2.56 (m, 1H), 2.46 (s, 3H).

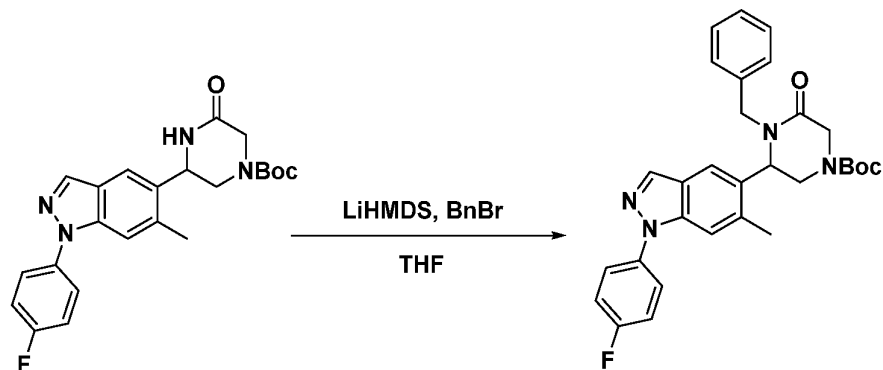
Intermediate Y:



[0260] To a solution of 6-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)piperazin-2-one **Intermediate X** (40.0 mg, 123 μmol) in DCM (1.50 mL) were added triethylamine (21.8 mg,

30.0 μ L, 216 μ mol) and Boc anhydride (32.3 mg, 34.0 μ L, 148 μ mol). The reaction mixture was stirred at rt for 1 hour before being quenched with sat. aq. NaHCO_3 (2 mL). The layers were separated, and the aqueous layer extracted with DCM (3 x 2 mL). Combined organic extracts were dried over MgSO_4 and concentrated in vacuo. The crude product was purified by chromatography on silica gel (4 g cartridge, 0-100% EtOAc/isohexane then isocratic 25% EtOH/EtOAc) to afford tert-butyl 3-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)-5-oxopiperazine-1-carboxylate **Intermediate Y** (47.0 mg, 0.11 mmol, 85 %) as a white solid; Rt 1.80 min (Method 9); m/z 425.2 (M+H)⁺ (ES⁺). δ H (DMSO- d_6 , 400 MHz) δ 8.40 (d, J = 3.3 Hz, 1H), 8.33 (s, 1H), 7.77 (s, 2H), 7.61 (m, 2H), 7.43 (t, J = 8.6 Hz, 2H), 4.88 (q, J = 3.8 Hz, 1H), 4.33 – 4.06 (m, 1H), 3.90 (m, 1H), 3.70 (m, 2H), 1.09 (m, 9H). 3H obscured under DMSO peak.

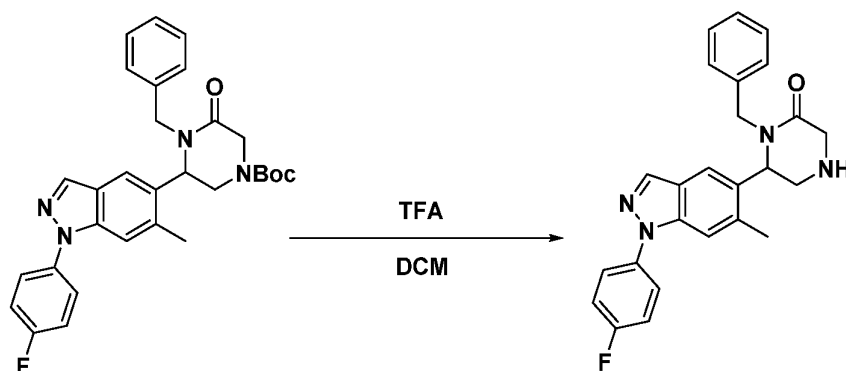
Intermediate Z: tert-butyl 4-benzyl-3-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)-5-oxopiperazine-1-carboxylate



[0261] To a solution of tert-butyl 3-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)-5-oxopiperazine-1-carboxylate **Intermediate Y** (35.0 mg, 82.5 μ mol) in THF (1.50 mL) at 0 °C was added lithium bis(trimethylsilyl)amide (1 M in toluene) (27.6 mg, 165 μ L, 1.00 molar, 165 μ mol). The reaction mixture was stirred at 0 °C for 20 mins before the addition of (bromomethyl)benzene (42.3 mg, 29.4 μ L, 247 μ mol). The reaction mixture was then stirred at 60 °C for 3 hours. After cooling to rt, the reaction mixture was quenched with sat. aqueous NH_4Cl (5 mL) and diluted with EtOAc (5 mL). The layers were separated, and the aqueous layer extracted with EtOAc (3 x 5 mL). Combined organic extracts were dried over MgSO_4 and concentrated in vacuo. The crude product was purified by chromatography on silica gel (4 g cartridge, 0-100% EtOAc/isohexane) to afford tert-butyl 4-benzyl-3-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)-5-oxopiperazine-1-carboxylate **Intermediate Z** (41.0 mg, 53

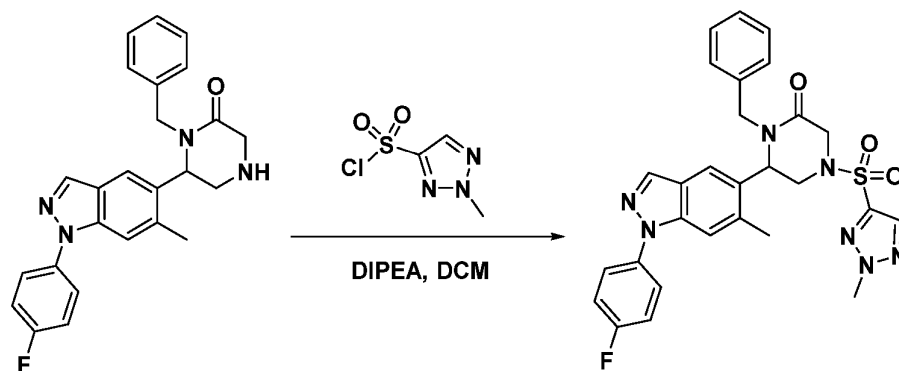
μmol, 53 %) as a pale tan solid; Rt 2.19 min (Method 9); m/z 515.2 (M+H)⁺ (ES⁺). δH (DMSO-d₆, 400 MHz) δ 8.32 (s, 1H), 7.73 (m, 3H), 7.56 – 7.15 (m, 8H), 5.31 (m, 1H), 4.71 (d, J = 3.1 Hz, 1H), 4.55 (m, 1H), 4.21 – 3.81 (m, 2H), 3.56 (m, 2H), 2.34 (s, 3H), 0.98 (m, 9H).

5 **Intermediate AA: 1-benzyl-6-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)piperazin-2-one**



[0262] To a solution of tert-butyl 4-benzyl-3-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)-5-oxopiperazine-1-carboxylate **Intermediate Z** (39.0 mg, 66% Wt, 50.0 μmol) in DCM (1.00 mL) was added 2,2,2-trifluoroacetic acid (149 mg, 100 μL, 1.31 mmol). The reaction mixture was stirred at rt for 2 hours before being diluted with toluene (2 mL) and concentrated *in vacuo*. The residue was dissolved in DCM (5 mL) and basified with sat. aq. NaHCO₃ (5 mL). The mixture was dried through a phase separator and the organics concentrated *in vacuo*. The crude product was purified by chromatography on silica gel (4 g cartridge, 0-10% (0.7 M Ammonia/MeOH)/DCM) to afford 1-benzyl-6-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)piperazin-2-one **Intermediate AA** (15.0 mg, 34 μmol, 69 %) as a flocculent white solid; Rt 1.46 min (Method 9); m/z 415.2 (M+H)⁺ (ES⁺). δH (DMSO-d₆, 400 MHz) δ 8.34 (d, J = 0.9 Hz, 1H), 7.84 – 7.76 (m, 2H), 7.69 (s, 1H), 7.63 (s, 1H), 7.43 (t, J = 8.8 Hz, 2H), 7.36 – 7.21 (m, 3H), 7.17 – 7.05 (m, 2H), 5.36 (d, J = 15.0 Hz, 1H), 4.62 (t, J = 4.5 Hz, 1H), 3.54 (q, J = 17.1 Hz, 2H), 3.19 (d, J = 13.0 Hz, 1H), 2.80 (d, J = 13.5 Hz, 1H), 2.19 (s, 3H). 2H obscured under DMSO.

Example 153: 3-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)-4-isobutyl-1-((2-methyl-2H-1,2,3-triazol-4-yl)sulfinyl)piperazin-2-one

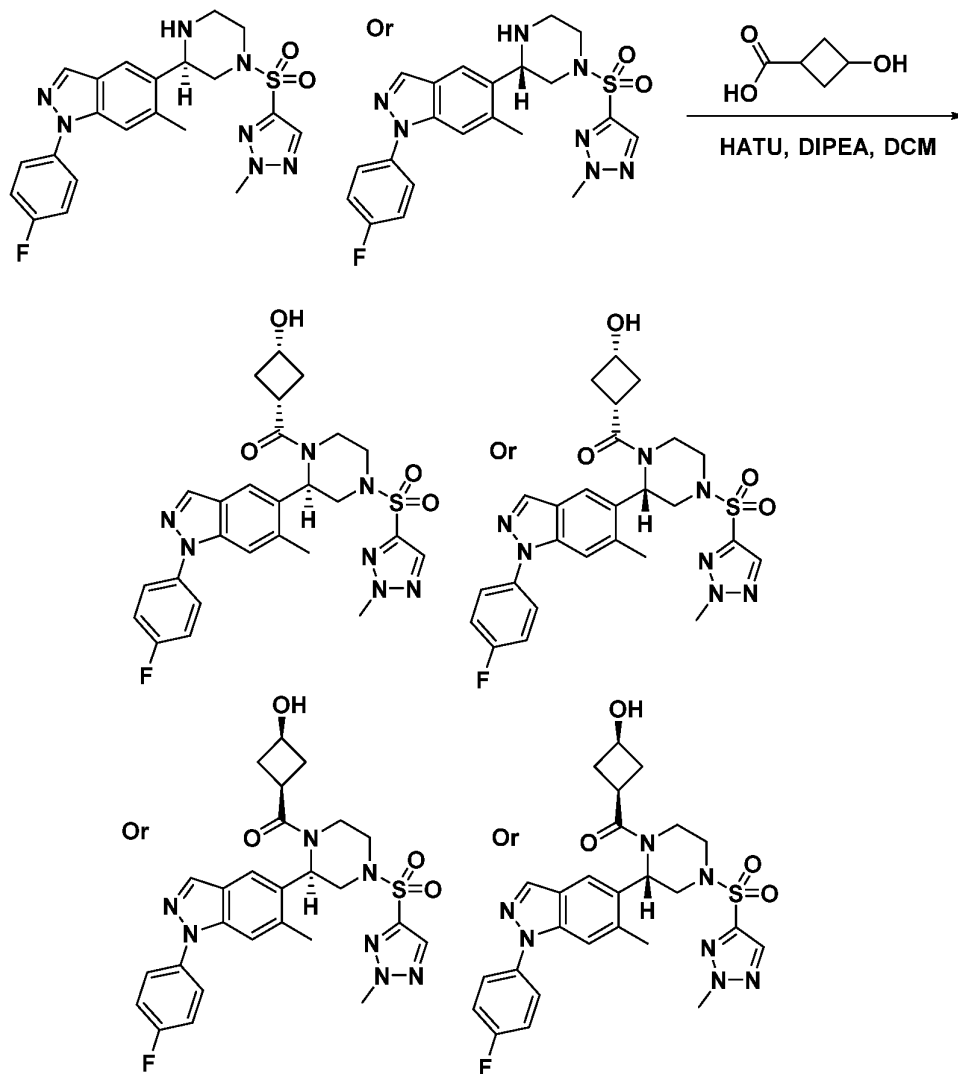


[0263] To a solution of 1-benzyl-6-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)piperazin-2-one **Intermediate AA** (14.0 mg, 133.8 μ mol) in DCM (0.50 mL) were added 2-methyl-2H-1,2,3-triazole-4-sulfonyl chloride (9.20 mg, 50.7 μ mol) and N-ethyl-N-isopropylpropan-2-amine (13.1 mg, 17.7 μ L, 101 μ mol). The reaction mixture was stirred at rt for 4 hours, before being quenched with sat. aq. NaHCO₃ (2 mL). The mixture was transferred to a phase separator and extracted with DCM (5 mL). Combined organic extracts were concentrated *in vacuo*. The crude product was purified by chromatography on silica gel (4 g cartridge, 0-100% EtOAc/isohexane) to afford the product at ~88% purity. This material was then further purified by reverse phase HPLC to afford 1-benzyl-6-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-2-one

Example 153 (6.20 mg, 11 μ mol, 31 %, 95% Purity) as a white solid; Rt 2.07 min (Method 9); m/z 560.2 (M+H)⁺ (ES⁺). δ H (DMSO-d₆, 400 MHz) δ 8.36 (s, 1H), 8.25 (s, 1H), 7.82 (dd, J = 8.9, 4.9 Hz, 2H), 7.67 (s, 1H), 7.63 (s, 1H), 7.44 (t, J = 8.6 Hz, 2H), 7.28 (m, 3H), 7.11 (d, J = 7.2 Hz, 2H), 5.24 (m, 1H), 4.77 (s, 1H), 4.19 (m, 4H), 3.89 (d, J = 16.3 Hz, 1H), 3.55 (d, J = 12.6 Hz, 1H), 3.47 (m, 2H), 2.26 (s, 3H).

Example 154: 3-((2-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-1-yl)methyl)cyclobutan-1-ol

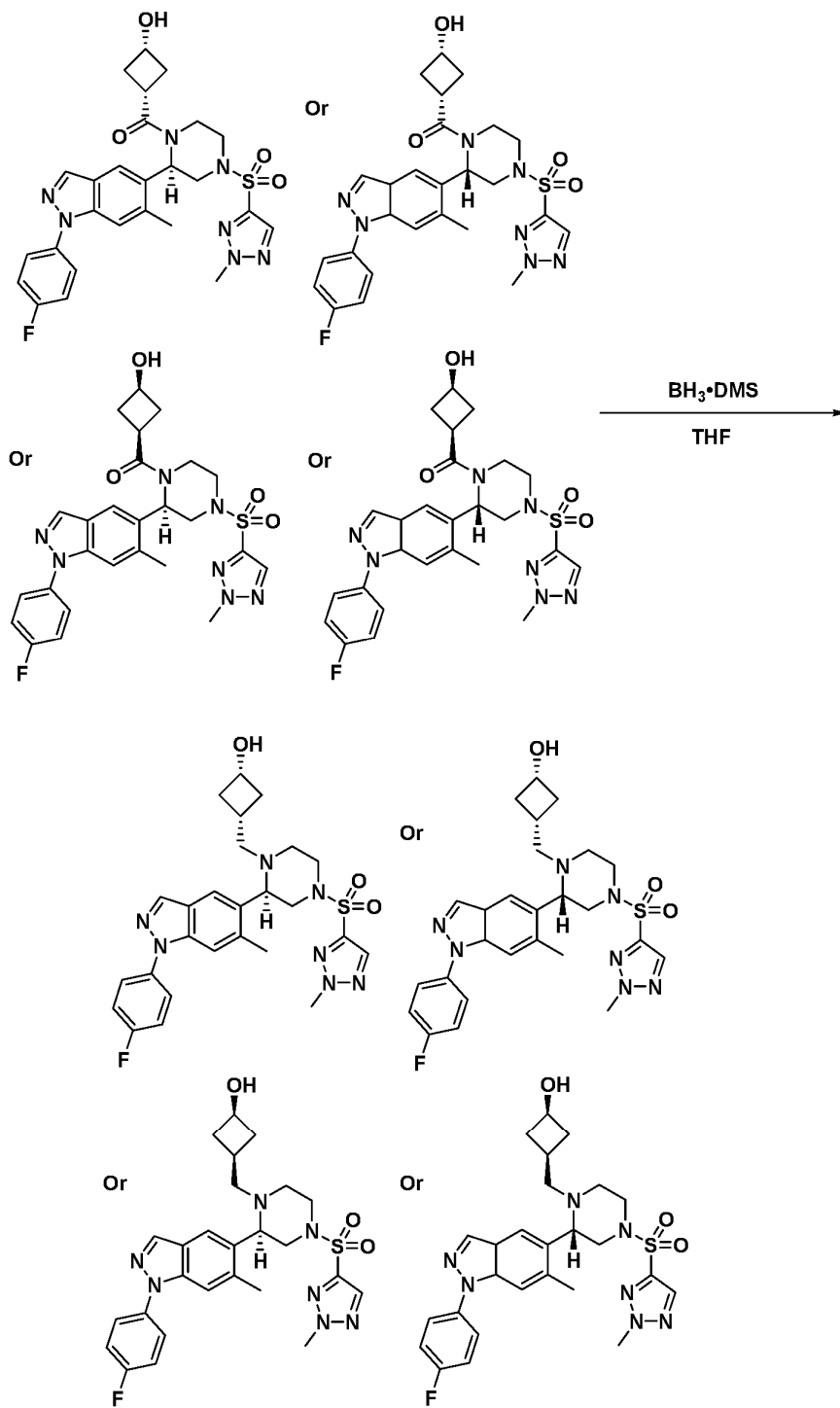
Intermediate AB: (2-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-1-yl)(3-hydroxycyclobutyl)methanone



[0264] To a solution of 3-hydroxycyclobutane-1-carboxylic acid (38.2 mg, 329 μ mol) in
 5 DCM (3.00 mL) were added N-ethyl-N-isopropylpropan-2-amine (85.1 mg, 114 μ L, 659 μ mol) and 2-(3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate(V) (125 mg, 329 μ mol). The reaction mixture was stirred for 10 mins before the addition of 1-(4-fluorophenyl)-6-methyl-5-(4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-2-yl)-1H-indazole (100 mg, 220 μ mol). The reaction mixture was then
 10 stirred at rt for 16 hours. The reaction mixture was then quenched with 1 M aq HCl (5 mL). The mixture was transferred to a phase separator and the aqueous layer extracted with DCM

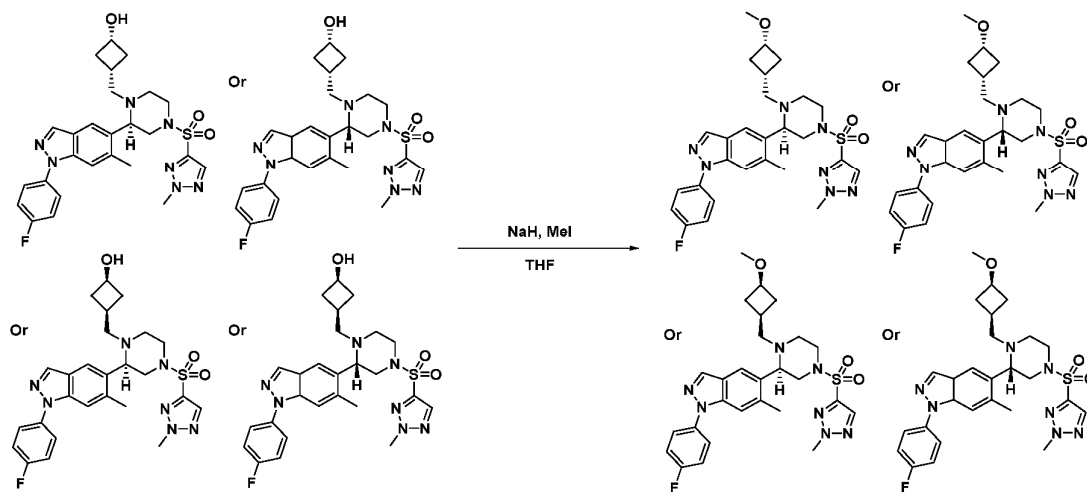
(2 x 4 mL). Combined organics were concentrated in vacuo. The crude product was purified by chromatography on silica gel (4 g cartridge, 0-100% EtOAc/isohexane) to afford (2-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-1-yl)(3-hydroxycyclobutyl)methanone **Intermediate AB** (120 mg, 0.13 mmol, 59 %, 60%) as a white solid; Rt 1.71 min (Method 9); m/z 554.2 (M+H)⁺ (ES⁺).

Example 154: 3-((2-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-1-yl)methyl)cyclobutan-1-ol



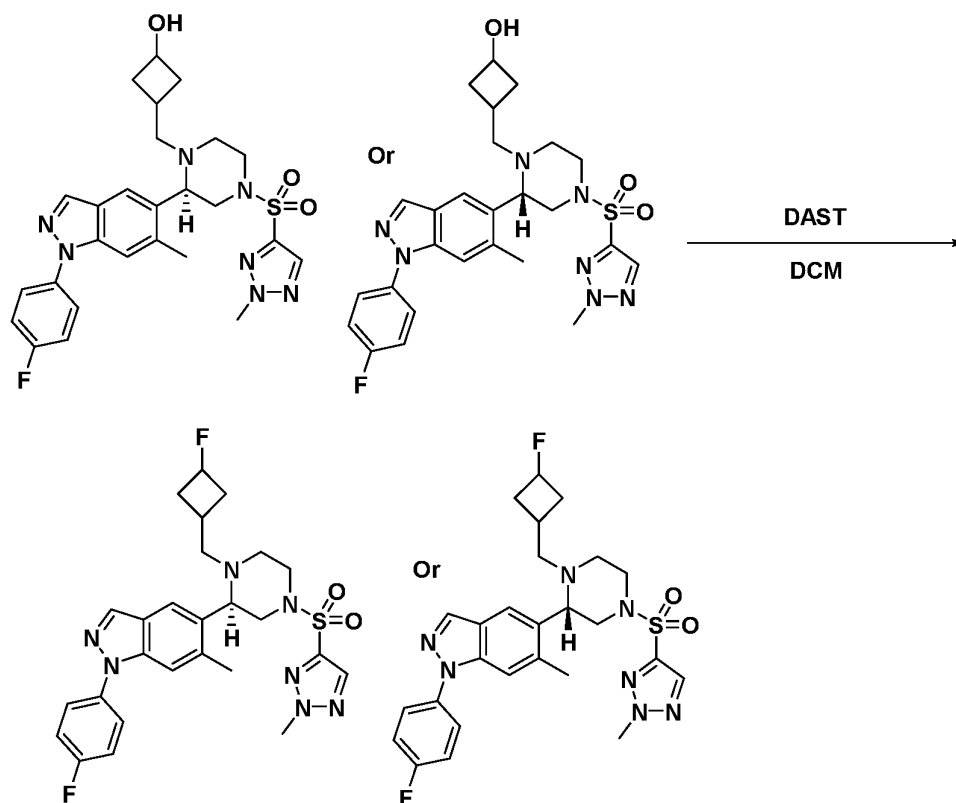
[0265] To a solution of (2-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-1-yl)(3-hydroxycyclobutyl)methanone **Intermediate AB** (120 mg, 70% Wt, 152 μ mol) in THF (2.00 mL) was added borane-methyl sulfide complex (2M in THF) (69.2 mg, 455 μ L, 2.00 molar, 910 μ mol). The reaction mixture was stirred at 40 °C for 3 hours. Additional borane-methyl sulfide complex (2M in THF) (45.6 mg, 300 μ L, 2.00 molar, 600 μ mol) was then added and the reaction mixture stirred at 40 °C for a further 2 hours. After cooling to rt, the reaction mixture was quenched with MeOH (1 mL), water (1 mL) and sat. aq. NH₄Cl (2 mL). DCM (5 mL) was added, and the layers separated. The aqueous layer was extracted with DCM (2 x 3 mL). Combined organic extracts were dried over MgSO₄ and concentrated *in vacuo*. The crude product was purified by chromatography on silica gel (2 x 4 g cartridge, 0-100% EtOAc/isohehexane) to afford 3-((2-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-1-yl)methyl)cyclobutan-1-ol **Example 154** (7.00 mg, 12 μ mol, 8.1 %, 95% Purity) as a white solid as an 8:1 mixture of diastereomers; Rt 1.48 and 1.53 min (Method 9); m/z 540.2 (M+H)⁺ (ES⁺). δ H (DMSO-d₆, 400 MHz) δ 8.29 (s, 1H), 8.27 (s, 1H), 7.84 (s, 1H), 7.79 (dd, J = 9.0, 4.8 Hz, 2H), 7.65 (s, 1H), 7.43 (t, J = 8.8 Hz, 2H), 4.79 (d, J = 6.8 Hz, 1H), 4.26 (s, 3H), 3.80 (q, J = 7.4 Hz, 1H), 3.70 (d, J = 11.7 Hz, 1H), 3.60 (dd, J = 10.2, 3.1 Hz, 1H), 3.45 (d, J = 11.9 Hz, 1H), 3.16 (d, J = 11.9 Hz, 1H), 2.68 (d, J = 11.2 Hz, 1H), 2.48 (obscured s, 3H), 2.41 – 2.27 (m, 3H), 2.20 (dq, J = 16.0, 7.5 Hz, 1H), 1.77 (dd, J = 14.8, 8.3 Hz, 2H), 1.17 (td, J = 19.9, 10.1 Hz, 2H). OH proton not observed.

Example 155: 1-(4-fluorophenyl)-5-(1-((3-methoxycyclobutyl)methyl)-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-2-yl)-6-methyl-1H-indazole



[0266] To a solution of 3-((2-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-1-yl)methyl)cyclobutan-1-ol **Example 154** (32.0 mg, 59.3 μ mol) in THF (1.00 mL) at 0 °C was added sodium hydride (60 wt% in mineral oil) (4.7 mg, 60% Wt, 119 μ mol) and the reaction mixture stirred for 30 mins. iodomethane (25.3 mg, 11.1 μ L, 178 μ mol) was then added and the reaction mixture stirred at rt for 18 hours. Additional sodium hydride (24 mg, 60% Wt, 593 μ mol) and iodomethane (126 mg, 55.4 μ L, 889 μ mol) were added and the reaction mixture stirred for a further 30 mins before being quenched with MeOH (1 mL) and sat. aq. NH₄Cl (2 mL). The crude product was purified by chromatography on silica gel (4 g cartridge, 0-100% EtOAc/isohexane) to afford 1-(4-fluorophenyl)-5-(1-((3-methoxycyclobutyl)methyl)-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-2-yl)-6-methyl-1H-indazole **Example 155** (11.0 mg, 19 μ mol, 32 %) as a white solid; Rt 1.72 min (Method 9); m/z 554.2 (M+H)⁺ (ES⁺). δ H (DMSO-d₆, 400 MHz) δ 8.29 (s, 1H), 8.27 (s, 1H), 7.83 (s, 1H), 7.82 – 7.75 (m, 2H), 7.65 (s, 1H), 7.43 (t, J = 8.8 Hz, 2H), 4.26 (s, 3H), 3.70 (d, J = 11.5 Hz, 1H), 3.65 – 3.52 (m, 2H), 3.45 (d, J = 12.0 Hz, 1H), 3.17 (d, J = 11.6 Hz, 1H), 2.98 (s, 3H), 2.72 – 2.63 (m, 1H), 2.48 (s, 3H), 2.37 (dd, J = 12.5, 8.6 Hz, 2H), 2.29 – 2.16 (m, 2H), 2.05 (dd, J = 12.6, 5.6 Hz, 1H), 1.92 (t, J = 7.6 Hz, 1H), 1.24 – 1.08 (m, 3H).

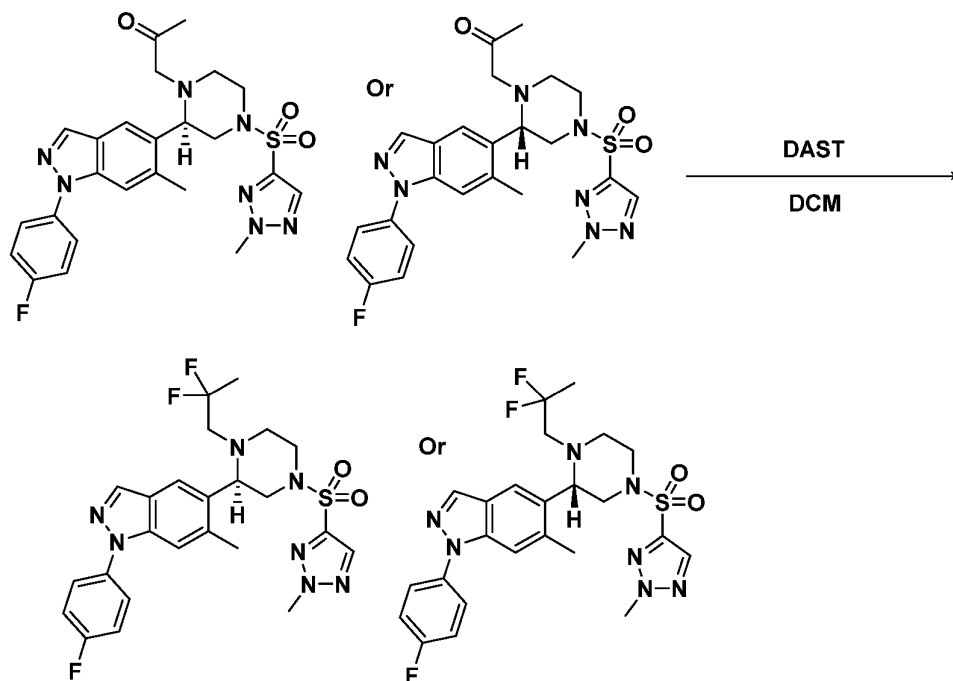
Example 156: 5-(1-((3-fluorocyclobutyl)methyl)-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-2-yl)-1-(4-fluorophenyl)-6-methyl-1H-indazole



- [0267] To a solution of 3-((2-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-1-yl)methyl)cyclobutan-1-ol (15.0 mg, 27.8 μmol) in DCM (0.30 mL) at -78 $^{\circ}\text{C}$ was added DAST (8.96 mg, 7.35 μL , 55.6 μmol). The reaction mixture was stirred for 2 hours, warming to rt, before being quenched with sat. aq. NaHCO_3 (1 mL) and diluted with DCM (1 mL). The layers were separated, and the aqueous layer extracted with DCM (3 x 1 mL). Combined organic extracts were dried over MgSO_4 and concentrated *in vacuo* to an orange solid. The crude mixture was dissolved in 0.9 mL with DMSO, filtered and purified by reversed phase preparative HPLC (Waters 2767 Sample Manager, Waters 2545 Binary Gradient Module, Waters Systems Fluidics Organiser, Waters 515 ACD pump, Waters 515 Makeup pump, Waters 2998 Photodiode Array Detector, Waters QDa) on a Waters X-Select CSH C18 ODB prep column, 130 $\text{\AA}$, 5 μm , 30 mm X 100 mm, flow rate 40 mL min $^{-1}$ eluting with a 0.1% Formic acid in water-MeCN gradient over 12.5 mins using UV across all wavelengths with PDA as well as a QDA and ELS detector. At-column dilution pump gives 2 mL min $^{-1}$ methanol over the entire method, which is included in the following MeCN percentages. Gradient information: 0.0-0.5 min, 50% MeCN; 0.5-10.5 min, ramped from 50% MeCN to 80% MeCN; 10.5-10.6 min, ramped from 80%

MeCN to 100% MeCN; 10.6-12.5 min, held at 100% MeCN to afford 5-(1-((3-fluorocyclobutyl)methyl)-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-2-yl)-1-(4-fluorophenyl)-6-methyl-1H-indazole (1.50 mg, 2.6 μ mol, 9.5 %, 95% Purity) was isolated as a mixture of isomers as an off-white solid; Rt 2.19, 2.21 and 2.24 min (Method 9); m/z 542.2 (M+H)⁺ (ES⁺).

Example 157: 5-(1-(2,2-difluoropropyl)-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-2-yl)-1-(4-fluorophenyl)-6-methyl-1H-indazole

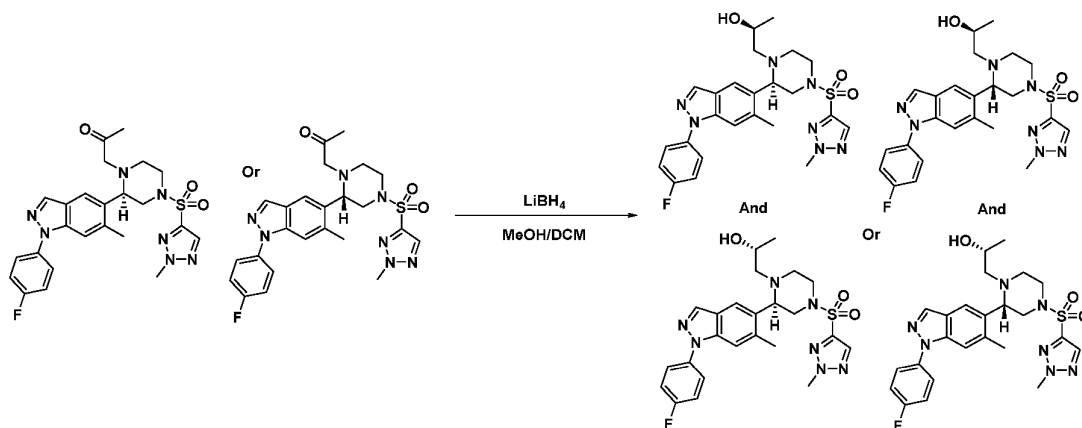


[0268] To a stirred solution of (R)-1-(2-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-1-yl)propan-2-one (75.0 mg, 1 Eq, 147 μ mol) **Example 125** in dry DCM (1.00 mL) under a nitrogen atmosphere at -20 °C was added DAST (122 mg, 100 μ L, 5.16 Eq, 757 μ mol). The reaction mixture was stirred for 30 minutes and then raised to 20 °C for 2 days. The reaction mixture was quenched with 2M NaOH (2mL) and transferred to a phase separator. The DCM layer was drawn off and adsorbed onto silica gel. The crude product was purified by chromatography on silica gel (4 g cartridge, 10-50% EtOAc/isohexane) to afford 5-(1-(2,2-difluoropropyl)-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-2-yl)-1-(4-fluorophenyl)-6-methyl-1H-indazole **Example 157** (34.0 mg, 61 μ mol, 41 %) as a white solid; Rt 2.24 min (Method 7); m/z 534.2 (M+H)⁺ (ES⁺). δ H (DMSO-d₆, 400 MHz) δ 8.36 – 8.18 (m, 2H), 7.88 (s, 1H), 7.83 – 7.74

(m, 2H), 7.66 (d, J = 1.1 Hz, 1H), 7.48 – 7.31 (m, 2H), 4.28 (s, 3H), 3.86 (dd, J = 10.4, 3.1 Hz, 1H), 3.70 (d, J = 11.7 Hz, 1H), 3.49 (d, J = 11.8 Hz, 1H), 3.29 (s, 1H), 2.88 – 2.76 (m, 1H), 2.70 – 2.60 (m, 2H), 2.59 – 2.52 (m, 2H), 2.51 (s, 3H), 1.47 (t, J = 19.2 Hz, 3H).

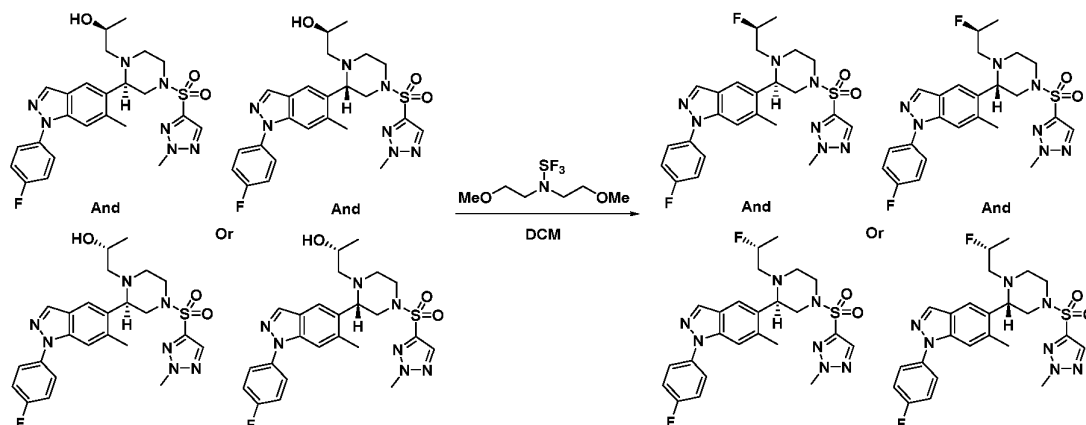
Example 158: 1-(4-fluorophenyl)-5-(1-(2-fluoropropyl)-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-2-yl)-6-methyl-1H-indazole

Intermediate AC: 1-(2-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-1-yl)propan-2-ol



[0269] To a solution of 1-(2-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-1-yl)propan-2-one **Example 125** (50.0 mg, 97.7 μ mol) in MeOH (977 μ L) and DCM (977 μ L) was added LiBH₄ (4.26 mg, 48.9 μ L, 4.00 molar in THF, 195 μ mol). The reaction mixture was stirred at 20 °C for 1 hour and then the volatiles were removed *in vacuo*. The residue was dissolved in DCM (2 mL) and transferred into a phase separator. The organic layer was washed with sat NH₄Cl (1 x 2 mL), water (2 mL) and then brine (2 mL). The organic layers was concentrated *in vacuo* to afford 1-(2-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-1-yl)propan-2-ol **Intermediate AC** (46.0 mg, 89.6 μ mol, 92 %) as a flocculent white solid; Rt 1.52 min (Method 7); m/z 514.4 (M+H)⁺ (ES⁺).

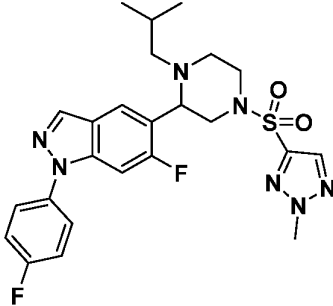
Example 158: 1-(4-fluorophenyl)-5-(1-(2-fluoropropyl)-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-2-yl)-6-methyl-1H-indazole



[0270] To a stirred solution of 1-(2-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-1-yl)propan-2-ol **Intermediate AC** (46.0 mg, 89.6 μ mol) in dry DCM (1.00 mL) under a nitrogen atmosphere at -10 $^{\circ}$ C was added deoxofluor (86.7 mg, 100 μ L, 50% Wt, 196 μ mol). The reaction mixture was stirred for 30 minutes and then raised to 20 $^{\circ}$ C and held for 18 hours. The reaction mixture was quenched with 2M NaOH (2 mL) and transferred into a phase separator. The organic layer was extracted and washed with brine. The organic layer was then adsorbed onto silica gel. The crude product was purified by chromatography on silica gel (4 g cartridge, 0-100% EtOAc/isohexane) to afford 1-(4-fluorophenyl)-5-(1-(2-fluoropropyl)-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-2-yl)-6-methyl-1H-indazole **Example 158** (15.8 mg, 29 μ mol, 33 %) as a white solid; Rt 2.09 and 2.10 min (Method 7); m/z 516.3 (M+H)⁺ (ES⁺).

Example 159: 6-fluoro-1-(4-fluorophenyl)-5-(1-isobutyl-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-2-yl)-1H-indazole

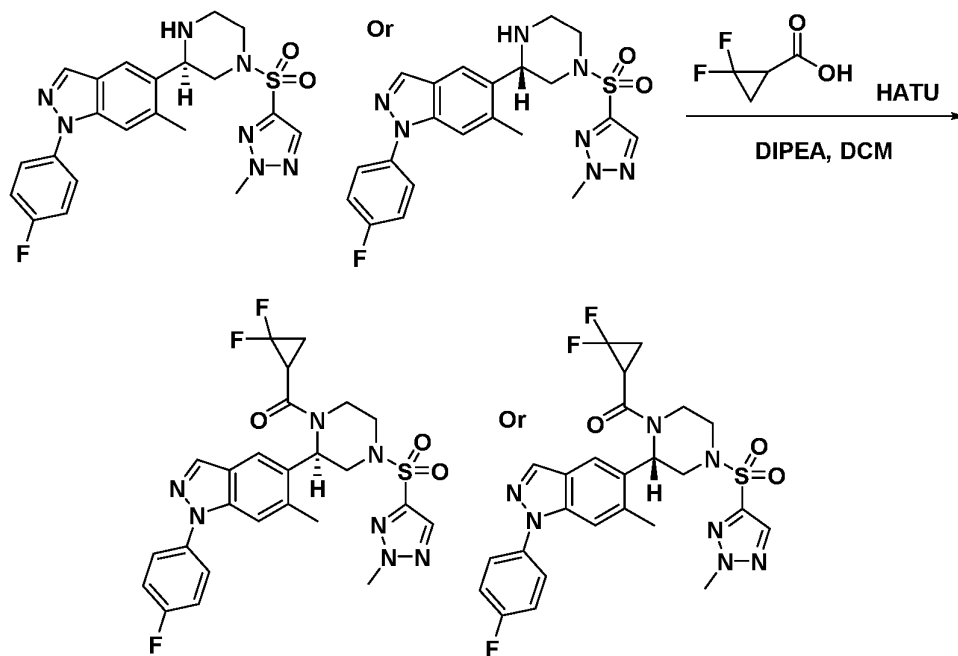
Table 17: The example shown in the table below was prepared by similar methods to those described in Example 1

Example	Structure	LC-MS analysis
159	 6-fluoro-1-(4-fluorophenyl)-5-(1-isobutyl-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-2-yl)-1H-indazole	R_t 2.03 min (Method 7); m/z 575.4 (M+H)⁺ (ES⁺)

5

Example 160: 5-(1-((2,2-difluorocyclopropyl)methyl)-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-2-yl)-1-(4-fluorophenyl)-6-methyl-1H-indazole

Intermediate AD: (2,2-difluorocyclopropyl)(2-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-1-yl)methanone

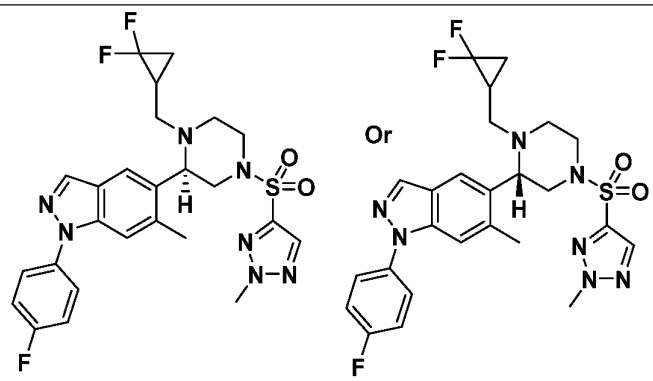


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[0271] To a solution of 1-(4-fluorophenyl)-6-methyl-5-(4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-2-yl)-1H-indazole (100 mg, 220 μ mol) in DCM (3.00 mL) were added 2,2-difluorocyclopropane-1-carboxylic acid (40.2 mg, 329 μ mol), DIPEA (85.1 mg, 115 μ L, 659 μ mol) and HATU (125 mg, 329 μ mol). The reaction mixture was stirred for 3 hours at rt before being quenched with sat. aq. NaHCO₃ (5 mL). The layers were separated, and the aqueous layer extracted with DCM (3 x 5 mL). Combined organic extracts were washed with brine (10 mL), dried over MgSO₄ and concentrated *in vacuo*. The crude product was purified by chromatography on silica gel (4 g cartridge, 0-100% EtOAc/isohexane) to afford (2,2-difluorocyclopropyl)(2-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-1-yl)methanone **Intermediate AD** (95 mg, 0.15 mmol, 70 %) as a mixture of diastereomers as an off-white solid; Rt 1.96 and 1.99 min (Method 9); m/z 560.2 (M+H)⁺ (ES⁺).

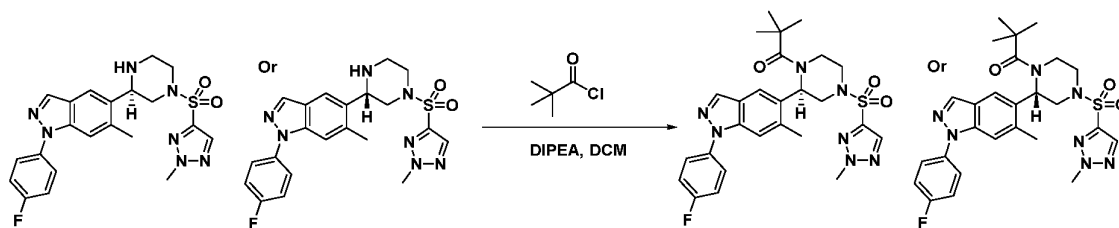
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Table 18: The example shown in the table below was prepared by similar methods to those described in Example 154 using Intermediate AD

Example	Structure	LC-MS analysis
160	 5-(1-((2,2-difluorocyclopropyl)methyl)-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-2-yl)-1-(4-fluorophenyl)-6-methyl-1H-indazole	R^t 2.13 and 2.16 min (Method 9); m/z 546.2 (M+H)⁺ (ES⁺)

Example 161: 1-(4-fluorophenyl)-6-methyl-5-(4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)-1-neopentylpiperazin-2-yl)-1H-indazole

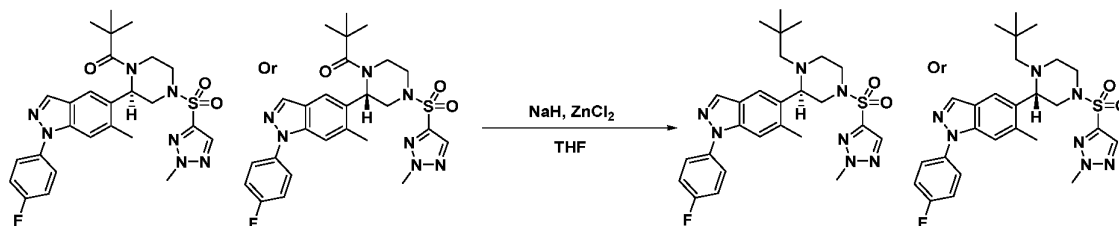
Intermediate AE: 1-(2-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-1-yl)-2,2-dimethylpropan-1-one



[0272] To a solution of 1-(4-fluorophenyl)-6-methyl-5-(4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-2-yl)-1H-indazole (100 mg, 220 μ mol) in DCM (2.50 mL) were added N-ethyl-N-isopropylpropan-2-amine (85.1 mg, 114 μ L, 659 μ mol) and pivaloyl chloride (31.8 mg, 32.4 μ L, 263 μ mol). The reaction mixture was stirred at rt for 16 hours. The reaction mixture was quenched with NaHCO₃ (3 mL) and the mixture transferred to a phase separator, where the aqueous was further extracted with DCM (2 x 3 mL). Combined organics were concentrated *in vacuo*. The crude product was purified by chromatography on silica gel (4 g cartridge, 0-100% EtOAc/isohexane) to afford 1-(2-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-1-yl)-2,2-

dimethylpropan-1-one **Intermediate AE** (89.0 mg, 0.16 mmol, 71 %, 95% Purity) as a flocculent white solid; Rt 2.06 min (Method 9); m/z 540.2 (M+H)⁺ (ES⁺). δ H (DMSO-d₆, 400 MHz) δ 8.33 (s, 1H), 8.31 (d, J = 0.9 Hz, 1H), 7.93 (s, 1H), 7.81 – 7.75 (m, 2H), 7.60 (s, 1H), 7.47 – 7.39 (m, 2H), 5.57 (t, J = 5.6 Hz, 1H), 4.25 (m, 4H), 3.83 (dd, J = 13.4, 6.1 Hz, 1H), 3.74 – 3.53 (m, 2H), 3.31 – 3.26 (m, 1H), 3.12 – 2.95 (m, 1H), 2.37 (s, 3H), 1.15 (s, 9H).

Example 161: 1-(4-fluorophenyl)-6-methyl-5-(4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)-1-neopentylpiperazin-2-yl)-1H-indazole

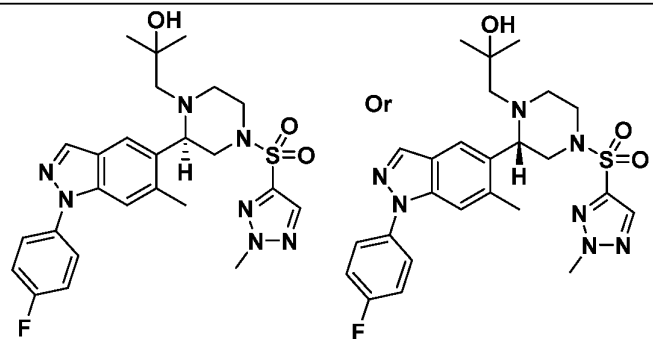


[0273] To a suspension of sodium hydride (60% in paraffin oil) (8.0 mg, 60% Wt, 200 μ mol) in THF (0.20 mL) was added zinc(II) chloride (0.5 M in THF) (13.6 mg, 200 μ L, 0.50 molar, 100 μ mol). The suspension was stirred at rt for 15 mins before the addition of 1-(2-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-1-yl)-2,2-dimethylpropan-1-one **Intermediate AE** (20.0 mg, 37.1 μ mol) (as a solution in THF (0.50 mL)). The reaction mixture was stirred at rt for 2 hours, at 40 °C for 2 hours and then at 50 °C for 18 hours. The reaction mixture was quenched with MeOH (0.5 mL) and water (3 mL). DCM (5 mL) was added, and the mixture transferred to a phase separator. The aqueous was further extracted with DCM (2 x 2 mL). Combined organic extracts were concentrated *in vacuo*. The crude product was purified by chromatography on silica gel (4 g cartridge, 0-100% EtOAc/isohehexane) to afford 1-(4-fluorophenyl)-6-methyl-5-(4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)-1-neopentylpiperazin-2-yl)-1H-indazole

Example 161 (1.60 mg, 2.9 μ mol, 7.8 %) as a white solid; Rt 2.12 min (Method 9); m/z 526.2 (M+H)⁺ (ES⁺). δ H (MeOD, 400 MHz) δ 8.17 (d, J = 0.9 Hz, 1H), 8.05 (s, 1H), 7.93 (s, 1H), 7.81 – 7.71 (m, 2H), 7.58 (s, 1H), 7.36 (t, J = 8.7 Hz, 2H), 4.33 (s, 3H), 3.76 (dd, J = 10.6, 3.3 Hz, 2H), 3.67 – 3.56 (m, 1H), 3.45 (d, J = 12.2 Hz, 1H), 2.94 (td, J = 11.9, 2.7 Hz, 1H), 2.77 (dd, J = 11.9, 10.5 Hz, 1H), 2.56 (s, 3H), 2.50 (td, J = 12.1, 3.0 Hz, 1H), 2.25 (d, J = 13.4 Hz, 1H), 1.90 (d, J = 13.4 Hz, 1H), 0.75 (s, 9H).

Example 162: 1-(2-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-1-yl)-2-methylpropan-2-ol

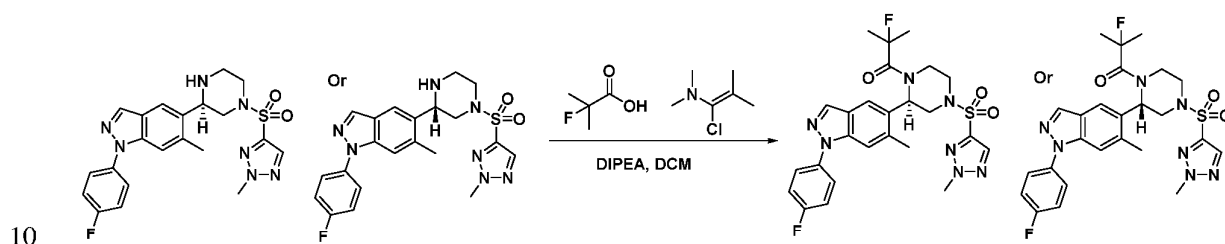
Table 19: The example shown in the table below was prepared by similar methods to those described in Example 161

Example	Structure	LC-MS analysis
162	 1-(2-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-1-yl)-2-methylpropan-2-ol	R_t 1.49 min (Method 9); m/z 528.2 (M+H)⁺ (ES⁺)

5

Example 162a: 5-(1-(2-fluoro-2-methylpropyl)-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-2-yl)-1-(4-fluorophenyl)-6-methyl-1H-indazole

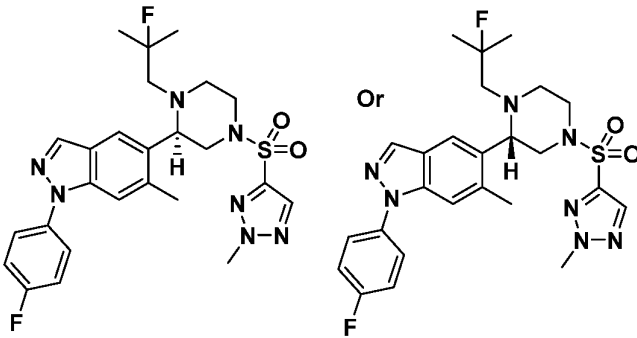
Intermediate AF: 2-fluoro-1-(2-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-1-yl)-2-methylpropan-1-one



[0274] To a solution of 2-fluoro-2-methylpropanoic acid (34.9 mg, 329 μ mol) in DCM (1.00 mL) were added 1-chloro-N,N,2-trimethylprop-1-en-1-amine (88.0 mg, 87.1 μ L, 659 μ mol) and DMF (2 drops). The reaction mixture was stirred at rt for 2 hours and then at 50 $^{\circ}$ C for 4 hours before being cooled to rt. In a separate vial, 1-(4-fluorophenyl)-6-methyl-5-(4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-2-yl)-1H-indazole (30.0 mg, 65.9 μ mol) was dissolved in DCM (1.00 mL) and treated with N-ethyl-N-isopropylpropan-2-amine (128

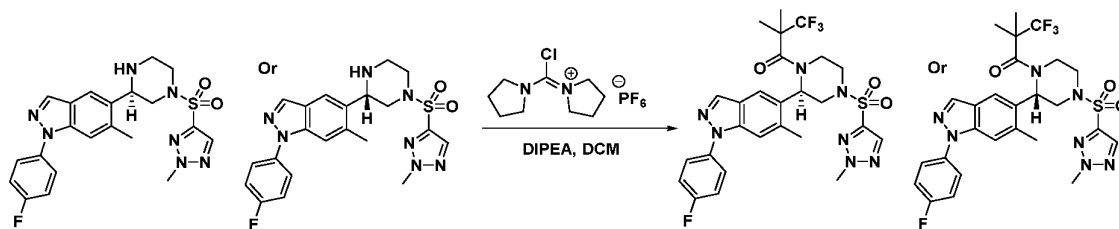
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- mg, 172 μ L, 988 μ mol). The solution of acid chloride generated was then added dropwise and the reaction mixture stirred at rt for 16 hours. The reaction mixture was then quenched with water (8 mL) and diluted with DCM (5 mL). The layers were separated, and the aqueous layer extracted with DCM (2 x 5 mL). Combined organic extracts were dried over MgSO_4 and concentrated *in vacuo*. The crude product was purified by chromatography on silica gel (4 g cartridge, 0-100% EtOAc/isohexane) to afford 2-fluoro-1-(2-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-1-yl)-2-methylpropan-1-one **Intermediate AF** (33.0 mg, 49 μ mol, 74 %) as an off-white solid; Rt 2.04 min (Method 9); m/z 544.2 (M+H)⁺ (ES⁺).
- 10 **Table 20: The example shown in the table below was prepared by similar methods to those described in Example 154 using Intermediate AF**

Example	Structure	LC-MS analysis
162a	 5-(1-(2-fluoro-2-methylpropyl)-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-2-yl)-1-(4-fluorophenyl)-6-methyl-1H-indazole	R _t 2.27 min (Method 9); m/z 530.2 (M+H) ⁺ (ES ⁺)

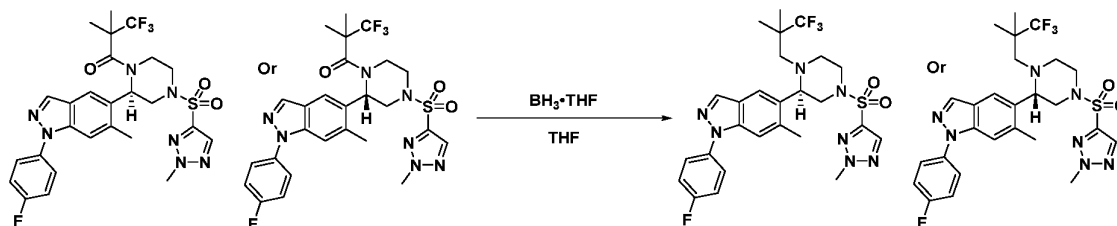
Example 163: 1-(4-fluorophenyl)-6-methyl-5-(4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)-1-(3,3,3-trifluoro-2,2-dimethylpropyl)piperazin-2-yl)-1H-indazole

- 15 **Intermediate AG: 3,3,3-trifluoro-1-(2-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-1-yl)-2,2-dimethylpropan-1-one**



[0275] To a solution of 3,3,3-trifluoro-2,2-dimethylpropanoic acid (34.3 mg, 220 μ mol) in DCM (1.00 mL) were added 1-(chloro(pyrrolidin-1-yl)methylene)pyrrolidin-1-ium hexafluorophosphate(V) (87.6 mg, 263 μ mol) and N-ethyl-N-isopropylpropan-2-amine (85.1 mg, 114 μ L, 3 Eq, 659 μ mol). The reaction mixture was stirred for 5 min at rt. 1-(4-fluorophenyl)-6-methyl-5-(4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-2-yl)-1H-indazole (100 mg, 220 μ mol) was then added and the reaction mixture heated in the microwave (150W) at 100 $^{\circ}$ C for 10 hours. The reaction mixture was diluted with DCM (2 mL) and transferred into a phase separator. The organic layer was washed with 2M NaOH (1 x 2 mL). The combined organic layers were collected and adsorbed onto silica gel. The crude product was purified by chromatography on silica gel (4 g cartridge, 25-100% EtOAc/isohexane) to afford 3,3,3-trifluoro-1-(2-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-1-yl)-2,2-dimethylpropan-1-one **Intermediate AG** (100 mg, 0.16 mmol, 71 %) as a clear colourless solid; Rt 2.13 min (Method 7); m/z 594.5 (M+H)⁺ (ES⁺).

Example 163: 1-(4-fluorophenyl)-6-methyl-5-(4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)-1-(3,3,3-trifluoro-2,2-dimethylpropyl)piperazin-2-yl)-1H-indazole

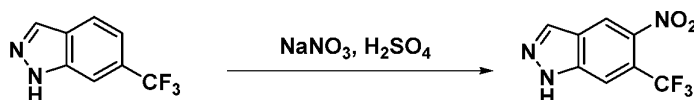


[0276] A suspension of 3,3,3-trifluoro-1-(2-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-1-yl)-2,2-dimethylpropan-1-one **Intermediate AG** (40.0 mg, 67.4 μ mol) was dosed with borane tetrahydrofuran complex (57.9 mg, 674 μ L, 1.00 molar, 674 μ mol) and the reaction mixture heated to 65 $^{\circ}$ C for 18 hours. An additional charge of borane tetrahydrofuran complex (57.9 mg, 674 μ L, 1.00 molar, 674 μ mol) was made and the reaction mixture heated for a further 5 hours. The reaction mixture was quenched with 2M NaOH and transferred into a phase separator. The cloudy solution was washed with DCM (5 mL). The organic layer was extracted and concentrated *in vacuo*. The concentrate was dissolved in 1.4 mL with DMSO, filtered and purified by reversed phase preparative HPLC (Waters 2767 Sample Manager, Waters 2545 Binary Gradient Module, Waters Systems Fluidics Organiser, Waters 515 ACD pump,

Waters 515 Makeup pump, Waters 2998 Photodiode Array Detector, Waters QDa) on a Waters X-Select CSH C18 ODB prep column, 130Å, 5 µm, 30 mm X 100 mm, flow rate 40 mL min⁻¹ eluting with a 0.1% formic acid in water-MeCN gradient over 12.5 mins using UV across all wavelengths with PDA as well as a QDA and ELS detector. At-column dilution pump gives 2 mL min⁻¹ methanol over the entire method, which is included in the following MeCN percentages. Gradient information: 0.0-0.5 min, 57.5% MeCN; 0.5-10.5 min, ramped from 57.5% MeCN to 87.5% MeCN; 10.5-10.6 min, ramped from 87.5% MeCN to 100% MeCN; 10.6-12.5 min, held at 100% MeCN. The clean fractions were evaporated in a Genevac prior to azeotroping with MeCN to afford 1-(4-fluorophenyl)-6-methyl-5-(4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)-1-(3,3,3-trifluoro-2,2-dimethylpropyl)piperazin-2-yl)-1H-indazole **Example 163** (3.80 mg, 6.2 µmol, 9.2 %) as a white solid; Rt 2.49 min (Method 7); m/z 580.2 (M+H)⁺ (ES⁺).

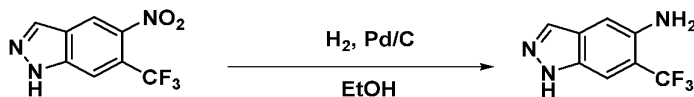
Example 164: 1-(4-fluorophenyl)-5-(1-isobutyl-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-2-yl)-6-(trifluoromethyl)-1H-indazole

Intermediate AH: 5-nitro-6-(trifluoromethyl)-1H-indazole



[0277] 6-(Trifluoromethyl)-1H-indazole (4400 mg, 23.64 mmol) was suspended in sulfuric acid (27.82 g, 15.12 mL, 50% Wt, 141.8 mmol) and the mixture was stirred for 5 mins before the addition of sodium nitrate (2.813 g, 33.09 mmol). Stirring continued for 60 mins before pouring the reaction mixture over ice and neutralising with 0.88 ammonia. The solid precipitate was collected by filtration, washed with water and dried in vac oven to give 5-nitro-6-(trifluoromethyl)-1H-indazole **Intermediate AH** (4.20 g, 18.2 mmol, 76.9 %, 100% Purity) as a cream coloured solid; Rt 1.54 min (Method 7); m/z 232.4 (M+H)⁺ (ES⁺).

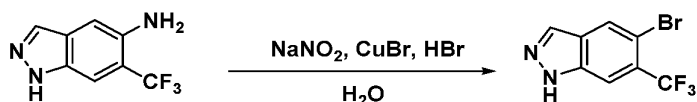
Intermediate AI: 6-(trifluoromethyl)-1H-indazol-5-amine



[0278] 5-Nitro-6-(trifluoromethyl)-1H-indazole **Intermediate AH** (4.50 g, 19.5 mmol) was dissolved in EtOH (50.0 mL) and treated with palladium on carbon (207 mg, 1.95 mmol). The mixture was purged with nitrogen (x3) then hydrogen (x3) before being hydrogenated at

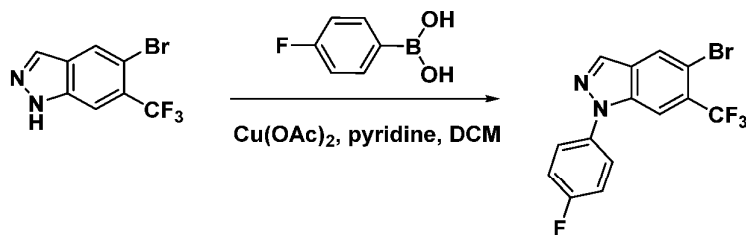
5 atm overnight at 40 °C. The catalyst was removed by filtration, washing with MeOH (2 x 20 mL). The solvent was removed *in vacuo* to give a pale yellow solid. The crude product was purified by chromatography on silica gel (120 g cartridge, 0-100% EtOAc/isohexane) to afford 6-(trifluoromethyl)-1H-indazol-5-amine **Intermediate AI** (3.60 g, 17.2 mmol, 88 %) as an off white solid; Rt 1.03 min (Method 7); m/z 201.8 (M+H)⁺ (ES⁺).

Intermediate AJ: 5-bromo-6-(trifluoromethyl)-1H-indazole



[0279] 6-(Trifluoromethyl)-1H-indazol-5-amine **Intermediate AI** (4770 mg, 23.71 mmol) was dissolved in HBr (25.3 g, 17.0 mL, 48% Wt, 150 mmol) and water (54.0 mL). The resulting solution was cooled to 0 °C and treated dropwise with a solution of sodium nitrite (1.800 g, 6.09 mmol) in water (68.0 mL). The reaction was stirred at 0°C for 15mins. This solution was then added dropwise into a stirring solution of copper(I) bromide (10.21 g, 3 Eq, 71.14 mmol) in HBr (50.7 g, 34.0 mL, 48% Wt, 12.7 Eq, 301 mmol) and water (70.0 mL) at room temperature and the reaction stirred overnight. The reaction was cooled to 0 °C and basified using concentrated ammonium hydroxide. The aqueous was extracted with DCM (3 x 100 mL), the bulked organic extracts were dried using sodium sulfate and concentrated *in vacuo* to give 5-bromo-6-(trifluoromethyl)-1H-indazole **Intermediate AJ** (5.05 g, 17 mmol, 72 %) as a mustard solid; Rt 1.74 min (Method 7); m/z 264.8/266.7 (M+H)⁺ (ES⁺).

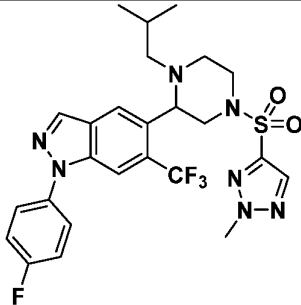
Intermediate AK: 5-bromo-1-(4-fluorophenyl)-6-(trifluoromethyl)-1H-indazole



20 [0280] Pyridine (2.98 g, 3.04 mL, 37.7 mmol) was added to a solution of 5-bromo-6-(trifluoromethyl)-1H-indazole **Intermediate AJ** (5.00 g, 18.9 mmol), (4-fluorophenyl)boronic acid (5.28 g, 37.7 mmol) and copper (II) acetate (3.43 g, 18.9 mmol) in DCM (50.0 mL). The reaction mixture was stirred at 20 °C for 48 hours. The reaction mixture was absorbed onto silica and the crude product was purified by chromatography on

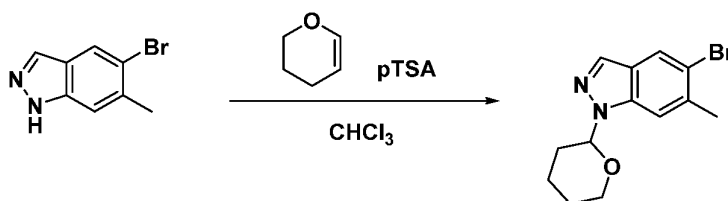
silica gel (220 g cartridge, 5-30% EtOAc/isohehexane) to afford 5-bromo-1-(4-fluorophenyl)-6-(trifluoromethyl)-1H-indazole (5.01 g, 12 mmol, 64 %) as a cream solid; Rt 2.32 min (Method 7); m/z 359.2/361.0 (M+H)⁺ (ES⁺). δ H (DMSO-d₆, 400 MHz) δ 8.51 (d, *J* = 0.9 Hz, 1H), 8.48 (s, 1H), 8.11 (s, 1H), 7.89 – 7.80 (m, 2H), 7.54 – 7.43 (m, 2H).

- 5 **Table 21: The example shown in the table below was prepared by similar methods to those described in Example 1 using Intermediate AK**

Example	Structure	LC-MS analysis
164	 1-(4-fluorophenyl)-5-(1-isobutyl-4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-2-yl)-6-(trifluoromethyl)-1H-indazole	R_t 2.48 min (Method 7); m/z 566.4 (M+H)⁺ (ES⁺)

Example 165: 1-methyl-5-(6-methyl-5-(4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)-1-(3,3,3-trifluoropropyl)piperazin-2-yl)-1H-indazol-1-yl)pyridin-2(1H)-one

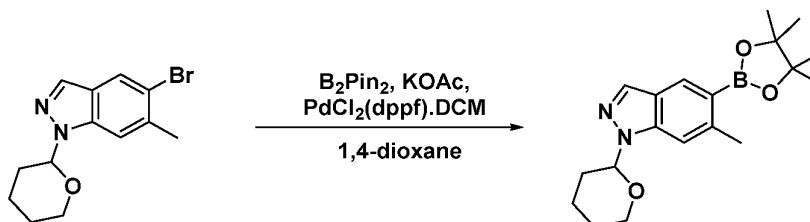
- 10 **Intermediate AL: 5-bromo-6-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole**



- 15 **[0281]** To a solution of 5-bromo-6-methyl-1H-indazole (25.00 g, 118.4 mmol) and dihydropyran (19.93 g, 21.5 mL, 236.9 mmol) in chloroform (400 mL) was added p-toluenesulfonic acid monohydrate (2.50 g, 13.1 mmol). The brown suspension was stirred at room temperature for 16 hours and then heated at reflux for 2 hours. The reaction mixture was washed with sodium bicarbonate (2 x 200mL) and then brine, (200mL), the organic layer was dried using magnesium sulfate and the solvent was removed under reduced pressure to

give 5-bromo-6-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole **Intermediate AL** (40.7 g, 0.10 mol, 87 %) as a brown oil; Rt 2.05 min (Method 7); m/z 295.2/297.2 (M+H)⁺ (ES⁺).

Intermediate AM: 6-methyl-1-(tetrahydro-2H-pyran-2-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole



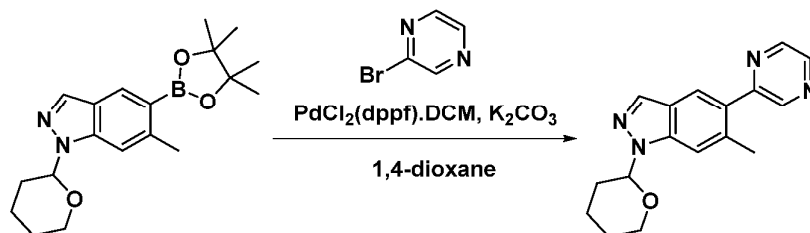
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[0282] To a mixture of 5-bromo-6-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole **Intermediate AL** (40.7 g, 138 mmol), potassium acetate (50.0 g, 509 mmol) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (53.6 g, 211 mmol) in dry 1,4-dioxane (689 mL) was added PdCl₂(dppf)-CH₂Cl₂ adduct (11.3 g, 13.8 mmol). The reaction mixture was stirred for 18 hours at 90 °C. The reaction mixture was filtered and the filtrate was concentrated in vacuo. The residue was taken up in EtOAc (400 mL). The solution was washed with 1:1 brine : distilled water (500 mL) and the organic layer extracted. The organic layer was washed with NaHCO₃ (1 x 500 mL). The combined organic layers were collected, dried over magnesium sulfate, filtered and concentrated in vacuo to afford 6-methyl-1-(tetrahydro-2H-pyran-2-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole **Intermediate AM** (52.0 g, 0.12 mol, 87 %) as a brown oil; Rt 2.28 min (Method 7); m/z 343.5 (M+H)⁺ (ES⁺).

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Intermediate AN: 6-methyl-5-(pyrazin-2-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole

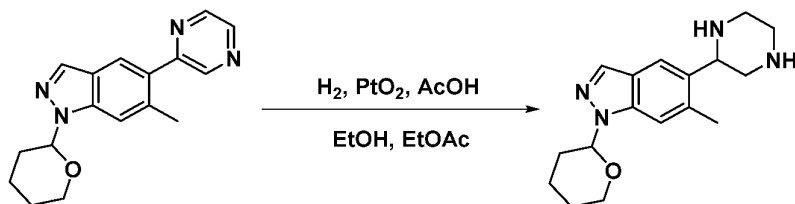


[0283] To a stirred solution of 6-methyl-1-(tetrahydro-2H-pyran-2-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole **Intermediate AM** (52.0 g, 50% Wt, 76.0 mmol) in dry 1,4-dioxane (304 mL) and water (76.0 mL) was added potassium carbonate (21.0 g, 152 mmol) and 2-bromopyrazine (19.5 g, 123 mmol). The reaction mixture was

20

sparged for 5 mins with N₂ prior to the addition of Pd(dppf)Cl₂.DCM (6.20 g, 0.1 Eq, 7.60 mmol). The reaction mixture was then heated to 90 °C and stirred for 16 hours. The reaction mixture was concentrated *in vacuo* and partitioned between DCM (400 mL) and water (400 mL). The DCM layer was drawn off and washed twice more with brine (2 x 400 mL). The organic layer was then concentrated *in vacuo* to afford 52g of crude brown oil. The crude product was purified by chromatography in 2 passes on silica gel (220 g cartridge, 20-100 EtOAc/isohexane) to afford 6-methyl-5-(pyrazin-2-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole **Intermediate AN** (8.61 g, 27 mmol, 36 %) as a light yellow solid. The batches were combined for analysis. Rt 1.57 min (Method 7); m/z 295.3 (M+H)⁺ (ES⁺). ¹H (DMSO-d₆, 400 MHz) δ 8.85 (d, J = 1.5 Hz, 1H), 8.74 (dd, J = 2.6, 1.5 Hz, 1H), 8.64 (d, J = 2.6 Hz, 1H), 8.13 (d, J = 0.9 Hz, 1H), 7.86 (s, 1H), 7.70 (d, J = 1.0 Hz, 1H), 5.87 (dd, J = 9.7, 2.6 Hz, 1H), 4.01 – 3.86 (m, 1H), 3.76 (ddd, J = 13.7, 7.1, 5.0 Hz, 1H), 2.46 (s, 3H), 2.44 – 2.35 (m, 1H), 2.14 – 1.93 (m, 2H), 1.84 – 1.67 (m, 1H), 1.66 – 1.55 (m, 2H).

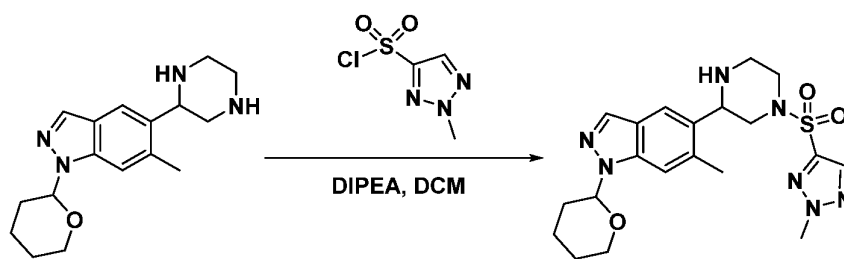
Intermediate AO: 6-methyl-5-(piperazin-2-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole



[0284] To a suspension of 6-methyl-5-(pyrazin-2-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (4.11 g, 98% Wt, 13.7 mmol) **Intermediate AN** in EtOH (230 mL) and acetic acid (24.7 g, 23.5 mL, 410 mmol) and EtOAc (50.0 mL) was added platinum(IV) oxide (500 mg, 2.20 mmol). The reaction mixture was stirred under an atmosphere of H₂ (5 bar) at 60 °C for 3 hours. The reaction mixture was then filtered and concentrated in vacuo. The residue was dissolved in EtOAc (250 mL) and washed with 2M NaOH (100 mL). The organic layer was then washed in brine. The combined aqueous layers were back-extracted with more EtOAc (250mL). Concentration of the organic layers afforded minimal product, which had preferentially partitioned into the aqueous layer. The crude product was loaded onto a column of SCX (50g) in water. The column was washed with distilled water (200mL), MeOH (250mL) and then the product was eluted with 0.7 M ammonia in MeOH. The resultant mixture was concentrated and azeotroped with MeCN in vacuo to afford 6-methyl-5-(piperazin-2-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (2.90 g, 8.7 mmol, 63 %, 90%

Purity) **Intermediate AO** as a sticky yellow oil; Rt 0.26 min (Method 7); m/z 301.4 (M+H)⁺ (ES⁺). δ H (MeOD, 400 MHz) δ 7.99 (s, 1H), 7.85 (s, 1H), 7.51 (s, 1H), 5.77 (dt, J = 9.9, 2.1 Hz, 1H), 4.14 – 4.04 (m, 1H), 4.07 – 3.95 (m, 1H), 3.90 – 3.75 (m, 1H), 3.16 – 3.07 (m, 1H), 3.06 – 2.93 (m, 4H), 2.92 – 2.81 (m, 1H), 2.65 (dd, J = 12.5, 10.4 Hz, 1H), 2.58 (s, 3H), 2.55 – 2.47 (m, 1H), 2.18 – 2.08 (m, 1H), 2.05 – 1.97 (m, 1H), 1.91 – 1.76 (m, 1H), 1.76 – 1.62 (m, 2H). 1 exchangeable NH not accounted for.

Intermediate AP: 6-methyl-5-(4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-2-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole



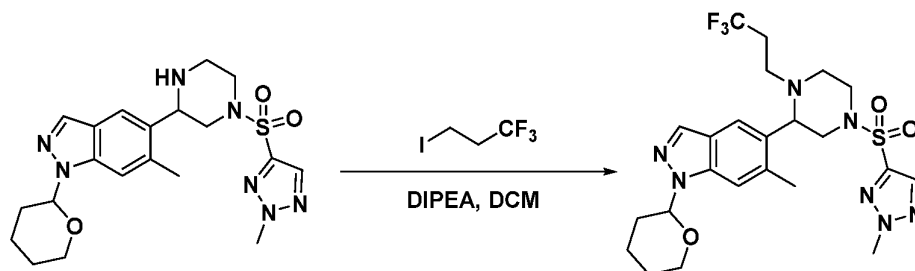
10 **[0285]** To a stirred solution of 6-methyl-5-(piperazin-2-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole **Intermediate AO** (2.90 g, 90% Wt, 8.69 mmol) and DIPEA (3.37 g, 4.54 mL, 26.1 mmol) in dry DCM (86.9 mL) under a nitrogen atmosphere at -3 °C (bath T) was added 2-methyl-2H-1,2,3-triazole-4-sulfonyl chloride (1.66 g, 9.12 mmol) dropwise over 10 minutes, as a DCM solution. The reaction mixture was stirred for 1 hour. The reaction

15 mixture was quenched with sat. NaHCO₃ (50 mL) and transferred into a separating funnel. The organic layer was extracted, and the aqueous layer washed with DCM (25 mL). The combined organic layers were collected, dried over magnesium sulfate, filtered and adsorbed onto silica *in vacuo*. The crude product was purified by chromatography on silica gel (80 g cartridge, 0-50% (0.7 M ammonia/MeOH)/DCM) and the clean fractions azeotroped in

20 MeCN twice to afford 6-methyl-5-(4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-2-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole **Intermediate AP** (3.55 g, 6.4 mmol, 73 %) as a sticky yellow solid; Rt 1.33 and 1.36 min (Method 7); m/z 446.1 (M+H)⁺ (ES⁺). δ H (MeOD, 400 MHz) δ 8.05 (d, J = 0.8 Hz, 1H), 7.97 (d, J = 0.9 Hz, 1H), 7.81 (s, 1H), 7.54 (s, 1H), 5.78 (dd, J = 10.0, 2.7 Hz, 1H), 4.29 (s, 3H), 4.15 (dd, J = 10.5, 2.9 Hz, 1H), 4.05 – 3.97 (m, 2H), 3.90 – 3.75 (m, 4H), 3.21 (ddd, J = 12.5, 3.3, 1.9 Hz, 1H), 3.12 – 3.00 (m, 1H), 2.90 – 2.70 (m, 1H), 2.50 (ddd, J = 12.0, 8.1, 5.1 Hz, 2H), 2.26 – 2.09 (m, 2H), 2.02 (dd, J = 12.0, 8.9 Hz, 2H), 1.85 – 1.62 (m, 3H).

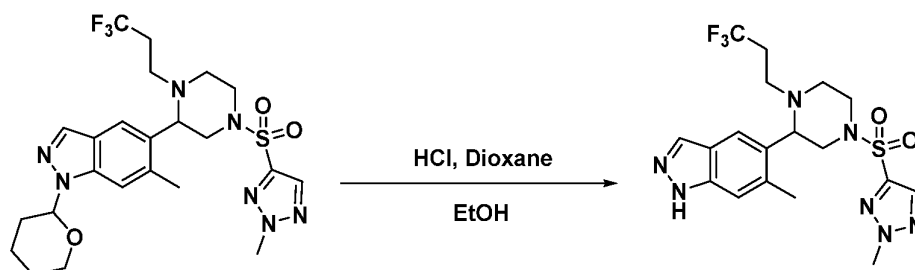
25

Intermediate AQ: 6-methyl-5-(4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)-1-(3,3,3-trifluoropropyl)piperazin-2-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole

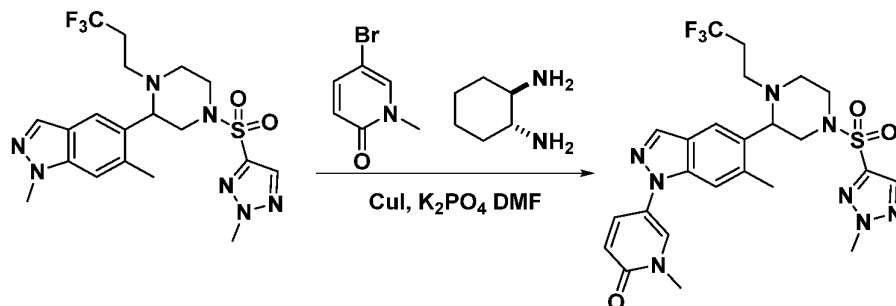


[0286] To a solution of 6-methyl-5-(4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)piperazin-2-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole **Intermediate AP** (3.55 g, 7.97 mmol) in MeCN (10.0 mL) were added N-ethyl-N-isopropylpropan-2-amine (6.18 g, 8.33 mL, 47.8 mmol) and 1,1,1-trifluoro-3-iodopropane (8.92 g, 4.67 mL, 39.8 mmol). The reaction mixture was then stirred at 150 °C for 1 hour in a CEM microwave (Pressure 300 psi, Power 150 W). Partial conversion was observed and so reaction was continued for an additional 5 hours at 150 °C. The reaction mixture was diluted with EtOAc (25 mL) and transferred into a separating funnel. The organic layer was washed with distilled water (1 x 50 mL) and then brine (1 x 50 mL) and then extracted. The combined aqueous layers were then back-extracted with EtOAc (1 x 50 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by chromatography on silica gel (80 g cartridge, 20-100% EtOAc/isohexane) to afford 6-methyl-5-(4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)-1-(3,3,3-trifluoropropyl)piperazin-2-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole **Intermediate AQ** (1.66 g, 2.1 mmol, 27 %) as a yellow semi-solid; Rt 2.09 min (Method 7); m/z 458.3 (M+H)⁺ (ES⁺).

Intermediate AR: 6-methyl-5-(4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)-1-(3,3,3-trifluoropropyl)piperazin-2-yl)-1H-indazole



- [0287] To a solution of 6-methyl-5-(4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)-1-(3,3,3-trifluoropropyl)piperazin-2-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole **Intermediate AQ** (1.70 g, 70% Wt, 2.20 mmol) in EtOH (5.00 mL) was added HCl (in dioxane) (10.5 g, 10.0 mL, 4 molar, 40.0 mmol). The reaction mixture was stirred at 20 °C for 16 hours prior to
- 5 being loaded onto an SCX column. The crude product was loaded onto a column of SCX (25 g) in MeOH. The column was washed with MeOH and then the product was eluted with 0.7 M ammonia in MeOH. The resultant mixture was concentrated *in vacuo* to afford 1.6 g material that was concentrated, dissolved in 10 vol% MeOH/DCM and loaded onto silica gel. The crude product was purified by chromatography on silica gel (24 g cartridge, 0-20% (0.7
- 10 M Ammonia/MeOH)/DCM) to afford 6-methyl-5-(4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)-1-(3,3,3-trifluoropropyl)piperazin-2-yl)-1H-indazole **Intermediate AR** (630 mg, 1.2 mmol, 56 %) as a sticky yellow solid; Rt 1.42 min (Method 8); m/z 458.3 (M+H)⁺ (ES⁺). δ H (DMSO-d₆, 400 MHz) δ 8.29 (s, 1H), 7.96 (s, 1H), 7.74 (s, 1H), 7.37 (s, 1H), 4.27 (s, 3H), 3.80 – 3.62 (m, 2H), 3.58 – 3.17 (m, 2H), 2.81 – 2.59 (m, 1H), 2.46 (m, 10H).
- 15 **Example 165: 1-methyl-5-(6-methyl-5-(4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)-1-(3,3,3-trifluoropropyl)piperazin-2-yl)-1H-indazol-1-yl)pyridin-2(1H)-one**

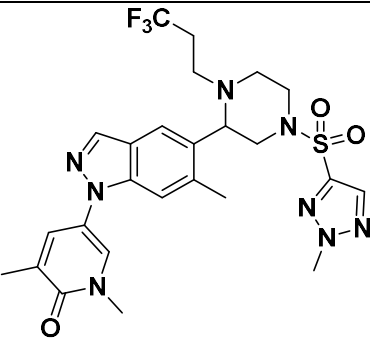


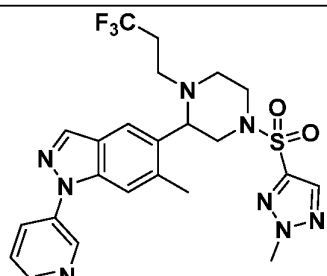
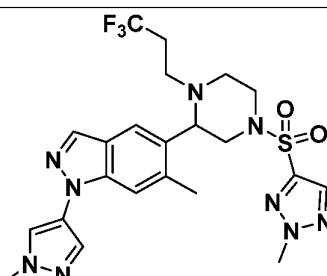
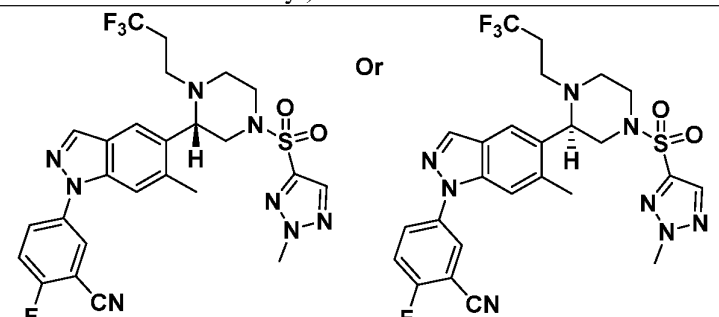
- [0288] A suspension of 6-methyl-5-(4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)-1-(3,3,3-trifluoropropyl)piperazin-2-yl)-1H-indazole **Intermediate AR** (75.0 mg, 90% Wt, 148
- 20 μ mol), 5-bromo-1-methylpyridin-2(1H)-one (41.6 mg, 221 μ mol), copper(I) iodide (14.1 mg, 73.8 μ mol) and potassium phosphate (62.6 mg, 295 μ mol) was degassed under vacuum 3 times prior to being suspended in DMF (1.50 mL) and (1R,2R)-cyclohexane-1,2-diamine (16.8 mg, 17.7 μ L, 148 μ mol) being added. The suspension was sparged with N₂ for 2 mins and the reaction mixture was then heated to 120 °C for 24 hours. The filtrate mixture was
- 25 diluted with EtOAc (10 mL) and transferred into a separating funnel. The layer was washed with 5 wt% LiCl (3 x 25 mL). The organic layer was collected, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The concentrate was dissolved in DMSO (2.1 mL),

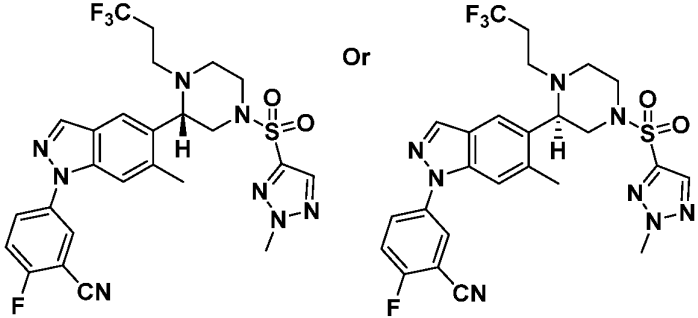
filtered and purified by reversed phase preparative HPLC (Waters 2767 Sample Manager, Waters 2545 Binary Gradient Module, Waters Systems Fluidics Organiser, Waters 515 ACD pump, Waters 515 Makeup pump, Waters 2998 Photodiode Array Detector, Waters QDa) on a Waters XBridge BEH C18 ODB prep column, 130Å, 5 µm, 30 mm X 100 mm, flow rate 40 mL min⁻¹ eluting with a 0.3% ammonia in water-MeCN gradient over 12.5 mins using UV across all wavelengths with PDA as well as a QDA and ELS detector. At-column dilution pump gives 2 mL min⁻¹ methanol over the entire method, which is included in the following MeCN percentages. Gradient information: 0.0-0.5 min, 32.5% MeCN; 0.5-10.5 min, ramped from 32.5% MeCN to 62.5% MeCN; 10.5-10.6 min, ramped from 62.5% MeCN to 100% MeCN; 10.6-12.5 min, held at 100% MeCN. Clean fractions were concentrated in vacuo to give 1-methyl-5-(6-methyl-5-(4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)-1-(3,3,3-trifluoropropyl)piperazin-2-yl)-1H-indazol-1-yl)pyridin-2(1H)-one **Example 165** (23.0 mg, 39 µmol, 26 %) as a yellow solid; Rt 1.71 min (Method 7); m/z 565.5 (M+H)⁺ (ES⁺). ¹H (DMSO-d₆, 400 MHz) δ 8.28 (s, 1H), 8.25 – 8.17 (m, 2H), 7.81 (s, 1H), 7.74 (dd, J = 9.6, 3.0 Hz, 1H), 7.53 (s, 1H), 6.56 (d, J = 9.6 Hz, 1H), 4.26 (s, 3H), 3.79 – 3.65 (m, 2H), 3.47 (d, J = 11.8 Hz, 1H), 3.28 – 3.11 (m, 1H), 2.78 – 2.60 (m, 2H), 2.49 – 2.47 (m, 5H), 2.46 – 2.31 (m, 5H), 2.28 – 2.14 (m, 1H).

Examples 166 – 170

Table 22: The examples shown in the table below were prepared by similar methods to those described in Example 165 using Intermediate AR

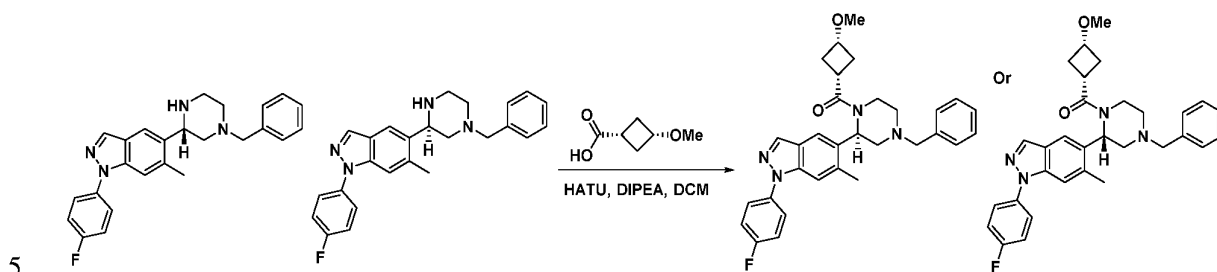
Example	Structure	LC-MS analysis
166	 1,3-dimethyl-5-(6-methyl-5-(4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)-1-(3,3,3-trifluoropropyl)piperazin-2-yl)-1H-indazol-1-yl)pyridin-2(1H)-one	R^t 1.95 min (Method 7); m/z 579.1 (M+H)⁺ (ES⁺)

Example	Structure	LC-MS analysis
167	 6-methyl-5-(4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)-1-(3,3,3-trifluoropropyl)piperazin-2-yl)-1-(pyridin-3-yl)-1H-indazole	R^t 1.88 min (Method 7); m/z 535.3 (M+H)⁺ (ES⁺)
168	 6-methyl-1-(1-methyl-1H-pyrazol-4-yl)-5-(4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)-1-(3,3,3-trifluoropropyl)piperazin-2-yl)-1H-indazole	R^t 1.83 min (Method 7); m/z 538.3 (M+H)⁺ (ES⁺)
169	 2-fluoro-5-(6-methyl-5-(4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)-1-(3,3,3-trifluoropropyl)piperazin-2-yl)-1H-indazol-1-yl)benzonitrile	R^t 2.19 min (Method 7); m/z 577.2 (M+H)⁺ (ES⁺)

Example	Structure	LC-MS analysis
170	 2-fluoro-5-(6-methyl-5-(4-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)-1-(3,3,3-trifluoropropyl)piperazin-2-yl)-1H-indazol-1-yl)benzonitrile	R_t 2.18 min (Method 7); m/z 577.4 (M+H)⁺ (ES⁺)

Examples 171 - 172

Intermediate AS: (4-benzyl-2-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)piperazin-1-yl)-3-methoxycyclobutyl)methanone



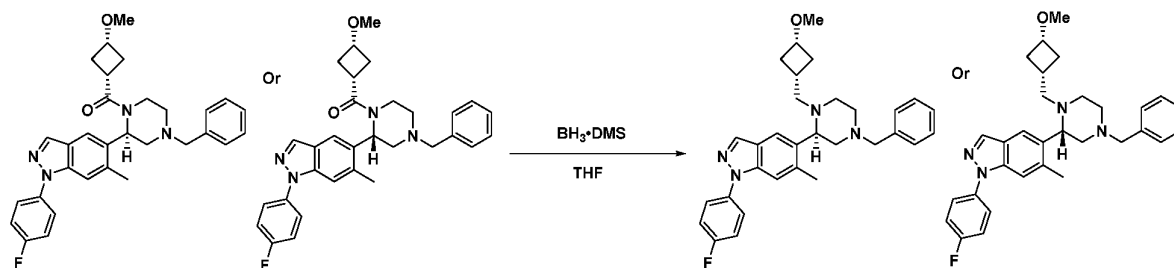
[0289] To a solution of (1s,3s)-3-methoxycyclobutane-1-carboxylic acid (390 mg, 3.00 mmol) in DCM (12.0 mL) were added DIPEA (968 mg, 1.30 mL, 7.49 mmol) and HATU (1.14 g, 1.2 Eq, 3.00 mmol). The reaction mixture was stirred at rt for 20 mins before the addition of 5-(4-benzylpiperazin-2-yl)-1-(4-fluorophenyl)-6-methyl-1H-indazole (1.00 g, 2.50 mmol) (as a solution in DCM (12.0 mL)). The reaction mixture was stirred for a further 16 hours at rt, before being quenched with water (20 mL) and sat. aq. NaHCO₃ (20 mL). The layers were separated, and the aqueous layer extracted with DCM (3 x 20 mL). Combined organic extracts were dried over MgSO₄ and concentrated *in vacuo*. The crude product was purified by chromatography on silica gel (40 g cartridge, 0-100% EtOAc/isohehexane) to afford (4-benzyl-2-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)piperazin-1-yl)-3-methoxycyclobutyl)methanone **Intermediate AS** (1.18 g, 2.1 mmol, 83 %) as a white solid; Rt 1.72 min (Method 9); m/z 513.2 (M+H)⁺ (ES⁺). δ H (DMSO-d₆, 400 MHz) δ 8.57 (s, 1H),

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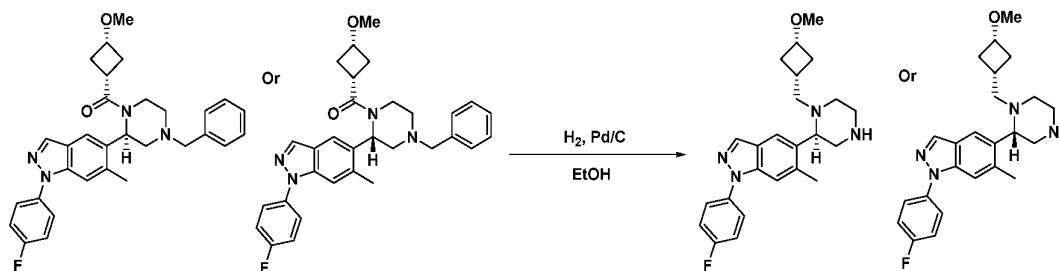
8.35 (d, $J = 0.9$ Hz, 1H), 7.86 – 7.69 (m, 2H), 7.56 (s, 1H), 7.41 (m, 7H), 5.75 (s, 1H), 3.87 – 3.65 (m, 1H), 3.63 – 3.41 (m, 3H), 3.14 (d, $J = 29.9$ Hz, 5H), 2.91 (d, $J = 11.5$ Hz, 2H), 2.44 – 2.29 (m, 6H), 2.04 – 1.88 (s, 3H).

Intermediate AT: 5-(4-benzyl-1-((3-methoxycyclobutyl)methyl)piperazin-2-yl)-1-(4-fluorophenyl)-6-methyl-1H-indazole



[0290] To a solution of 4-benzyl-2-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)piperazin-1-yl)-3-methoxycyclobutyl)methanone **Intermediate AS** (1.18 g, 2.30 mmol) in THF (24.0 mL) was added borane-methyl sulfide complex (2 M in THF) (699 mg, 4.60 mL, 2.00 molar, 9.21 mmol) and the reaction mixture stirred at 40 °C for 16 hours. After cooling to rt, the reaction mixture was quenched with MeOH (3 mL) and then sat. aq. NH_4Cl (15 mL). EtOAc (30 mL) was added, and the layers separated. The aqueous layer was extracted with EtOAc (3 x 20 mL). Combined organic extracts were washed with water (15 mL) and then brine (5 mL) and then dried over MgSO_4 before being concentrated *in vacuo*. The crude product was purified by chromatography on silica gel (24 g cartridge, 0-100% EtOAc/isohexane), but LCMS of the major fraction showed multiple peaks of the same m/z . This material was dissolved in THF (20 mL) and 1M aq HCl (20 mL) added. The solution was stirred vigorously for 1 hour before being diluted with water (30 mL) and EtOAc (30 mL). The layers were separated, and the aqueous layer extracted with EtOAc (3 x 10 mL). Combined organic extracts were dried over MgSO_4 and concentrated *in vacuo* to afford 5-(4-benzyl-1-((3-methoxycyclobutyl)methyl)piperazin-2-yl)-1-(4-fluorophenyl)-6-methyl-1H-indazole **Intermediate AT** (502 mg, 0.86 mmol, 37 %) as an off-white solid; Rt 1.63 min (Method 9); m/z 499.2 (M+H)⁺ (ES⁺). δH (DMSO- d_6 , 400 MHz) δ 8.30 (s, 1H), 7.91 (s, 1H), 7.86 – 7.72 (m, 2H), 7.57 (s, 1H), 7.48 – 7.34 (m, 2H), 7.34 – 7.18 (m, 5H), 3.47 (m, 3H), 3.11 – 3.02 (m, 1H), 2.99 (s, 3H), 2.83 (d, $J = 10.3$ Hz, 1H), 2.66 (d, $J = 11.4$ Hz, 1H), 2.46 – 2.14 (m, 8H), 2.05 – 1.80 (m, 3H), 1.36 (s, 1H), 1.30 – 1.11 (m, 2H).

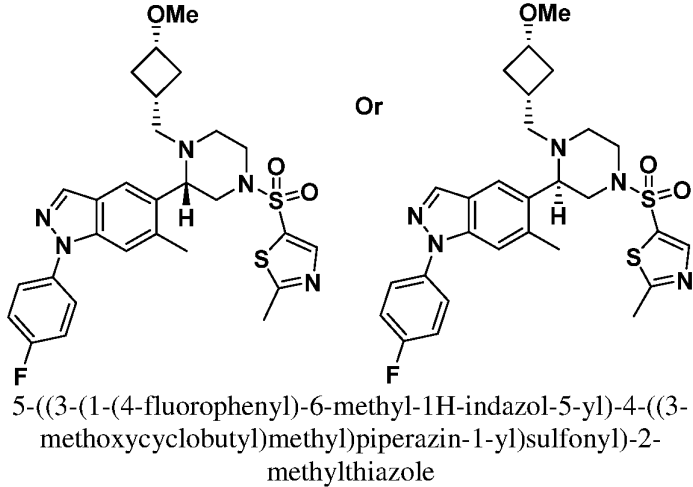
Intermediate AU: 1-(4-fluorophenyl)-5-(1-((3-methoxycyclobutyl)methyl)piperazin-2-yl)-6-methyl-1H-indazole



[0291] To a solution of 5-(4-benzyl-1-((3-methoxycyclobutyl)methyl)piperazin-2-yl)-1-(4-fluorophenyl)-6-methyl-1H-indazole **Intermediate AT** (375 mg, 752 μ mol) in EtOH (15.0 mL) was added palladium (120 mg, 10% Wt, 113 μ mol) and the reaction mixture stirred at 70 °C for 16 hours. The reaction mixture was filtered through glass microfibre filter pad and concentrated *in vacuo*. The residue was azeotroped in toluene 3 times to remove residual EtOH to afford 280 mgs of crude material as yellow oil. 100 mgs of this material was purified chromatography on silica gel (4 g cartridge, 0-100% 0.7M ammonia in MeOH/DCM) to afford 1-(4-fluorophenyl)-5-(1-((3-methoxycyclobutyl)methyl)piperazin-2-yl)-6-methyl-1H-indazole **Intermediate AU** (40 mg, 91 μ mol, 12%) as a colourless oil; Rt 1.25 min (Method 7); m/z 409.4 (M+H)⁺ (ES⁺).

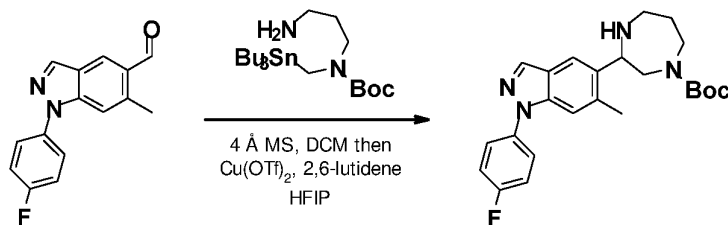
Table 23: The examples shown in the table below were prepared by similar methods to those described in Example 36 using Intermediate AU

Example	Structure	LC-MS analysis
171	4-((3-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)-4-((3-methoxycyclobutyl)methyl)piperazin-1-yl)sulfonyl)-2-methylthiazole	R_t 1.79 min (Method 7); m/z 570.1 (M+H)⁺ (ES⁺)

Example	Structure	LC-MS analysis
172	 5-((3-(1-(4-fluorophenyl)-6-methyl-1H-indazol-5-yl)-4-((3-methoxycyclobutyl)methyl)piperazin-1-yl)sulfonyl)-2-methylthiazole	R^t 1.76 min (Method 7); m/z 570.4 (M+H)⁺ (ES⁺)

Example 173: 1-(4-fluorophenyl)-6-methyl-5-(4-(2-methylthiazol-4-yl)sulfonyl)-1-(3,3,3-trifluoropropyl)-1,4-diazepan-2-ylindazole

Intermediate BA: tert-butyl 3-(1-(4-fluorophenyl)-6-methyl-indazol-5-yl)-1,4-diazepane-1-carboxylate

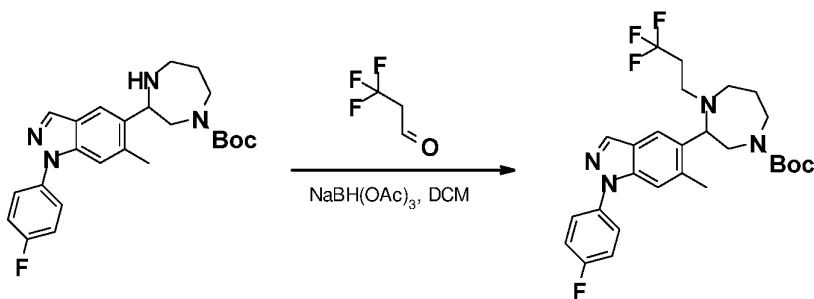


- [0292] To a solution of 1-(4-fluorophenyl)-6-methyl-indazole-5-carbaldehyde (245 mg, 0.960 mmol) in DCM (5.0 mL) at rt was added *tert*-butyl *N*-(3-aminopropyl)-*N*-(tributylstannylmethyl)carbamate (460 mg, 0.960 mmol), followed by 4 Å molecular sieves (4 pellets). The resulting mixture was maintained at rt for 4 hours, then diluted with further DCM (16.0 mL). Simultaneously, Cu(OTf)₂ (349 mg, 0.960 mmol) and 2,6-lutidine (112 µL, 0.960 mmol) were stirred in hexafluoro isopropanol (HFIP) (4.0 mL) for 4 hours. To the resulting homogeneous suspension was added the pre-formed solution of imine at rt and the mixture was maintained at rt for 60 hours. The crude mixture was diluted with DCM (20.0 mL) and 10% aq NH₃:brine (1:1, 20.0 mL) and vigorously stirred for 15 minutes. The biphasic mixture that formed was separated, the aqueous phase extracted with further DCM (2 x 20.0 mL) and the combined organic extracts dried (phase separator) and evaporated *in*

vacuo. The residue thus obtained was purified by flash column chromatography (25 g cartridge, 0-2.5% 2 M NH₃ in MeOH in DCM) to afford *tert*-butyl 3-(1-(4-fluorophenyl)-6-methyl-indazol-5-yl)-1,4-diazepane-1-carboxylate (180 mg, 0.420 mmol, 44%) as a yellow gum; R_t 1.48 min (Method 12); m/z 369.2 (M+H-tBu)⁺ (ES⁺); ¹H NMR (400 MHz,

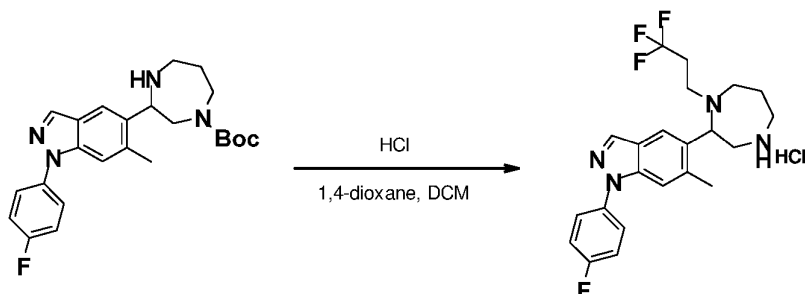
- 5 Chloroform-*d*) δ 8.08 (d, *J* = 6.3 Hz, 1H), 7.94 (d, *J* = 3.9 Hz, 1H), 7.71 – 7.61 (m, 2H), 7.45 (s, 1H), 7.26 – 7.18 (m, 2H), 4.16 – 3.82 (m, 3H), 3.36 – 3.18 (m, 2H), 2.92 – 2.70 (m, 2H), 2.59 (d, *J* = 17.2 Hz, 3H), 2.18 – 1.95 (m, 1H), 1.95 – 1.82 (m, 1H), 1.50 (d, *J* = 1.9 Hz, 9H). NH not observed.

10 **Intermediate BB: *tert*-butyl 3-(1-(4-fluorophenyl)-6-methyl-indazol-5-yl)-4-(3,3,3-trifluoropropyl)-1,4-diazepane-1-carboxylate**



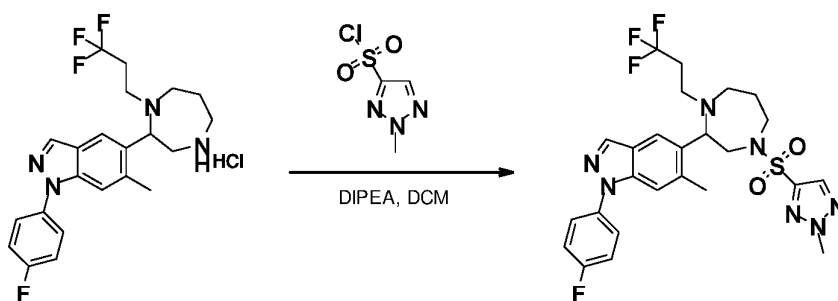
- [0293] To a solution of *tert*-butyl 3-(1-(4-fluorophenyl)-6-methyl-indazol-5-yl)-1,4-diazepane-1-carboxylate (180 mg, 0.420 mmol) in DCM (5.0 mL) at rt was 3,3,3-trifluoropropanal (73 μ L, 0.850 mmol), followed by NaBH(OAc)₃ (270 mg, 1.27 mmol). The
- 15 resulting mixture was maintained at rt for 18 hours, then diluted with sat aq NaHCO₃ and EtOAc. The biphasic mixture was separated, and the organic extracts washed with further EtOAc. The combined organic layers were washed with further sat aq NaHCO₃, dried (Na₂SO₄) and evaporated *in vacuo*. The residue thus obtained was purified by flash column chromatography (10 g cartridge, 0-20% EtOAc in heptane) to afford *tert*-butyl 3-(1-(4-
- 20 fluorophenyl)-6-methyl-indazol-5-yl)-4-(3,3,3-trifluoropropyl)-1,4-diazepane-1-carboxylate (174 mg, 0.330 mmol, 79%) as a colourless gum; R_t 2.10 min (Method 12); m/z 465.2 (M+H-tBu)⁺ (ES⁺); ¹H NMR (400 MHz, Chloroform-*d*) δ 8.10 (apparent d, 1H), 7.89 (apparent d, 1H), 7.72 – 7.63 (m, 2H), 7.45 (s, 1H), 7.23 (apparent m, 2H, obscured by solvent), 4.04 – 3.69 (over-lapping m, 3H), 3.25 – 2.94 (over-lapping m, 2.5H), 3.01 (dd, *J* = 14.8, 10.0 Hz,
- 25 0.5H), 2.84 – 2.65 (m, 2H), 2.65 – 2.48 (over-lapping m + 2 x s, 4H), 2.23 – 1.85 (over-lapping m, 4H), 1.49 (s, 4.5 H), 1.43 (s, 4.5 H). Restricted rotation observed.

Intermediate BC: 1-(4-fluorophenyl)-6-methyl-5-(1-(3,3,3-trifluoropropyl)-1,4-diazepan-2-yl)indazole hydrochloride



- [0294] To a solution of *tert*-butyl 3-(1-(4-fluorophenyl)-6-methyl-indazol-5-yl)-4-(3,3,3-trifluoropropyl)-1,4-diazepan-1-carboxylate (174 mg, 0.330 mmol) in DCM (1.0 mL) at rt was added HCl (3.7-4.2 N in 1,4-dioxane, 2.0 mL, 0.330 mmol). The resulting mixture was maintained at rt for 4 hours and then evaporated *in vacuo*. The residue obtained was azeotroped with DCM (x4) and dried *in vacuo* to give 1-(4-fluorophenyl)-6-methyl-5-(1-(3,3,3-trifluoropropyl)-1,4-diazepan-2-yl)indazole hydrochloride (172 mg) as a white solid;
 10 R_t 1.47 min (Method 12); m/z 421.2 (M+H)⁺ (ES⁺). This material was used in the subsequent step without further purification.

Example 173: 1-(4-fluorophenyl)-6-methyl-5-(4-(2-methyltriazol-4-yl)sulfonyl-1-(3,3,3-trifluoropropyl)-1,4-diazepan-2-yl)indazole

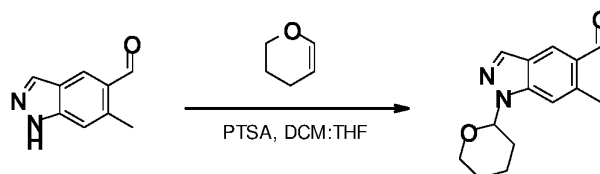


- [0295] To a solution of 1-(4-fluorophenyl)-6-methyl-5-(1-(3,3,3-trifluoropropyl)-1,4-diazepan-2-yl)indazole hydrochloride (54.0 mg, 0.120 mmol) and DIPEA (82 μ L, 0.470 mmol) in DCM (2.0 mL) at rt was added 2-methyltriazole-4-sulfonyl chloride (25.8 mg, 0.140 mmol) dropwise. The resulting mixture was maintained at rt for 18 hours and then dry loaded onto silica and purified by flash column chromatography (10 g cartridge, 0-50%
 20 EtOAc in heptane) to afford 1-(4-fluorophenyl)-6-methyl-5-(4-(2-methyltriazol-4-

yl)sulfonyl-1-(3,3,3-trifluoro propyl)-1,4-diazepan-2-yl)indazole (38.7 mg, 0.0700 mmol, 56%) as a white solid; R^t 2.92 min (Method 11); m/z 566.2 (M+H)⁺ (ES⁺); δ H NMR (400 MHz, DMSO-*d*₆) δ 8.29 (d, J = 0.9 Hz, 1H), 8.25 (s, 1H), 7.92 (s, 1H), 7.83 – 7.77 (m, 2H), 7.65 (q, J = 0.9 Hz, 1H), 7.46 – 7.39 (m, 2H), 4.20 (s, 3H), 4.00 (dd, J = 9.8, 2.8 Hz, 1H), 3.57 – 3.52 (m, 1H), 3.48 (dd, J = 15.5, 2.5 Hz, 1H), 3.24 – 3.18 (m, 2H), 3.07 (dt, J = 11.2, 5.2 Hz, 1H), 2.74 (dd, J = 13.9, 8.7 Hz, 1H), 2.66 – 2.57 (m, 1H), 2.54 (d, J = 1.0 Hz, 3H), 2.53 – 2.50 (m, assume 1H, obscured by solvent), 2.40 – 2.24 (m, 2H), 2.14 – 2.01 (m, 1H), 1.98 – 1.87 (m, 1H).

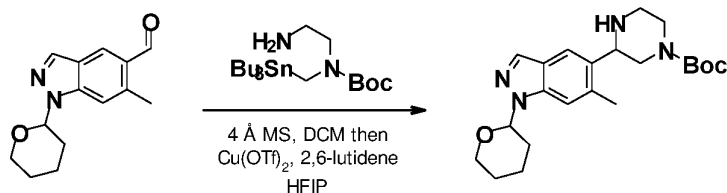
Example 174: 5-(5-(4-(1-ethylpyrazol-4-yl)sulfonyl-1-(3,3,3-trifluoropropyl)piperazin-2-yl)-6-methyl-indazol-1-yl)-1,3-dimethyl-pyridin-2-one

Intermediate CA: 6-methyl-1-tetrahydropyran-2-yl-indazole-5-carbaldehyde



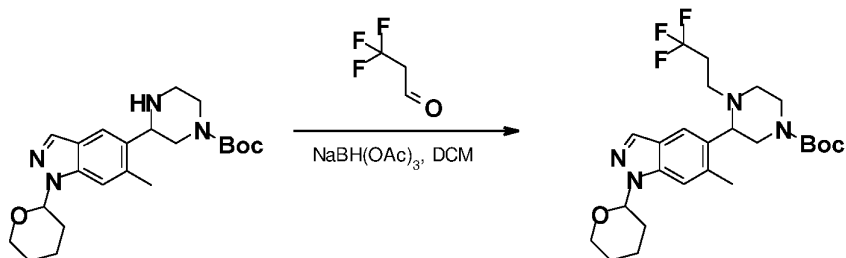
[0296] To a suspension of 6-methyl-1H-indazole-5-carbaldehyde (940 mg, 5.87 mmol) in THF:DCM (1:1, 20 mL) at rt was added 3,4-dihydro-2H-pyran (1.61 mL, 17.6 mmol) and PTSA monohydrate (223 mg, 1.17 mmol). The resulting mixture was maintained at rt for 20 hours and then evaporated *in vacuo*. The residue thus obtained was purified by flash column chromatography (50 g cartridge, 0-25% EtOAc in heptane) to afford 6-methyl-1-tetrahydropyran-2-yl-indazole-5-carbaldehyde (992 mg, 4.06 mmol, 69%) as an off-white gum; δ H NMR (400 MHz, Chloroform-*d*) δ 10.22 (s, 1H), 8.20 (s, 1H), 8.12 (d, J = 0.9 Hz, 1H), 7.41 (s, 1H), 5.72 (dd, J = 9.4, 2.8 Hz, 1H), 4.09 – 4.00 (m, 1H), 3.82 – 3.72 (m, 1H), 2.80 (d, J = 0.9 Hz, 3H), 2.62 – 2.44 (m, 1H), 2.23 – 2.03 (m, 2H), 1.85 – 1.63 (over-lapping m, 3H).

Intermediate CB: *tert*-butyl 3-(6-methyl-1-tetrahydropyran-2-yl-indazol-5-yl)piperazine-1-carboxylate



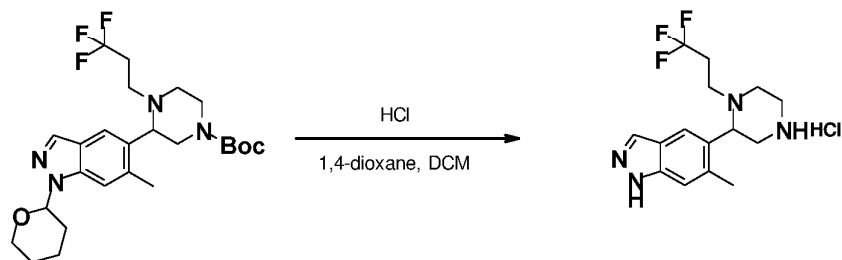
- [0297] To a solution of 6-methyl-1-tetrahydropyran-2-yl-indazole-5-carbaldehyde (0.990 g, 4.05 mmol) in DCM (18.0 mL) at rt was added *tert*-butyl N-(2-aminoethyl)-N-(tributylstannylmethyl)carbamate (1.88 g, 4.05 mmol), followed by 4 Å molecular sieves (20 pellets). The resulting mixture was maintained at rt for 4 hours, then diluted with further DCM (60.0 mL). Simultaneously, Cu(OTf)₂ (1.47 g, 4.05 mmol) and 2,6-lutidine (472 µL, 4.05 mmol) were stirred in HFIP (16.6 mL) for 4 hours. To the resulting homogeneous suspension was added the pre-formed solution of imine at rt and the mixture was maintained at rt for 72 hours. The crude mixture was diluted with DCM (20.0 mL) and 10% aq NH₃:brine (1:1, 60.0 mL) and vigorously stirred for 15 minutes. The biphasic mixture that formed was separated, the aqueous phase extracted with further DCM (2 x 20.0 mL) and the combined organic extracts dried (Na₂SO₄) and evaporated *in vacuo*. The residue thus obtained was purified by flash column chromatography (120 g cartridge, 0-4% 2 M NH₃ in MeOH in DCM) to afford *tert*-butyl 3-(6-methyl-1-tetrahydropyran-2-yl-indazol-5-yl)piperazine-1-carboxylate (0.88 g, 0.208 mmol, 51%) as a light yellow gum; R_t 1.36 min (Method 12); m/z 345.2(M+H-tBu)⁺ (ES⁺); ¹H NMR (400 MHz, Chloroform-*d*) δ 7.95 (br d, 1H), 7.93 (s, 1H), 7.38 (s, 1H), 5.68 (dt, *J* = 9.5, 2.5 Hz, 1H), 4.21 – 3.96 (over-lapping br s +dd, 3H), 3.96 – 3.89 (m, 1H), 3.80 – 3.69 (m, 1H), 3.18 – 3.05 (m, 1H), 3.04 – 2.86 (m, 2H), 2.71 – 2.48 (over-lapping m+s, 5H), 2.21 – 2.11 (m, 1H), 2.06 (d, *J* = 13.6 Hz, 1H), 1.83 – 1.59 (m, 4H), 1.48 (s, 9H).

Intermediate CC: *tert*-butyl 3-(6-methyl-1-tetrahydropyran-2-yl-indazol-5-yl)-4-(3,3,3-trifluoropropyl)piperazine-1-carboxylate



[0298] To a solution of *tert*-butyl 3-(6-methyl-1-tetrahydropyran-2-yl-indazol-5-yl)piperazine-1-carboxylate (875 mg, 2.18 mmol) in DCM (15.0 mL) at rt was added 3,3,3-trifluoropropanal (377 μ L, 4.37 mmol), followed by NaBH(OAc)₃ (1.39 g, 6.55 mmol). The resulting mixture was maintained at rt for 18 hours, then diluted with sat aq NaHCO₃ and DCM and stirred for 10 minutes. The biphasic mixture was separated, and the organic extracts washed with further DCM. The combined organic layers were dried (Na₂SO₄) and evaporated *in vacuo*. The residue thus obtained was purified by flash column chromatography (50 g cartridge, 0-25% EtOAc in heptane) to afford *tert*-butyl 3-(6-methyl-1-tetrahydropyran-2-yl-indazol-5-yl)-4-(3,3,3-trifluoropropyl)piperazine-1-carboxylate (803 mg, 1.62 mmol, 74%) as a colourless gum; R_t 2.03 min (Method 12); m/z 441.2 (M+H-tBu)⁺ (ES⁺); δ H NMR (400 MHz, Chloroform-*d*) δ 7.95 (s, 1H), 7.84 (s, 1H), 7.39 (s, 1H), 5.74 – 5.60 (m, 1H), 4.27 – 3.83 (over-lapping m, 3H), 3.83 – 3.71 (m, 1H), 3.52 – 3.34 (m, 1H), 3.19 – 2.89 (over-lapping m, 2H), 2.91 – 2.54 (over-lapping m, 3H), 2.52 (s, 3H), 2.33 – 2.04 (over-lapping m, 6H), 1.85 – 1.60 (over-lapping m, 3H), 1.46 (s, 9H).

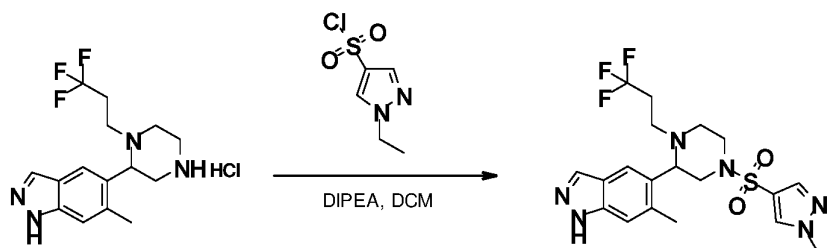
Intermediate CD: 6-methyl-5-[1-(3,3,3-trifluoropropyl)piperazin-2-yl]-1H-indazole hydrochloride



[0299] A solution of *tert*-butyl 3-(6-methyl-1-tetrahydropyran-2-yl-indazol-5-yl)-4-(3,3,3-trifluoropropyl)piperazine-1-carboxylate (802 mg, 1.62 mmol) and HCl (1.25 M in ethanol,

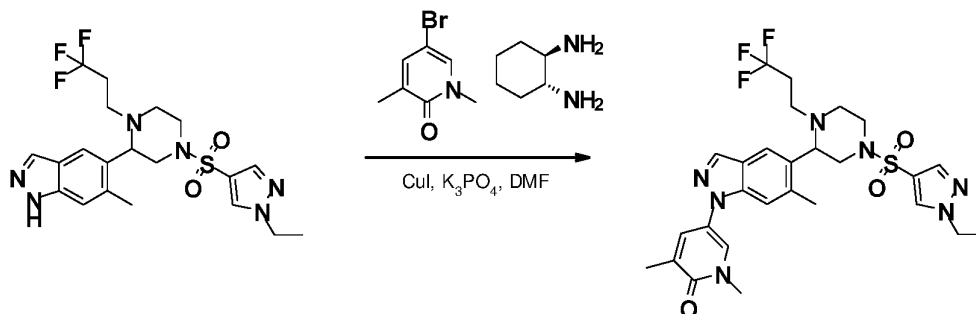
8.0 mL, 10.0 mmol) was stirred at rt for 1 hour. The mixture was heated to 50 °C, maintained at this temperature for 4 hours and then evaporated *in vacuo* to give 6-methyl-5-(1-(3,3,3-trifluoropropyl)piperazin-2-yl)-1H-indazole hydrochloride (647 mg) as a white solid; R^t 1.19 min (Method 12); m/z 313.2 (M+H)⁺ (ES⁺). This material was used in the subsequent step without further purification.

Intermediate CE: 5-(4-(1-ethylpyrazol-4-yl)sulfonyl-1-(3,3,3-trifluoropropyl)piperazin-2-yl)-6-methyl-1H-indazole



[0300] To a solution of 6-methyl-5-(1-(3,3,3-trifluoropropyl)piperazin-2-yl)-1H-indazole hydrochloride (69.0 mg, 0.180 mmol) and DIPEA (125 μ L, 0.716 mmol) in DCM (2.0 mL) at rt was added a solution of 1-ethylpyrazole-4-sulfonyl chloride (33.1 mg, 0.170 mmol) in DCM (0.5 mL) dropwise. The resulting mixture was maintained at rt for 30 minutes and then diluted with water. The resulting biphasic mixture was separated and the organic extracts dry loaded onto silica and purified by flash column chromatography (12 g cartridge, 0-3% MeOH in DCM) to afford 5-(4-(1-ethylpyrazol-4-yl)sulfonyl-1-(3,3,3-trifluoropropyl)piperazin-2-yl)-6-methyl-1H-indazole (75.0 mg, 0.159 mmol, 89%) as a white solid; R^t 1.69 min (Method 12); m/z 471.2 (M+H)⁺ (ES⁺); δ H NMR (400 MHz, Chloroform-*d*) δ 9.97 (br s, 1H), 7.99 (s, 1H), 7.75 (br s, J = 17.7 Hz, 1H), 7.71 (s, 1H), 7.68 (d, J = 0.7 Hz, 1H), 7.32 (br s, 1H), 4.20 (q, J = 7.3 Hz, 2H), 3.84 – 3.68 (over-lapping m, 2H), 3.64 – 3.56 (m, 1H), 3.26 – 3.10 (m, 1H), 2.91 – 2.72 (m, 1H), 2.68 – 2.46 (over-lapping m+s, 5H), 2.36 – 2.06 (over-lapping m, 4H), 1.51 (t, J = 7.3 Hz, 3H).

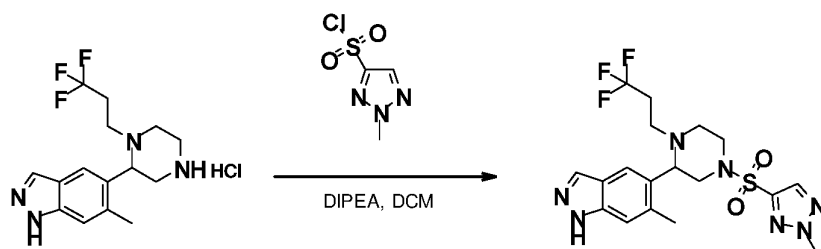
Example 174: 5-(5-(4-(1-ethylpyrazol-4-yl)sulfonyl-1-(3,3,3-trifluoropropyl)piperazin-2-yl)-6-methyl-indazol-1-yl)-1,3-dimethyl-pyridin-2-one



- [0301] A suspension of 5-(4-(1-ethylpyrazol-4-yl)sulfonyl-1-(3,3,3-trifluoropropyl)piperazin-2-yl)-6-methyl-1H-indazole (75.0 mg, 0.159 mmol), 5-bromo-1,3-dimethyl-pyridin-2-one (48.3 mg, 0.239 mmol), CuI (15.2 mg, 0.0797 mmol) and K₃PO₄ (67.7 mg, 0.319 mmol) in DMF (2.0 mL) was degassed for 10 minutes and then treated with a solution of (1*R*,2*R*)-cyclohexane-1,2-diamine (18.4 mg, 0.160 mmol) in DMF (0.5 mL). The resulting mixture was degassed for a further 5 minutes and then heated at 120 °C for 18 hours. Further (1*R*,2*R*)-cyclohexane-1,2-diamine (18.4 mg, 0.160 mmol), CuI (15.2 mg, 0.0797 mmol) and K₃PO₄ (67.7 mg, 0.319 mmol) were added, and the reaction mixture heated at 120 °C for 4 hours. After cooling to rt the mixture was diluted with EtOAc and filtered through a pad celite. The filtrate was partitioned with water and the phases separated. The aqueous layer was diluted with brine and extracted with further EtOAc (x3). The combined organic extracts were washed with brine (x2), dried (Na₂SO₄), and evaporated *in vacuo*. The residue thus obtained was purified by flash column chromatography (12 g cartridge, 0-3% MeOH/DCM). Further purification by preparative HPLC (Method AA) afforded 5-(5-(4-(1-ethylpyrazol-4-yl)sulfonyl-1-(3,3,3-trifluoropropyl)piperazin-2-yl)-6-methyl-indazol-1-yl)-1,3-dimethyl-pyridin-2-one (28.1 mg, 0.0467 mmol, 29%) as a white solid; R_t 2.45 min (Method 11); m/z 592.2 (M+H)⁺ (ES⁺); ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.36 (s, 1H), 8.19 (d, *J* = 1.0 Hz, 1H), 8.06 (dd, *J* = 3.0, 0.8 Hz, 1H), 7.81 – 7.76 (overlapping d+s, 2H), 7.68 – 7.58 (m, 1H), 7.52 (s, 1H), 4.18 (q, *J* = 7.3 Hz, 2H), 3.72 (dd, *J* = 10.3, 3.0 Hz, 1H), 3.66 – 3.59 (m, 1H), 3.54 (s, 3H), 3.43 – 3.35 (m, 1H), 3.29 – 3.20 (m, 1H), 2.71 – 2.59 (m, 1H), 2.48 (s, 3H), 2.46 – 2.36 (overlapping m, 4H), 2.24 – 2.06 (overlapping m+s, 5H), 1.37 (t, *J* = 7.3 Hz, 3H).

Example 175: 2,4-dimethyl-6-(6-methyl-5-(4-(2-methyltriazol-4-yl)sulfonyl-1-(3,3,3-trifluoropropyl)piperazin-2-yl)indazol-1-yl)pyridazin-3-one

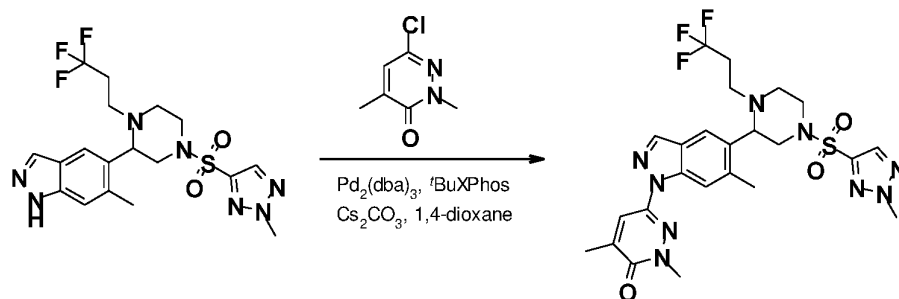
Intermediate DA: 6-methyl-5-(4-(2-methyltriazol-4-yl)sulfonyl-1-(3,3,3-trifluoropropyl)piperazin-2-yl)-1H-indazole



5

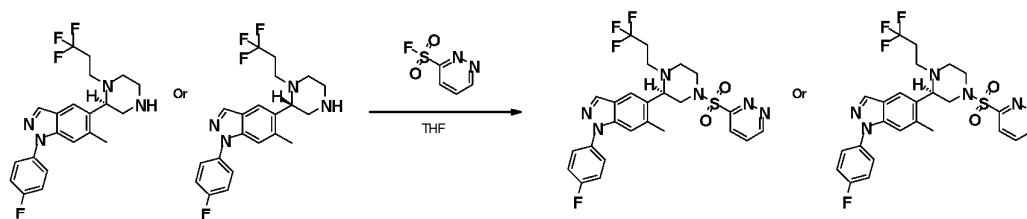
- [0302] To a solution of 6-methyl-5-(1-(3,3,3-trifluoropropyl)piperazin-2-yl)-1H-indazole hydrochloride (523 mg, 1.36 mmol) and DIPEA (946 μ L, 5.43 mmol) in DCM (13.6 mL) at rt was added a solution of 2-methyltriazole-4-sulfonyl chloride (234 mg, 1.29 mmol) in DCM (2.0 mL) dropwise. The resulting mixture was maintained at rt for 30 minutes and then
- 10 diluted with water. The resulting biphasic mixture was separated, and the organic extracts evaporated *in vacuo*. The residue thus obtained was purified by flash column chromatography (24 g cartridge, 0-2% MeOH in DCM) to afford 6-methyl-5-[4-(2-methyltriazol-4-yl)sulfonyl-1-(3,3,3-trifluoropropyl)piperazin-2-yl]-1H-indazole (543 mg, 1.19 mmol, 87%) as a white solid; R^t 1.71 min (Method 12); m/z 458.0 ($M+H$)⁺ (ES^+); δ H NMR (400 MHz, DMSO- d_6) δ 12.92 (s, 1H), 8.28 (s, 1H), 7.95 (s, 1H), 7.71 (s, 1H), 7.36 (s, 1H), 4.26 (s, 3H), 3.72 (dd, J = 11.5, 1.9 Hz, 1H), 3.66 (dd, J = 10.4, 3.1 Hz, 1H), 3.46 (dt, J = 11.8, 2.6 Hz, 1H), 3.25 (apparent d, 1H), 2.76 - 2.60 (m, 2H), 2.45 (s, 3H), 2.43 - 2.26 (over-lapping m, 4H), 2.17 (ddd, J = 13.2, 8.2, 5.3 Hz, 1H).
- 15

- Example 175: 2,4-dimethyl-6-(6-methyl-5-(4-(2-methyltriazol-4-yl)sulfonyl-1-(3,3,3-trifluoropropyl)piperazin-2-yl)indazol-1-yl)pyridazin-3-one**
- 20



- [0303] A suspension of 6-methyl-5-(4-(2-methyltriazol-4-yl)sulfonyl-1-(3,3,3-trifluoropropyl) piperazin-2-yl)-1H-indazole (50.0 mg, 0.109 mmol), 6-chloro-2,4-dimethylpyridazin-3-one (17.3 mg, 0.109 mmol), Pd₂(dba)₃ (3.14 mg, 0.00550 mmol), ^tBuXPhos (4.64 mg, 0.0109 mmol) and Cs₂CO₃ (53.4 mg, 0.164 mmol) in 1,4-dioxane (0.5 mL) was degassed for 5 minutes and then heated at 105 °C for 18 hours. After cooling to rt the mixture was partitioned between water (10 mL) and EtOAc (10 mL). The organic phase was separated, dried (phase separator) and evaporated *in vacuo*. The residue thus obtained was purified by flash column chromatography (4 g cartridge, 0-80% EtOAc in heptane). The white solid so obtained was taken up into DCM and subjected to SCX capture and release.
- After evaporation *in vacuo* the resulting white solid was taken up in DCM (2.0 mL) and washed with water (2.0 mL). The biphasic mixture was passed through a phase separator and the organic extracts evaporated *in vacuo* to afford 2,4-dimethyl-6-(6-methyl-5-(4-(2-methyltriazol-4-yl)sulfonyl-1-(3,3,3-trifluoropropyl)piperazin-2-yl)indazol-1-yl)pyridazin-3-one (26.0 mg, 0.0426 mmol, 39%) as a white solid; R_t 2.68 min (Method 11); m/z 580.2 (M+H)⁺ (ES⁺); δH NMR (400 MHz, DMSO-*d*₆) δ 8.35 (d, *J* = 0.9 Hz, 1H), 8.29 (s, 1H), 8.22 (s, 1H), 8.08 (q, *J* = 1.2 Hz, 1H), 7.86 (s, 1H), 4.27 (s, 3H), 3.79 (s, 3H), 3.77 - 3.70 (m, 2H), 3.51 (dt, *J* = 12.0, 2.5 Hz, 1H), 3.27 (apparent d, 1H), 2.73 (td, *J* = 11.5, 2.6 Hz, 1H), 2.67 - 2.58 (m, 1H), 2.55 (s, 3H), 2.47 - 2.31 (over-lapping m, 4H), 2.22 (d, *J* = 1.3 Hz, 3H), 2.27 - 2.17 (m, 1H).

Example 176: 1-(4-fluorophenyl)-6-methyl-5-(4-pyridazin-3-ylsulfonyl-1-(3,3,3-trifluoropropyl)piperazin-2-yl)indazole (Route D)

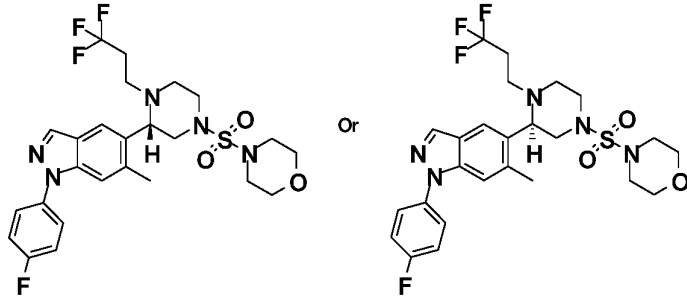
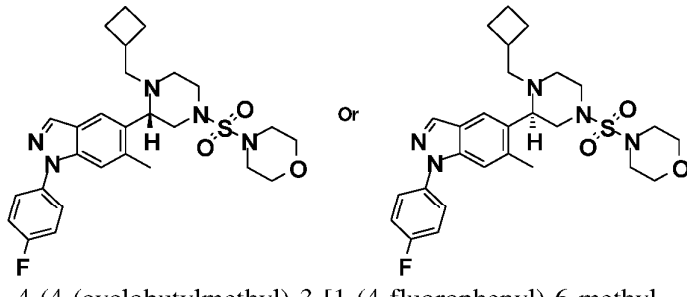


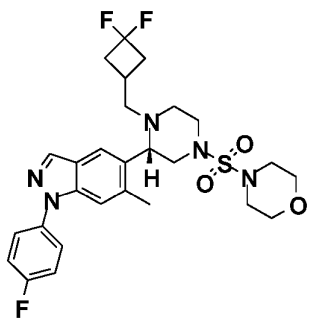
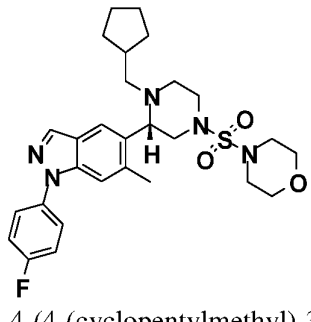
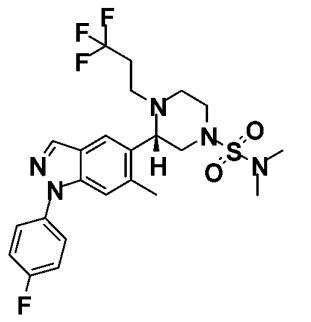
- [0304] To a solution of pyridazine-3-sulfonyl fluoride (22.5 mg, 0.132 mmol) in THF (0.7 mL) at 0 °C was added a solution of 1-(4-fluorophenyl)-6-methyl-5-[1-(3,3,3-trifluoropropyl) piperazin-2-yl]indazole (67.5 mg, 0.166 mmol) in THF (0.3 mL). The resulting mixture was warmed to rt and maintained at this temperature for 48 hours, then partitioned between water (2 mL) and DCM (5 mL). The layers were separated and the aqueous extracted with further DCM (2 x 5 mL). The combined organic extracts were dried (phase separator) and evaporated *in vacuo*. The residue thus obtained was purified by flash column chromatography

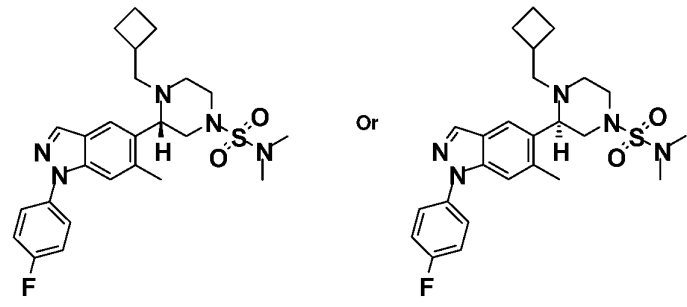
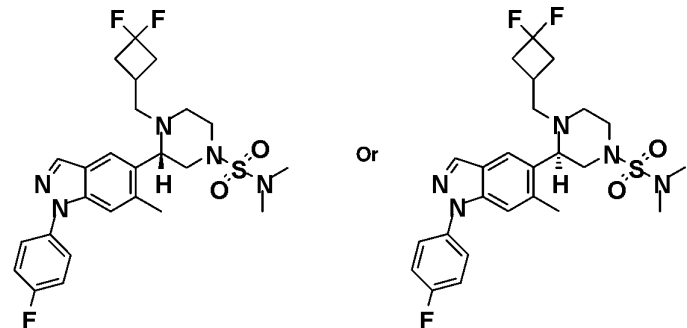
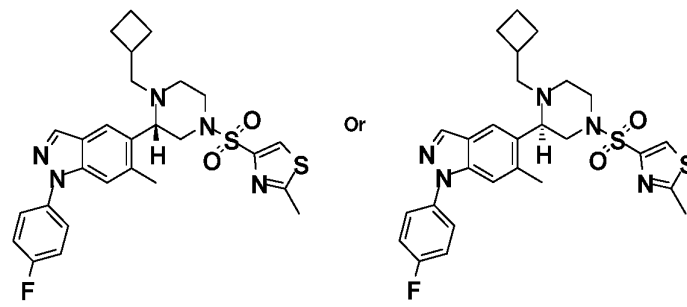
(4 g cartridge, 0-4% MeOH in DCM) to afford 1-(4-fluorophenyl)-6-methyl-5-(4-pyridazin-3-ylsulfonyl-1-(3,3,3-trifluoropropyl)piperazin-2-yl)indazole (34.1 mg, 0.0609 mmol, 46%) as a white solid; R^t 2.81 min (Method 11); m/z 549.0 ($M+H$)⁺ (ES⁺); δ H NMR (400 MHz, DMSO-*d*₆) δ 9.50 (dd, J = 5.1, 1.5 Hz, 1H), 8.26 (d, J = 0.9 Hz, 1H), 8.20 (dd, J = 8.6, 1.6 Hz, 1H), 8.02 (dd, J = 8.6, 5.1 Hz, 1H), 7.86 (s, 1H), 7.82 - 7.76 (m, 2H), 7.65 (s, 1H), 7.46 - 7.37 (m, 2H), 3.88 (d, J = 12.1 Hz, 1H), 3.72 (dd, J = 10.3, 3.2 Hz, 1H), 3.65 (d, J = 12.4 Hz, 1H), 3.27 (d, J = 12.3 Hz, 1H), 3.06 - 2.97 (m, 1H), 2.77 - 2.60 (m, 2H), 2.47 - 2.31 (m, 3H), 2.24 - 2.12 (m, 1H). Methyl signal obscured by solvent but presence confirmed by 2D NMR.

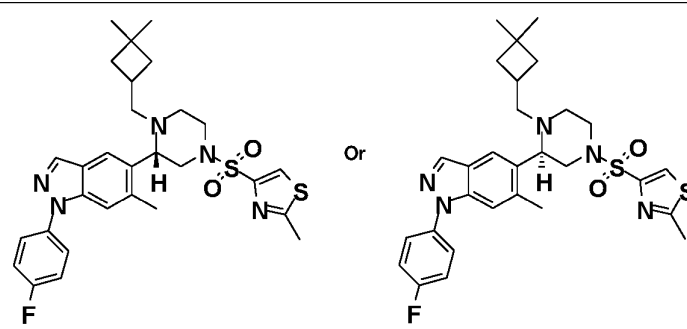
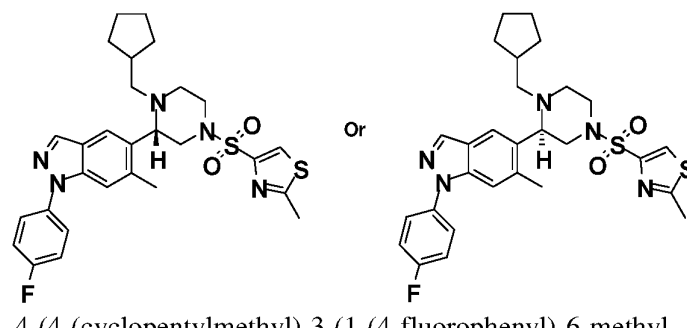
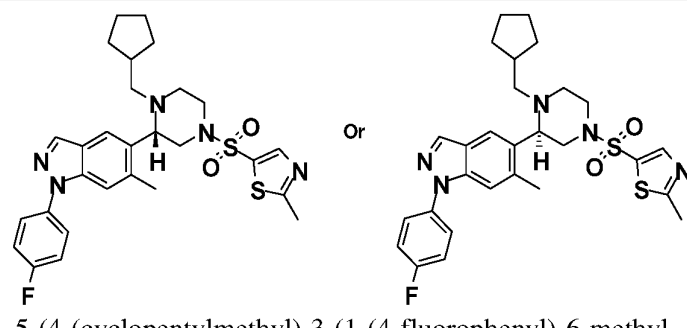
Examples 177 - 215

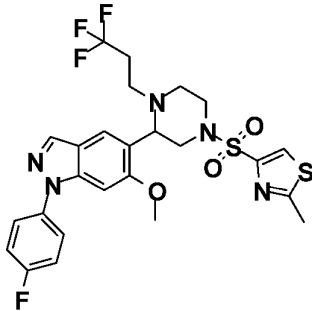
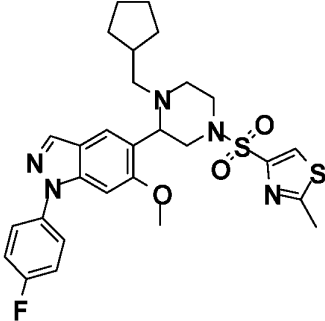
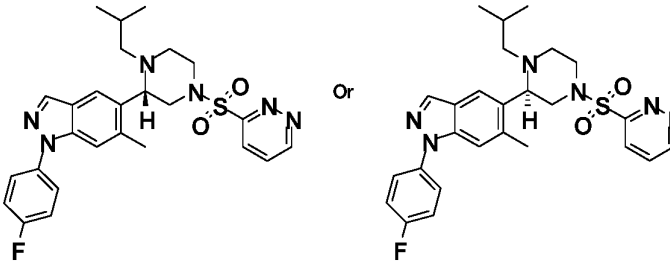
10 **Table 24:** The examples shown in the table below were prepared by method in the Example indicated for the synthesis method

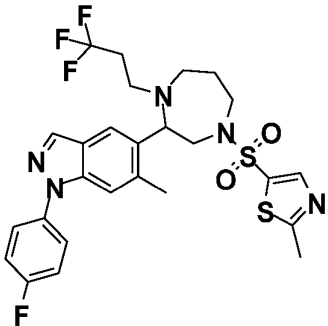
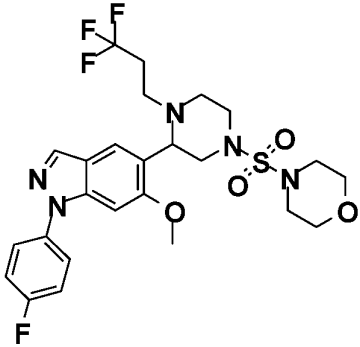
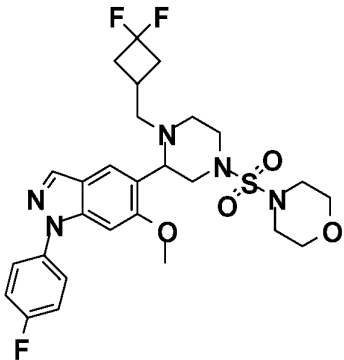
Ex.	Structure	LC-MS analysis	Synthesis Method
177	 4-(3-(1-(4-fluorophenyl)-6-methyl-indazol-5-yl)-4-(3,3,3-trifluoropropyl)piperazin-1-yl)sulfonylmorpholine	R^t 2.91 min (Method 11); m/z 556.2 ($M+H$) ⁺ (ES ⁺)	1
178	 4-(4-(cyclobutylmethyl)-3-[1-(4-fluorophenyl)-6-methyl-indazol-5-yl]piperazin-1-yl)sulfonylmorpholine	R^t 2.16 min (Method 11); m/z 528.2 ($M+H$) ⁺ (ES ⁺)	1

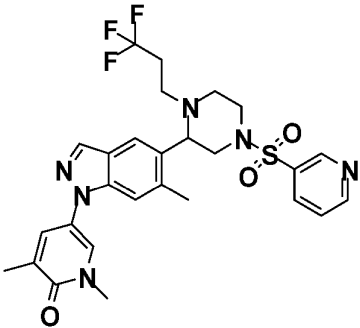
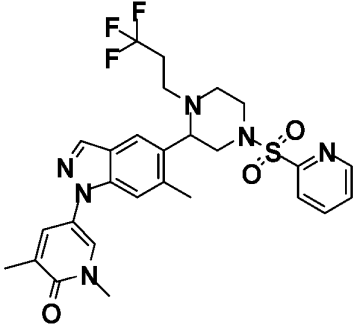
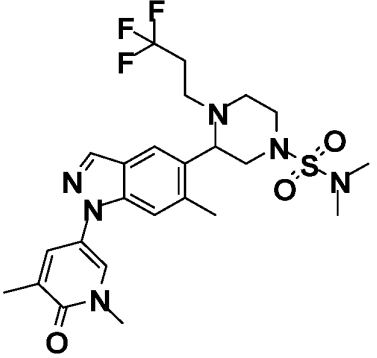
Ex.	Structure	LC-MS analysis	Synthesis Method
179	 4-(4-((3,3-difluorocyclobutyl)methyl)-3-(1-(4-fluorophenyl)-6-methyl-indazol-5-yl)piperazin-1-yl)sulfonylmorpholine	R^t 2.56 min (Method 11); m/z 564.2 (M+H)⁺ (ES⁺)	1
180	 4-(4-(cyclopentylmethyl)-3-(1-(4-fluorophenyl)-6-methyl-indazol-5-yl)piperazin-1-yl)sulfonylmorpholine	R^t 2.40 min (Method 11); m/z 542.2 (M+H)⁺ (ES⁺)	1
181	 3-(1-(4-fluorophenyl)-6-methyl-indazol-5-yl)-N,N-dimethyl-4-(3,3,3-trifluoropropyl)piperazine-1-sulfonamide	R^t 2.95 min (Method 11); m/z 514.1 (M+H)⁺ (ES⁺)	1

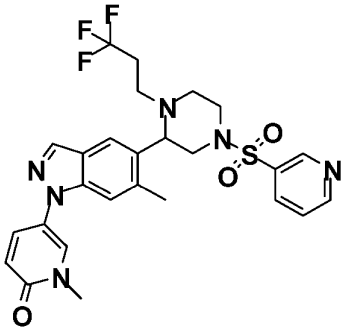
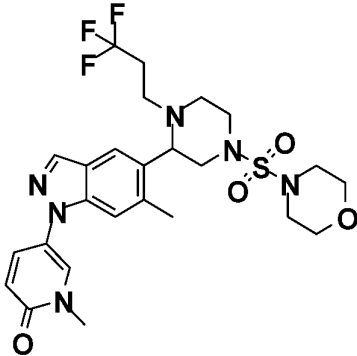
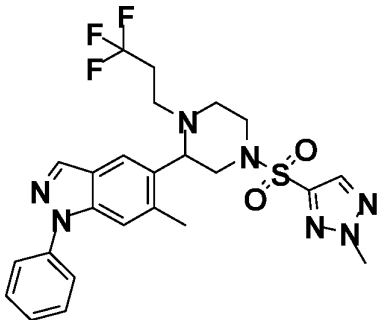
Ex.	Structure	LC-MS analysis	Synthesis Method
182	 4-(cyclobutylmethyl)-3-(1-(4-fluorophenyl)-6-methyl-indazol-5-yl)-<i>N,N</i>-dimethyl-piperazine-1-sulfonamide	R ^t 2.15 min (Method 11); m/z 486.2 (M+H) ⁺ (ES ⁺)	1
183	 4-((3,3-difluorocyclobutyl)methyl)-3-(1-(4-fluorophenyl)-6-methyl-indazol-5-yl)-<i>N,N</i>-dimethyl-piperazine-1-sulfonamide	R ^t 2.56 min (Method 11); m/z 522.2 (M+H) ⁺ (ES ⁺)	1
184	 4-(4-(cyclobutylmethyl)-3-(1-(4-fluorophenyl)-6-methyl-indazol-5-yl)piperazin-1-yl)sulfonyl-2-methyl-thiazole	R ^t 2.36 min (Method 11); m/z 540.2 (M+H) ⁺ (ES ⁺)	1

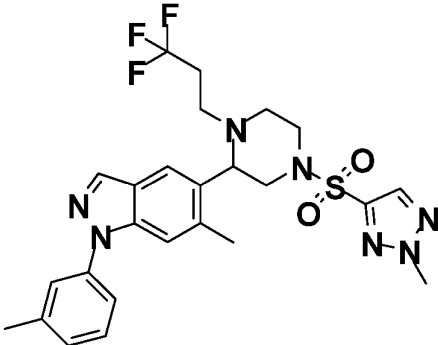
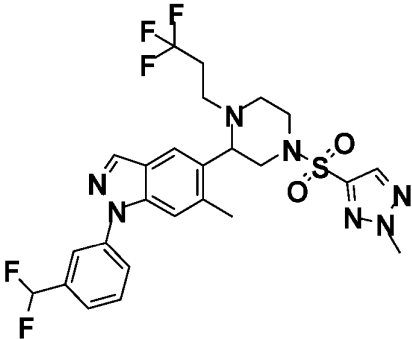
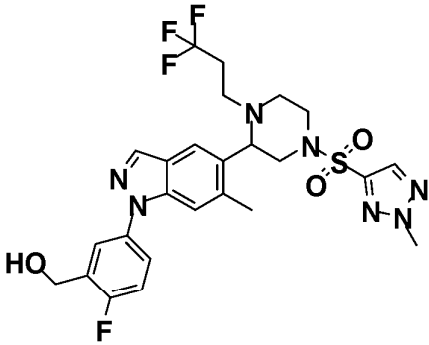
Ex.	Structure	LC-MS analysis	Synthesis Method
185	 4-((3,3-dimethylcyclobutyl)methyl)-3-(1-(4-fluorophenyl)-6-methyl-indazol-5-yl)piperazin-1-yl)sulfonyl-2-methyl-thiazole	R ^t 2.60 min (Method 11); m/z 568.2 (M+H) ⁺ (ES ⁺)	1
186	 4-(4-(cyclopentylmethyl)-3-(1-(4-fluorophenyl)-6-methyl-indazol-5-yl)piperazin-1-yl)sulfonyl-2-methyl-thiazole	R ^t 2.60 min (Method 11); m/z 554.2 (M+H) ⁺ (ES ⁺)	1
187	 5-(4-(cyclopentylmethyl)-3-(1-(4-fluorophenyl)-6-methyl-indazol-5-yl)piperazin-1-yl)sulfonyl-2-methyl-thiazole	R ^t 2.86 min (Method 11); m/z 554.2 (M+H) ⁺ (ES ⁺)	1

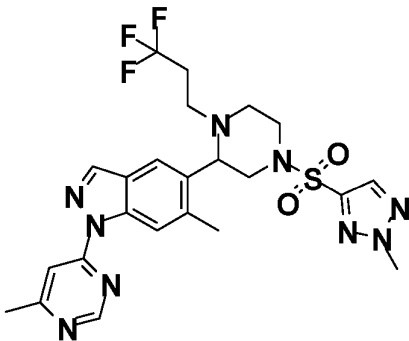
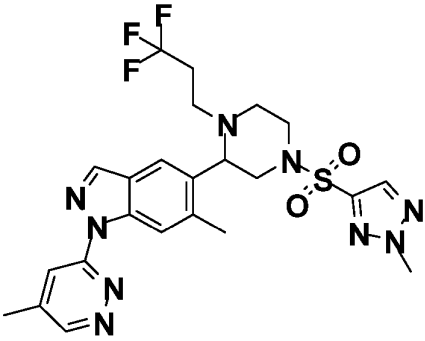
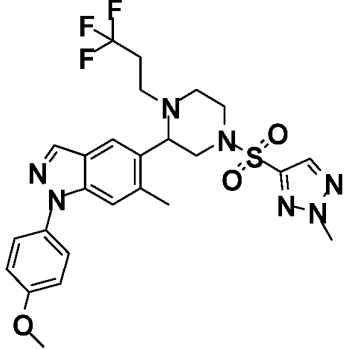
Ex.	Structure	LC-MS analysis	Synthesis Method
188	 4-(3-(1-(4-fluorophenyl)-6-methoxy-indazol-5-yl)-4-(3,3,3-trifluoropropyl)piperazin-1-yl)sulfonyl-2-methyl-thiazole	R ^t 2.84 min (Method 11); m/z 584.0 (M+H) ⁺ (ES ⁺)	1
189	 4-(4-(cyclopentylmethyl)-3-(1-(4-fluorophenyl)-6-methoxy-indazol-5-yl)piperazin-1-yl)sulfonyl-2-methyl-thiazole	R ^t 2.17 min (Method 11); m/z 570.2 (M+H) ⁺ (ES ⁺)	1
190	 1-(4-fluorophenyl)-5-(1-isobutyl-4-pyridazin-3-yl)sulfonyl-piperazin-2-yl)-6-methyl-indazole	R ^t 2.23 min (Method 11); m/z 509.2 (M+H) ⁺ (ES ⁺)	176

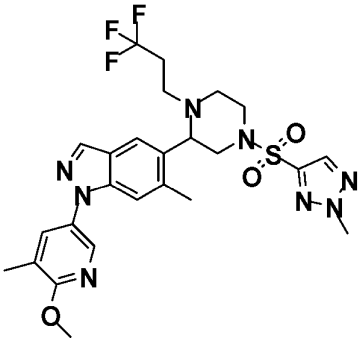
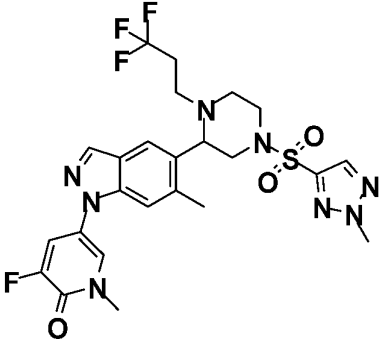
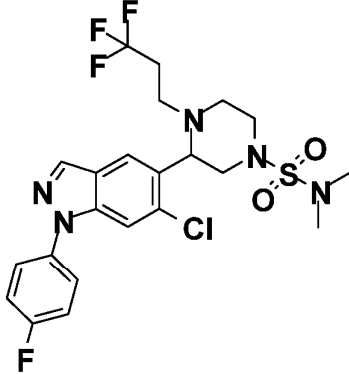
Ex.	Structure	LC-MS analysis	Synthesis Method
191	 5-((3-(1-(4-fluorophenyl)-6-methyl-indazol-5-yl)-4-(3,3,3-trifluoropropyl)-1,4-diazepan-1-yl)sulfonyl)-2-methyl-thiazole	R ^t 3.01 min (Method 11); m/z 582.2 (M+H) ⁺ (ES ⁺)	173
192	 4-(3-(1-(4-fluorophenyl)-6-methoxy-indazol-5-yl)-4-(3,3,3-trifluoropropyl)piperazin-1-yl)sulfonylmorpholine	R ^t 2.70 min (Method 11); m/z 572.2 (M+H) ⁺ (ES ⁺)	1
193	 4-(4-((3,3-difluorocyclobutyl)methyl)-3-(1-(4-fluorophenyl)-6-methoxy-indazol-5-yl)piperazin-1-yl)sulfonylmorpholine	R ^t 2.16 min (Method 11); m/z 580.2 (M+H) ⁺ (ES ⁺)	1

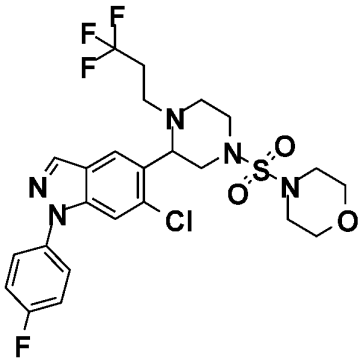
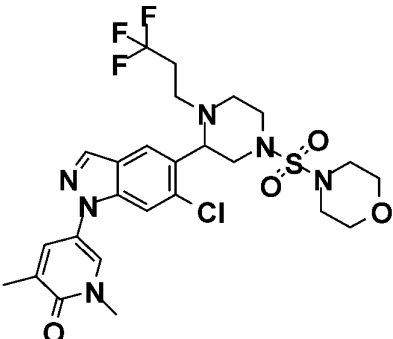
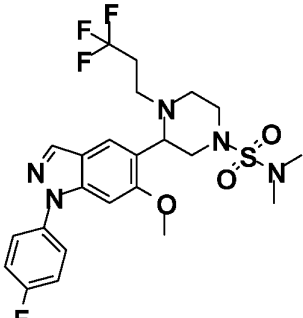
Ex.	Structure	LC-MS analysis	Synthesis Method
194	 1,3-dimethyl-5-(6-methyl-5-(4-(3-pyridylsulfonyl)-1-(3,3,3-trifluoropropyl)piperazin-2-yl)indazol-1-yl)pyridin-2-one	R ^t 2.43 min (Method 11); m/z 575.2 (M+H) ⁺ (ES ⁺)	174
195	 1,3-dimethyl-5-(6-methyl-5-(4-(2-pyridylsulfonyl)-1-(3,3,3-trifluoropropyl)piperazin-2-yl)indazol-1-yl)pyridin-2-one	R ^t 2.47 min (Method 11); m/z 575.2 (M+H) ⁺ (ES ⁺)	174
196	 3-(1-(1,5-dimethyl-6-oxo-3-pyridyl)-6-methyl-indazol-5-yl)-N,N-dimethyl-4-(3,3,3-trifluoropropyl)piperazine-1-sulfonamide	R ^t 2.44 min (Method 11); m/z 541.2 (M+H) ⁺ (ES ⁺)	174

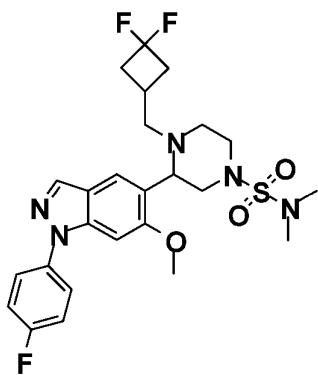
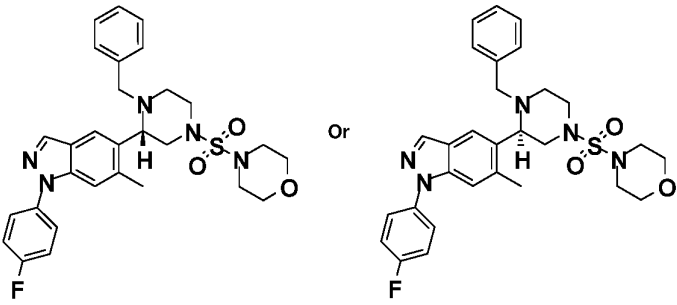
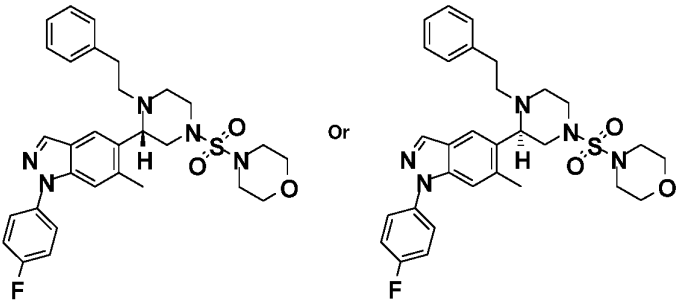
Ex.	Structure	LC-MS analysis	Synthesis Method
197	 1-methyl-5-(6-methyl-5-(4-(3-pyridylsulfonyl)-1-(3,3,3-trifluoropropyl)piperazin-2-yl)indazol-1-yl)pyridin-2-one	R ^t 2.31 min (Method 11); m/z 561.2 (M+H) ⁺ (ES ⁺)	174
198	 1-methyl-5-(6-methyl-5-(4-morpholin sulfonyl)-1-(3,3,3-trifluoropropyl)piperazin-2-yl)indazol-1-yl)pyridin-2-one	R ^t 2.28 min (Method 11); m/z 569.2 (M+H) ⁺ (ES ⁺)	174
199	 6-methyl-5-(4-(2-methyltriazol-4-yl)sulfonyl)-1-(3,3,3-trifluoropropyl)piperazin-2-yl)-1-phenyl-indazole	R ^t 2.91 min (Method 11); m/z 534.0 (M+H) ⁺ (ES ⁺)	174

Ex.	Structure	LC-MS analysis	Synthesis Method
200	 6-methyl-5-(4-(2-methyltriazol-4-yl)sulfonyl-1-(3,3,3-trifluoropropyl)piperazin-2-yl)-1-(m-tolyl)indazole	R ^t 3.01 min (Method 11); m/z 548.0 (M+H) ⁺ (ES ⁺)	174
201	 1-(3-(difluoromethyl)phenyl)-6-methyl-5-(4-(2-methyltriazol-4-yl)sulfonyl-1-(3,3,3-trifluoropropyl)piperazin-2-yl)indazole	R ^t 2.98 min (Method 11); m/z 584.1 (M+H) ⁺ (ES ⁺)	174
202	 (2-fluoro-5-(6-methyl-5-(4-(2-methyltriazol-4-yl)sulfonyl-1-(3,3,3-trifluoropropyl)piperazin-2-yl)indazol-1-yl)phenyl)methanol	R ^t 2.67 min (Method 11); m/z 582.2 (M+H) ⁺ (ES ⁺)	174

Ex.	Structure	LC-MS analysis	Synthesis Method
203	 6-methyl-1-(6-methylpyrimidin-4-yl)-5-(4-(2-methyltriazol-4-yl)sulfonyl-1-(3,3,3-trifluoropropyl)piperazin-2-yl)indazole	R ^t 2.77 min (Method 11); m/z 550.0 (M+H) ⁺ (ES ⁺)	174
204	 6-methyl-1-(5-methylpyridazin-3-yl)-5-(4-(2-methyltriazol-4-yl)sulfonyl-1-(3,3,3-trifluoropropyl)piperazin-2-yl)indazole	R ^t 2.69 min (Method 11); m/z 550.2 (M+H) ⁺ (ES ⁺)	174
205	 1-(4-methoxyphenyl)-6-methyl-5-(4-(2-methyltriazol-4-yl)sulfonyl-1-(3,3,3-trifluoropropyl)piperazin-2-yl)indazole	R ^t 2.87 min (Method 11); m/z 564.2 (M+H) ⁺ (ES ⁺)	174

Ex.	Structure	LC-MS analysis	Synthesis Method
206	 1-(6-methoxy-5-methyl-3-pyridyl)-6-methyl-5-(4-(2-methyltriazol-4-yl)sulfonyl-1-(3,3,3-trifluoropropyl)piperazin-2-yl)indazole	R ^t 2.97 min (Method 11); m/z 579.2 (M+H) ⁺ (ES ⁺)	174
207	 3-fluoro-1-methyl-5-(6-methyl-5-(4-(2-methyltriazol-4-yl)sulfonyl-1-(3,3,3-trifluoropropyl)piperazin-2-yl)indazol-1-yl)pyridin-2-one	R ^t 2.40 min (Method 11); m/z 583.0 (M+H) ⁺ (ES ⁺)	174
209	 3-(6-chloro-1-(4-fluorophenyl)indazol-5-yl)-N,N-dimethyl-4-(3,3,3-trifluoropropyl)piperazine-1-sulfonamide	R ^t 3.01 min (Method 11); m/z 534.1 (M+H) ⁺ (ES ⁺)	174

Ex.	Structure	LC-MS analysis	Synthesis Method
210	 4-(3-(6-chloro-1-(4-fluorophenyl)indazol-5-yl)-4-(3,3,3-trifluoropropyl)piperazin-1-yl)sulfonylmorpholine	R ^t 2.51 min (Method 11); m/z 603.2 (M+H) ⁺ (ES ⁺)	174
211	 5-(6-chloro-5-(4-morpholinosulfonyl-1-(3,3,3-trifluoropropyl)piperazin-2-yl)indazol-1-yl)-1,3-dimethylpyridin-2-one	R ^t 2.51 min (Method 11); m/z 603.2 (M+H) ⁺ (ES ⁺)	174
212	 3-(1-(4-fluorophenyl)-6-methoxy-indazol-5-yl)-N,N-dimethyl-4-(3,3,3-trifluoropropyl)piperazine-1-sulfonamide	R ^t 2.60 min (Method 11); m/z 530.2 (M+H) ⁺ (ES ⁺)	1

Ex.	Structure	LC-MS analysis	Synthesis Method
213	 4-((3,3-difluorocyclobutyl)methyl)-3-(1-(4-fluorophenyl)-6-methoxy-indazol-5-yl)-<i>N,N</i>-dimethyl-piperazine-1-sulfonamide	R ^t 2.09 min (Method 11); m/z 538.2 (M+H) ⁺ (ES ⁺)	1
214	 4-(4-benzyl-3-(1-(4-fluorophenyl)-6-methyl-indazol-5-yl)piperazin-1-yl)sulfonylmorpholine	R ^t 2.75 min (Method 11); m/z 550.2 (M+H) ⁺ (ES ⁺)	1
215	 4-(3-(1-(4-fluorophenyl)-6-methyl-indazol-5-yl)-4-(2-phenylethyl)piperazin-1-yl)sulfonylmorpholine	R ^t 2.51 min (Method 11); m/z 564.2 (M+H) ⁺ (ES ⁺)	1

VII. BIOLOGICAL EXAMPLES

Example 1: GR Binding Assay

- [0305] Binding of test compounds to the glucocorticoid receptor (GR) is determined using
5 a fluorescence polarisation (FP) assay utilising a recombinant ligand binding domain (LBD)

of GR. The test compounds are assessed by their ability to displace a fluorescently tagged ligand and detection of the resulting decrease in fluorescence polarisation. Fluorescence polarisation values are converted to % inhibition using the high (1% DMSO only) and low (1 μ M) controls and IC₅₀ values are calculated from non-linear regression curves fitted using
5 Dotmatics software.

Example 2: Hep G2 TAT Ki

[0306] Glucocorticoid mediated activation of TAT occurs by transactivation of glucocorticoid response elements in the TAT promoter by glucocorticoid receptor–agonist complex. The following protocol describes an assay for measuring induction of TAT by
10 dexamethasone in HepG2 cells (a human liver hepatocellular carcinoma cell line; ECACC, UK).

[0307] TAT activity was measured as outlined in the literature by A. Ali *et al.*, J. Med. Chem., 2004, 47, 2441-2452. Dexamethasone induced TAT production with an average EC₅₀ value (half-maximal effect) of 20nM.

15 [0308] HepG2 cells were cultured using MEME media supplemented with 10% (v/v) foetal bovine serum; 2mM L-glutamine and 1% (v/v) NEAA at 37°C, 5%/95% (v/v) CO₂/air. The HepG2 cells were counted and adjusted to yield a density of 0.2 x 10⁶ cells/ml in RPMI 1640 without phenol red, 10% (v/v) charcoal stripped FBS, 2mM L-glutamine and seeded at 40,000 cells/well in 200 μ l into 96 well, sterile, tissue culture micro titre plates, and incubated
20 at 37°C, 5% CO₂ for 24 hours

[0309] Growth media was removed and replaced with assay media {RPMI 1640 without phenol red, 2mM L-glutamine + 10 μ M forskolin}. Test compounds were screened against a challenge of 100nM dexamethasone. Compounds were serially half log diluted in 100% (v/v) dimethylsulphoxide from a 10mM stock. Then an 8-point half-log dilution curve was
25 generated followed by a 1:100 dilution into assay media to give a 10x final assay [compound]; this resulted in final assay [compound] that ranged 10 to 0.003 μ M in 0.1% (v/v) dimethylsulfoxide.

[0310] 100 nM of dexamethasone was added to the test compounds which were then subsequently incubated for 18-24 hr at 37°C, 5/95 (v/v) CO₂/air to allow optimal TAT
30 induction.

[0311] HepG2 cells were then lysed with 30µl of cell lysis buffer containing a protease inhibitor cocktail for 15 minutes at 4°C. 155µl of substrate mixture was then added containing 5.4mM Tyrosine sodium salt, 10.8mM alpha ketoglutarate and 0.06mM pyridoxal 5' phosphate in 0.1M potassium phosphate buffer (pH 7.4). After 2 hours incubation at 37°C the reaction was terminated by the addition of 15µl of 10M aqueous potassium hydroxide solution, and the plates incubated for a further 30 minutes at 37°C. The TAT activity product was measured by absorbance at λ 340nm.

[0312] IC_{50} values were calculated by plotting % inhibition (normalised to 100nM dexamethasone TAT stimulation) v. [compound] and fitting the data to a 4 parameter logistic equation. IC_{50} values were converted to K_i (equilibrium dissociation constant) using the Cheng and Prusoff equation, assuming the antagonists were competitive inhibitors with respect to dexamethasone.

Table 25: Activity Data

Example No.	HepG2 TAT K_i (nM)
1	35
2	81
3	85
4	41
5	420
6	46
7	62
8	66
9	72
10	430
11	20
12	68
13	97
14	62
15	260
16	520
17	110
18	330
19	140
20	130
21	120
22	57
23	13
24	73
25	77

Example No.	HepG2 TAT Ki (nM)
26	180
27	47
28	230
29	74
30	90
31	11
32	19
33	11
34	430
35	770
36	50
37	76
38	46
39	57
40	53
41	60
42	40
43	76
44	93
45	510
46	310
47	23
48	23
49	31
50	64
51	28
52	24
53	41
54	31
55	19
56	65
57	19
58	15
59	22
60	28
61	64
62	44
63	20
64	50
65	370
66	260
67	390
68	58
69	180
70	170
71	160

Example No.	HepG2 TAT Ki (nM)
72	330
73	170
74	160
75	140
76	22
77	13
78	13
79	29
80	150
81	73
82	43
83	33
84	14
85	29
86	180
87	54
88	35
89	34
92	86
93	36
94	74
95	100
96	43
97	23
98	25
99	19
100	42
101	28
102	39
103	35
104	19
105	46
106	33
107	22
108	44
109	12
110	27
111	65
112	36
113	
114	55
115	24
116	25
117	38
118	190
119	19

Example No.	HepG2 TAT Ki (nM)
120	65
121	270
122	110
123	71
124	14
125	87
126	62
127	22
128	14
129	13
130	7.7
131	13
132	13
133	11
134	6.5
135	23
136	57
137	33
138	35
139	37
140	47
141	14
142	13
143	25
144	15
145	8.5
146	7.5
147	11
148	38
149	56
150	19
151	35
152	120
153	380
154	24
155	11
156	28
157	43
158	45
159	220
160	32
161	57
162	260
162a	57
163	44
164	170

Example No.	HepG2 TAT Ki (nM)
165	81
166	28
167	59
168	100
169	66
170	91
171	24
172	36

Example 3: Hep G2 TAT IC50

[0313] Glucocorticoid mediated activation of TAT occurs by transactivation of glucocorticoid response elements in the TAT promoter by glucocorticoid receptor/agonist complex. The following protocol describes an assay for measuring induction of TAT by dexamethasone in HepG2 cells (a human liver hepatocellular carcinoma cell line; ATCC, cat. HB-8065, UK).

[0314] TAT activity was measured as outlined in the literature by A. Ali *et al.*, J. Med. Chem., 2004, 47, 2441-2452. Dexamethasone induced TAT production with an average EC₅₀ value (half-maximal effect) of 20 nM.

[0315] HepG2 cells were cultured using MEME media supplemented with 10% (v/v) foetal bovine serum, 2 mM L-glutamine, 1% (v/v) NEAA, and 1% (v/v) penstrep, at 37 °C, 5%/95% (v/v) CO₂/air. The HepG2 cells were counted and adjusted to yield a density of 0.5 x 10⁶ cells/mL in RPMI 1640 without phenol red, 10% (v/v) charcoal stripped FBS, 2 mM L-glutamine, and 1% (v/v) penstrep and seeded at 10,000 cells/well in 20 µL into a 384 well, sterile, tissue culture micro titre plates, and incubated at 37 °C, 5% CO₂ for 24 hours.

[0316] Growth media was removed and replaced with assay media {RPMI 1640 without phenol red, 2 mM L-glutamine, 1% (v/v) penstrep + 10 µM forskolin}. Test compounds were screened against a challenge of 100 nM dexamethasone. Compounds were diluted from a 10 mM stock via an Echo Acoustic liquid handler into 10 µL assay media to generate a 10-point half-log dilution curve. After the compound was dispensed, an additional 30 µL of assay media was added to give 2x the final compound concentration: this resulted in a final assay compound concentration that ranged from 30 to 0.001 µM in 0.3% (v/v) dimethylsulfoxide.

[0317] 100 nM of dexamethasone was added to the test compounds which were then subsequently incubated for 18-22 hours at 37 °C, 5/95 (v/v) CO₂/air to allow optimal TAT induction.

- [0318] HepG2 cells were then lysed with 8 µL of cell lysis buffer containing a protease inhibitor cocktail for 15 minutes at 25 °C. 39 µL of substrate mixture was then added, containing 5.4 mM tyrosine sodium salt, 10.8 mM alpha ketoglutarate and 0.06 mM pyridoxal 5' phosphate in 0.1 M potassium phosphate buffer (pH 7.5). After a 2-hour incubation at 37 °C the reaction was terminated by the addition of 8 µL of 5 M aqueous potassium hydroxide solution, and the plates incubated for a further 30 minutes at 37 °C.
- 10 [0319] IC₅₀ values were calculated by plotting % inhibition (normalised to 100 nM dexamethasone TAT stimulation) v. [compound] and fitting the data to a 4-parameter logistic equation.

Table 26: Activity Data

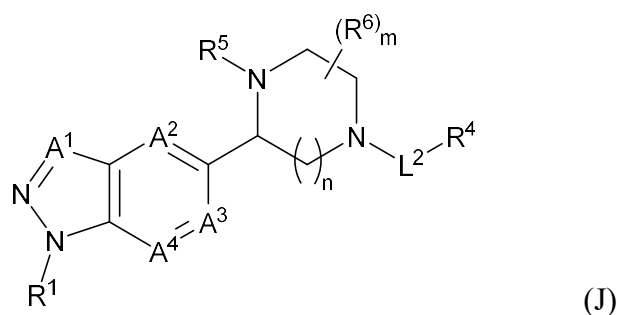
Example	HepG2 TAT IC ₅₀ (nM)
173	2750
174	191
175	1245
176	841
177	2455
178	3428
179	2018
180	2089
181	1660
182	3589
183	2661
184	1161
185	1216
186	2399
187	1660
188	1318
189	1660
190	1072
191	4027
192	3162
193	2786
194	443
195	253
196	284

Example	HepG2 TAT IC50 (nM)
197	1000
198	1279
199	1318
200	4012
201	3846
202	1035
203	9333
204	3846
205	2884
206	6119
207	933
209	3126
210	2541
211	589
212	1445
213	2239
214	2754
215	3981

[0320] Although the foregoing invention has been described in some detail by way of illustration and Examples for purposes of clarity of understanding, one of skill in the art will appreciate that certain changes and modifications may be practiced within the scope of the appended claims. In addition, each reference provided herein is incorporated by reference in its entirety to the same extent as if each reference was individually incorporated by reference. Where a conflict exists between the instant application and a reference provided herein, the instant application shall dominate.

WHAT IS CLAIMED IS:

Claim 1. A compound of Formula J:



or a pharmaceutically acceptable salt thereof, wherein

R¹ is heterocycloalkyl having 3 to 12 ring members and 1 to 4 heteroatoms each N, O or S, phenyl or heteroaryl having 5 to 10 ring members and 1 to 5 heteroatoms each N, O or S, each independently substituted with 0 to 5 R^{1a} groups;

each R^{1a} is independently C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkoxyalkyl, C₁₋₆ hydroxyalkyl, halogen, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, -OH, oxo, -CN, -C(O)N(R^{1b})(R^{1c}), C₃₋₁₀ cycloalkyl, or heterocycloalkyl having 3 to 12 ring members and 1 to 4 heteroatoms each N, O or S;

each R^{1b} and R^{1c} is independently hydrogen, C₁₋₆ alkyl or a 3 to 8 membered heterocycloalkyl having 1 to 3 heteroatoms each independently N, O or S;

A¹, A², A³ and A⁴ are each independently =CR²- or =N-;

each R² is independently hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₂₋₆ alkoxyalkyl, halogen, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, hydroxy or -CN;

L² is -C(O)-, -C(O)O-, -C(O)N(R³)-, -S(O)₂- or -S(O)₂N(R³)-;

R³ is hydrogen, or C₁₋₆ alkyl;

R⁴ is C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₂₋₆ alkoxyalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ haloalkyl, C₃₋₈ cycloalkyl, C₁₋₆ alkyl-C₃₋₈ cycloalkyl, heterocycloalkyl, C₁₋₆ alkyl-heterocycloalkyl, C₆₋₁₂ aryl, C₁₋₆ alkyl-C₆₋₁₂ aryl, -O-C₆₋₁₂ aryl, heteroaryl, or C₁₋₆ alkyl-heteroaryl,

wherein each heterocycloalkyl independently has 3 to 12 ring members and 1 to 3 heteroatoms each independently N, O or S,

wherein each heteroaryl independently has 5 to 10 ring members and 1 to 4 heteroatoms each independently N, O or S, and

wherein the cycloalkyl, heterocycloalkyl, aryl and heteroaryl are each independently substituted with 0 to 5 R^{4a} groups;

alternatively, R³ and R⁴ are combined with the atoms to which they are attached to form a heterocycloalkyl having 3 to 12 ring members and 1 to 3 additional heteroatoms each independently N, O or S, wherein the heterocycloalkyl is substituted with 0, 1 or 2 C₁₋₆ alkyl groups;

each R^{4a} is independently C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ alkoxy, C₂₋₆ alkoxyalkyl, C₁₋₆ hydroxyalkyl, halogen, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, -CN, -OH, oxo, -C(O)R^{4b}, -C(O)OR^{4b}, -OC(O)R^{4b}, -OC(O)OR^{4b}, -C(O)N(R^{4b})(R^{4c}), -N(R^{4b})C(O)R^{4c}, -OC(O)N(R^{4b})(R^{4c}), -N(R^{4b})C(O)OR^{4c}, -S(O)₂R^{4b}, -S(O)₂N(R^{4b})(R^{4c}), -N(R^{4b})S(O)₂R^{4c}, C₃₋₈ cycloalkyl, C₁₋₆ alkyl-C₃₋₈ cycloalkyl, heterocycloalkyl, C₁₋₆ alkyl-heterocycloalkyl, C₆₋₁₂ aryl, C₁₋₆ alkyl-C₆₋₁₂ aryl, -O-C₆₋₁₂ aryl, heteroaryl, or C₁₋₆ alkyl-heteroaryl, wherein each heterocycloalkyl independently has 3 to 12 ring members and 1 to 3 heteroatoms each independently N, O or S, wherein each heteroaryl independently has 5 to 10 ring members and 1 to 4 heteroatoms each independently N, O or S, and wherein each cycloalkyl, heterocycloalkyl, aryl and heteroaryl is substituted with 0, 1 or 2 C₁₋₆ alkyl groups;

each R^{4b} and R^{4c} is hydrogen or C₁₋₆ alkyl;

R⁵ is C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₂₋₆ alkoxyalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ haloalkyl, C₁₋₆ alkyl-OR^{5a}, -C(O)R^{5a}, C₁₋₆ alkyl-C(O)R^{5a}, -C(O)OR^{5a}, -C(O)N(R^{5a})(R^{5b}), -S(O)₂R^{5a}, -S(O)₂N(R^{5a})(R^{5b}), C₃₋₈ cycloalkyl, C₁₋₆ alkyl-C₃₋₈ cycloalkyl, heterocycloalkyl, C₁₋₆ alkyl-heterocycloalkyl, C₆₋₁₂ aryl, C₁₋₆ alkyl-C₆₋₁₂ aryl, heteroaryl, or C₁₋₆ alkyl-heteroaryl, wherein each heterocycloalkyl independently has 3 to 12 ring members and 1 to 3 heteroatoms each independently N, O or S, wherein each heteroaryl independently has 5 to 10 ring members and 1 to 4 heteroatoms each independently N, O or S, and wherein each cycloalkyl, heterocycloalkyl, aryl and heteroaryl is independently substituted with 0 to 4 R^{5c} groups;

each R^{5a} and R^{5b} is independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₂₋₆ alkoxyalkyl, hydroxy, C₁₋₆ hydroxyalkyl, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, C₃₋₈ cycloalkyl, C₁₋₆ alkyl-C₃₋₈ cycloalkyl, heterocycloalkyl, C₁₋₆ alkyl-heterocycloalkyl, C₆₋₁₂ aryl, C₁₋₆ alkyl-C₆₋₁₂ aryl, heteroaryl, or C₁₋₆ alkyl-

heteroaryl, wherein each heterocycloalkyl independently has 3 to 12 ring members and 1 to 3 heteroatoms each independently N, O or S, wherein each heteroaryl independently has 5 to 10 ring members and 1 to 4 heteroatoms each independently N, O or S, and wherein each cycloalkyl, heterocycloalkyl, aryl and heteroaryl is substituted with 0 to 4 R^{5d} groups;

alternatively, R^{5a} and R^{5b} are combined with the atoms to which they are attached to form a heterocycloalkyl having 3 to 12 ring members and 1 to 3 additional heteroatoms each independently N, O or S, wherein the heterocycloalkyl is substituted with 0, 1 or 2 C₁₋₆ alkyl groups;

each R^{5c} is independently C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ alkoxy, C₂₋₆ alkoxyalkyl, C₁₋₆ hydroxyalkyl, halogen, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, -CN, oxo, -OH, -C(O)R^{5c1}, -C(O)OR^{5c1}, -OC(O)R^{5c1}, -OC(O)OR^{5c1}, -C(O)N(R^{5c1})(R^{5c2}), -N(R^{5c1})C(O)R^{5c2}, -OC(O)N(R^{5c1})(R^{5c2}), -N(R^{5c1})C(O)OR^{5c2}, -S(O)₂R^{5c1}, -S(O)₂N(R^{5c1})(R^{5c2}), -N(R^{5c1})S(O)₂R^{5c2}, C₃₋₈ cycloalkyl, C₁₋₆ alkyl-C₃₋₈ cycloalkyl, heterocycloalkyl, C₁₋₆ alkyl-heterocycloalkyl, C₆₋₁₂ aryl, C₁₋₆ alkyl-C₆₋₁₂ aryl, heteroaryl, or C₁₋₆ alkyl-heteroaryl, wherein each heterocycloalkyl independently has 3 to 12 ring members and 1 to 3 heteroatoms each independently N, O or S, wherein each heteroaryl independently has 5 to 10 ring members and 1 to 4 heteroatoms each independently N, O or S, and wherein each heterocycloalkyl and heteroaryl is substituted with 0, 1 or 2 C₁₋₆ alkyl groups;

each R^{5c1} and R^{5c2} is independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₂₋₆ alkoxyalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ haloalkyl, C₃₋₈ cycloalkyl, C₁₋₆ alkyl-C₃₋₈ cycloalkyl, heterocycloalkyl, C₁₋₆ alkyl-heterocycloalkyl, C₆₋₁₂ aryl, C₁₋₆ alkyl-C₆₋₁₂ aryl, heteroaryl, or C₁₋₆ alkyl-heteroaryl, wherein each heterocycloalkyl independently has 3 to 12 ring members and 1 to 3 heteroatoms each independently N, O or S, wherein each heteroaryl independently has 5 to 10 ring members and 1 to 4 heteroatoms each independently N, O or S, and wherein each heterocycloalkyl and heteroaryl is substituted with 0, 1 or 2 C₁₋₆ alkyl groups;

alternatively, R^{5c1} and R^{5c2} are combined with the atoms to which they are attached to form a heterocycloalkyl having 3 to 12 ring members and 1 to 3 heteroatoms each independently N, O or S, wherein the heterocycloalkyl is substituted with 0, 1 or 2 C₁₋₆ alkyl groups;

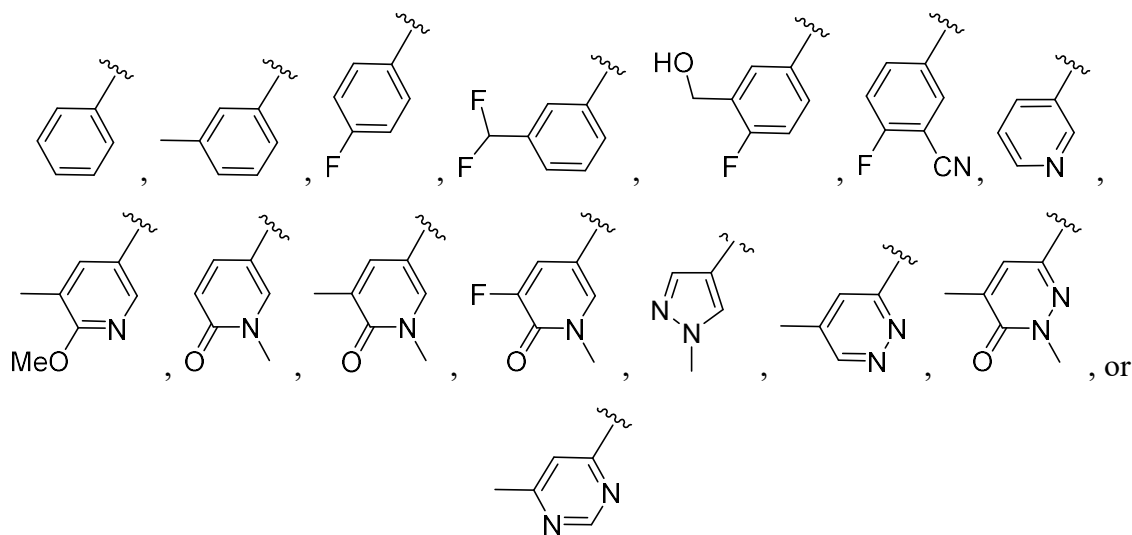
each R^{5d} is independently C₁₋₆ alkyl or halogen;

each R⁶ is independently hydrogen, C₁₋₆ alkyl, halogen, C₁₋₆ haloalkyl, or oxo;

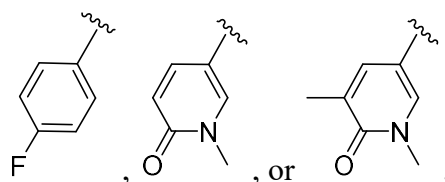
subscript m is 0, 1, 2, 3, 4, or 5; and

subscript n is 1 or 2.

Claim 2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R¹ is



Claim 3. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein R¹ is



Claim 4. The compound of any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, wherein

A¹, A² and A⁴ are each =CH-; and

A³ is =C(Me)-, =C(OMe)-, =C(F)-, =C(Cl)-, or =C(CF₃)-.

Claim 5. The compound of any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein

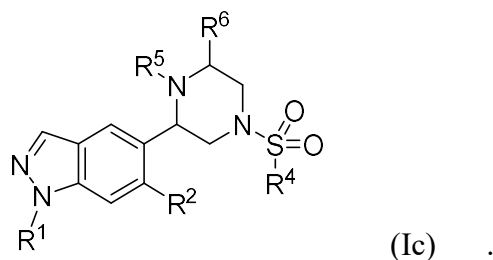
A¹, A² and A⁴ are each =CH-; and

A³ is =C(Me)-.

Claim 6. The compound of any one of claims 1 to 5, or a pharmaceutically acceptable salt thereof, wherein L^2 is $-C(O)-$, $-S(O)_2-$ or $-S(O)_2N(Me)-$.

Claim 7. The compound of any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof, wherein L^2 is $-S(O)_2-$.

Claim 8. The compound of any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, having the structure of Formula Ic:



Claim 9. The compound of any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof, wherein

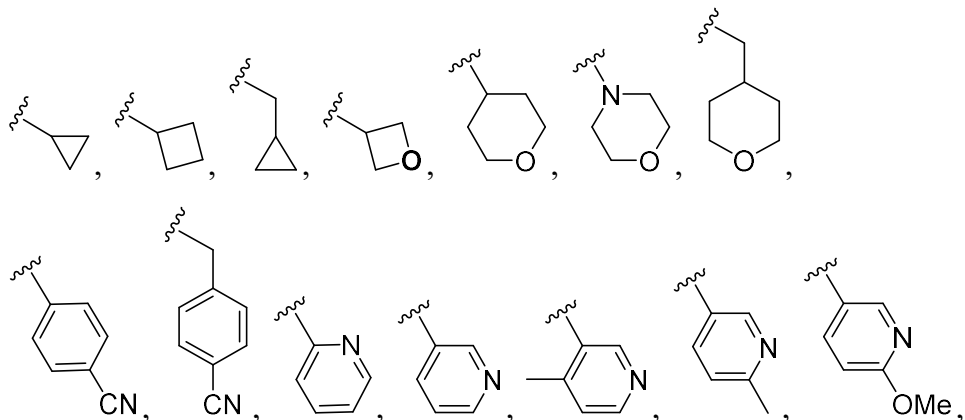
R^4 is pyridine, pyrazole, thiazole, or triazole, each substituted with 0 to 2 R^{4a} groups;

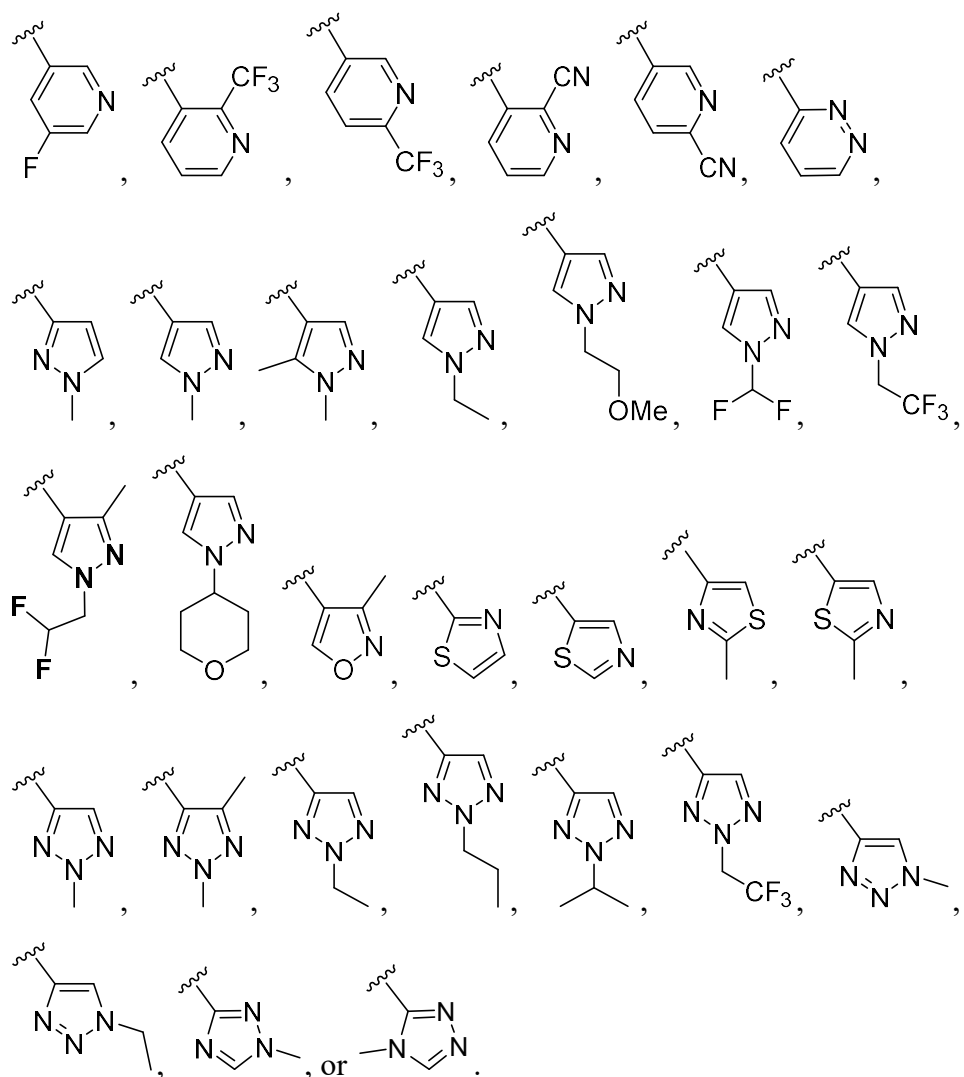
and

each R^{4a} is independently methyl, ethyl, n-propyl, iso-propyl, methoxy, methoxyethyl, fluoro, $-CHF_2$, $-CF_3$, $-CH_2CHF_2$, $-CH_2CF_3$, $-CN$, or tetrahydropyran.

Claim 10. The compound of any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof, wherein

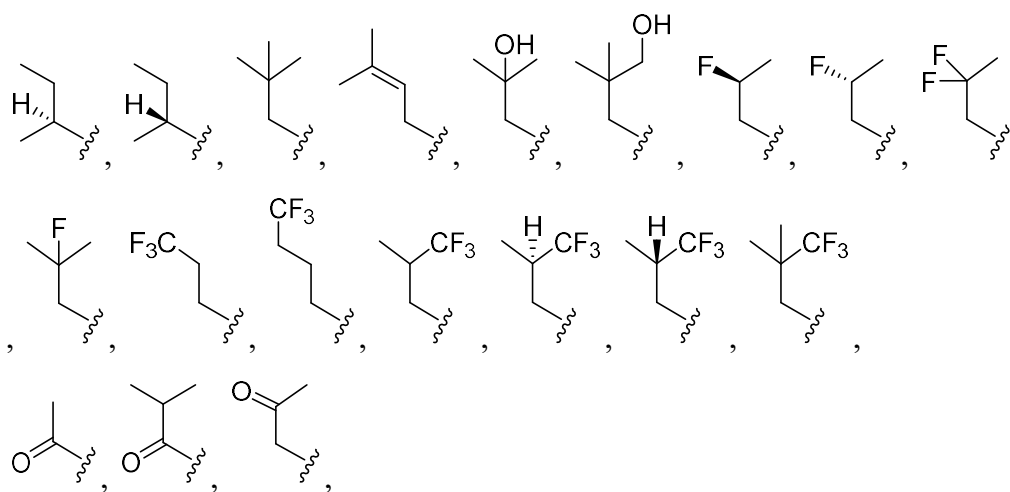
R^4 is methyl, n-propyl, iso-butyl, $-CH(OH)CH_3$, methoxyethyl, isopropoxyethyl, CH_2CF_3 ,

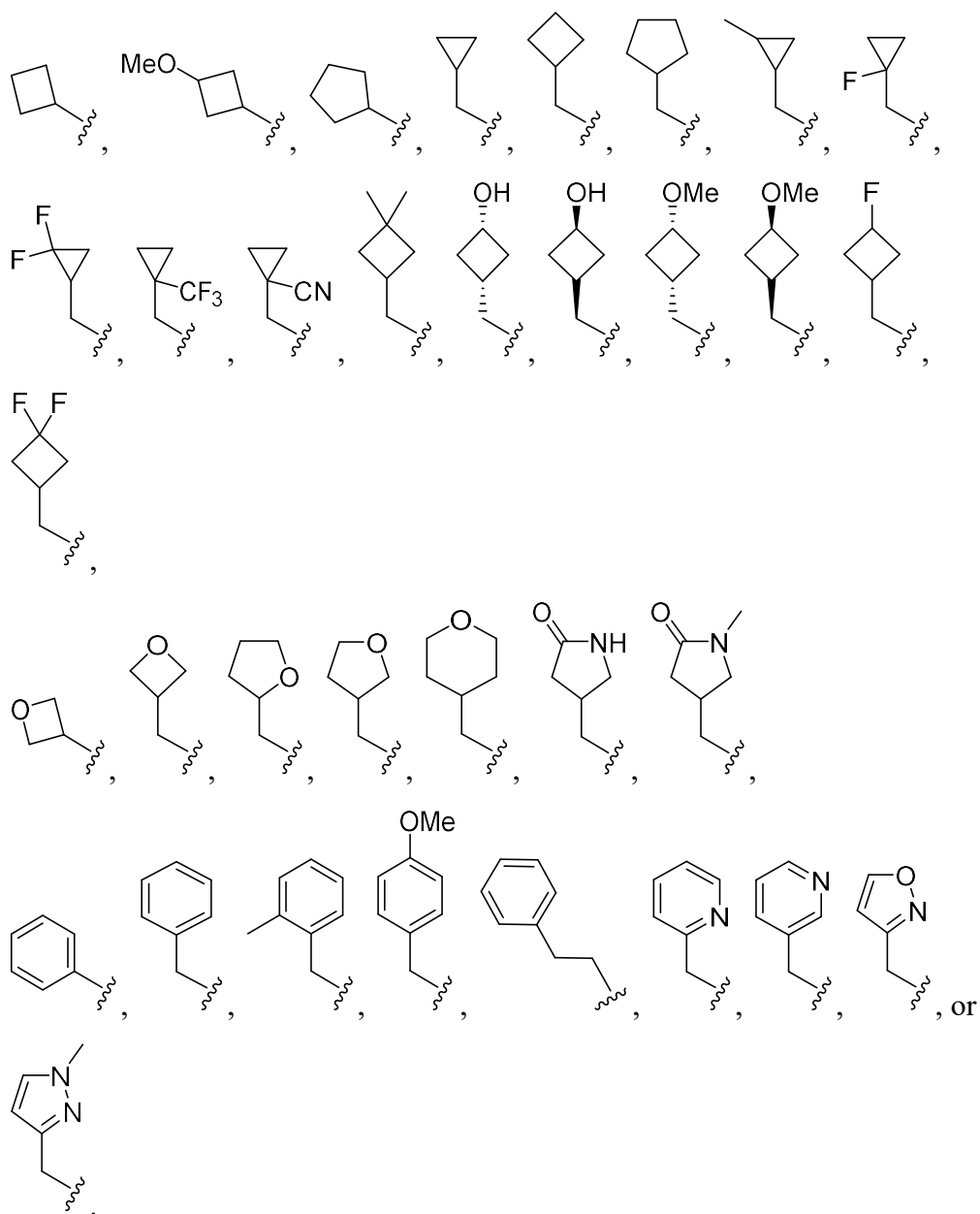




Claim 11. The compound of any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof, wherein

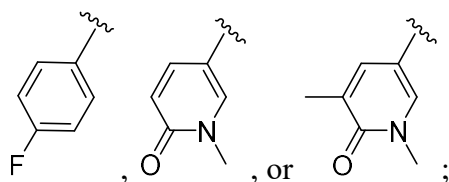
R⁵ is ethyl, iso-propyl, iso-butyl,





Claim 12. The compound of any one of claims 1 to 11, or a pharmaceutically acceptable salt thereof, wherein

R^1 is



A^1 , A^2 and A^4 are each $=CH-$;

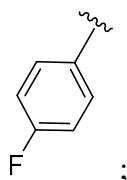
A^3 is $=C(Me)-$;

L^2 is $-S(O)_2-$;

R^4 is pyridine, pyrazole, thiazole, or triazole, each substituted with 0 to 2 R^{4a} groups;
each R^{4a} is independently methyl, ethyl, n-propyl, iso-propyl, methoxy, methoxyethyl,
fluoro, $-\text{CHF}_2$, $-\text{CF}_3$, $-\text{CH}_2\text{CHF}_2$, $-\text{CH}_2\text{CF}_3$, $-\text{CN}$, or tetrahydropyran;
 R^5 is C_{1-6} alkyl, C_{1-6} haloalkyl, or C_{1-2} alkyl- C_{3-6} cycloalkyl, wherein each
cycloalkyl is independently substituted with 0 to 2 R^{5c} groups;
each R^{5c} is independently C_{1-3} alkyl, C_{1-3} alkoxy, halogen, C_{1-3} haloalkyl, $-\text{CN}$, oxo or
 $-\text{OH}$;
subscript m is 0; and
subscript n is 1.

Claim 13. The compound of any one of claims 1 to 11, or a
pharmaceutically acceptable salt thereof, wherein

R^1 is



A^1 , A^2 and A^4 are each $=\text{CH}-$;

A^3 is $=\text{C}(\text{Me})-$;

L^2 is $-\text{S}(\text{O})_2-$;

R^4 is pyrazole or triazole, each substituted with 1 R^{4a} groups;

R^{4a} is methyl, ethyl, n-propyl, or iso-propyl;

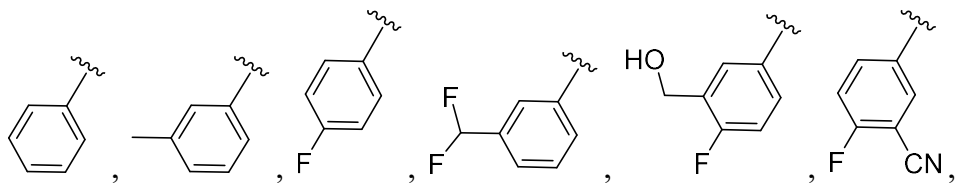
R^5 is C_{1-6} haloalkyl;

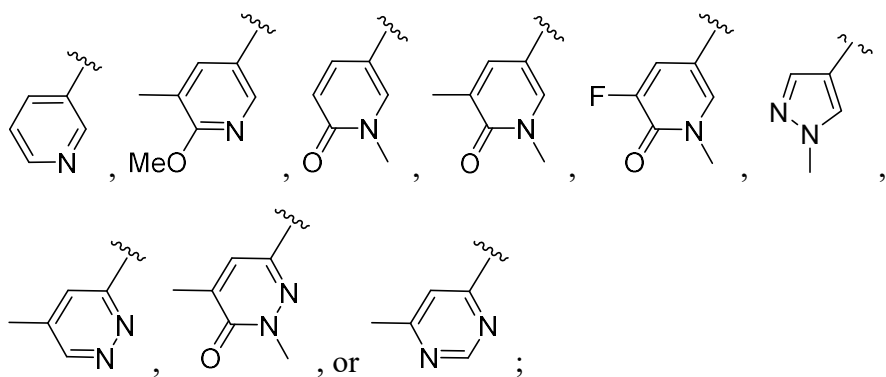
subscript m is 0; and

subscript n is 1.

Claim 14. The compound of any one of claims 1 to 11, or a
pharmaceutically acceptable salt thereof, wherein

R^1 is



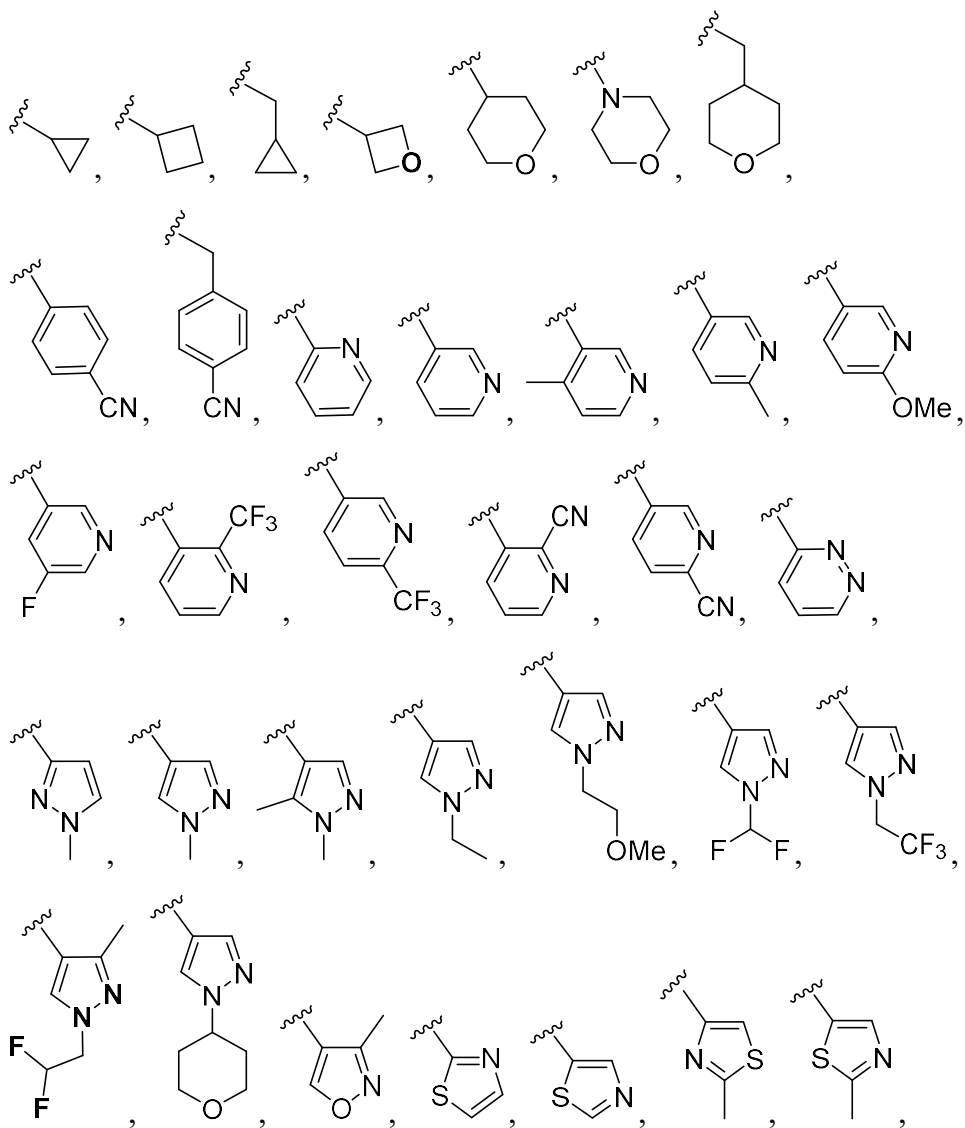


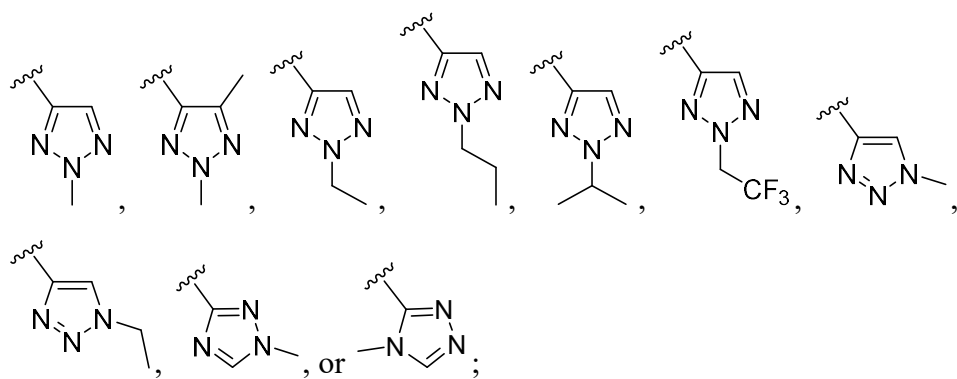
A^1 , A^2 and A^4 are each $=CH-$;

A^3 is $=C(Me)-$, $=C(OMe)-$, $=C(F)-$, $=C(Cl)-$, or $=C(CF_3)-$;

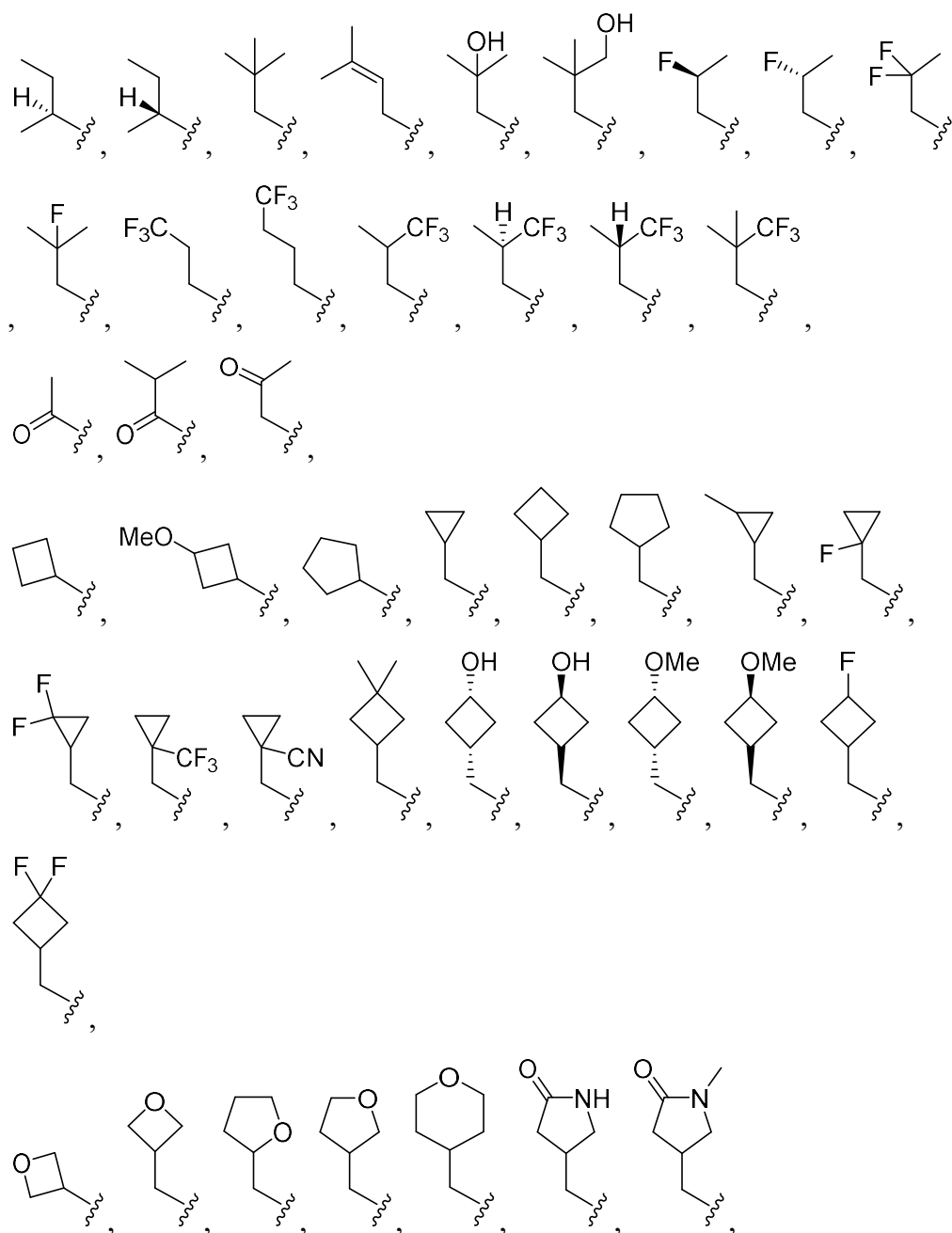
L^2 is $-C(O)-$, $-S(O)_2-$ or $-S(O)_2N(Me)-$;

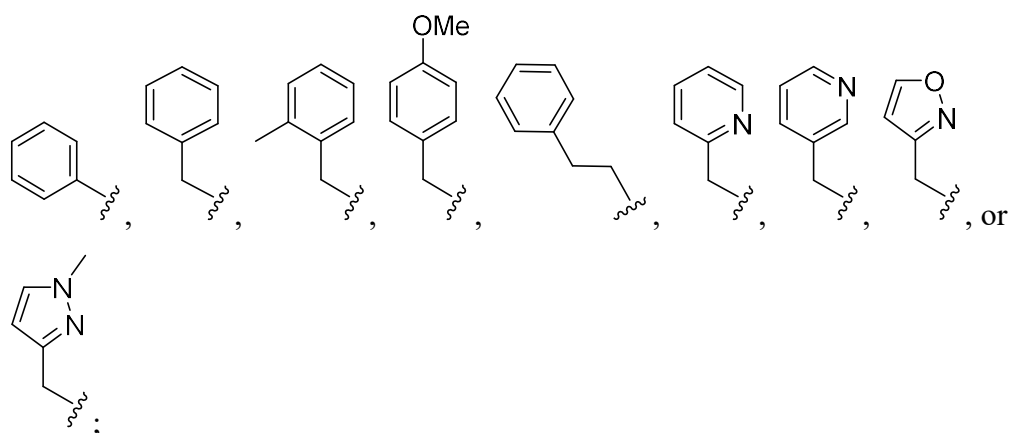
R^4 is methyl, n-propyl, iso-butyl, $-CH(OH)CH_3$, methoxyethyl, isopropoxyethyl, CH_2CF_3 ,





R^5 is ethyl, iso-propyl, iso-butyl,

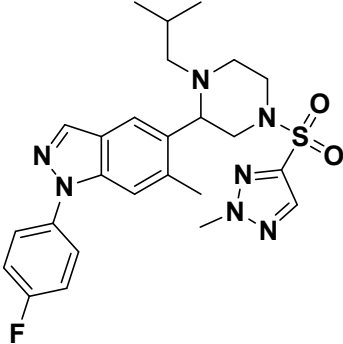
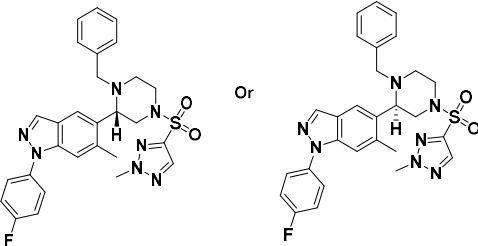
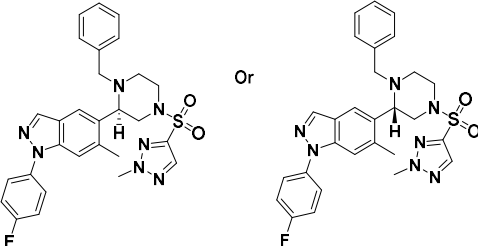
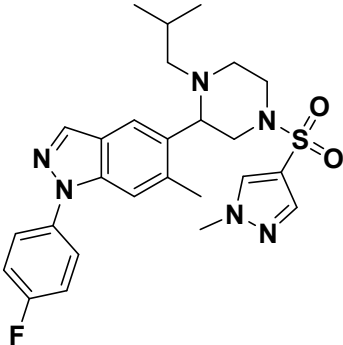
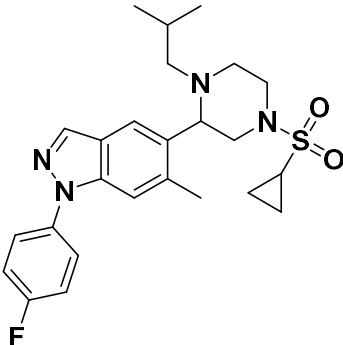


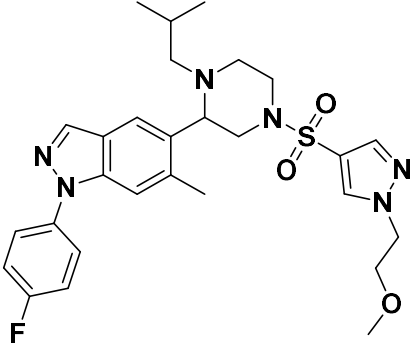
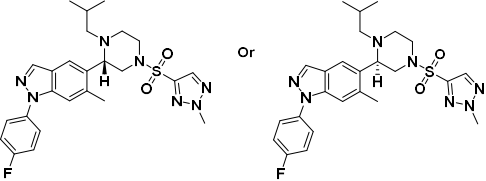
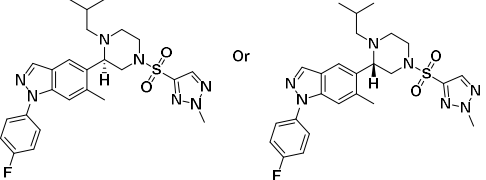
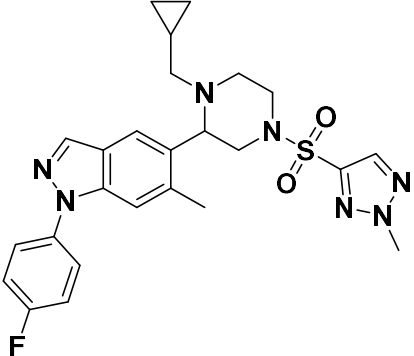
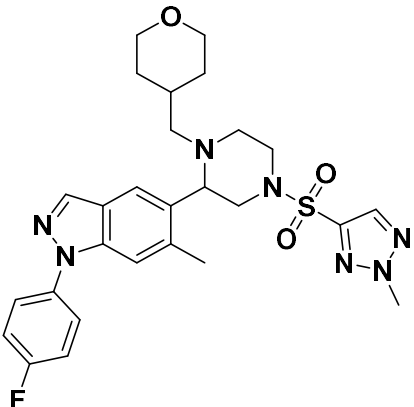


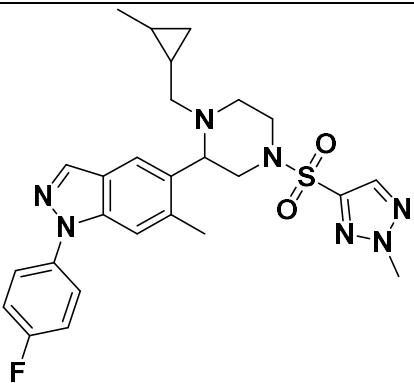
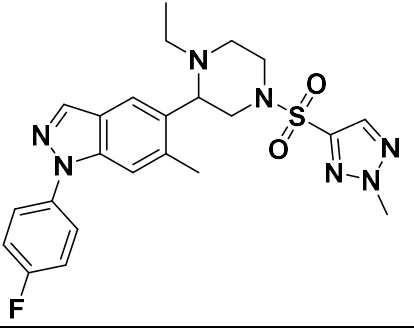
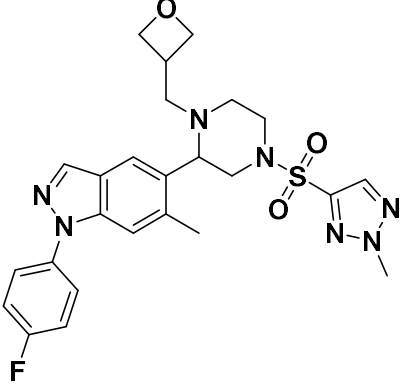
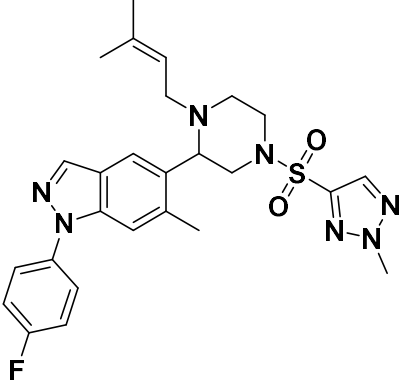
R^6 is hydrogen, methyl, or oxo; and
 subscript m is 0, 1 or 2.

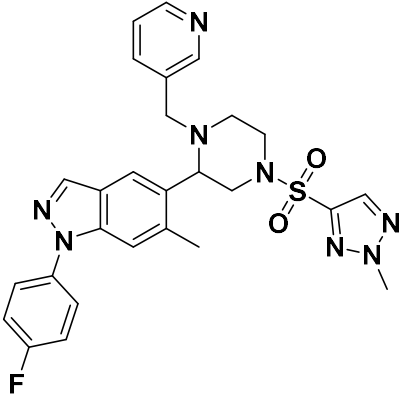
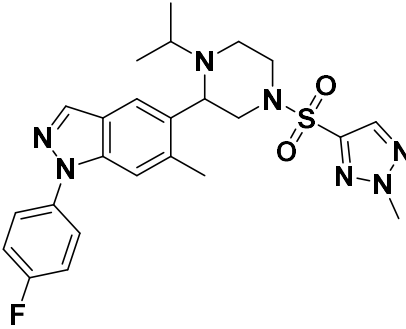
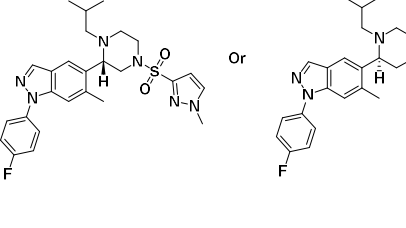
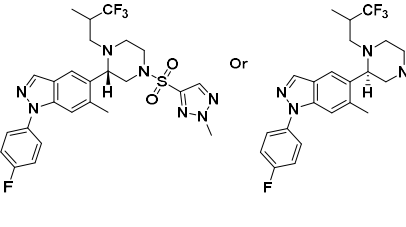
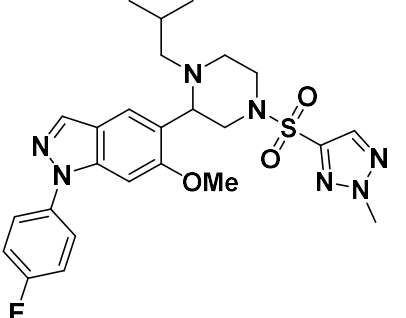
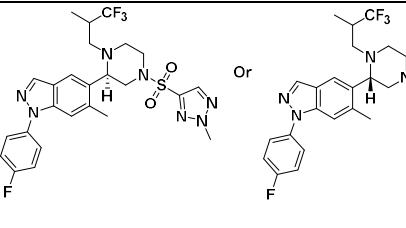
Claim 15. The compound of any one of claims 1 to 14, or a
 pharmaceutically acceptable salt thereof, having the structure:

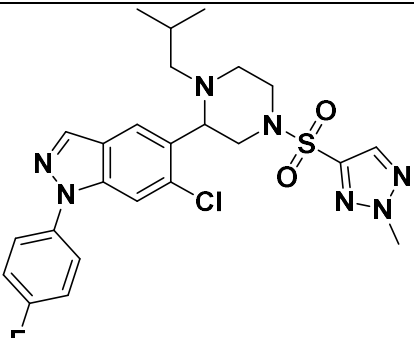
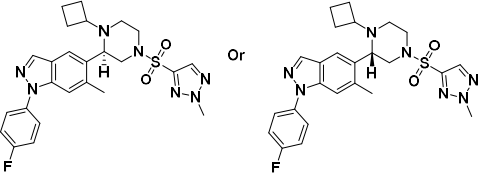
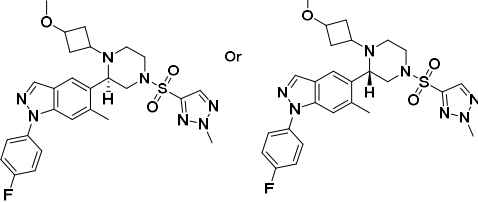
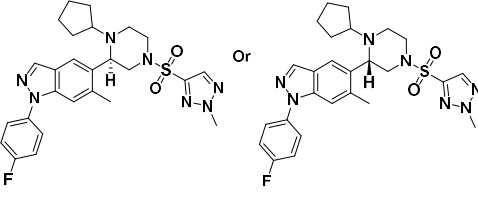
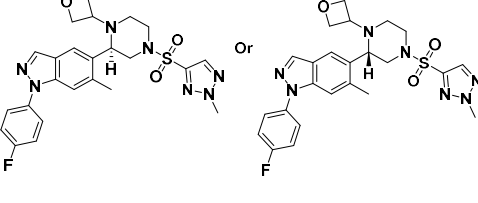
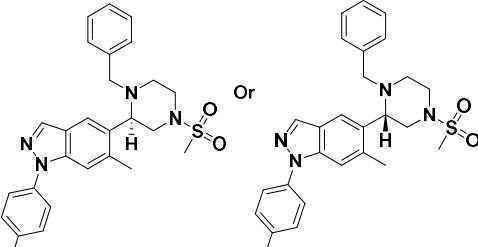
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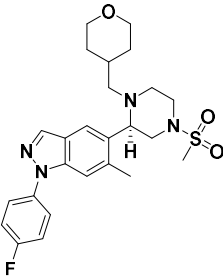
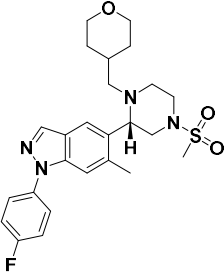
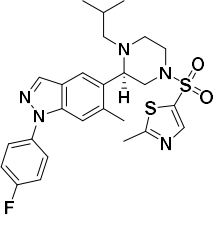
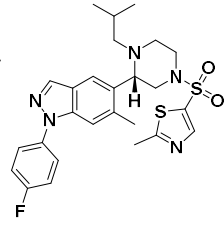
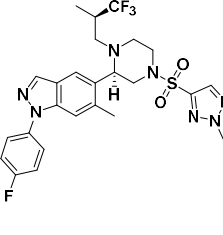
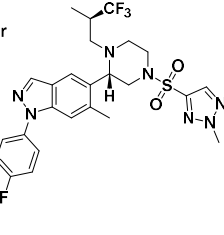
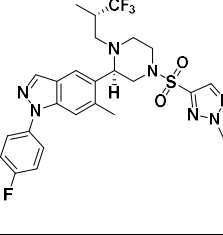
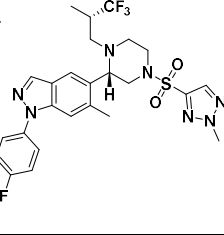
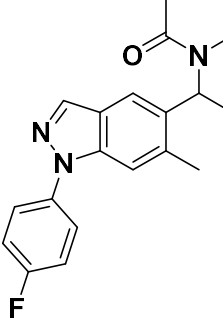
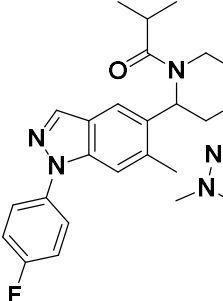
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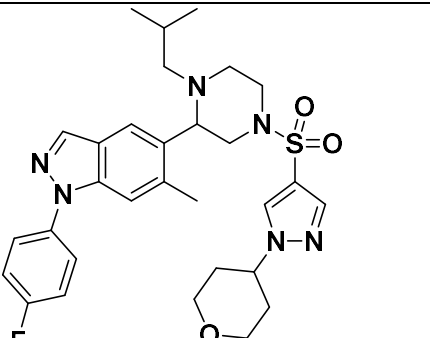
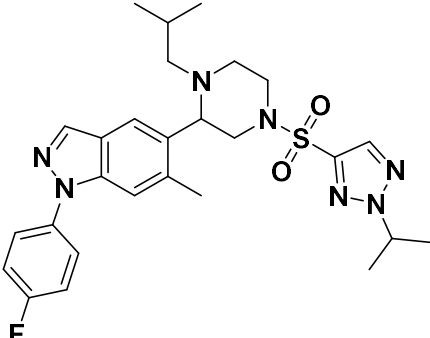
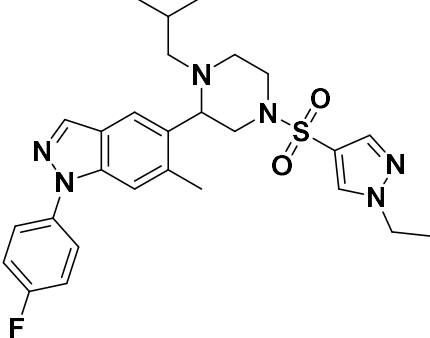
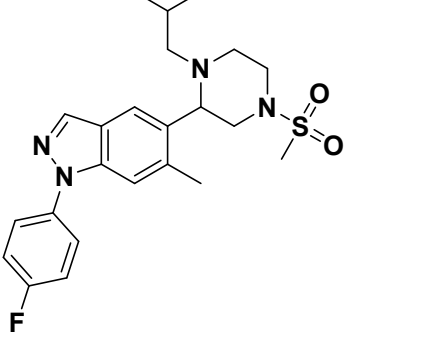
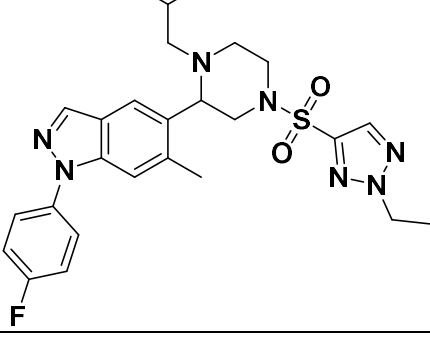
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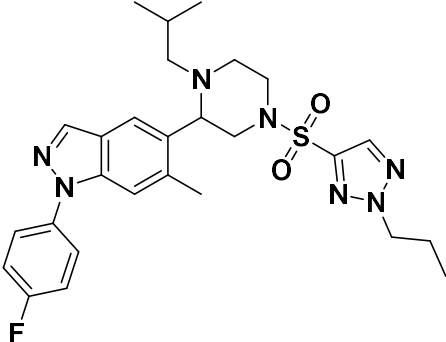
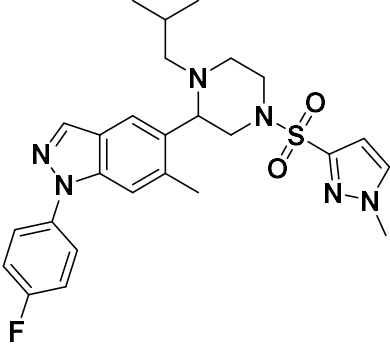
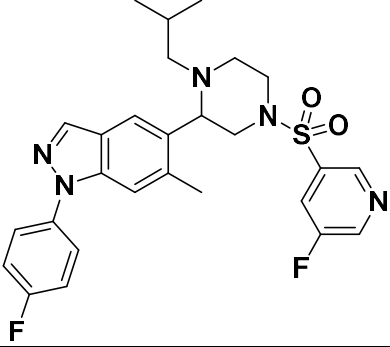
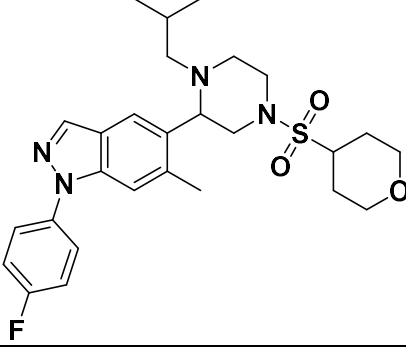
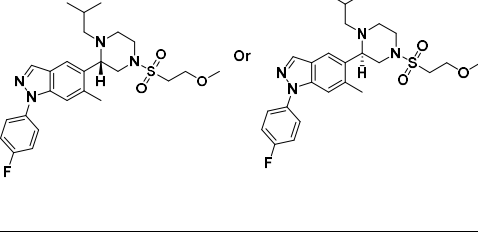
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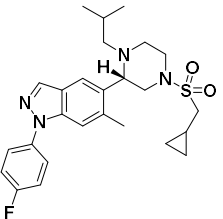
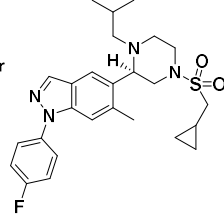
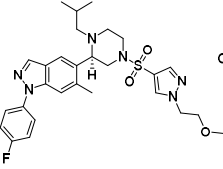
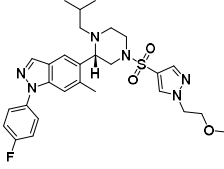
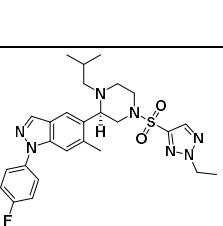
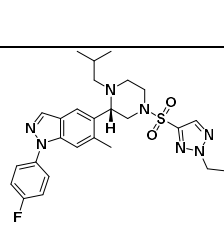
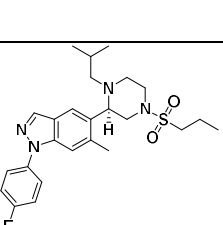
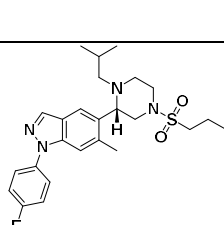
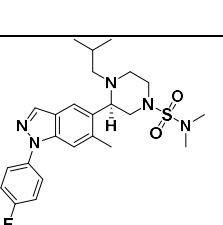
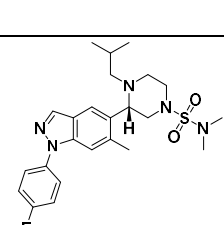
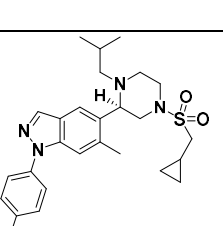
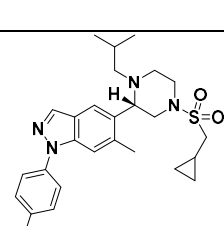
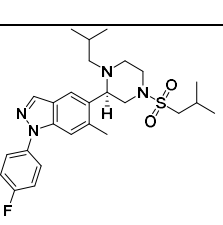
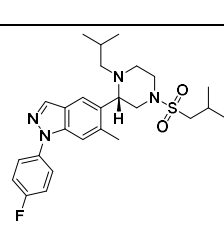
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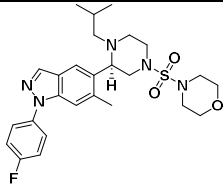
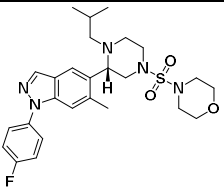
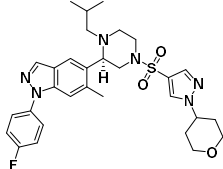
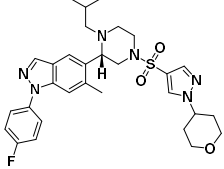
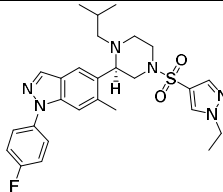
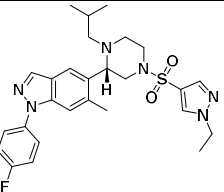
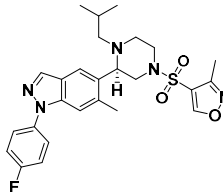
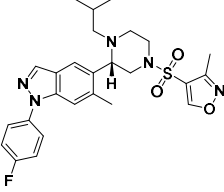
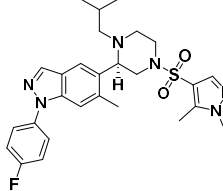
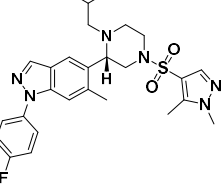
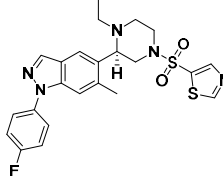
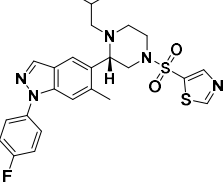
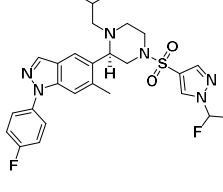
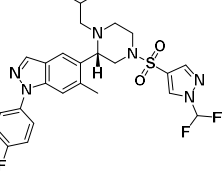
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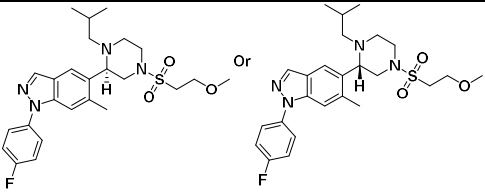
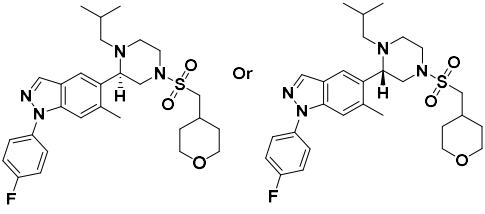
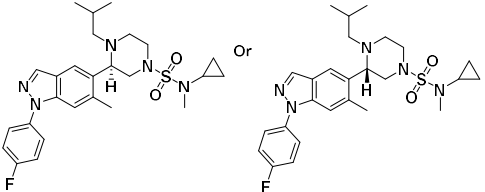
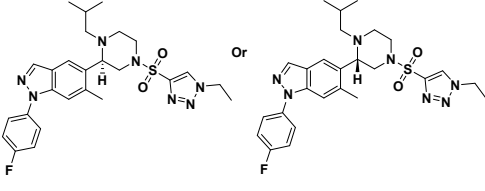
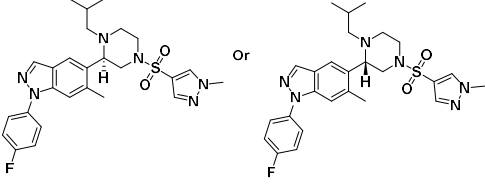
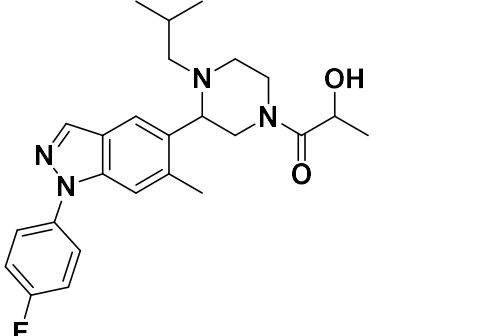
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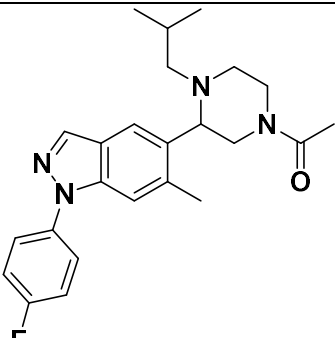
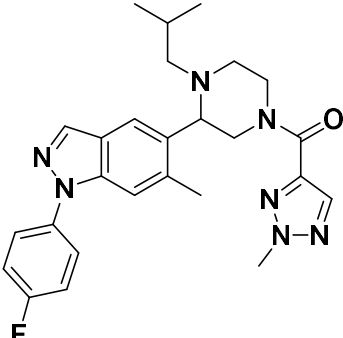
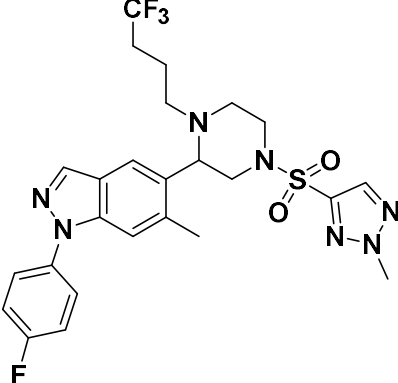
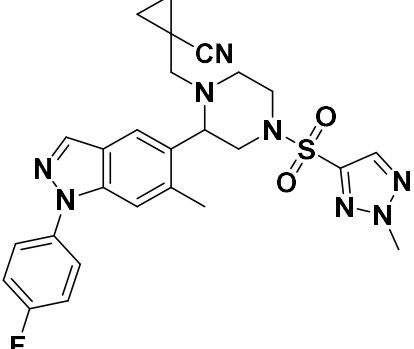
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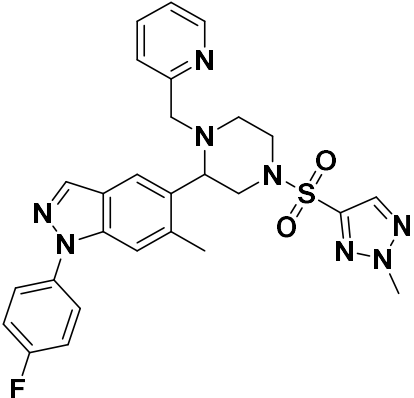
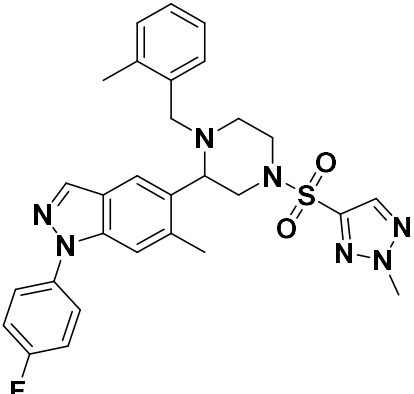
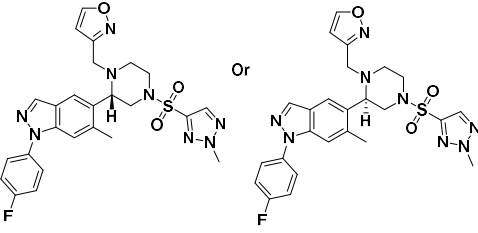
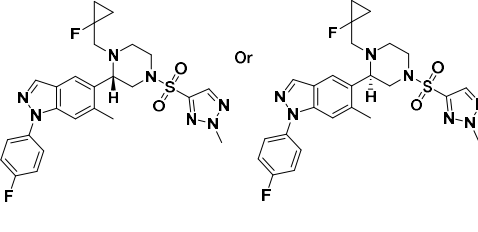
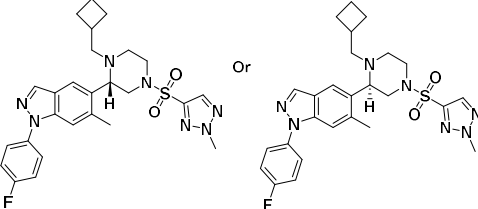
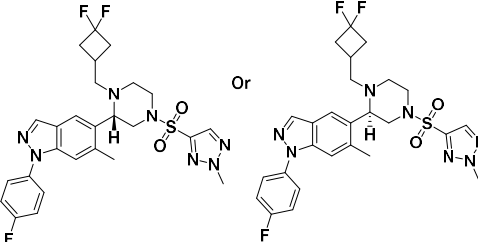
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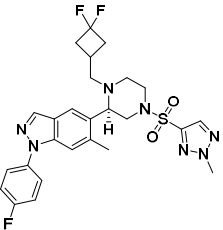
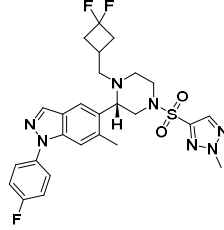
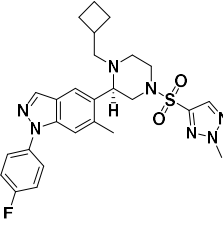
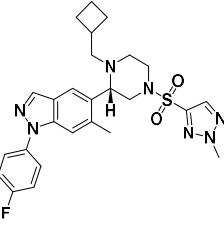
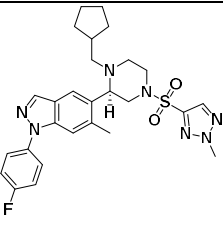
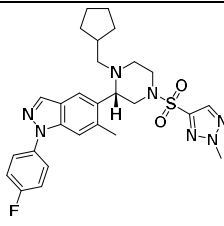
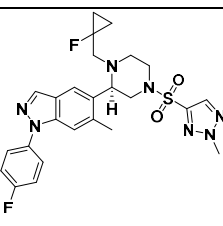
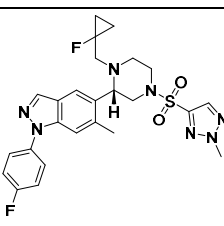
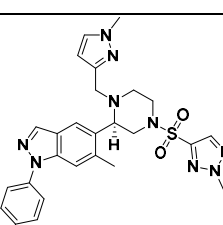
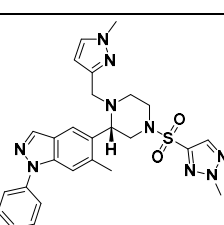
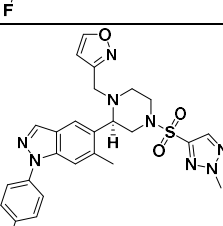
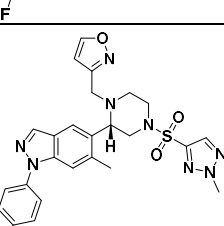
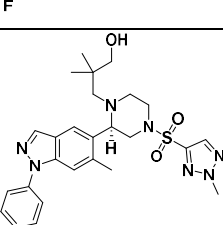
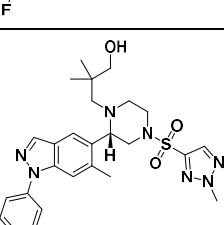
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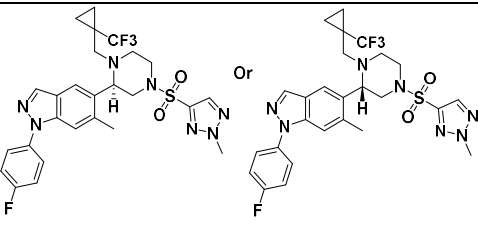
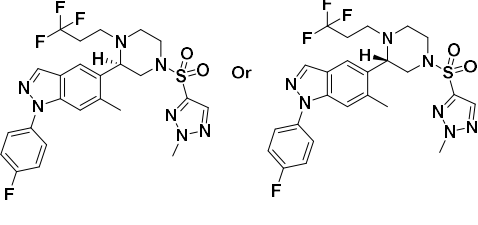
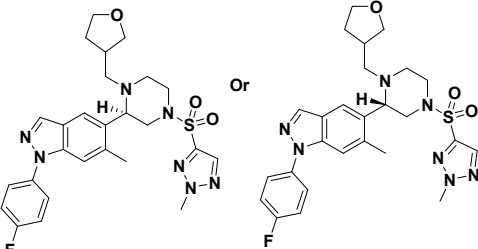
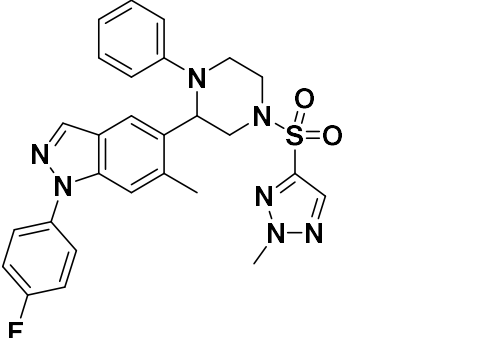
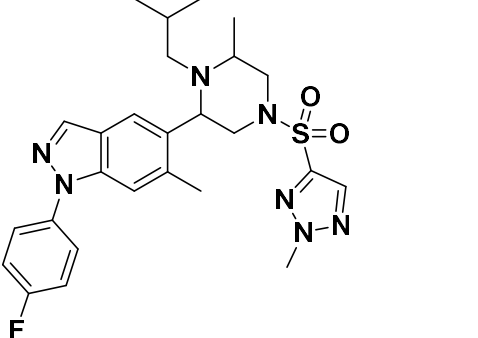
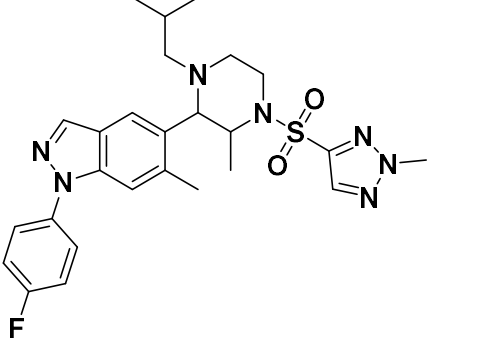
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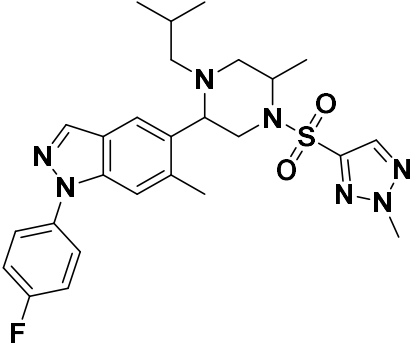
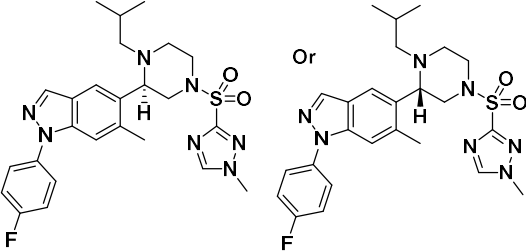
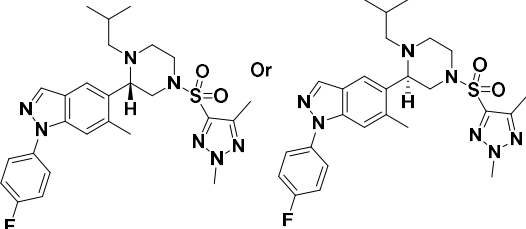
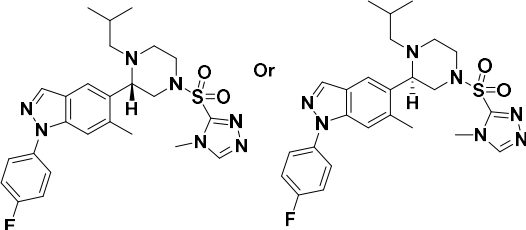
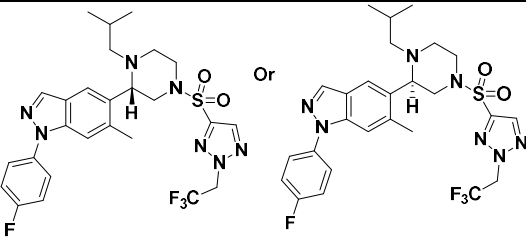
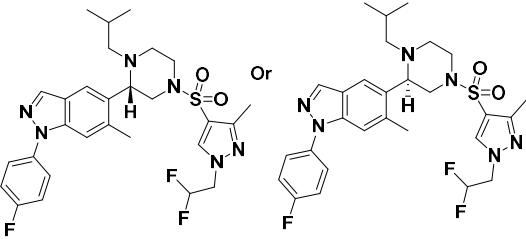
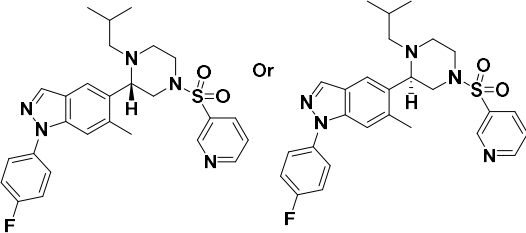
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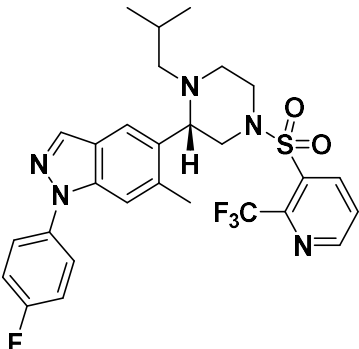
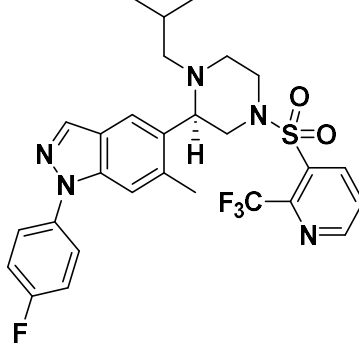
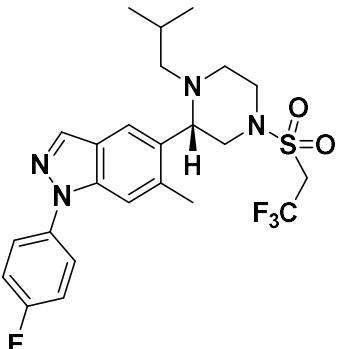
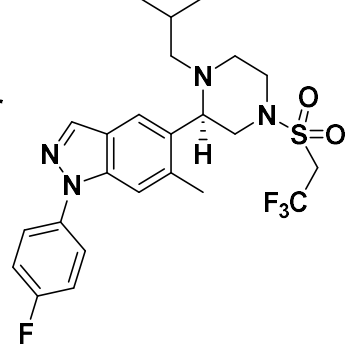
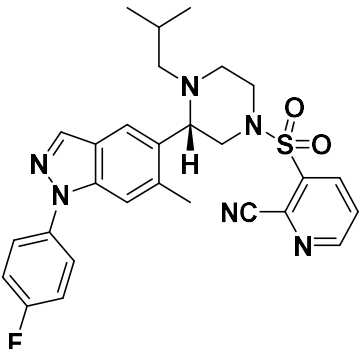
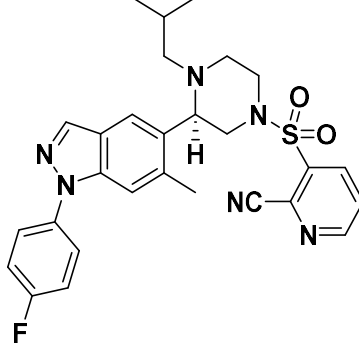
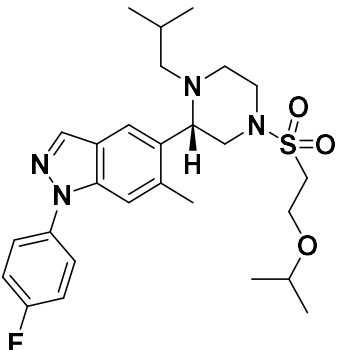
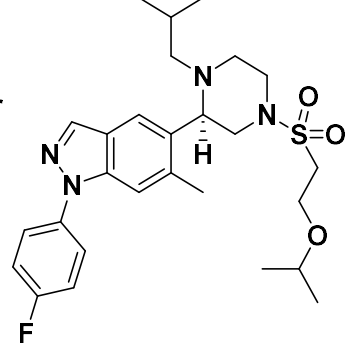
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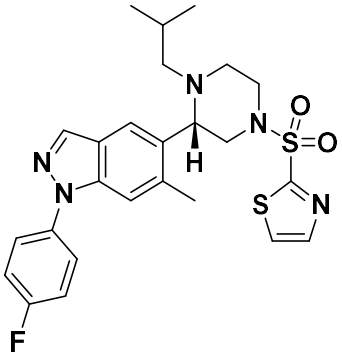
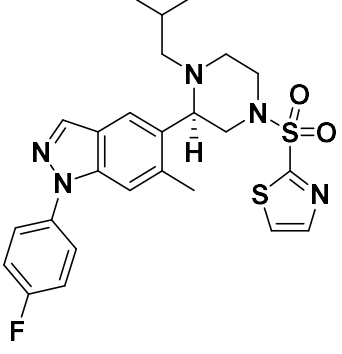
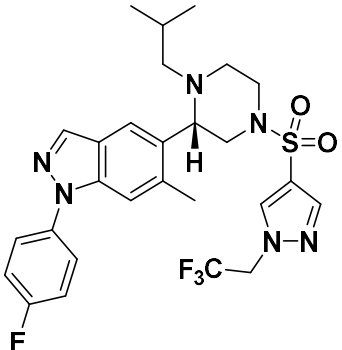
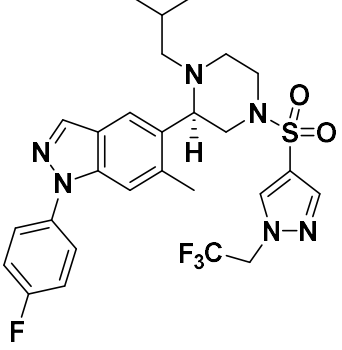
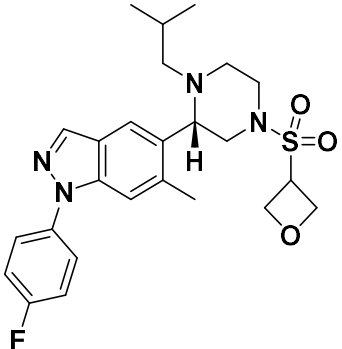
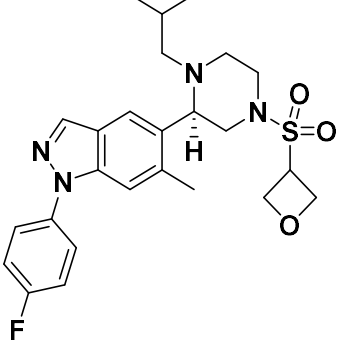
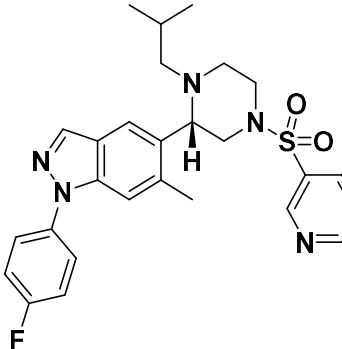
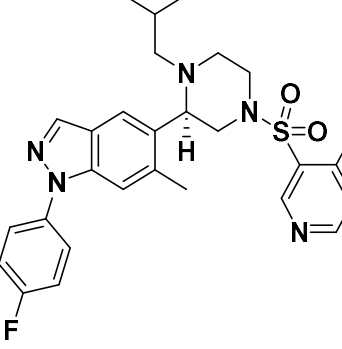
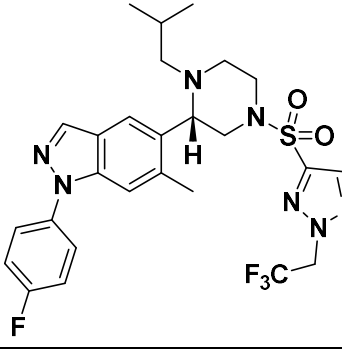
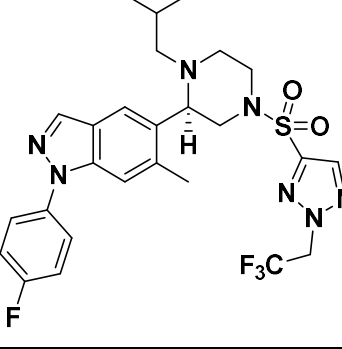
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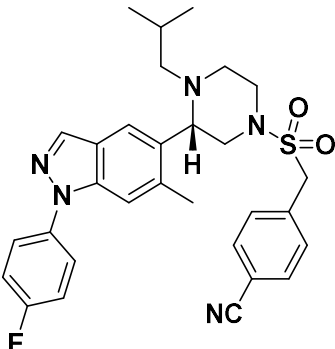
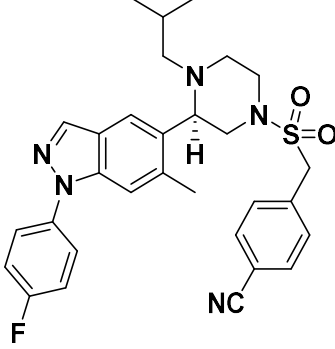
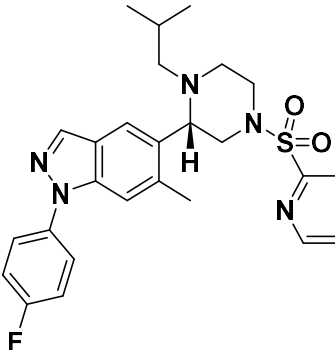
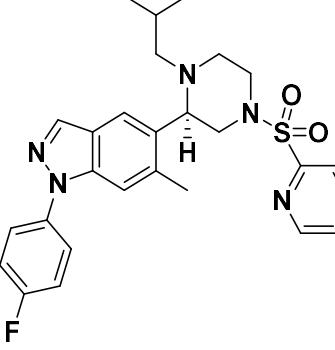
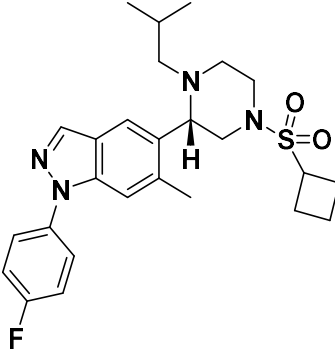
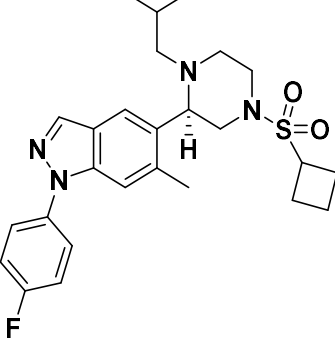
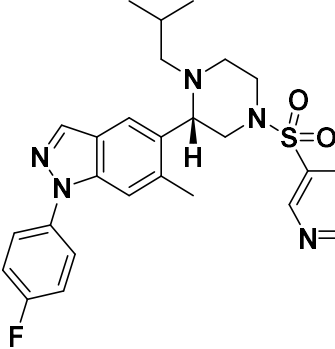
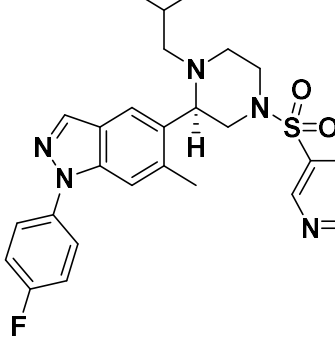
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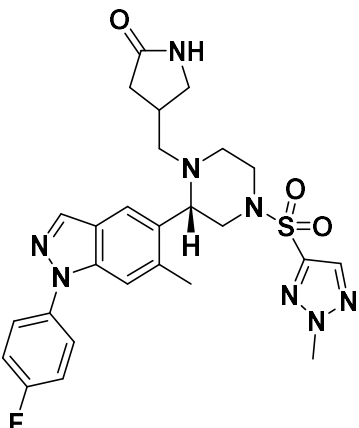
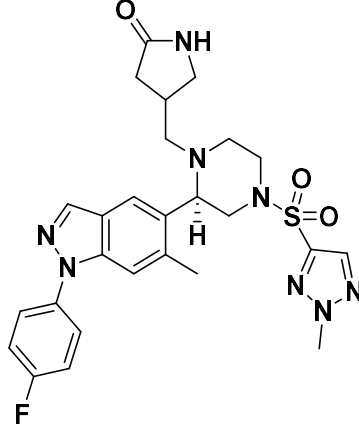
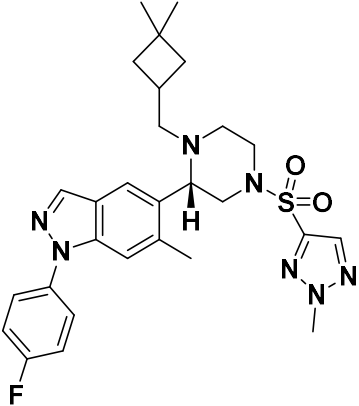
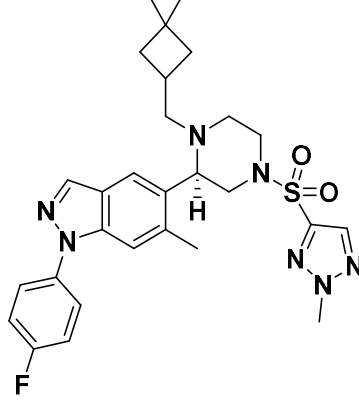
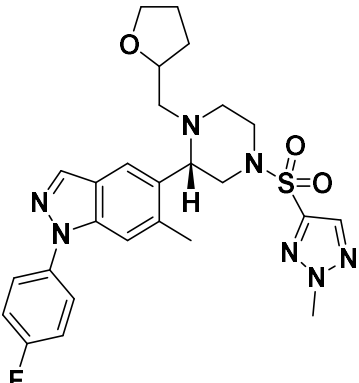
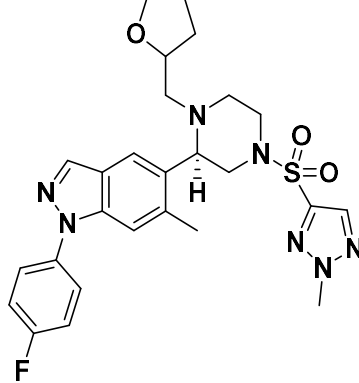
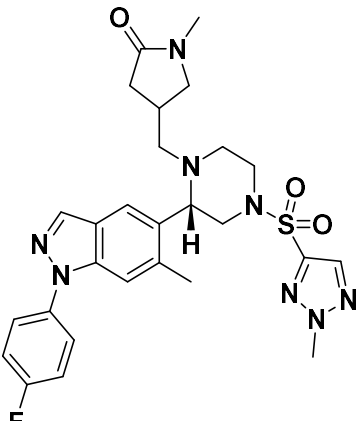
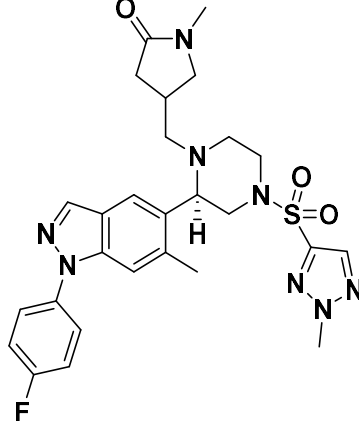
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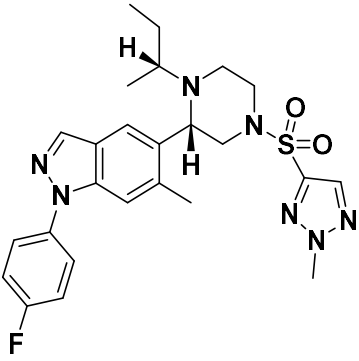
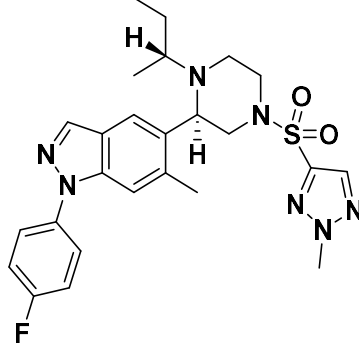
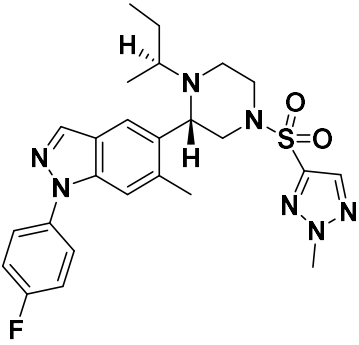
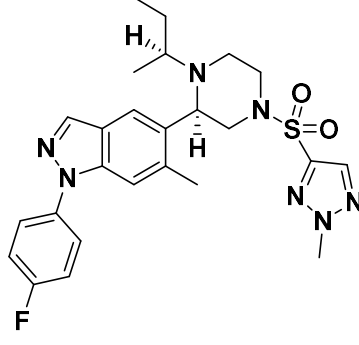
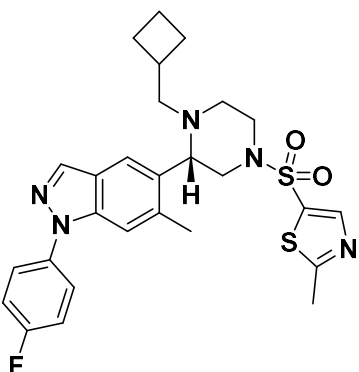
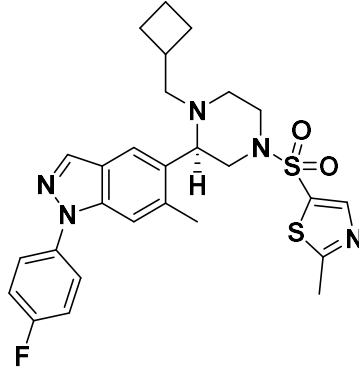
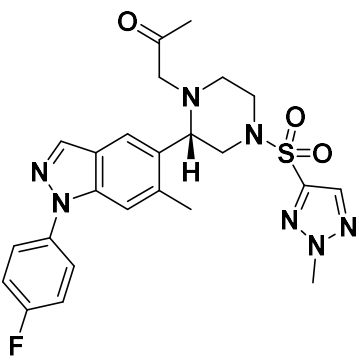
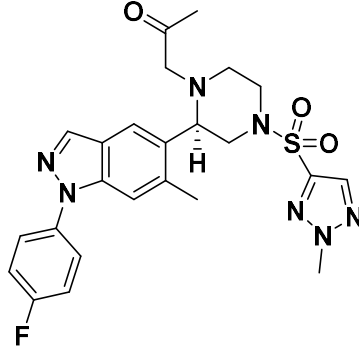
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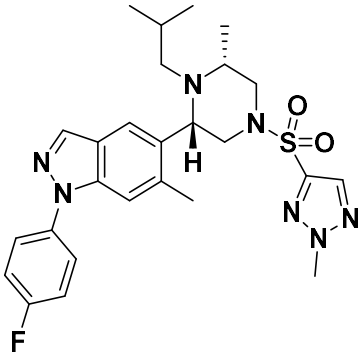
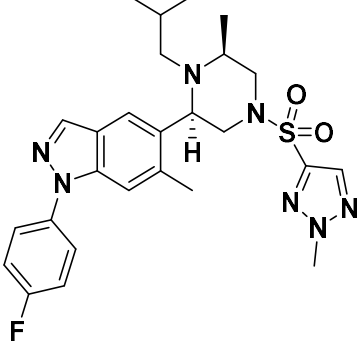
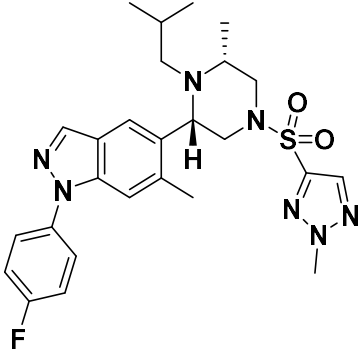
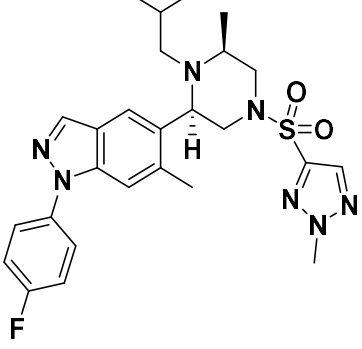
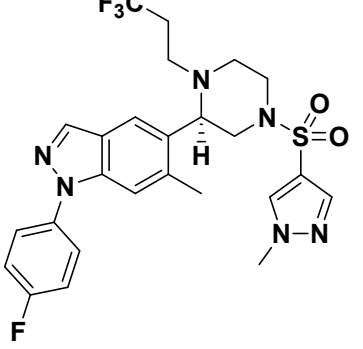
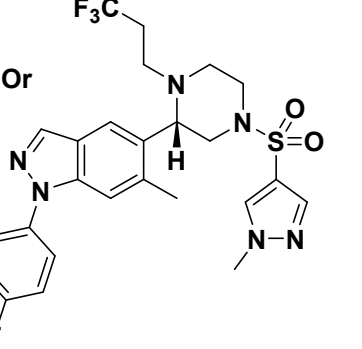
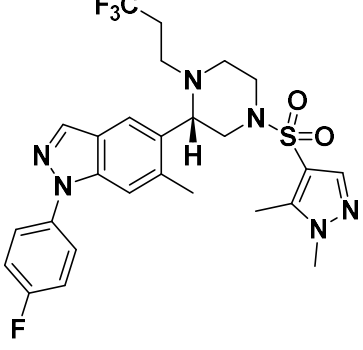
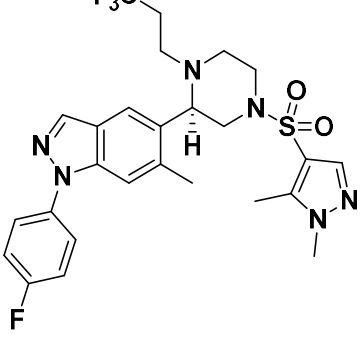
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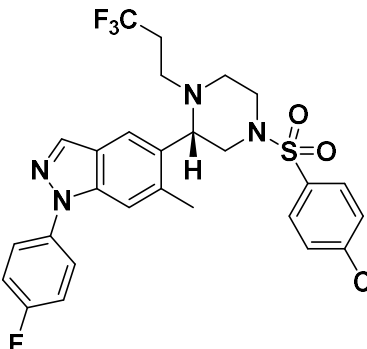
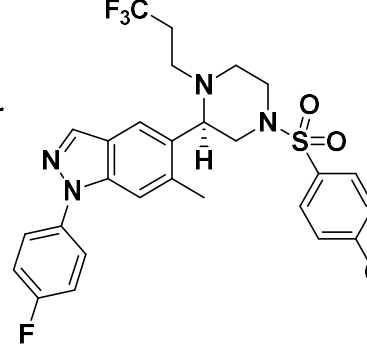
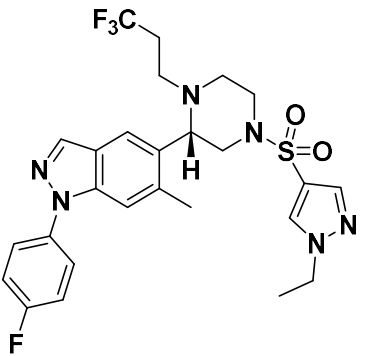
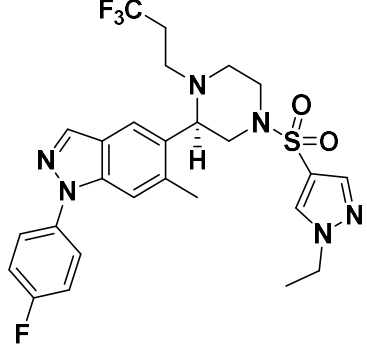
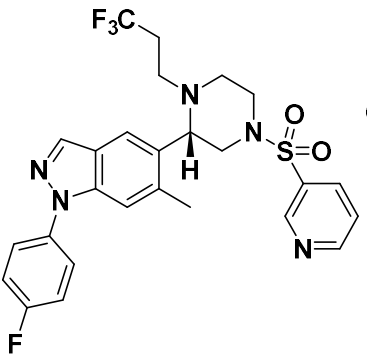
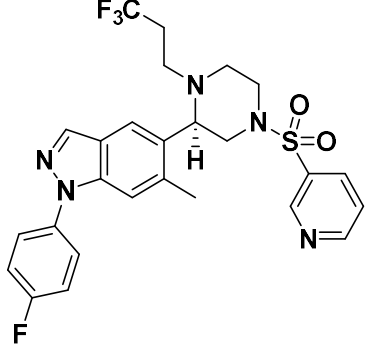
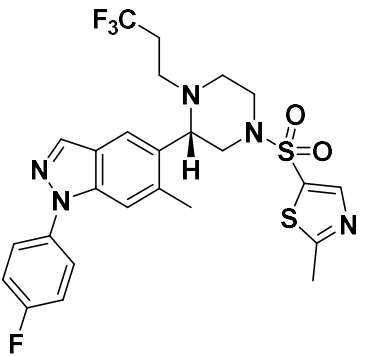
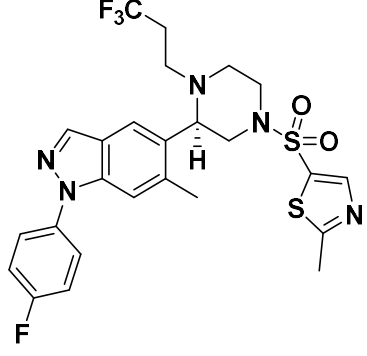
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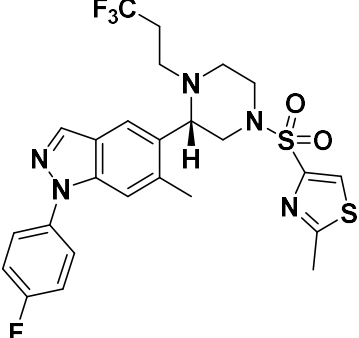
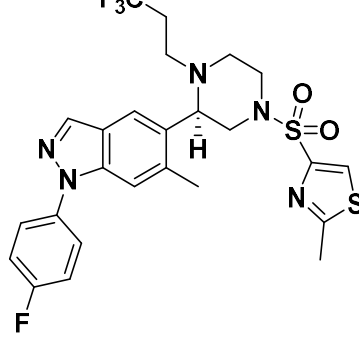
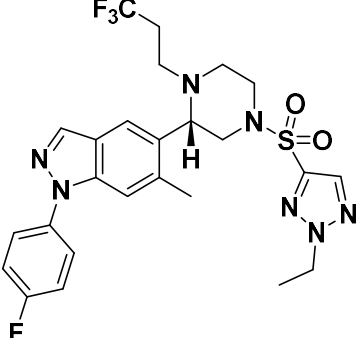
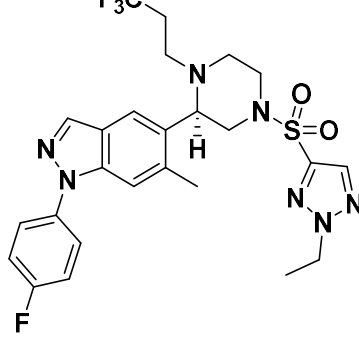
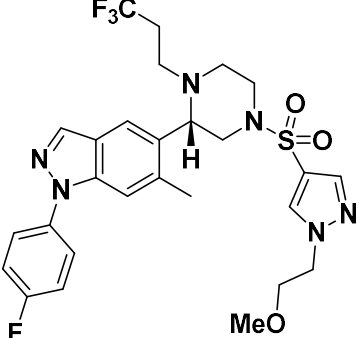
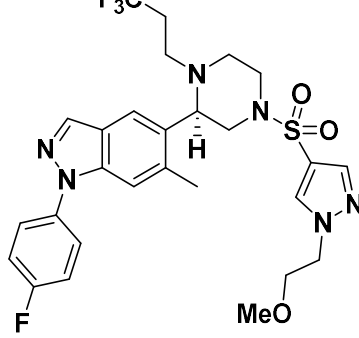
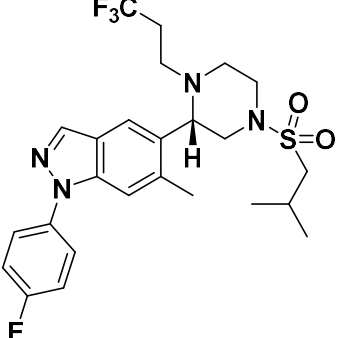
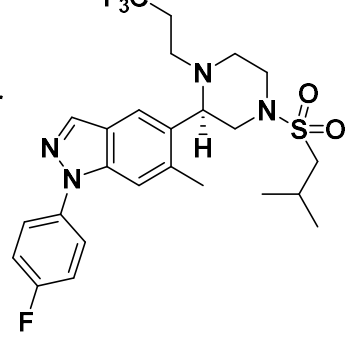
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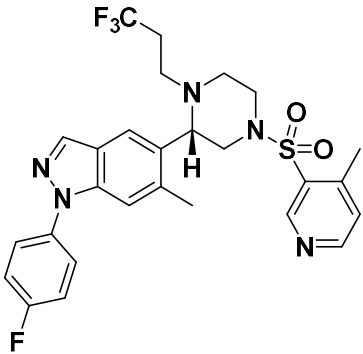
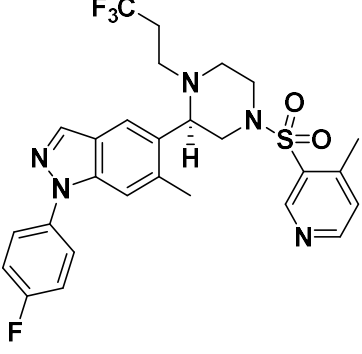
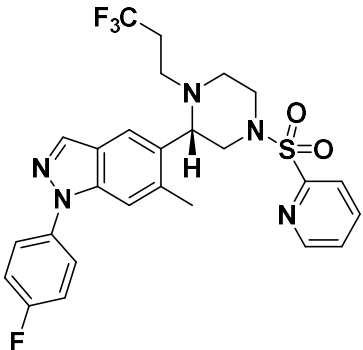
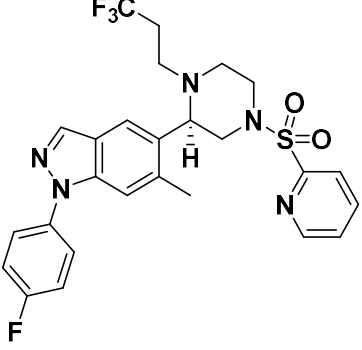
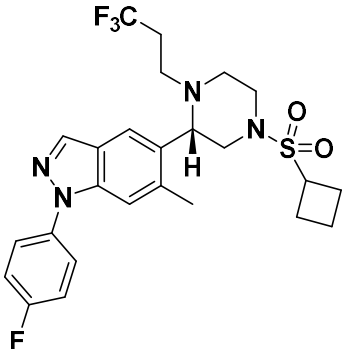
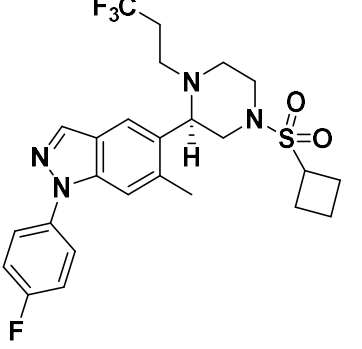
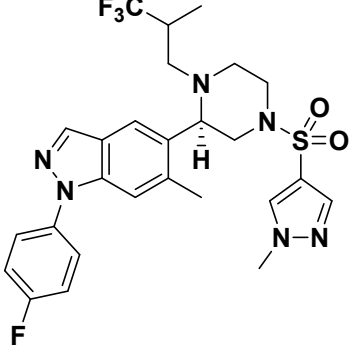
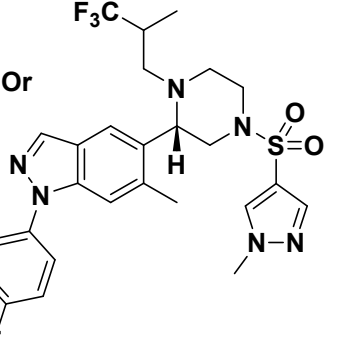
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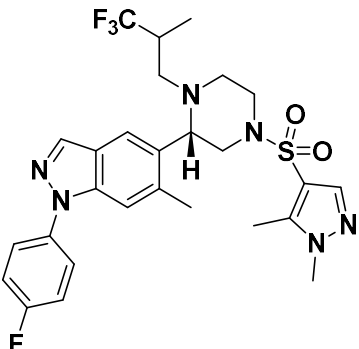
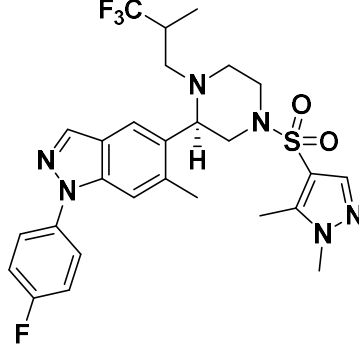
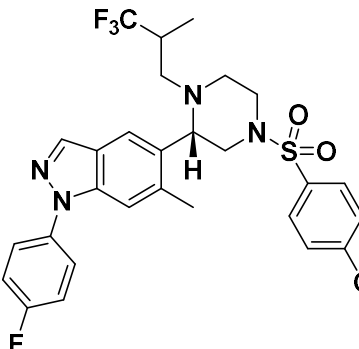
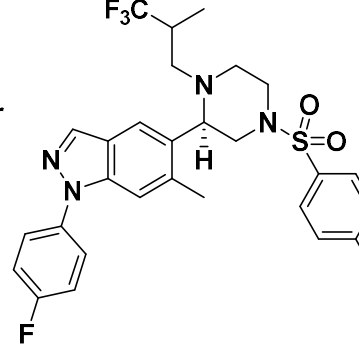
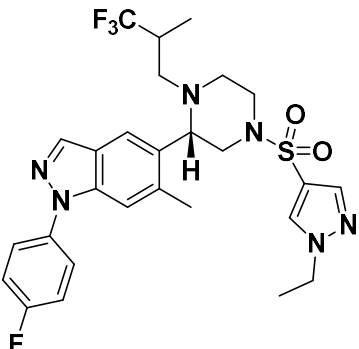
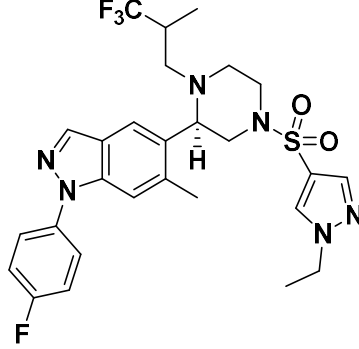
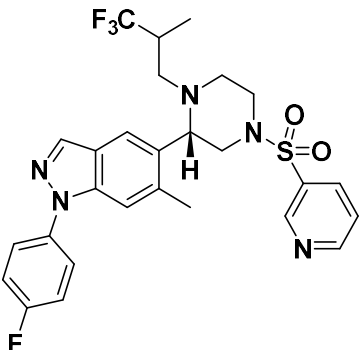
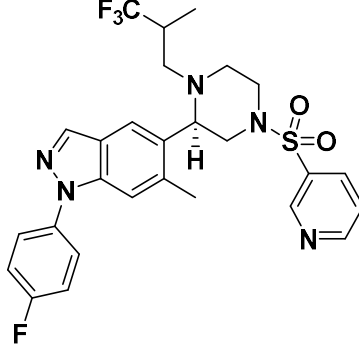
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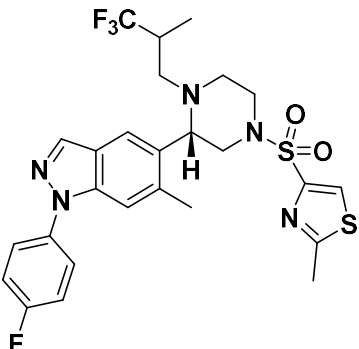
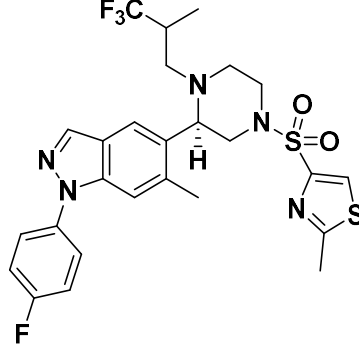
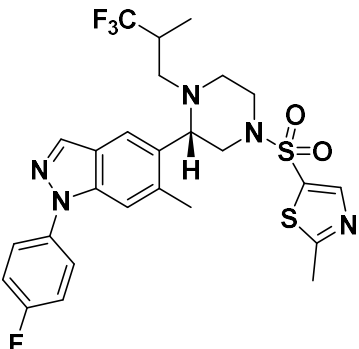
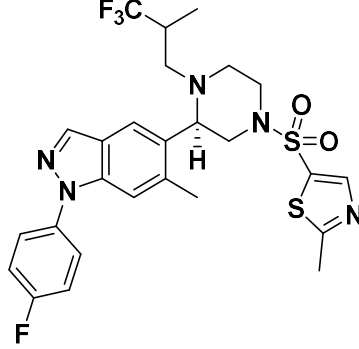
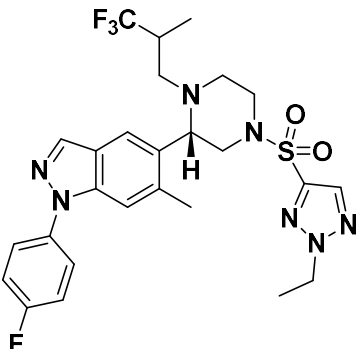
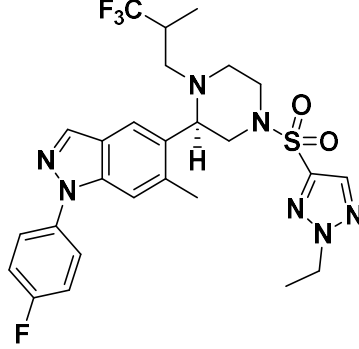
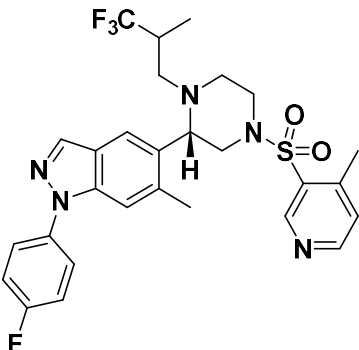
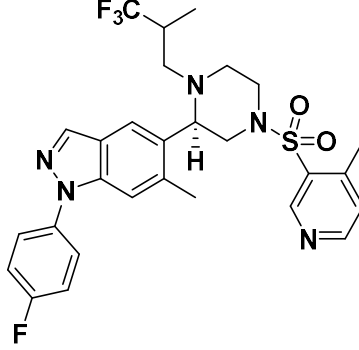
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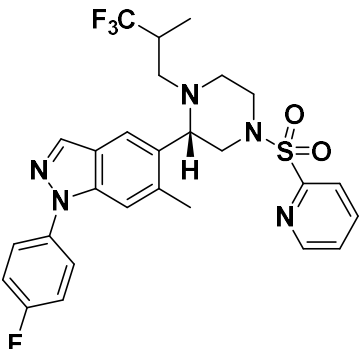
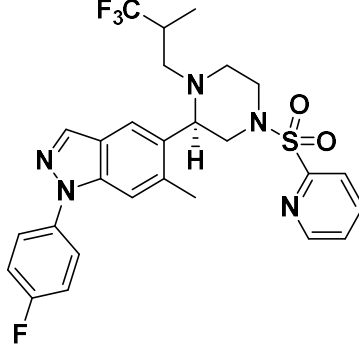
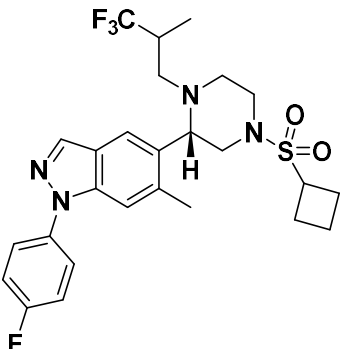
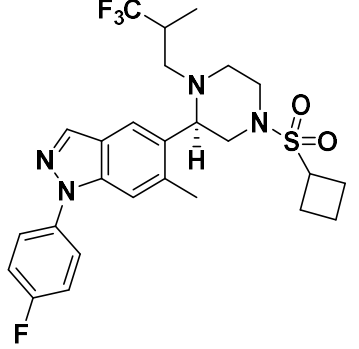
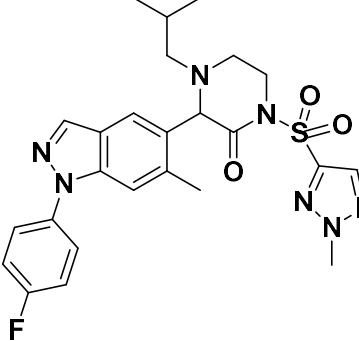
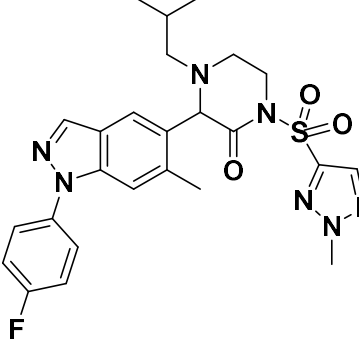
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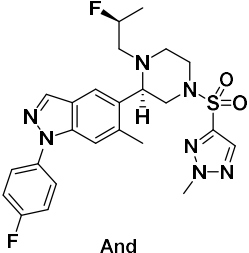
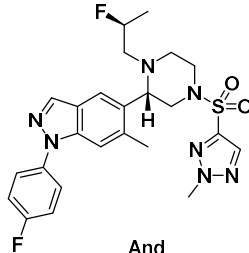
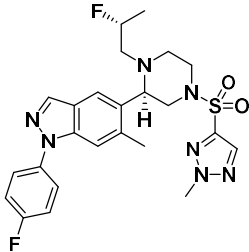
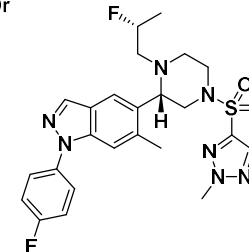
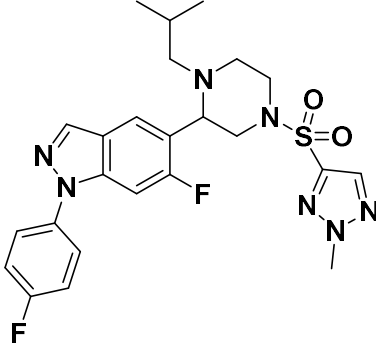
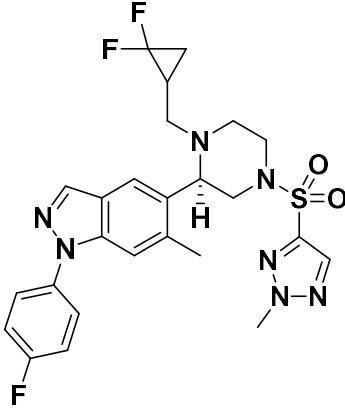
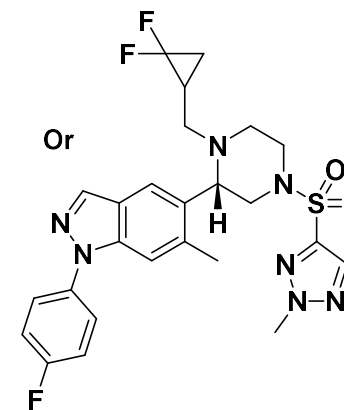
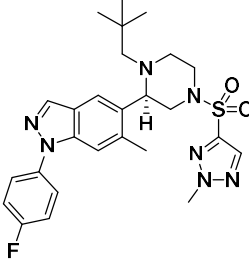
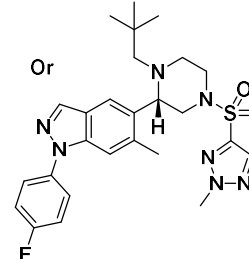
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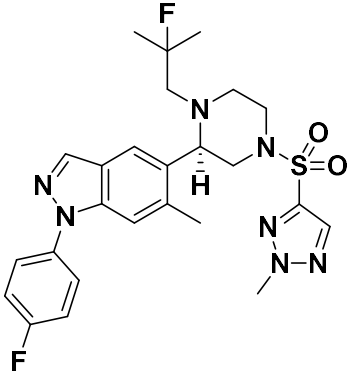
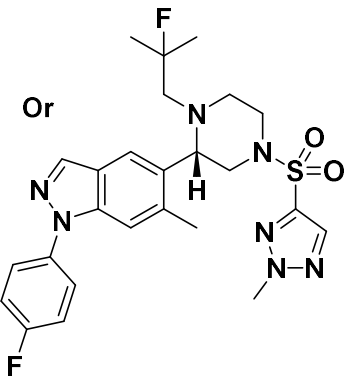
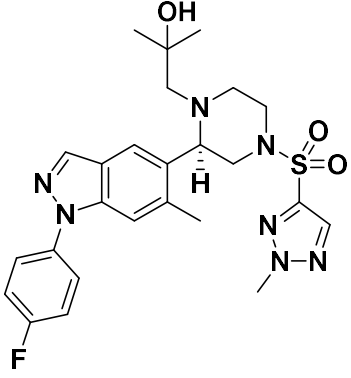
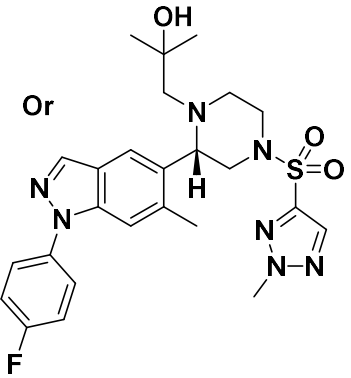
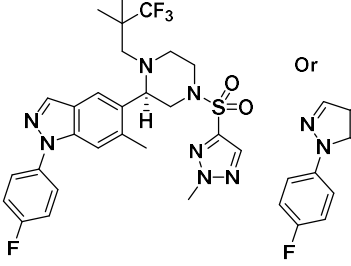
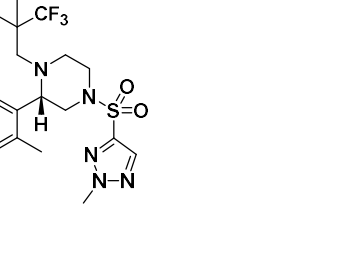
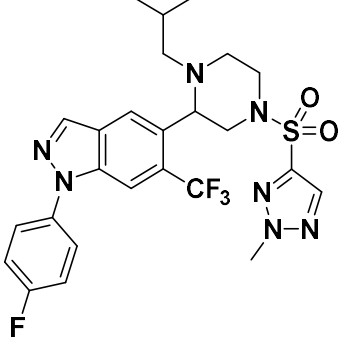
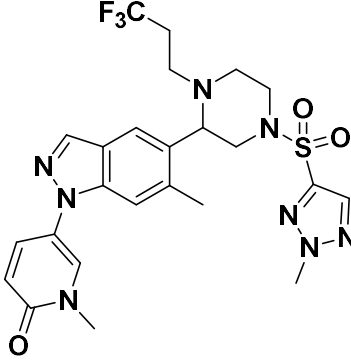
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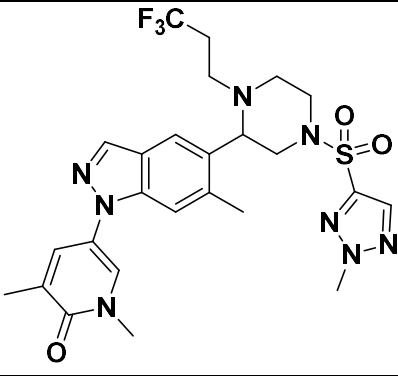
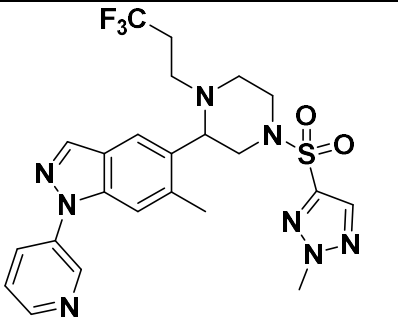
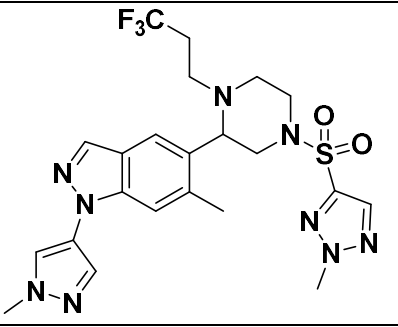
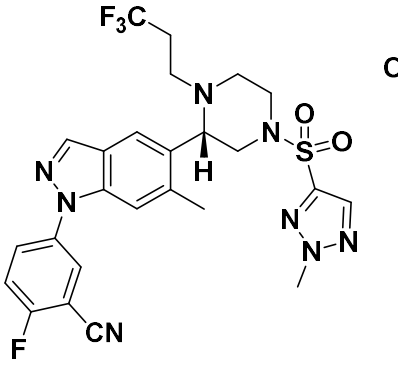
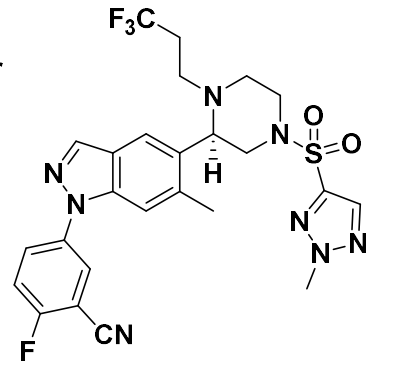
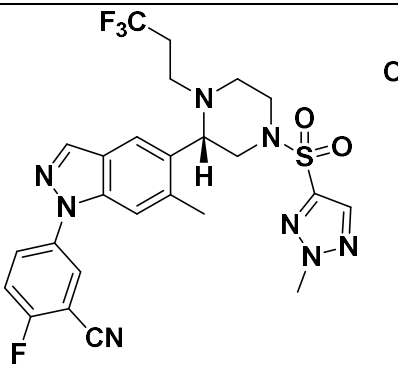
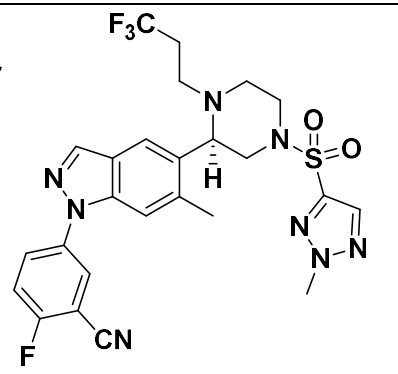
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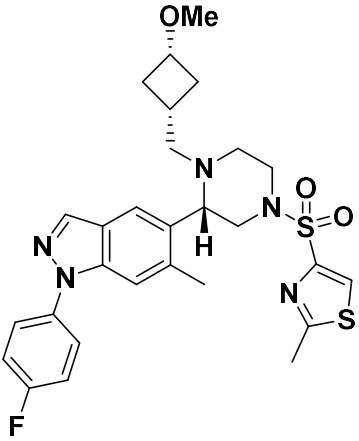
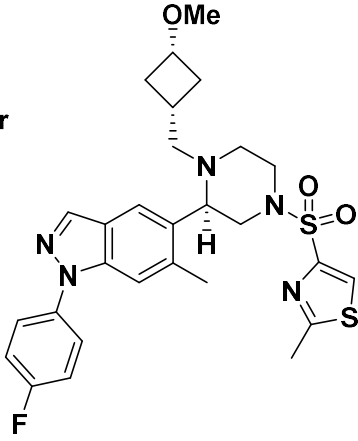
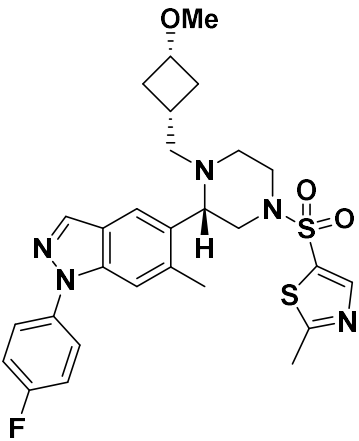
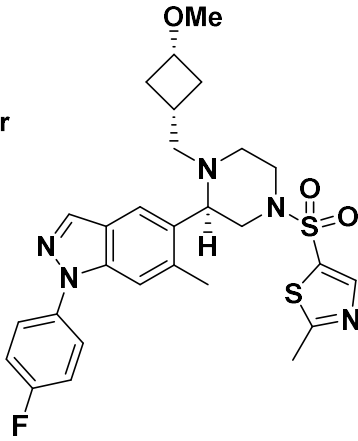
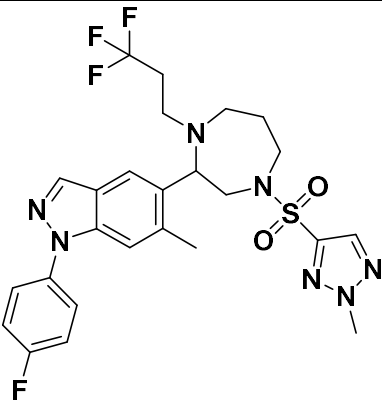
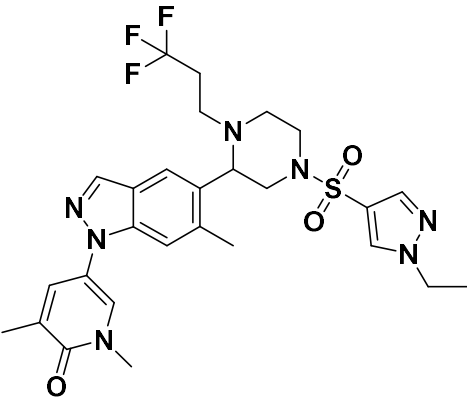
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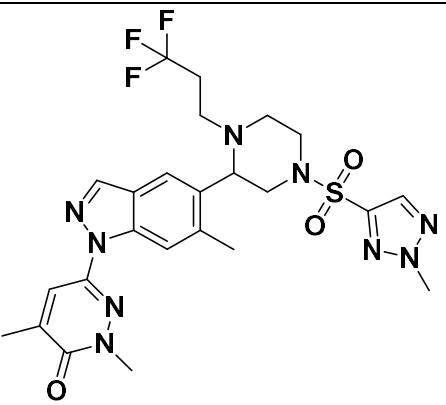
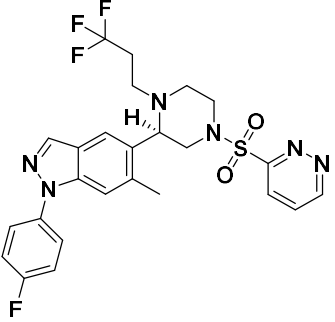
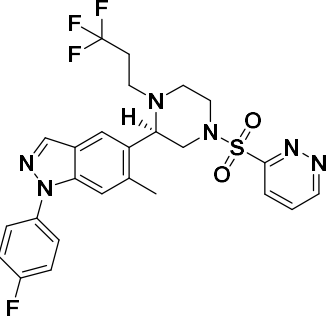
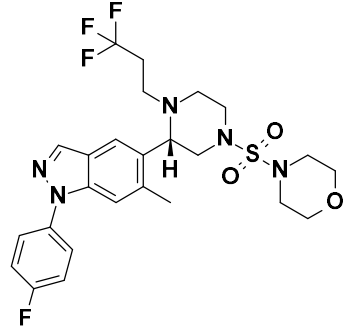
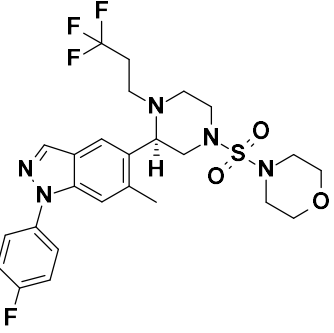
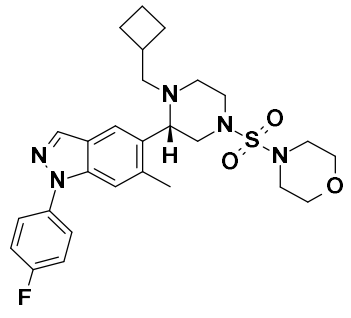
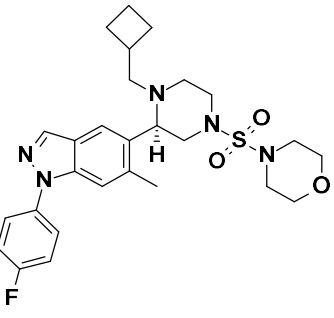
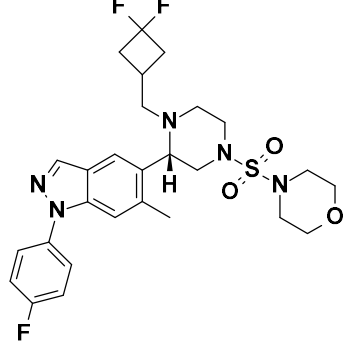
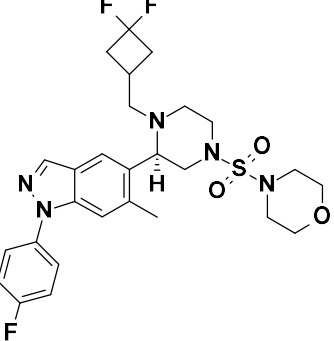
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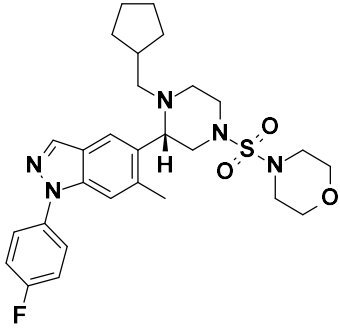
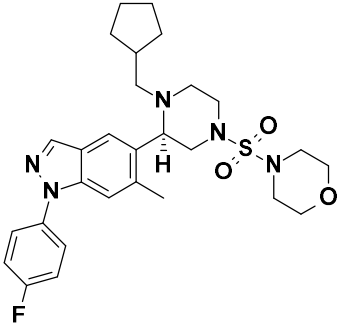
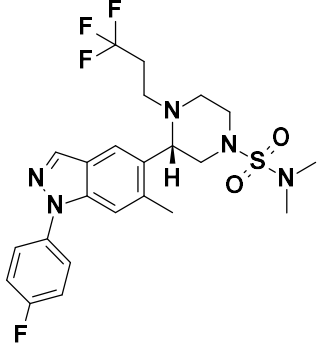
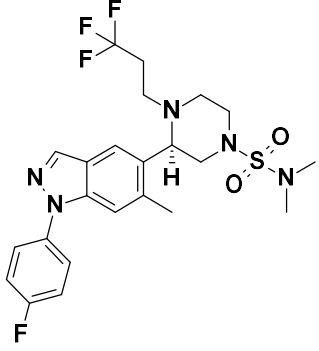
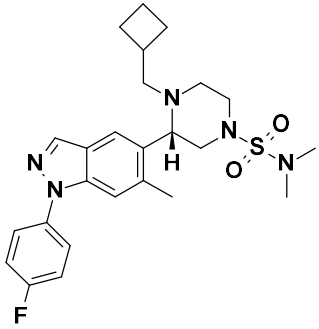
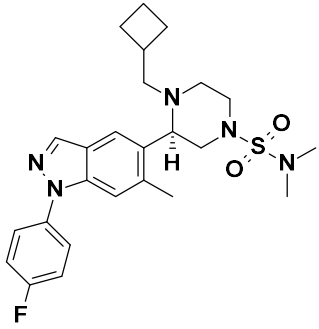
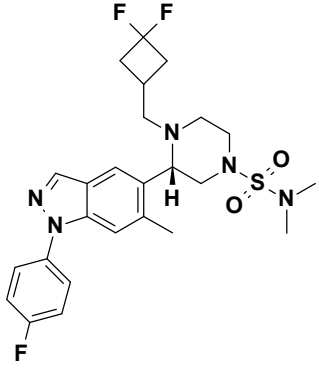
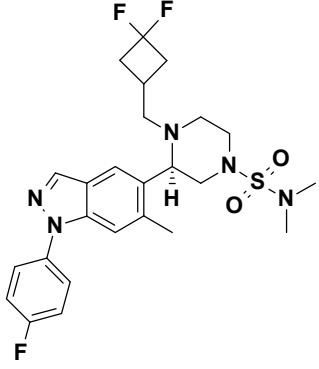
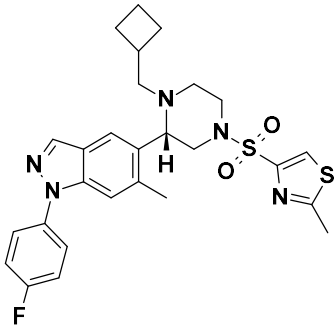
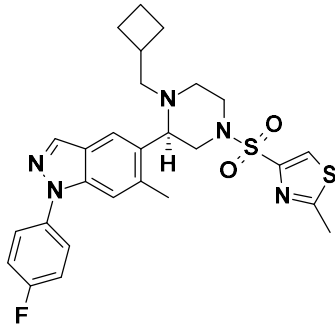
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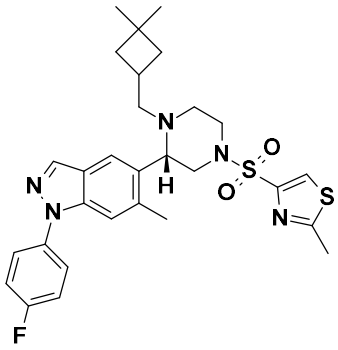
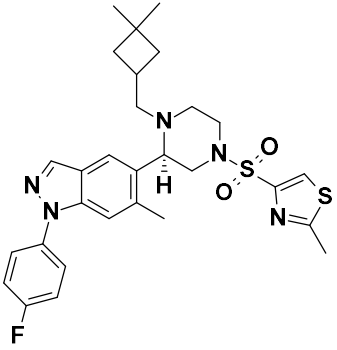
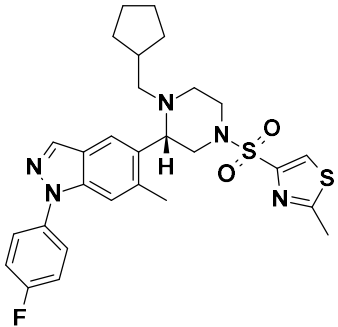
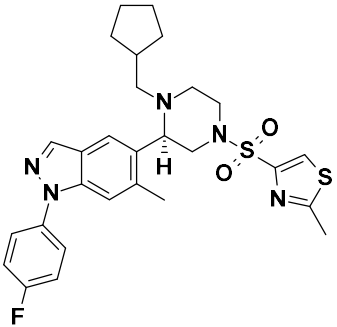
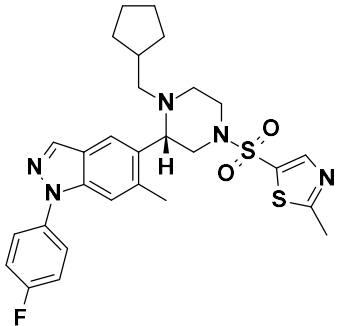
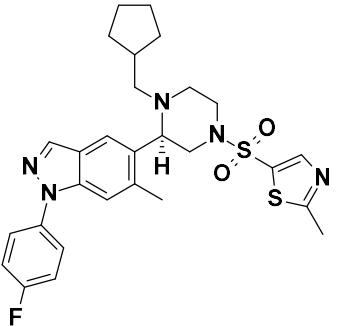
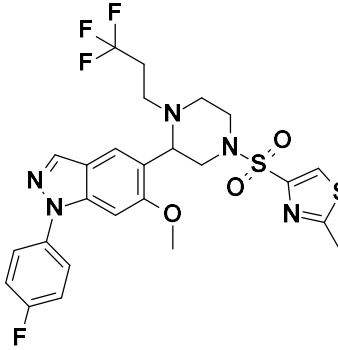
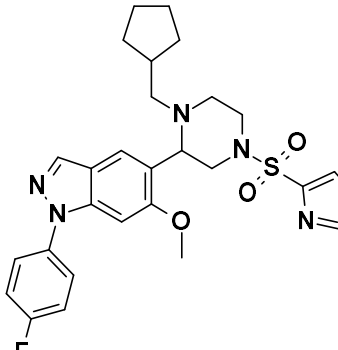
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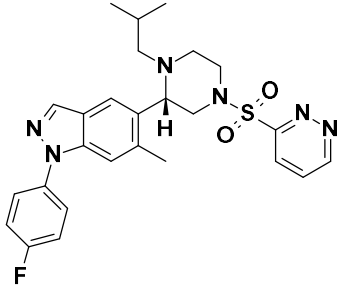
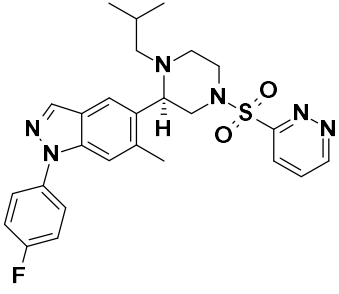
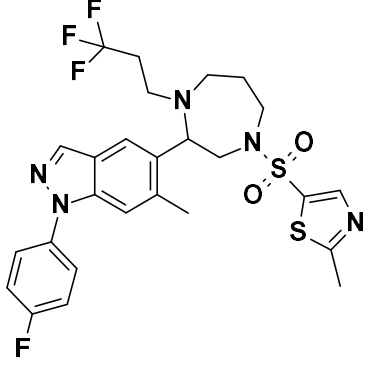
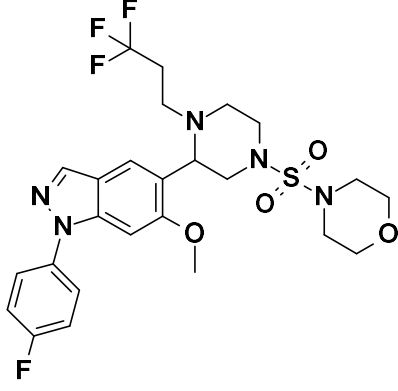
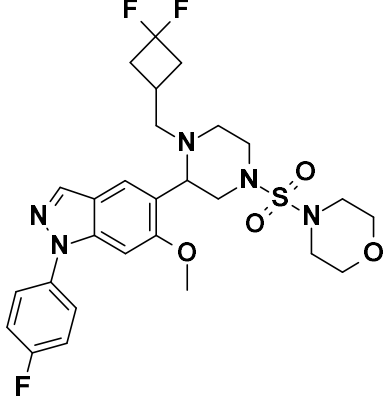
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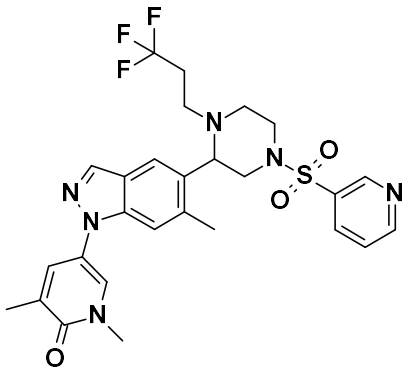
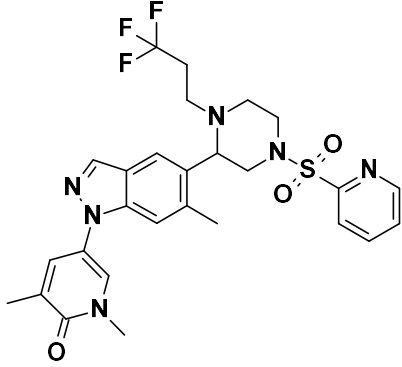
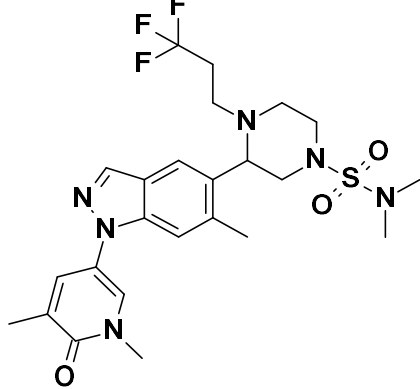
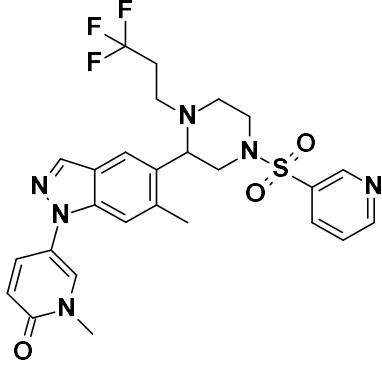
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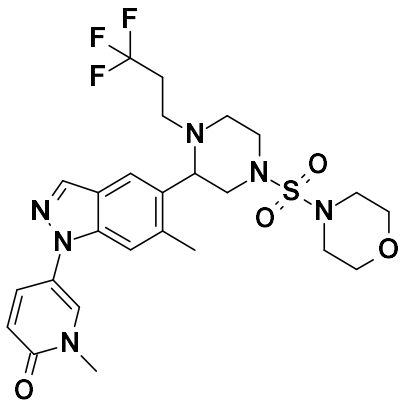
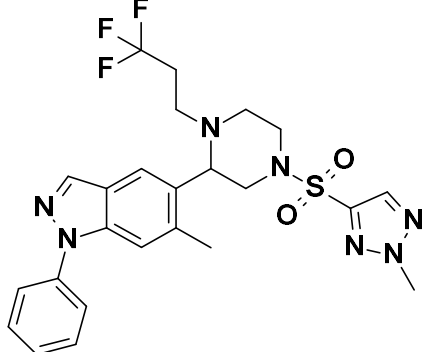
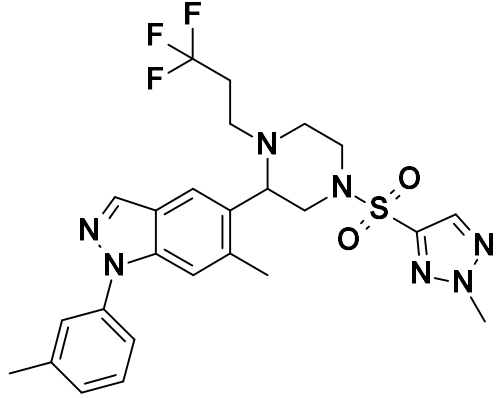
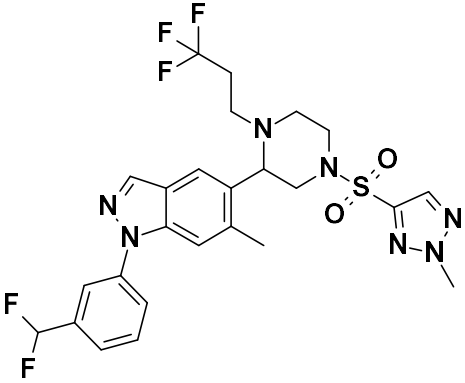
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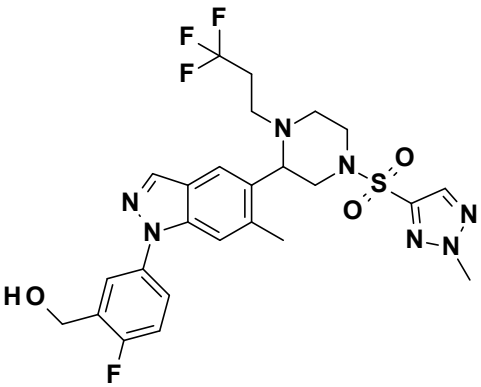
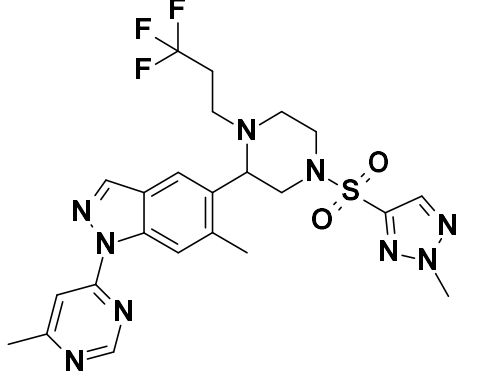
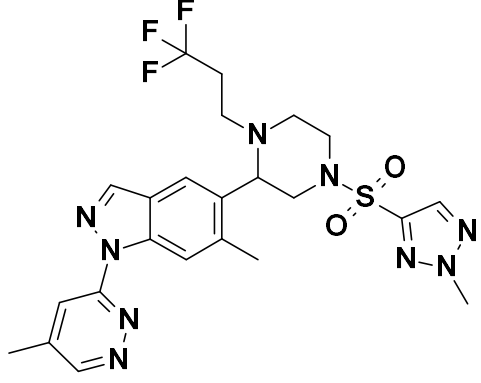
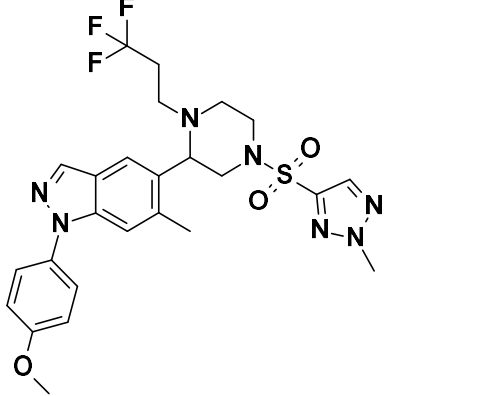
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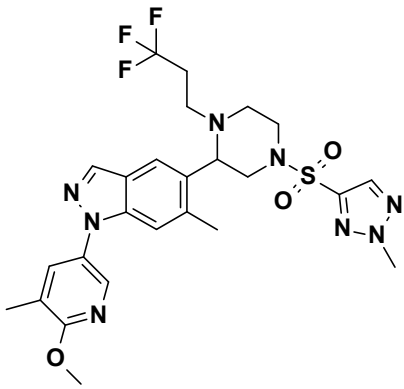
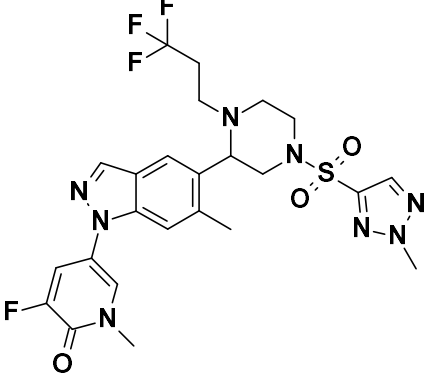
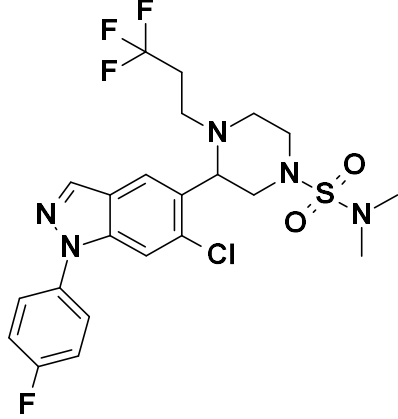
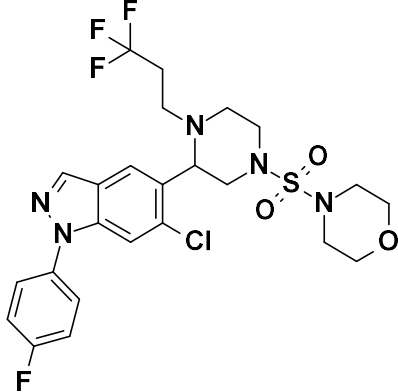
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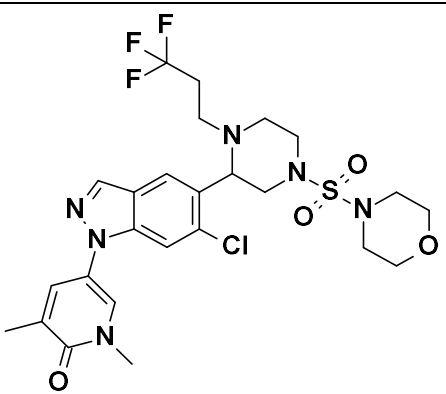
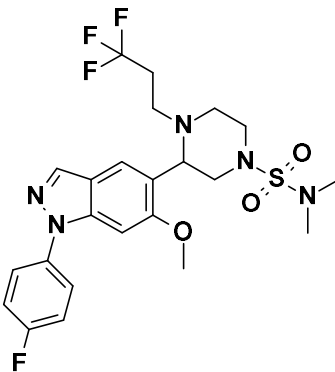
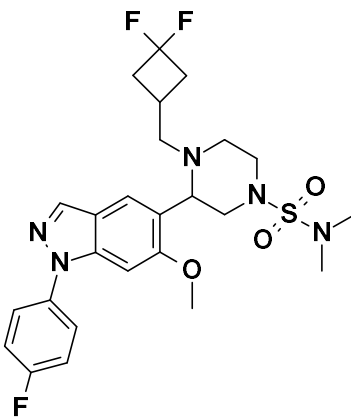
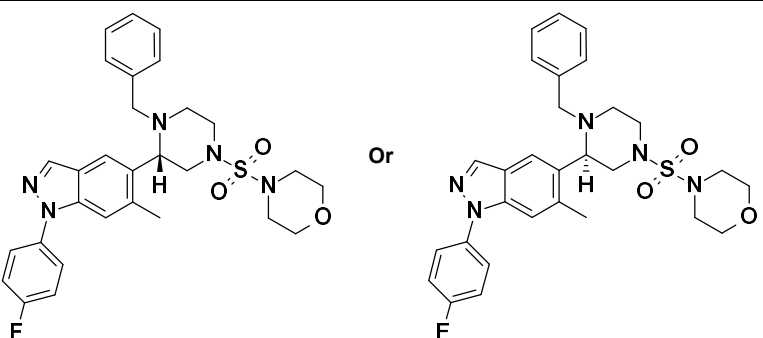
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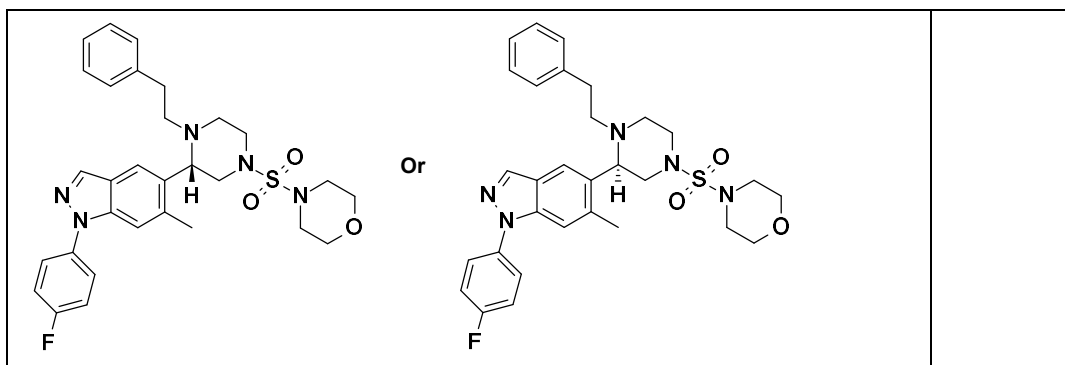
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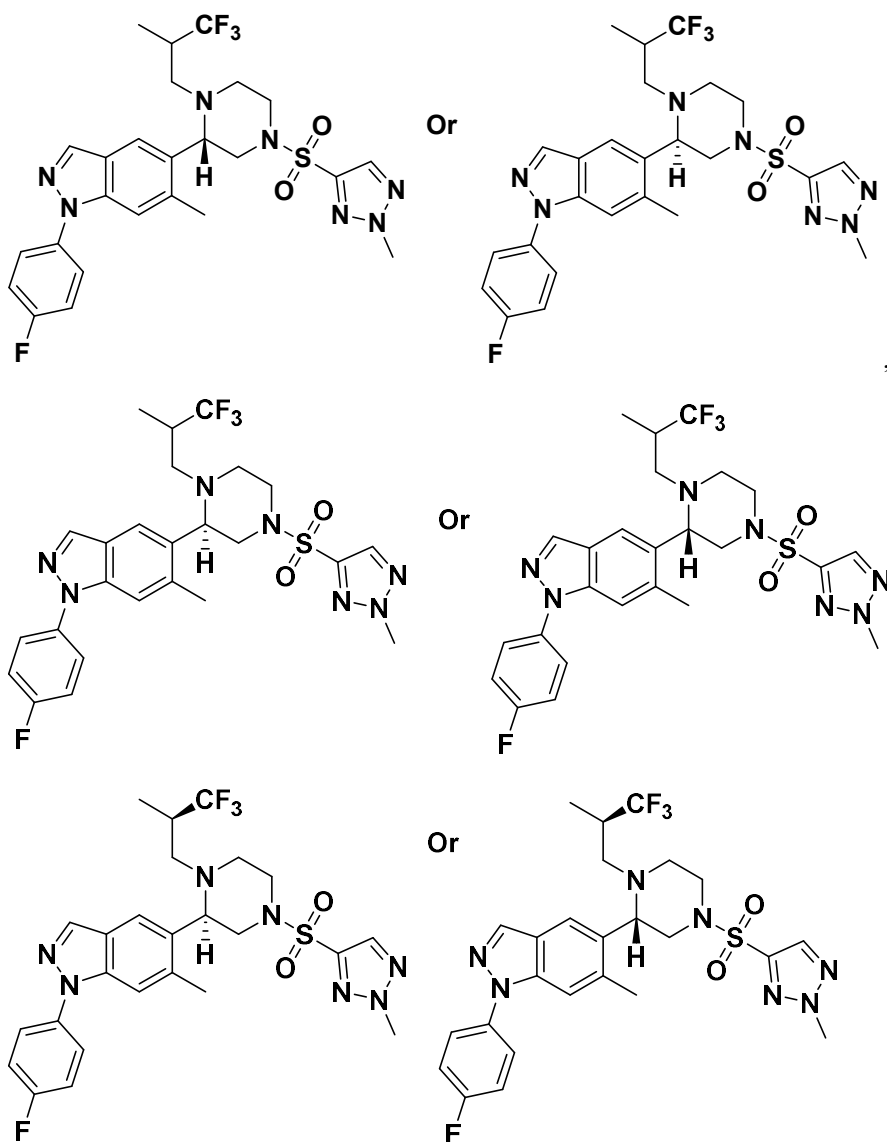
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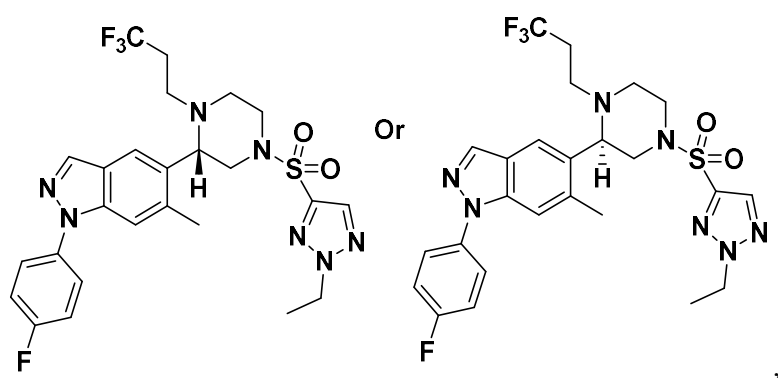
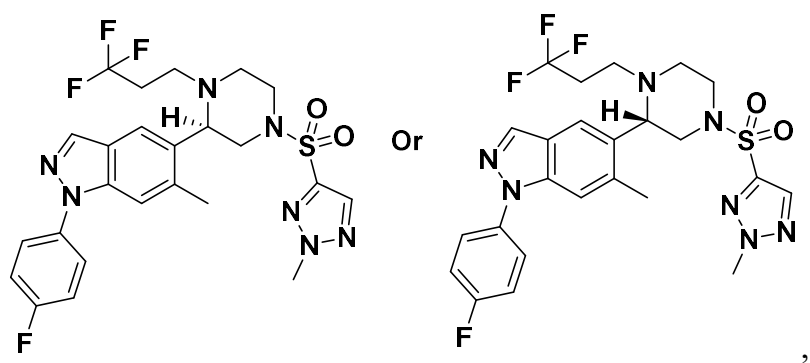
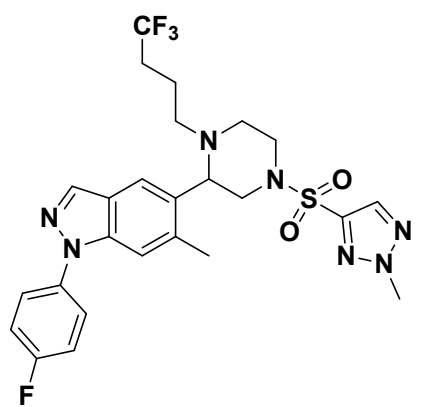
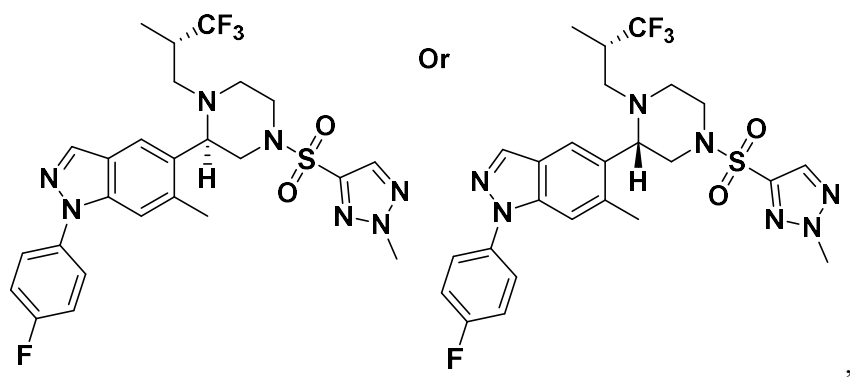
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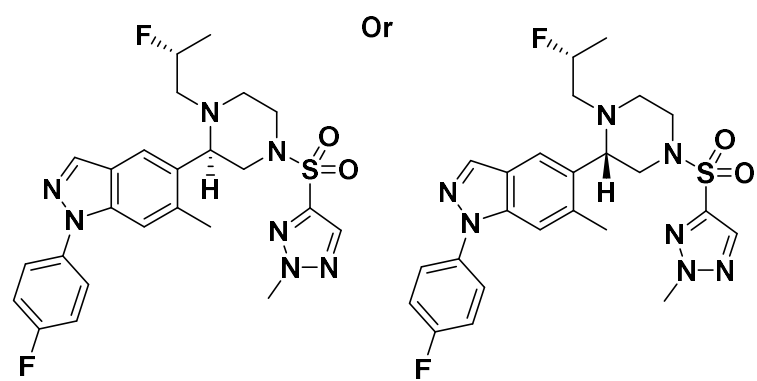
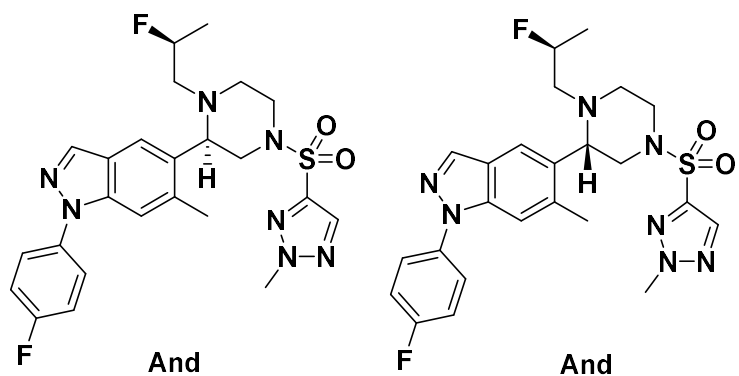
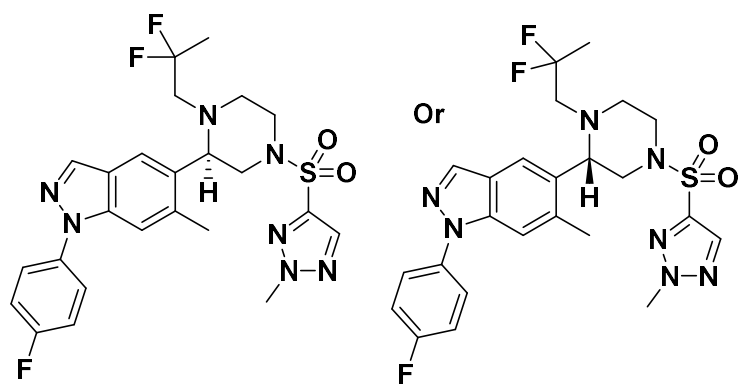
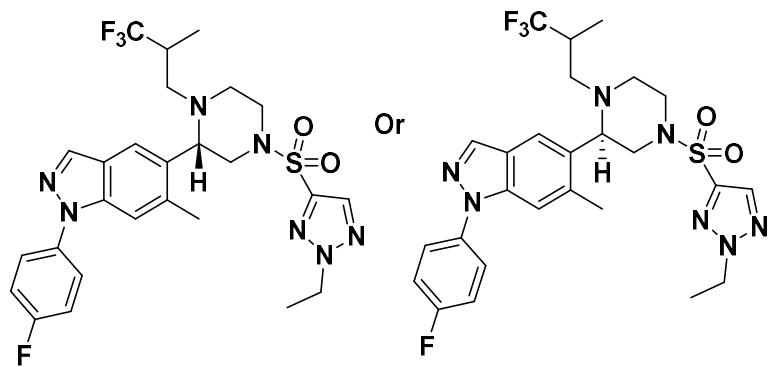
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	; or

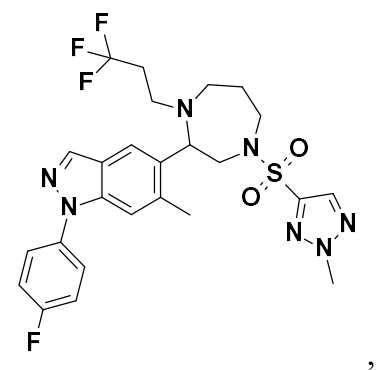
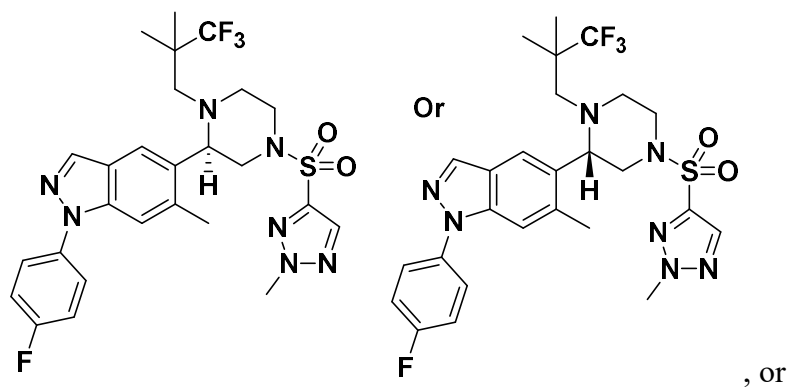
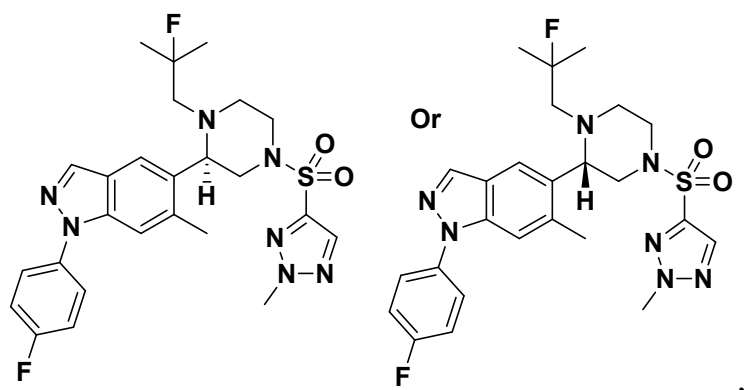


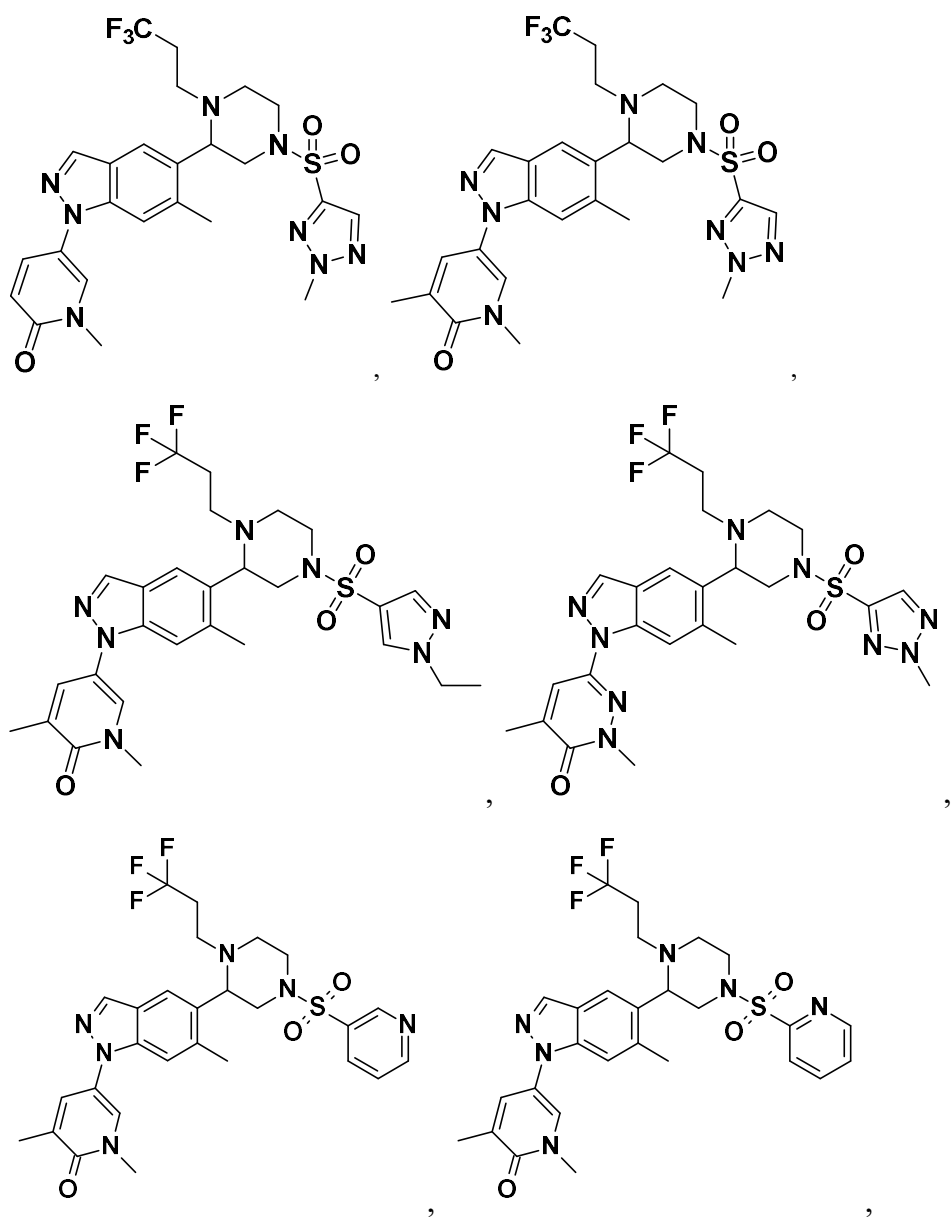
Claim 16. The compound of any one of claims 1 to 15, or a pharmaceutically acceptable salt thereof, is the compound having the structure:

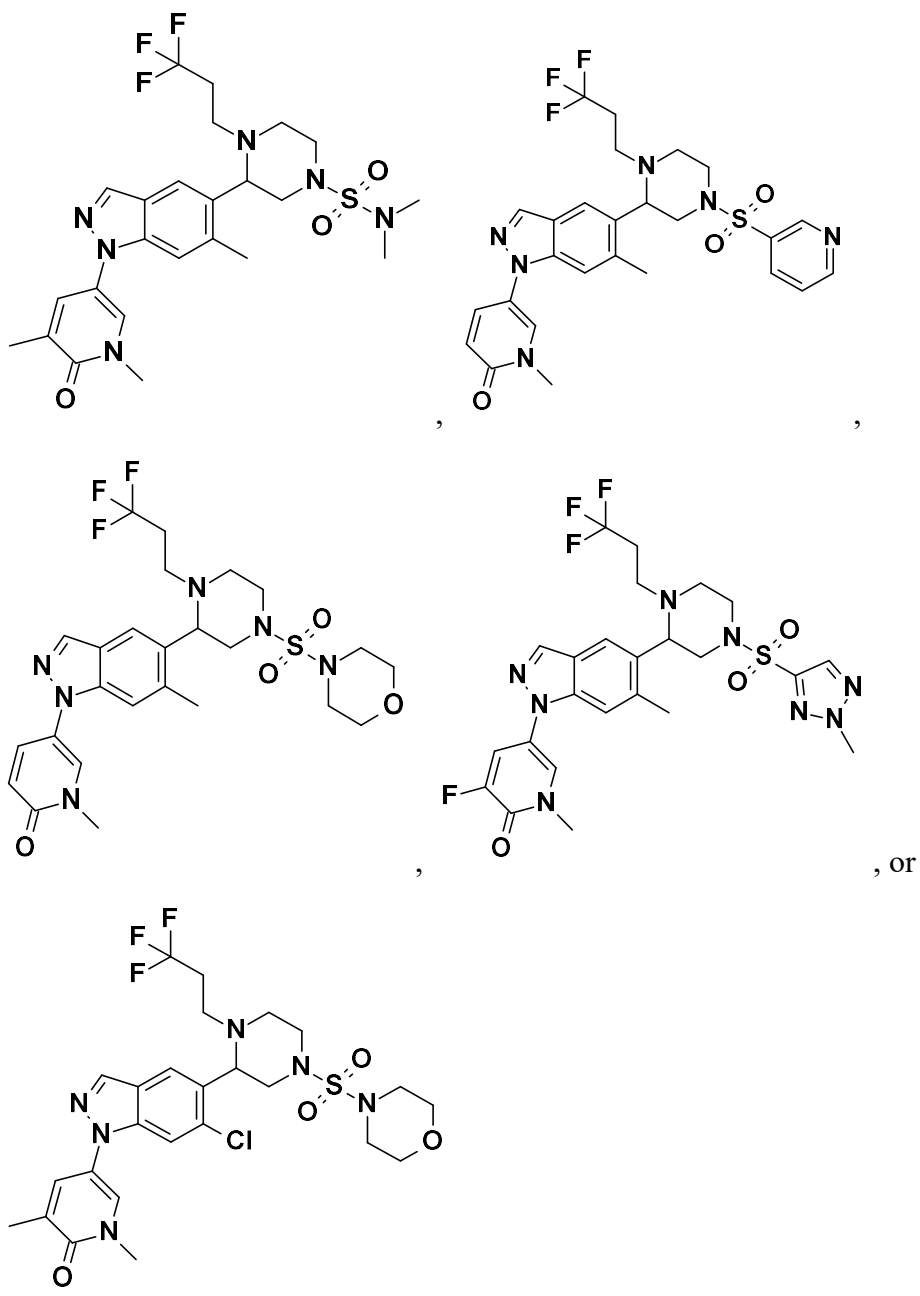




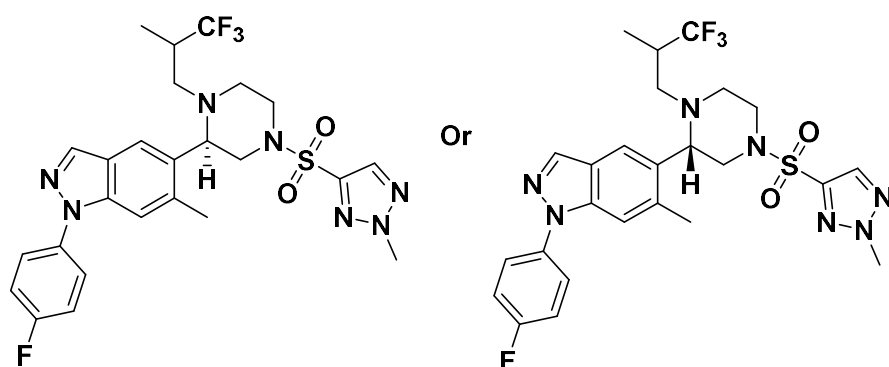




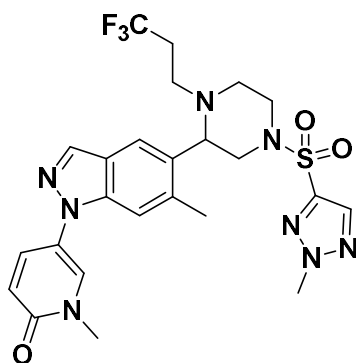




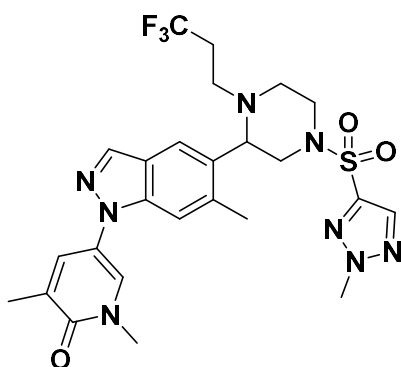
Claim 17. The compound of any one of claims 1 to 16, or a pharmaceutically acceptable salt thereof, is the compound having the structure



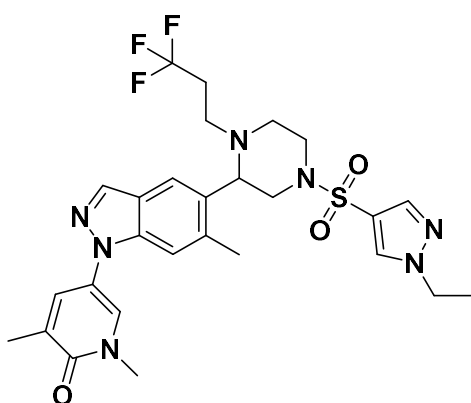
Claim 18. The compound of any one of claims 1 to 16, or a pharmaceutically acceptable salt thereof, is the compound having the structure



Claim 19. The compound of any one of claims 1 to 16, or a pharmaceutically acceptable salt thereof, is the compound having the structure



Claim 20. The compound of any one of claims 1 to 16, or a pharmaceutically acceptable salt thereof, is the compound having the structure



Claim 21. A pharmaceutical composition comprising a compound of any one of claims 1 to 20, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

Claim 22. A compound of any one of claims 1 to 20, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 21, for use in a method of treating a disorder or condition through modulating or antagonizing a glucocorticoid receptor.

Claim 23. The compound or pharmaceutical composition for use of claim 22, wherein the disorder or condition is selected from the group consisting of Alzheimer's disease, amyotrophic lateral sclerosis (ALS), antipsychotic induced weight gain, cancer, Cushing Disease, Cushing's Syndrome, major psychotic depression, Nonalcoholic steatohepatitis, and obesity.

Claim 24. Use of a compound of any one of claims 1 to 20, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 21, in the manufacture of a medicament for treating a disorder or condition through modulating a glucocorticoid receptor.

Claim 25. Use of claim 24, wherein the disorder or condition is selected from the group consisting of Alzheimer's disease, amyotrophic lateral sclerosis (ALS), antipsychotic induced weight gain, cancer, Cushing Disease, Cushing's Syndrome, major psychotic depression, Nonalcoholic steatohepatitis, and obesity.