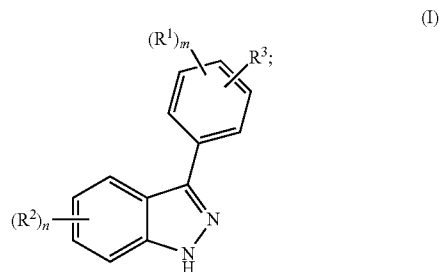




US 20140051679A1

(19) **United States**(12) **Patent Application Publication****Pauls et al.**(10) **Pub. No.: US 2014/0051679 A1**(43) **Pub. Date: Feb. 20, 2014**(54) **KINASE INHIBITORS AND METHOD OF
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NETWORKS**, Toronto (CA)(21) Appl. No.: **13/650,762**(22) Filed: **Oct. 12, 2012****Related U.S. Application Data**(60) Provisional application No. 61/546,533, filed on Oct.
12, 2011.**Publication Classification**(51) **Int. Cl.**
C07D 231/56 (2006.01)
C07D 401/12 (2006.01)
C07D 413/14 (2006.01)
C07D 409/12 (2006.01)
C07D 451/06 (2006.01)
C07D 413/04 (2006.01)
C07D 413/10 (2006.01)**C07D 403/10** (2006.01)
C07D 405/14 (2006.01)
C07D 401/10 (2006.01)
C07D 409/14 (2006.01)
C07D 401/14 (2006.01)(52) **U.S. Cl.**
CPC **C07D 231/56** (2013.01); **C07D 409/14**
(2013.01); **C07D 401/12** (2013.01); **C07D**
413/14 (2013.01); **C07D 409/12** (2013.01);
C07D 401/14 (2013.01); **C07D 413/04**
(2013.01); **C07D 413/10** (2013.01); **C07D**
403/10 (2013.01); **C07D 405/14** (2013.01);
C07D 401/10 (2013.01); **C07D 451/06**
(2013.01)
USPC ... **514/210.21**; 544/140; 514/234.5; 544/371;
514/254.06; 546/199; 514/322; 548/361.1;
514/406; 544/105; 514/230.5; 546/187;
514/316; 546/146; 514/307; 540/552;
514/211.09; 540/569; 514/221; 546/194;
514/318; 546/126; 514/304(57) **ABSTRACT**The present teachings provide a compound represented by
Structural Formula (I):or a pharmaceutically acceptable salt thereof. Also described
are pharmaceutical compositions and methods of use thereof.

KINASE INHIBITORS AND METHOD OF TREATING CANCER WITH SAME

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of and priority to U.S. Provisional Application No. 61/546,533, filed Oct. 12, 2011. The entire contents of this application are incorporated herein by reference.

BACKGROUND OF THE INVENTION

[0002] Protein kinases have been the subject of extensive study in the search for new therapeutic agents in various diseases, for example, cancer. Protein kinases are known to mediate intracellular signal transduction by effecting a phosphoryl transfer from a nucleoside triphosphate to a protein acceptor that is involved in a signaling pathway. There are a number of kinases and pathways through which extracellular and other stimuli cause a variety of cellular responses to occur inside the cell.

[0003] Human TTK protein kinase (TTK), also known as tyrosine threonine kinase, dual specificity protein kinase TTK, Monopolar Spindle 1 (Mps1) and Phosphotyrosine-Picked Threonine Kinase (PYT), is a conserved multispecific kinase that is capable of phosphorylating serine, threonine and tyrosine residues when expressed in *E. coli* (Mills et al., *J. Biol. Chem.* 22(5): 16000-16006 (1992)). TTK mRNA is not expressed in the majority of physiologically normal tissues in human (Id). TTK mRNA is expressed in some rapidly proliferating tissues, such as testis and thymus, as well as in some tumors (for example, TTK mRNA was not expressed in renal cell carcinoma, was expressed in 50% of breast cancer samples, was expressed in testicular tumors and ovarian cancer samples) (Id). TTK is expressed in some cancer cell lines and tumors relative to normal counterparts (Id.; see also WO 02/068444 A1).

[0004] Therefore, agents which inhibit a protein kinase, in particular TTK, have the potential to treat cancer. There is a need for additional agents which can act as protein kinase inhibitors, in particular TTK inhibitors.

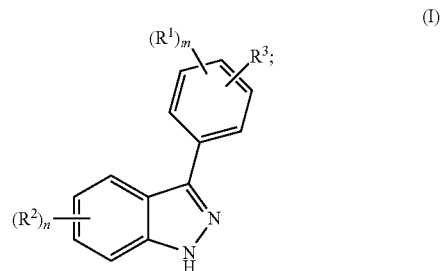
[0005] In addition, cancer recurrence, drug resistance or metastasis is one of the major challenges in cancer therapies. Cancer patients who responded favorably to the initial anti-cancer therapy often develop drug resistance and secondary tumors that lead to the relapse of the disease. Recent research evidences suggest that the capability of a tumor to grow and propagate is dependent on a small subset of cells within the tumor. These cells are termed tumor-initiating cells (TICs) or cancer stem cells. It is thought that the TICs are responsible for drug resistance, cancer relapse and metastasis. Compounds that can inhibit the growth and survival of these tumor-initiating cells can be used to treat cancer, metastasis or prevent recurrence of cancer. Therefore, a need exists for new compounds that can inhibit the growth and survival of tumor-initiating cells.

SUMMARY OF THE INVENTION

[0006] Applicants have now discovered that certain indazole compounds are potent kinase inhibitors, such as TTK protein kinase, polo-like kinase 4 (PLK4) and Aurora kinases (see Example B-D). Applicants have also now discovered that these indazole compounds have potent anticancer activity against breast cancer cells, colon cancer cells, and ovarian

cancer cells in cell culture study (see Example E). Based on these discoveries, indazole compounds, pharmaceutical compositions thereof, and methods of treating cancer with the indazole compounds are disclosed herein.

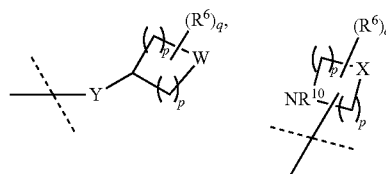
[0007] The present teachings are directed, at least in part, to an indazole compound represented by the following structural formula:



or a pharmaceutically acceptable salt thereof, wherein:

[0008] each R^1 is independently selected from H, -halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{NR}^a\text{R}^b$, $-\text{S}(\text{O})_i\text{R}^c$, $-\text{NR}^d\text{S}(\text{O})_i\text{R}^c$, $-\text{S}(\text{O})_i\text{NR}^e\text{R}^f$, $-\text{C}(=\text{O})\text{OR}^c$, $-\text{OC}(=\text{O})\text{OR}^c$, $-\text{C}(=\text{S})\text{OR}^c$, $-\text{O}(\text{C}=\text{S})\text{R}^c$, $-\text{C}(=\text{O})\text{NR}^e\text{R}^f$, $-\text{NR}^d\text{C}(=\text{O})\text{R}^c$, $-\text{C}(=\text{S})\text{NR}^e\text{R}^f$, $-\text{NR}^d\text{C}(=\text{S})\text{R}^c$, $-\text{NR}^d(\text{C}=\text{O})\text{OR}^c$, $-\text{O}(\text{C}=\text{O})\text{NR}^e\text{R}^f$, $-\text{NR}^d(\text{C}=\text{S})\text{OR}^c$, $-\text{O}(\text{C}=\text{S})\text{NR}^e\text{R}^f$, $-\text{NR}^d(\text{C}=\text{O})\text{NR}^e\text{R}^f$, $-\text{NR}^d(\text{C}=\text{S})\text{NR}^e\text{R}^f$, $-\text{C}(=\text{S})\text{R}^c$, $-\text{C}(=\text{O})\text{R}^c$, heterocycloalkyl or alkyl, wherein the heterocycloalkyl or the alkyl is optionally substituted with 1 to 3 substituents independently selected from -halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{NR}^a\text{R}^b$, $-\text{S}(\text{O})_i\text{R}^c$, $-\text{NR}^d\text{S}(\text{O})_i\text{R}^c$, $-\text{S}(\text{O})_i\text{NR}^e\text{R}^f$, $-\text{C}(=\text{O})\text{OR}^c$, $-\text{OC}(=\text{O})\text{OR}^c$, $-\text{C}(=\text{S})\text{OR}^c$, $-\text{O}(\text{C}=\text{S})\text{R}^c$, $-\text{C}(=\text{O})\text{NR}^e\text{R}^f$, $-\text{NR}^d\text{C}(=\text{O})\text{R}^c$, $-\text{C}(=\text{S})\text{NR}^e\text{R}^f$, $-\text{NR}^d\text{C}(=\text{S})\text{R}^c$, $-\text{NR}^d(\text{C}=\text{O})\text{OR}^c$, $-\text{O}(\text{C}=\text{O})\text{NR}^e\text{R}^f$, $-\text{NR}^d(\text{C}=\text{S})\text{OR}^c$, $-\text{O}(\text{C}=\text{S})\text{NR}^e\text{R}^f$, $-\text{NR}^d(\text{C}=\text{O})\text{NR}^e\text{R}^f$, $-\text{NR}^d(\text{C}=\text{S})\text{NR}^e\text{R}^f$, $-\text{C}(=\text{S})\text{R}^c$ and $-\text{C}(=\text{O})\text{R}^c$;

[0009] each R^2 is independently selected from: $-(\text{CH}_2)_{0-2}\text{C}(=\text{O})\text{NR}^4(\text{CH}_2)_{0-2}\text{Z}-\text{R}^5$, $-(\text{CH}_2)_{0-2}\text{NR}^4\text{C}(=\text{O})(\text{CH}_2)_{0-2}\text{Z}-\text{R}^5$ and $-(\text{CH}_2)_{0-2}\text{NR}^4(\text{C}=\text{O})\text{NR}^4(\text{CH}_2\text{Z}-\text{R}^5)$;



[0010] R^3 is or $-\text{O}-(\text{C}_1-\text{C}_6)\text{alkyl}-\text{NR}^a\text{R}^b$; or R^3 taken together with an instance of R^1 and the phenyl ring to which they are attached form a fused ring heteroaryl or heterocycloalkyl, wherein the heteroaryl or heterocycloalkyl are optionally substituted with 1 to 3 (C_1-C_3) alkyl, provided that R^3 is meta or para to the indazole ring;

[0011] W is $-\text{O}-$, $-\text{NR}^7-$, $-\text{S}(\text{O})_i-$ or $-\text{CR}_8\text{R}_9-$;

[0012] X is $-\text{O}-$, $-\text{CR}^8\text{R}^9-$, $-\text{NR}^{11}-$ or $-\text{S}(\text{O})_i-$;

[0013] Y is $-\text{O}-(\text{CH}_2)_r-$, $-\text{NR}^{12}-(\text{CH}_2)_r-$, $-\text{CH}_2-$ or $-\text{S}(\text{O})_i-(\text{CH}_2)_r-$;

[0014] R^4 is $-H$ or an alkyl group optionally substituted with 1 to 3 substituents independently selected from halogen, hydroxy and (C_1-C_3) alkoxy;

[0015] R^5 is alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl, each of which is optionally substituted with 1 to 3 groups individually represented by R^{15} or R^{16} ;

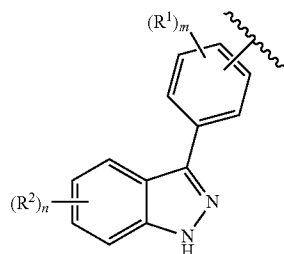
[0016] Z is a bond or $-CR^{13}R^{14}-$;

[0017] R^6 is halogen, hydroxyl, (C_1-C_3) alkyl, (C_1-C_3) alkoxy, (C_1-C_3) alkyl- OR^c or $-NR^aR^b$; or two instances of R^6 on the same carbon are taken together form $=O$; or two instances of R^6 on different carbons, together with the ring to which they are attached, form a bridged bicyclic group;

[0018] R^7 is $-H$, (C_1-C_6) alkyl, cycloalkyl, cycloalkyl(C_1-C_6)alkyl, heterocycloalkyl, heterocycloalkyl(C_1-C_6)alkyl, $-C(=O)R^c$ or $-C(=O)OR^c$, wherein each of the (C_1-C_6) alkyl, cycloalkyl, cycloalkyl(C_1-C_6)alkyl, heterocycloalkyl and heterocycloalkyl(C_1-C_6)alkyl groups is optionally substituted with 1 to 3 substituents independently selected from halogen, hydroxy, (C_1-C_3) alkoxy and $-C(=O)NR^eR^f$;

[0019] R^8 and R^9 are each independently selected from $-H$, $-OR^c$, and (C_1-C_6) alkyl, wherein the (C_1-C_6) alkyl group is optionally substituted with 1 to 3 substituents independently selected from halogen, hydroxy and (C_1-C_3) alkoxy;

[0020] R^{10} is $-H$ or (C_1-C_3) alkyl, or is absent when the nitrogen to which it is attached is attached directly to the



moiety;

[0021] R^{11} is $-H$, (C_1-C_6) alkyl, cycloalkyl, cycloalkyl(C_1-C_6)alkyl, heterocycloalkyl, heterocycloalkyl(C_1-C_6)alkyl, $-C(=O)R^c$ or $-C(=O)OR^c$, wherein each of the (C_1-C_6) alkyl, cycloalkyl, cycloalkyl(C_1-C_6)alkyl, heterocycloalkyl and heterocycloalkyl(C_1-C_6)alkyl groups is optionally substituted with 1 to 3 substituents independently selected from halogen, hydroxy, (C_1-C_3) alkoxy and $-C(=O)NR^eR^f$;

[0022] R^{12} is $-H$ or (C_1-C_3) alkyl;

[0023] R^{13} and R^{14} are each independently selected from $-H$, alkyl, $-OR^c$, $-NR^aR^b$, $-(C_1-C_3)$ alkylene- NR^aR^b , $-(C_1-C_3)$ alkylene- OR^c , $-(C_1-C_3)$ alkylene-OH, cycloalkyl, $-O$ -cycloalkyl and heterocycloalkyl, wherein each of the cycloalkyl or heterocycloalkyl groups is optionally substituted with 1 to 3 substituents independently selected from (C_1-C_3) alkyl and (C_1-C_3) alkoxy, provided that R^{13} and R^{14} are not both selected from $-OR^c$ and $-NR^aR^b$;

[0024] each R^{15} and R^{16} are independently selected from halogen, $-CN$, $-NO_2$, $=O$, $-OR^c$, $-NR^aR^b$, $-S(O)_pR^c$, $-NR^dS(O)_pR^c$, $-S(O)_pNR^eR^f$, $C(=O)OR^c$, $-OC(=O)OR^c$, $-C(=S)OR^c$, $-O(C=S)R^c$, $-C(=O)NR^eR^f$, $-NR^dC(=O)R^c$, $-C(=S)NR^eR^f$, $-NR^dC(=S)R^c$, $-NR^d(C=O)OR^c$, $-O(C=O)NR^eR^f$, $-NR^d(C=S)OR^c$,

$-O(C=S)NR^eR^f$, $-NR^d(C=O)NR^eR^f$, $-NR^d(C=S)NR^eR^f$, $-C(=S)R^e$, $-C(=O)R^c$, (C_1-C_6) alkyl, aryl, aryl(C_1-C_3)alkyl, heterocycloalkyl and heteroaryl; wherein each (C_1-C_6) alkyl, aryl, aryl(C_1-C_3)alkyl, heterocycloalkyl and heteroaryl represented by R^{15} is optionally substituted with 1 to 3 substituents independently selected from $-halogen$, $-CN$, $-OR^c$, (C_1-C_6) alkyl, halo(C_1-C_6)alkyl, (C_1-C_3) alkoxy, halo(C_1-C_3)alkoxy, (C_1-C_3) alkoxy(C_1-C_6)alkyl, 3 to 8 membered heterocycloalkyl and 3 to 8 membered heteroaryl;

[0025] R^a and R^b are each independently selected from $-H$ and (C_1-C_6) alkyl, optionally substituted with 1 to 3 substituents independently selected from halogen, hydroxy, $-NR^eR^f$ and (C_1-C_3) alkoxy;

[0026] R^c is $-H$ or (C_1-C_6) alkyl, optionally substituted with 1 to 3 substituents independently selected from halogen, $-NR^eR^f$, hydroxy and (C_1-C_3) alkoxy;

[0027] R^d is $-H$ or (C_1-C_6) alkyl, optionally substituted with 1 to 3 substituents independently selected from halogen, $-NR^eR^f$, hydroxy and (C_1-C_3) alkoxy;

[0028] R^e and R^f are each independently selected from $-H$ and (C_1-C_6) alkyl optionally substituted with 1 to 3 substituents independently selected from halogen, $-NR^eR^f$, hydroxy and (C_1-C_3) alkoxy;

[0029] R^e and R^f , together with the nitrogen to which they are attached, form a 3-8 membered ring optionally substituted with 1 to 3 substituents independently selected from halogen, $-NR^eR^f$, $-CN$, (C_1-C_6) alkyl, halo(C_1-C_6)alkyl, (C_1-C_3) alkoxy, halo(C_1-C_3)alkoxy, and (C_1-C_3) alkoxy(C_1-C_6)alkyl;

[0030] R^g and R^h are each independently selected from $-H$, (C_1-C_6) alkyl, halo(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl and (C_1-C_3) alkoxy(C_1-C_6)alkyl;

[0031] i is 0, 1 or 2;

[0032] n is an integer from 1 to 4;

[0033] m is an integer from 1 to 4;

[0034] each p is 1, 2 or 3;

[0035] q is 0, 1 or 2; and

[0036] r is 0, 1, 2 or 3.

[0037] In another embodiment, the present teachings include a pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and a compound represented by Structural Formula (I) described above or a pharmaceutically acceptable salt thereof.

[0038] Another embodiment of the present teachings provides a method of treating a subject having cancer comprising administering to the subject an effective amount of a compound of Structural Formula (I) or a pharmaceutically acceptable salt thereof.

[0039] Another embodiment of the present teachings provides a method of inhibiting TTK activity in a subject in need of inhibition of TTK activity, comprising administering to the subject an effective amount of a compound represented by Structural Formula (I) or a pharmaceutically acceptable salt thereof.

[0040] Another embodiment of the present teachings includes the use of a compound represented by Structural Formula (I) or a pharmaceutically acceptable salt thereof in therapy. In some embodiments, the therapy is for treating a subject with cancer. Alternatively, the therapy is for inhibiting TTK activity in a subject in need of inhibition of TTK activity.

[0041] Another embodiment of the present teachings includes the use of a compound represented by Structural

Formula (I) or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for treating a subject with cancer.

[0042] Another embodiment of the present teachings includes the use of a compound represented by Structural Formulas (I) or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for inhibiting TTK activity in a subject in need of inhibition of TTK activity.

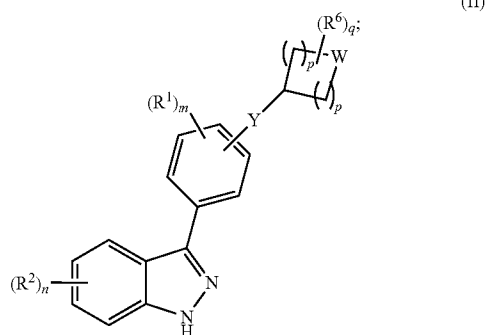
DETAILED DESCRIPTION OF THE INVENTION

[0043] In one embodiment, the present teachings are directed to a compound represented by Structural Formula (I) or a pharmaceutically acceptable salt thereof; and values and alternative values for the variables in Structural Formula (I) are provided in the following paragraphs:

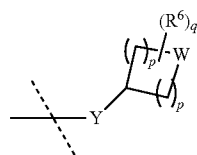
[0044] In a first embodiment, W is —O— or —NR⁷—; X is —O—, —CR⁸R⁹— or —NR¹¹—; and Y is —O—(CH₂)_r—, —NR¹²—(CH₂)_r— or —CH₂—; and values and alternative values for the remainder of the variables are as described for Structural Formula (I).

[0045] In a second embodiment, R⁵ is cycloalkyl, heterocycloalkyl, aryl or heteroaryl, each of which is optionally substituted with 1 to 3 groups individually represented by R¹⁵ or R¹⁶; and values and alternative values for the remainder of the variables are as described for Structural Formula (I) or in the first embodiment.

[0046] In a third embodiment, the compound is represented by structural formula:

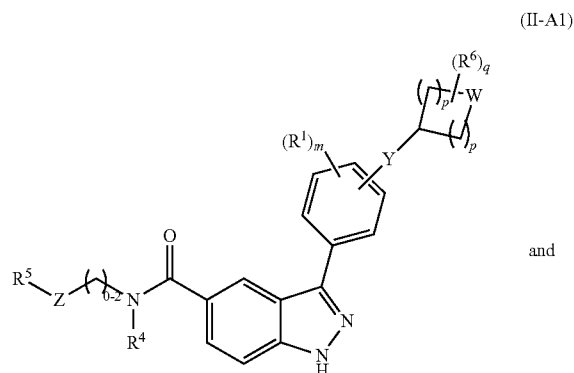


or a pharmaceutically acceptable salt thereof, wherein the group represented by

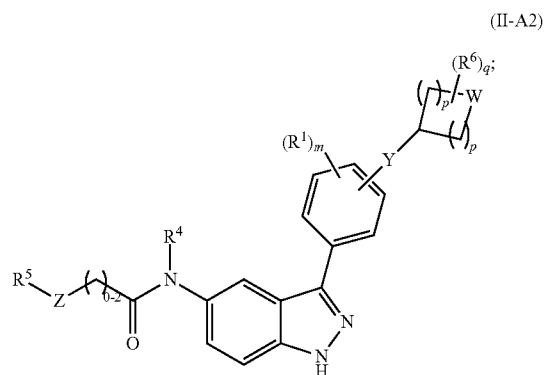


is meta or para to the indazole ring; and values and alternative values for the remainder of the variables are as described for Structural Formula (I) or in the first or second embodiment.

[0047] In a fourth embodiment, the compound is represented by a structural formula selected from:

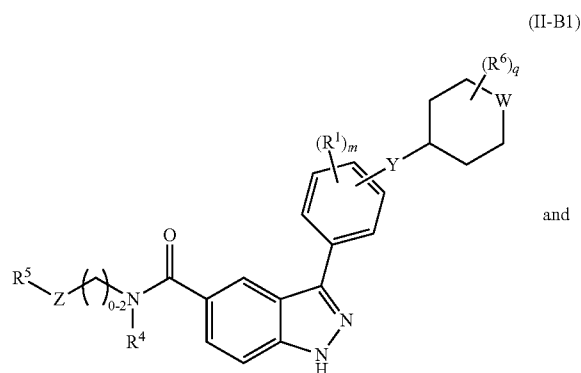


and



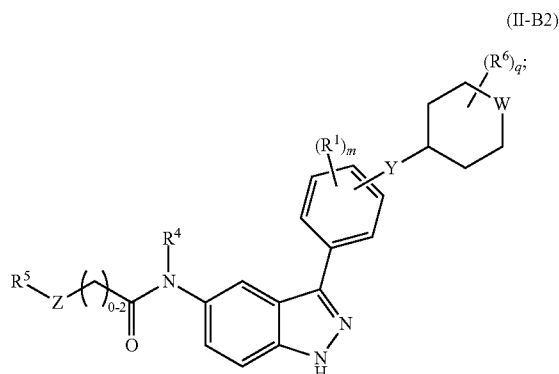
or a pharmaceutically acceptable salt thereof; and values and alternative values for the remainder of the variables are as described for Structural Formula (I) or in the first or second embodiment.

[0048] In a fifth embodiment, the compound is represented by a structural formula selected from:

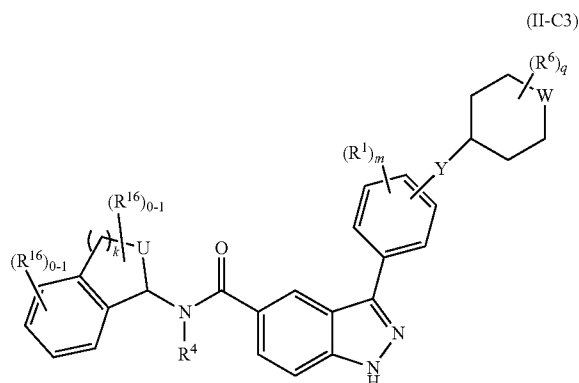


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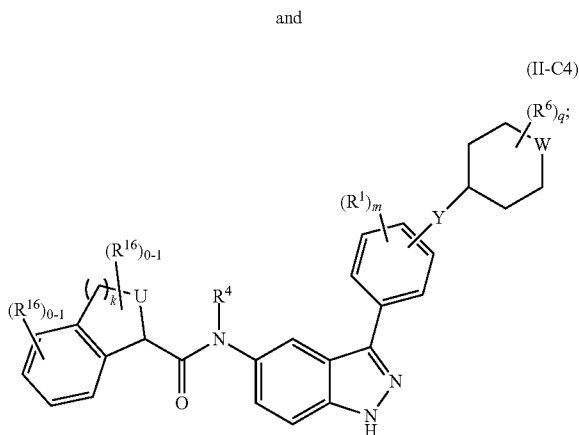
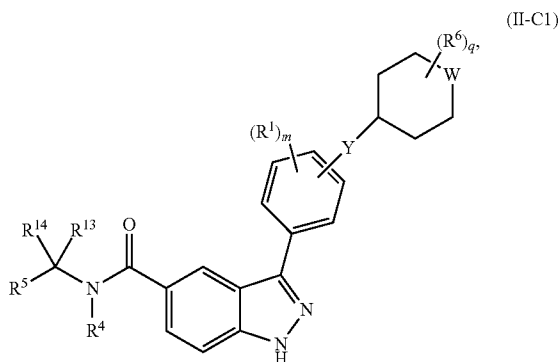
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or a pharmaceutically acceptable salt thereof; and values and alternative values for the remainder of the variables are as described for Structural Formula (I) or in the first or second embodiment.

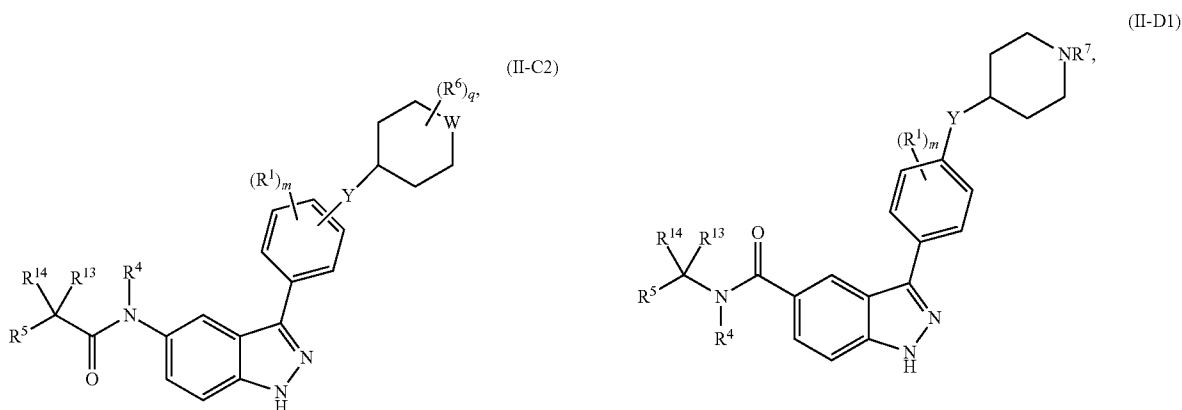
[0049] In one embodiment, for compounds described in Structural Formula (I) or in the first, second, third, fourth or fifth embodiment, Z is a bond. In another embodiment, for compounds described in Structural Formula (I) or in the first, second, third, fourth or fifth embodiment, Z is $-\text{CR}^{13}\text{R}^{14}-$.

[0050] In a sixth embodiment, the compound is represented by a structural formula selected from:

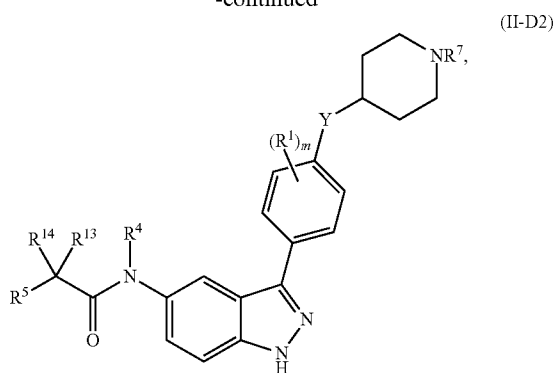


or a pharmaceutically acceptable salt thereof; wherein U is $-\text{CH}_2-$, $-\text{CHR}^{15}-$, $-\text{NH}-$, $-\text{NR}^{15}-$ or $-\text{O}-$; k is 1 or 2; and values and alternative values for the remainder of the variables are as described for Structural Formula (I) or in the first or second embodiment.

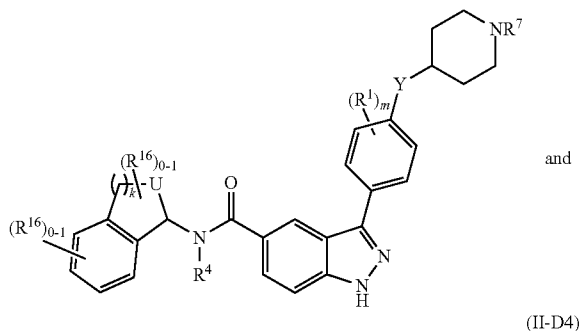
[0051] In a seventh embodiment, the compound is represented by a structural formula selected from:



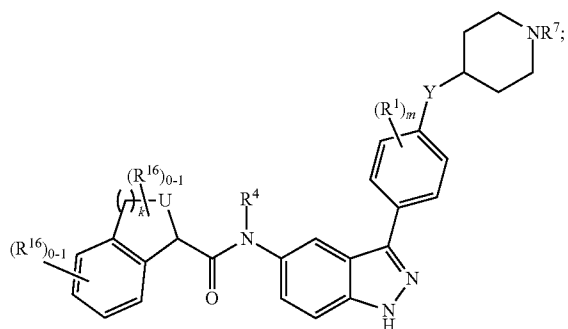
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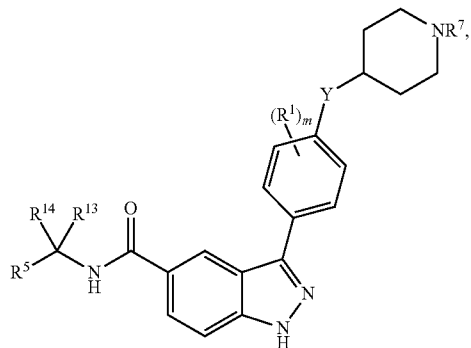
and



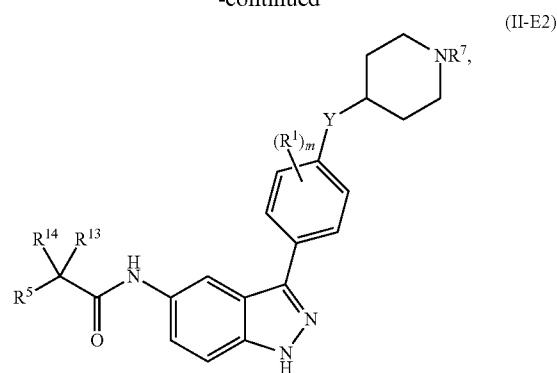
or a pharmaceutically acceptable salt thereof; and values and alternative values for the remainder of the variables are as described for Structural Formula (I) or in the first or second embodiment.

[0052] In an eighth embodiment, the compound is represented by a structural formula selected from:

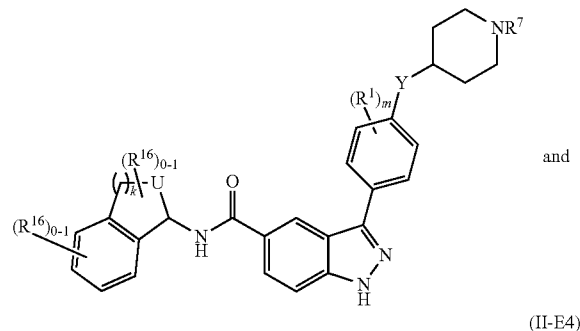
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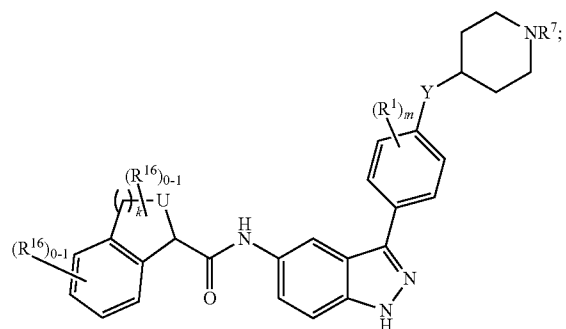
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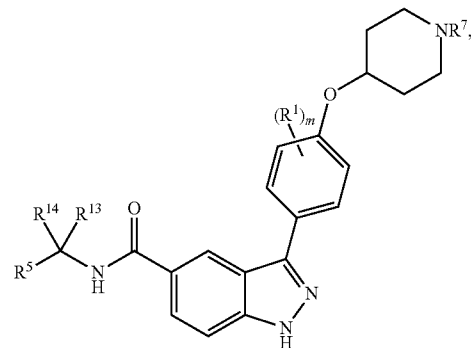
and



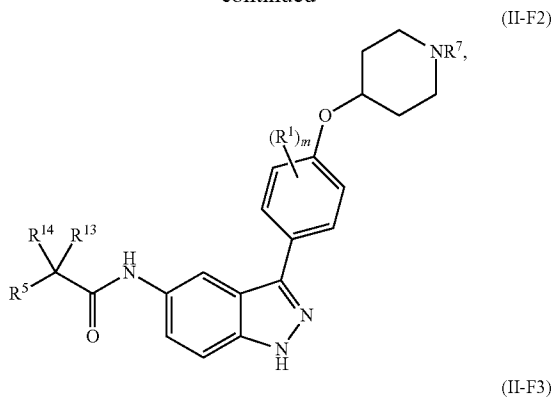
or a pharmaceutically acceptable salt thereof; and values and alternative values for the remainder of the variables are as described for Structural Formula (I) or in the first or second embodiment.

[0053] In a ninth embodiment, the compound is represented by a structural formula selected from:

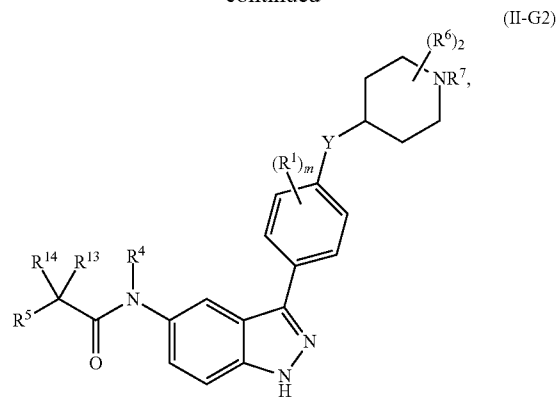
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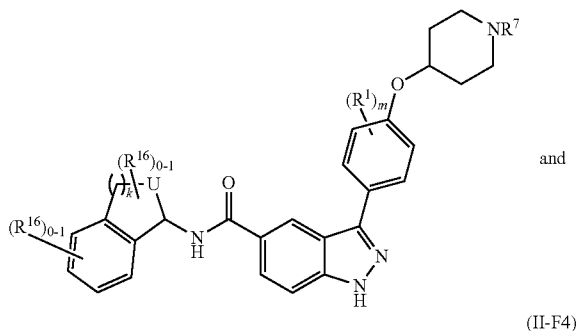


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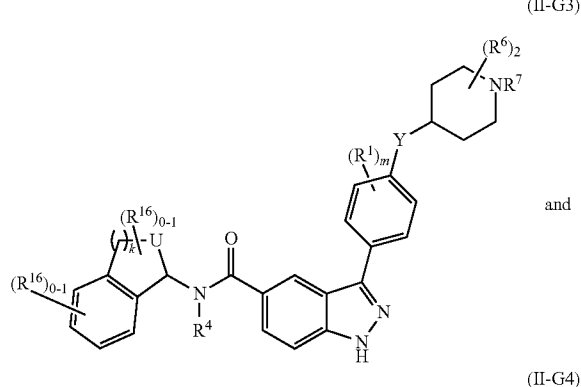


(II-F3)

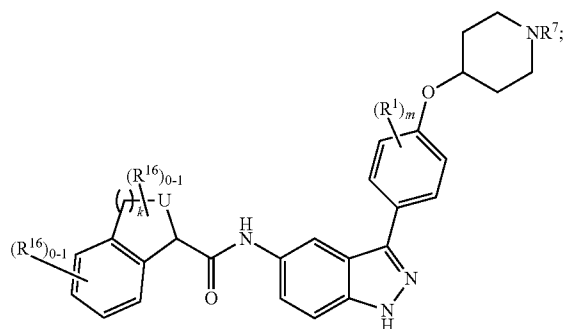
(II-G3)



and



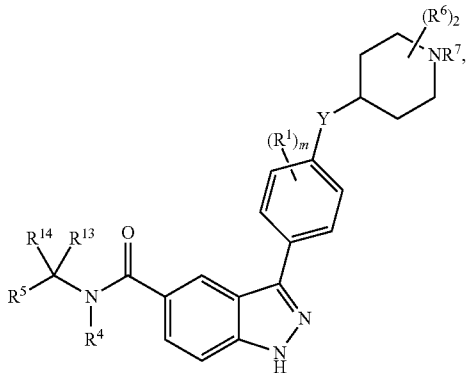
and



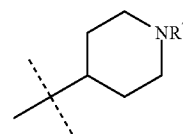
or a pharmaceutically acceptable salt thereof; and values and alternative values for the remainder of the variables are as described for Structural Formula (I) or in the first or second embodiment.

[0054] In a tenth embodiment, the compound is represented by a structural formula selected from:

(II-G1)

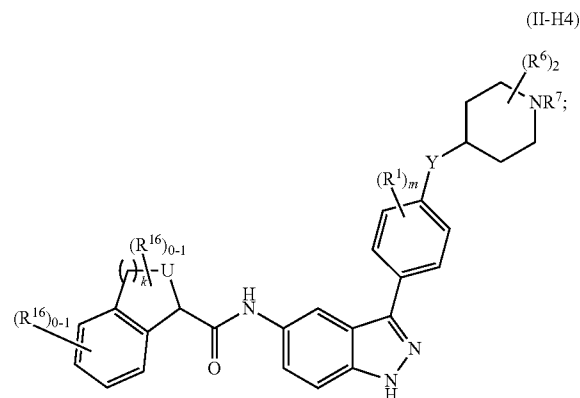
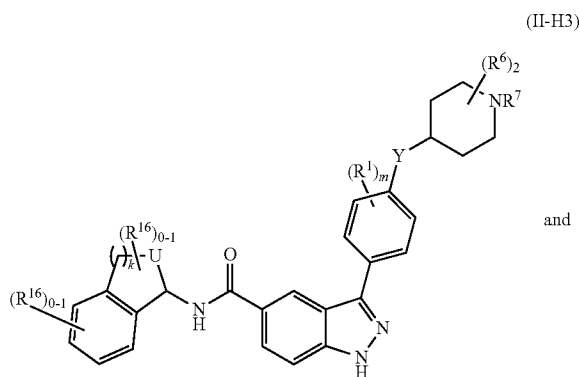
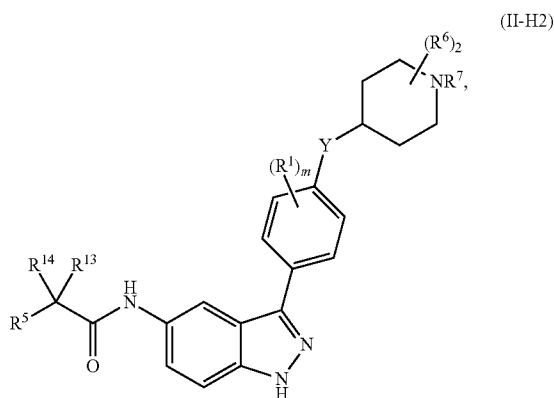
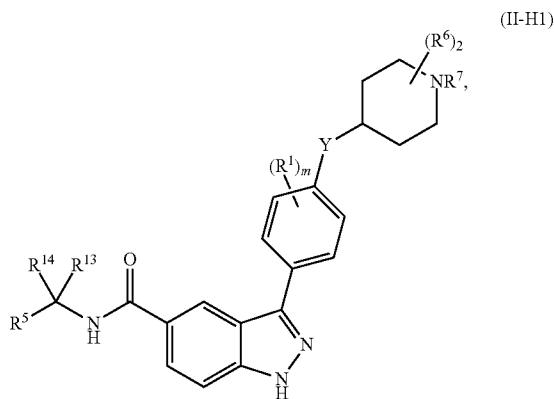


or a pharmaceutically acceptable salt thereof; wherein the two R⁶ groups, together with the

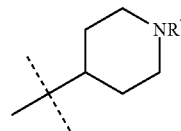


ring to which they are attached, form a 7 to 9 membered bridged bicyclic group containing 1 or 2 ring heteroatoms, wherein the bridged bicyclic group is optionally substituted with —OH, halogen, —NH₂ or (C₁–C₃)alkyl; and values and alternative values for the remainder of the variables are as described for Structural Formula (I) or in the first or second embodiment.

[0055] In an eleventh embodiment, the compound is represented by a structural formula selected from:

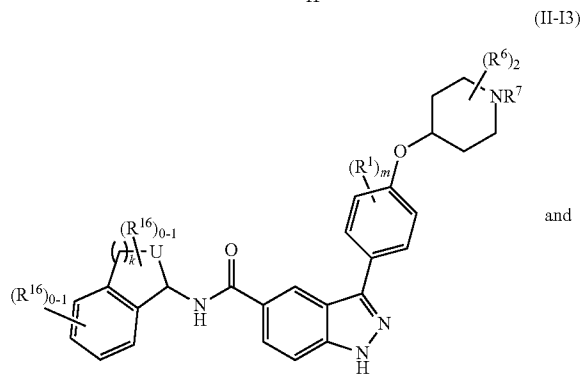
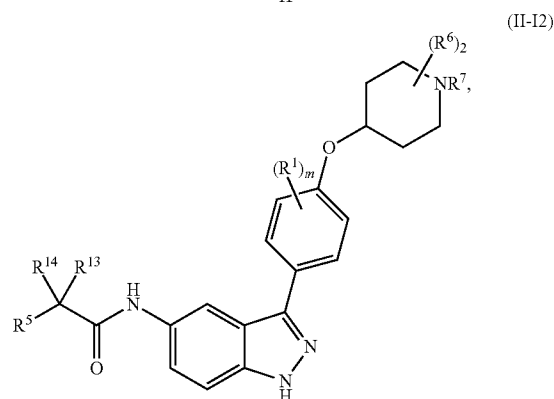
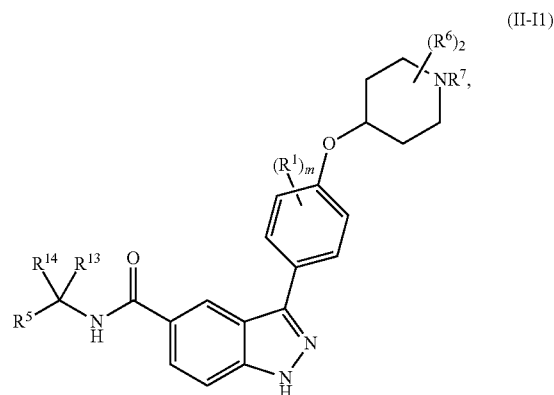


or a pharmaceutically acceptable salt thereof; wherein the two R⁶ groups, together with the

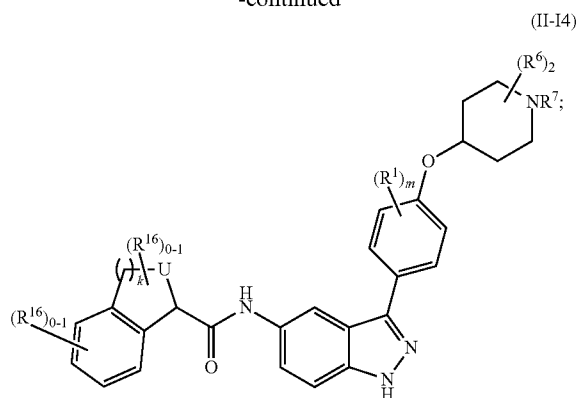


ring to which they are attached, form a 7 to 9 membered bridged bicyclic group containing 1 or 2 ring heteroatoms, wherein the bridged bicyclic group is optionally substituted with —OH, halogen, —NH₂ or (C₁-C₃)alkyl; and values and alternative values for the remainder of the variables are as described for Structural Formula (I) or in the first or second embodiment.

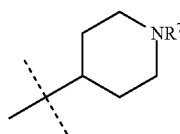
[0056] In a twelfth embodiment, the compound is represented by a structural formula selected from:



-continued



or a pharmaceutically acceptable salt thereof; wherein the two R^6 groups, together with the



ring to which they are attached, form a 7 to 9 membered bridged bicyclic group containing 1 or 2 ring heteroatoms, wherein the bridged bicyclic group is optionally substituted with $-\text{OH}$, halogen, $-\text{NH}_2$ or $(\text{C}_1\text{-C}_3)\text{alkyl}$; and values and alternative values for the remainder of the variables are as described for Structural Formula (I) or in the first or second embodiment.

[0057] In some embodiments, for compounds described in the tenth, eleventh or twelfth embodiment, the bridge formed by two R^6 groups is exo to the $-\text{Y}$ -indazole moiety or the $-\text{O}$ -indazole moiety; and values and alternative values for the remainder of the variables are as described in Structural Formula (I) or the first or second embodiment. In other embodiments, for compounds described in the tenth, eleventh or twelfth embodiment, the bridge formed by two R^6 groups is endo to the $-\text{Y}$ -indazole moiety or the $-\text{O}$ -indazole moiety; and values and alternative values for the remainder of the variables are as described for Structural Formula (I) or in the first or second embodiment.

[0058] In a thirteenth embodiment, for compounds represented by any one of structural formulas (I), (II) or (II-A1)-(II-I4), the group represented by Y is $-\text{O}-(\text{CH}_2)_n-$, or $-\text{NR}^{12}-$;

[0059] R^4 is $-\text{H}$ or an alkyl group optionally substituted with a substituent selected from halogen, hydroxy and $(\text{C}_1\text{-C}_3)\text{alkoxy}$;

[0060] R^7 is $-\text{H}$, $(\text{C}_1\text{-C}_6)\text{alkyl}$, cycloalkyl, heterocycloalkyl, $-\text{C}(=\text{O})\text{R}^c$ or $-\text{C}(=\text{O})\text{OR}^c$, wherein each of the $(\text{C}_1\text{-C}_6)\text{alkyl}$, cycloalkyl, and heterocycloalkyl groups is optionally substituted with a substituent independently selected from halogen, hydroxy, $(\text{C}_1\text{-C}_3)\text{alkoxy}$ and $-\text{C}(=\text{O})\text{NR}^a\text{R}^b$;

[0061] R^{13} and R^{14} are each independently selected from $-\text{H}$, alkyl, $-\text{OR}^c$, $-(\text{C}_1\text{-C}_3)\text{alkylene-OR}^c$, $-(\text{C}_1\text{-C}_3)\text{alkylene-OH}$, $(\text{C}_3\text{-C}_8)\text{cycloalkyl}$, $-\text{O}-(\text{C}_3\text{-C}_8)\text{cycloalkyl}$ and 3 to 8 membered heterocycloalkyl, provided that R^{13} and R^{14}

are not both $-\text{OR}^c$, wherein each of the cycloalkyl or heterocycloalkyl groups is optionally substituted with a $(\text{C}_1\text{-C}_3)\text{alkyl}$;

[0062] n is an integer from 1 to 2;

[0063] m is an integer from 1 to 2;

[0064] each p is 1 or 2; and values and alternative values for the remainder of the variables are as described for Structural Formula (I) or in the first or second embodiment.

[0065] In a fourteenth embodiment, for compounds represented by any one of structural formulas (I), (II) or (II-A1)-(II-I4), each R^1 is independently selected from $-\text{H}$, -halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{OR}^c$, $-\text{NR}^a\text{R}^b$, $-\text{S}(\text{O})_i\text{R}^c$, $-\text{C}(=\text{O})\text{OR}^c$, $-\text{OC}(=\text{O})\text{OR}^c$, $-\text{C}(=\text{O})\text{NR}^a\text{R}^b$, $-\text{NR}^a\text{C}(=\text{O})\text{R}^c$, $-\text{C}(=\text{O})\text{R}^c$ or $(\text{C}_1\text{-C}_6)\text{alkyl}$, wherein the alkyl is optionally substituted with a substituent selected from -halogen, $-\text{OR}^c$, $-\text{NR}^a\text{R}^b$, and $-\text{S}(\text{O})_i\text{R}^c$;

[0066] R^5 is (a) cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, morpholinyl, thiomorpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, piperazinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, azetidiny, dihydroimidazole, dihydrofuranyl, dihydropyranal, dihydropyridinyl, dihydropyrimidinyl, dihydrothienyl, dihydrothiophenyl, dihydrothiopyranal, tetrahydroimidazole, tetrahydrofuranyl, tetrahydropyranal, tetrahydrothienyl, tetrahydropyridinyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranal, phenyl, furanyl, imidazolyl, oxazolyl, isoxazolyl, oxadiazolyl, pyrazolyl, pyrrolyl, pyridyl, pyrimidinyl, pyridazinyl, thiazolyl, isothiazolyl, triazolyl, tetrazolyl or thienyl, each of which is optionally substituted with 1 to 3 groups represented by R^{15} or (b) bicyclooctanyl, decahydronaphthyl, octahydroindenyl, dihydronaphthalenyl, tetrahydronaphthalenyl, dihydroindolyl, dihydroisindolyl, dihydrobenzimidazolyl, dihydrobenzothienyl, dihydrobenzofuranyl, dihydroisobenzofuranyl, dihydrobenzotriazolyl, dihydrobenzothiazolyl, dihydrobenzoxazolyl, dihydrobenzisoxazolyl, dihydroquinolinyl, tetrahydroquinolinyl, dihydroisoquinolinyl, tetrahydroisoquinolinyl, dihydroindazolyl, dihydroacridinyl, tetrahydroacridinyl, chromanyl, isochromanyl, chromenyl, isochromenyl, naphthyl, anthracenyl, fluorenyl, indenyl, indenyl, carbazolyl, benzimidazolyl, benzothienyl, benzofuranyl, isobenzofuranyl, indolyl, isindolyl, benzotriazolyl, benzothiazolyl, benzoxazolyl, benzisoxazolyl, quinolinyl, isoquinolinyl, indazolyl or acridinyl, each of which is optionally substituted with 1 to 3 groups represented by R^{16} ;

[0067] R^6 is absent, halogen or $(\text{C}_1\text{-C}_4)\text{alkyl}$; or two instances of R^6 on different carbons, together with the ring to which they are attached, form an azabicyclooctanyl, a diazabicyclooctanyl, an oxabicyclooctanyl, a dioxabicyclooctanyl, an oxa-azabicyclooctanyl, an azabicyclononanyl, a diazabicyclononanyl, an oxabicyclononanyl, a dioxabicyclononanyl, or an oxa-azabicyclononanyl;

[0068] R^7 is $-\text{H}$, $(\text{C}_1\text{-C}_4)\text{alkyl}$, halo $(\text{C}_1\text{-C}_4)\text{alkyl}$, hydroxy $(\text{C}_1\text{-C}_4)\text{alkyl}$, methoxy $(\text{C}_1\text{-C}_4)\text{alkyl}$, $-(\text{C}_1\text{-C}_4)\text{alkyl-C}(=\text{O})\text{NMe}_2$, $-\text{C}(=\text{O})-(\text{C}_1\text{-C}_4)\text{alkyl-NMe}_2$, morpholinyl, thiomorpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, piperazinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, azetidiny, dihydroimidazole, dihydrofuranyl, dihydropyranal, dihydropyridinyl, dihydropyrimidinyl, dihydrothienyl, dihydrothiophenyl, dihydrothiopyranal, tetrahydroimidazole, tetrahydrofuranyl, tetrahydropyranal, tetrahydrothienyl, tetrahydropyridinyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranal, $-\text{C}(=\text{O})\text{R}^c$ or

—C(=O)OR^c, and wherein each R^c is independently selected from —H, (C₁-C₄)alkyl, amino(C₁-C₄)alkyl or dimethylamino(C₁-C₄)alkyl;

[0069] R¹³ is H and R¹⁴ is —H, (C₁-C₆)alkyl, —OR^c, —(C₁-C₃)alkylene-OR^c, —(C₁-C₃)alkylene-OH, a cycloalkyl selected from cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl, a —O-cycloalkyl selected from —O-cyclopropyl, —O-cyclobutyl, and —O-cyclopentyl, —O-cyclohexyl, or a heterocycloalkyl selected from morpholinyl, thiomorpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, piperazinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, azetidiny, dihydroimidazole, dihydrofuranyl, dihydropyrany, dihydropyridinyl, dihydropyrimidinyl, dihydrothienyl, dihydrothiophenyl, dihydrothiopyranyl, tetrahydroimidazole, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothienyl, tetrahydropyridinyl, tetrahydropyrimidinyl, tetrahydrothiophenyl and tetrahydrothiopyranyl, provided that R¹³ and R¹⁴ are not both —OR^c, wherein each of the —O-cycloalkyl, cycloalkyl or heterocycloalkyl groups is optionally substituted with a (C₁-C₃)alkyl; and R^c is —H, or (C₁-C₆)alkyl;

[0070] each R¹⁵ is independently selected from halogen, —CN, —NO₂, =O, —OR^c, —NR^aR^b, —C(=O)OR^c, —OC(=O)OR^c, —C(=O)NR^eR^f, —NR^dC(=O)R^c, —NR^d(C=O)OR^c, —O(C=O)NR^eR^f, —NR^d(C=O)NR^eR^f, —C(=O)R^c, (C₁-C₆)alkyl, morpholinyl, thiomorpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, piperazinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, azetidiny, dihydroimidazole, dihydrofuranyl, dihydropyranyl, dihydropyridinyl, dihydropyrimidinyl, dihydrothienyl, dihydrothiophenyl, dihydrothiopyranyl, tetrahydroimidazole, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothienyl, tetrahydropyridinyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, phenyl, benzyl, furanyl, imidazolyl, oxazolyl, isoxazolyl, oxadiazolyl, pyrazolyl, pyrrolyl, pyridyl, pyrimidinyl, pyridazinyl, thiazolyl, isothiazolyl, triazolyl, tetrazolyl, and thienyl; wherein the (C₁-C₆)alkyl represented by R¹⁵ is optionally substituted with a substituent selected from —halogen, —OR^c, (C₁-C₆)alkyl, (C₁-C₃)alkoxy, morpholinyl, thiomorpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, piperazinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, azetidiny, dihydroimidazole, dihydrofuranyl, dihydropyranyl, dihydropyridinyl, dihydropyrimidinyl, dihydrothienyl, dihydrothiophenyl, dihydrothiopyranyl, tetrahydroimidazole, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothienyl, tetrahydropyridinyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, phenyl, benzyl, furanyl, imidazolyl, oxazolyl, isoxazolyl, oxadiazolyl, pyrazolyl, pyrrolyl, pyridyl, pyrimidinyl, pyridazinyl, thiazolyl, isothiazolyl, triazolyl, tetrazolyl, and thienyl;

[0071] each R¹⁶ is independently selected from halogen, —OR^c, —NR^aR^b, —C(=O)OR^c, —C(=O)NR^eR^f, —NR^dC(=O)R^c, —C(=O)R^c, (C₁-C₆)alkyl, phenyl, phenyl(C₁-C₃)alkyl, morpholinyl, thiomorpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, piperazinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, azetidiny, dihydroimidazole, dihydrofuranyl, dihydropyranyl, dihydropyridinyl, dihydropyrimidinyl, dihydrothienyl, dihydrothiophenyl, dihydrothiopyranyl, tetrahydroimidazole, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothienyl, tetrahydrothiopyranyl, furanyl, imidazolyl, oxazolyl, isoxazolyl, oxadiazolyl, pyrazolyl, pyrrolyl, pyridyl, pyrimidinyl, pyridazinyl, thiazolyl, isothiazolyl, triazolyl, tetrazolyl, and thienyl; and

values and alternative values for the remainder of the variables are as described for Structural Formula (I) or in the first, second or thirteenth embodiment.

[0072] In a fifteenth embodiment, for compounds represented by any one of structural formulas (I), (II) or (II-A1)-(II-14), R¹ is selected from —H, —halogen, —OCH₃, —N(CH₃)₂, —S(O)₂CH₃, or methyl;

[0073] R⁵ is (a) cyclopentyl, cyclohexyl, morpholinyl, pyrrolidinyl, piperidinyl, dihydropyridinyl, tetrahydropyridinyl, dihydropyrimidinyl, tetrahydropyrimidinyl, phenyl, furanyl, imidazolyl, pyrrolyl, pyridyl, pyrimidinyl or thienyl, each of which is optionally substituted with 1 to 3 groups represented by R¹⁵ or (b) chromanyl, chromenyl, dihydroindolyl, dihydroisoindolyl, dihydrobenzothienyl, dihydrobenzofuranyl, dihydroisobenzofuranyl, dihydrobenzotriazolyl, dihydroquinolinyl, tetrahydroquinolinyl, dihydroisoquinolinyl, tetrahydroisoquinolinyl, dihydrobenzisoquinolinyl, naphthyl, anthracenyl, fluorenyl, indanyl, indenyl, dihydronaphthalene, tetrahydronaphthalene, carbazolyl, benzimidazolyl, benzothienyl, benzofuranyl, isobenzofuranyl, indolyl, quinolinyl, isoquinolinyl or isoindolyl, each of which is optionally substituted with 1 to 3 groups represented by R¹⁶;

[0074] R⁶ is absent, halogen or (C₁-C₄)alkyl; or two instances of R⁶ on different carbons, together with the ring to which they are attached, form an azabicyclooctanyl, a diazabicyclooctanyl, an oxa-azabicyclooctanyl, an azabicyclononanyl, a diazabicyclononanyl, or an oxa-azabicyclononanyl;

[0075] R⁷ is —H, methyl, ethyl, propyl, isopropyl, methoxyethyl, hydroxyethyl, fluoroethyl, —C(=O)H, —C(=O)CH₂N(CH₃)₂, —CH₂—C(=O)N(CH₃)₂, oxetanyl, tetrahydrofuranyl, —CH₂C(=O)N(CH₃)₂, —C(=O)O(C₁-C₄)alkyl;

[0076] R¹³ is —H and R¹⁴ is —H, (C₁-C₆)alkyl, —OR^c, —(C₁-C₃)alkylene-OR^c, —(C₁-C₃)alkylene-OH, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, —O-cyclopropyl, —O-cyclobutyl, —O-cyclopentyl, —O-cyclohexyl, morpholinyl, thiomorpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, piperazinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, azetidiny, dihydroimidazole, dihydrofuranyl, dihydropyranyl, dihydropyridinyl, dihydropyrimidinyl, dihydrothienyl, dihydrothiophenyl, dihydrothiopyranyl, tetrahydroimidazole, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothienyl, tetrahydropyridinyl, tetrahydropyrimidinyl, tetrahydrothiophenyl or tetrahydrothiopyranyl; and R^c is —H, or (C₁-C₆)alkyl;

[0077] each R¹⁵ is independently selected from halogen, —OR^c, —NR^aR^b, (C₁-C₆)alkyl, morpholinyl, thiomorpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, piperazinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, azetidiny, dihydroimidazole, dihydrofuranyl, dihydropyranyl, dihydropyridinyl, dihydropyrimidinyl, dihydrothienyl, dihydrothiophenyl, dihydrothiopyranyl, tetrahydroimidazole, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothienyl, tetrahydropyridinyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, furanyl, imidazolyl, isoxazolyl, oxadiazolyl, oxazolyl, pyrazolyl, pyrrolyl, pyridyl, pyrimidinyl, pyridazinyl, thiazolyl, isothiazolyl, triazolyl, tetrazolyl and thienyl; wherein the (C₁-C₆)alkyl represented by R¹⁵ is optionally substituted with a substituent selected from —halogen, —OR^c, (C₁-C₃)alkoxy, morpholinyl, thiomorpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, piperazinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, azetidiny, dihydroimidazole, dihydrofuranyl, dihydropyra-

nyl, dihydropyridinyl, dihydropyrimidinyl, dihydrothienyl, dihydrothiophenyl, dihydrothiopyranyl, tetrahydroimidazole, tetrahydrofuran, tetrahydropyranyl, tetrahydrothienyl, tetrahydropyridinyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, furanyl, imidazolyl, isoxazolyl, oxadiazolyl, oxazolyl, pyrazolyl, pyrrolyl, pyridyl, pyrimidinyl, pyridazinyl, thiazolyl, isothiazolyl, triazolyl, tetrazolyl and thienyl;

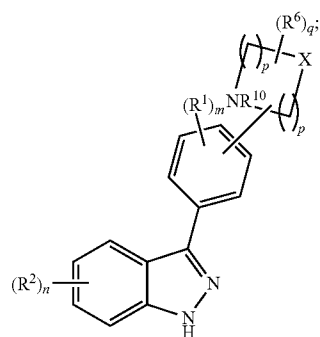
[0078] each R^{16} is independently selected from halogen, $-OR^c$, $-NR^aR^b$, and $(C_1-C_6)alkyl$;

[0079] m is 1; and values and alternative values for the remainder of the variables are as described for Structural Formula (I) or in the first, second, thirteenth or fourteenth embodiment.

[0080] In a sixteenth embodiment, for compounds represented by any one of structural formulas (II-C1)-(II-I4), U is $-CH_2-$, $-NH-$, or $-O-$; each $(R^{16})_{0-1}$ is absent; and values and alternative values for the remainder of the variables are as described for Structural Formula (I) or in the first, second, thirteenth, fourteenth or fifteenth embodiment.

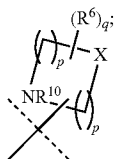
[0081] In a seventeenth embodiment, for compounds represented by any one of structural formulas (I) and (II-A1)-(II-I4), two instances of R^6 on different carbons, together with the ring to which they are attached, form an 8-azabicyclo[3.2.1]octanyl, a 9-azabicyclo[3.3.1]nonanyl, a 3-oxa-9-azabicyclo[3.3.1]nonanyl or a 3,9-diazabicyclo[3.3.1]nonanyl; and values and alternative values for the remainder of the variables are as described for Structural Formula (I) or in the first, second, thirteenth, fourteenth, fifteenth or sixteenth embodiment.

[0082] In an eighteenth embodiment, the compound is represented by structural formula



(III)

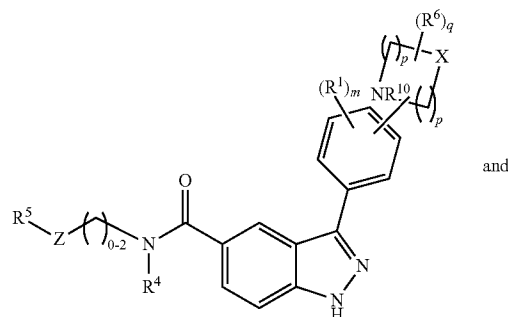
or a pharmaceutically acceptable salt thereof; wherein the group represented by



is meta or para to the indazole ring; and values and alternative values for the remainder of the variables are as described for Structural Formula (I) or in the first or second embodiment.

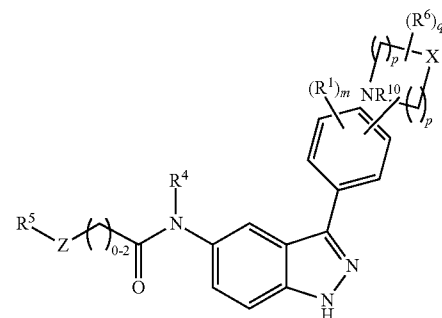
[0083] In a nineteenth embodiment, the compound is represented by a structural formula selected from:

(III-A1)



and

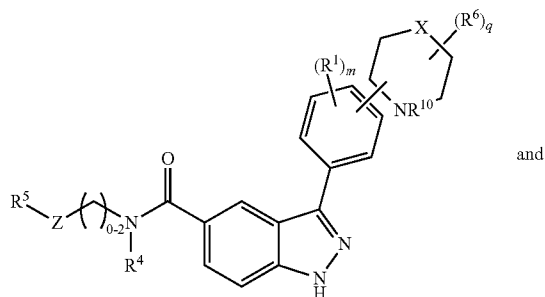
(III-A2)



or a pharmaceutically acceptable salt thereof; and values and alternative values for the remainder of the variables are as described for Structural Formula (I) or in the first or second embodiment.

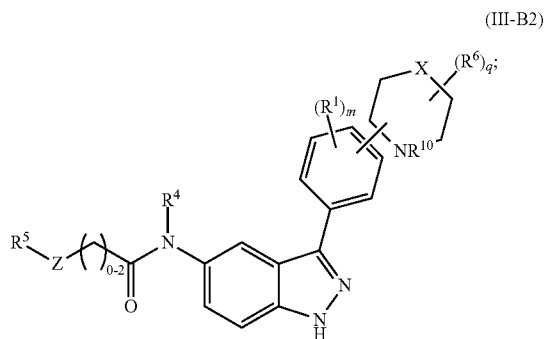
[0084] In a twentieth embodiment, the compound is represented by a structural formula selected from:

(III-B1)

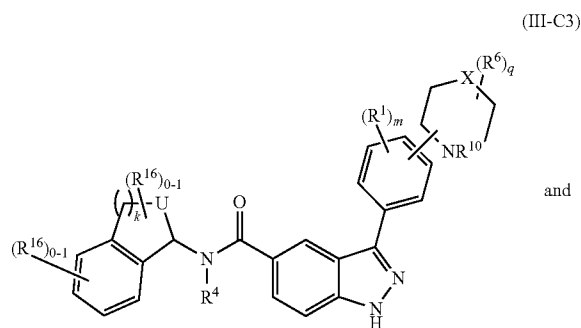


and

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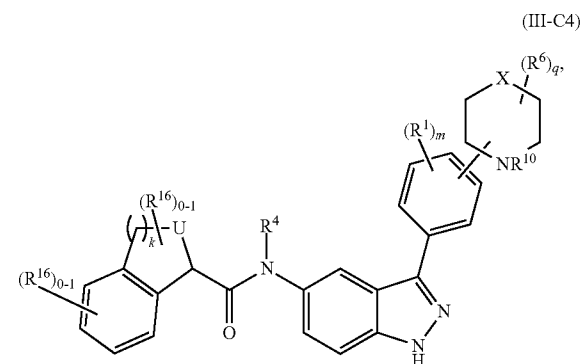
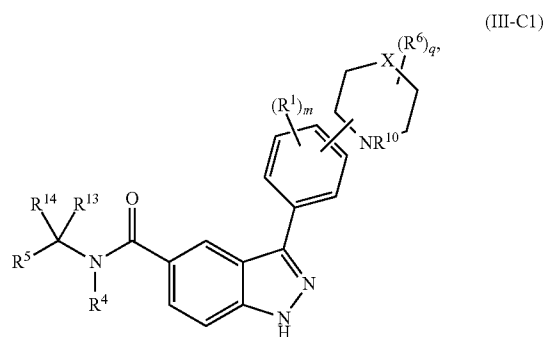
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or a pharmaceutically acceptable salt thereof; and values and alternative values for the remainder of the variables are as described for Structural Formula (I) or in the first or second embodiment.

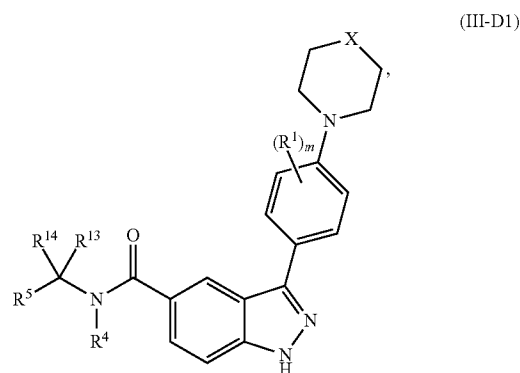
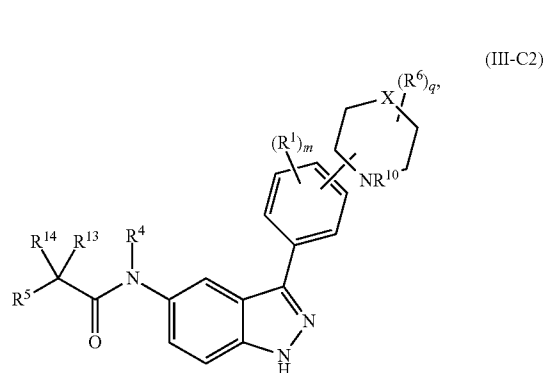
[0085] In one embodiment, for compounds described in Structural Formula (I) or in the eighteenth, nineteenth or twentieth embodiment, Z is a bond. In another embodiment, for compounds described in Structural Formula (I) or in the first, second, third, fourth or fifth embodiment, Z is $-\text{CR}^{13}\text{R}^{14}$.

[0086] In a twenty-first embodiment, the compound is represented by a structural formula selected from:



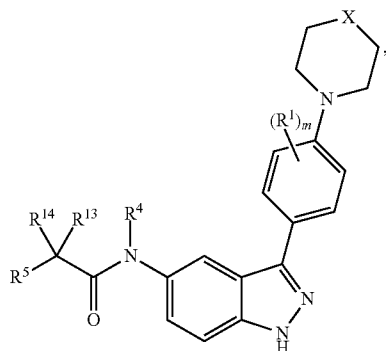
or a pharmaceutically acceptable salt thereof; wherein U is $-\text{CH}_2-$, $-\text{CHR}^{15}-$, $-\text{NH}-$, $-\text{NR}^{15}-$ or $-\text{O}-$; k is 1 or 2; and values and alternative values for the remainder of the variables are as described for Structural Formula (I) or in the first or second embodiment.

[0087] In a twenty-second embodiment, the compound is represented by a structural formula selected from:



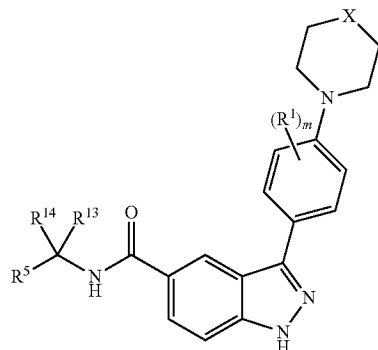
-continued

(III-D2)

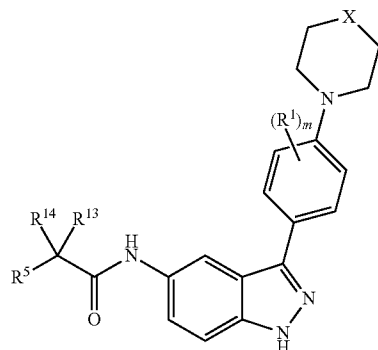


[0088] In a twenty-third embodiment, the compound is represented by a structural formula selected from:

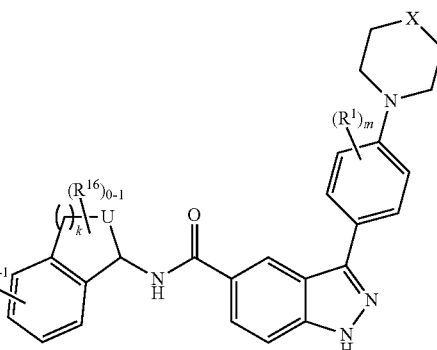
(III-E1)



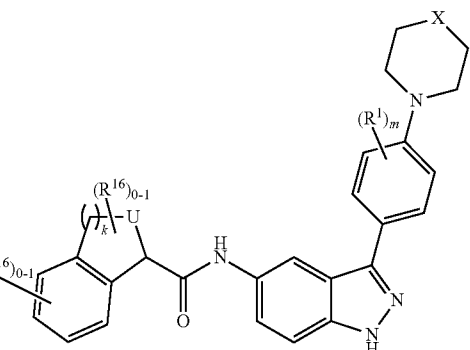
(III-E2)



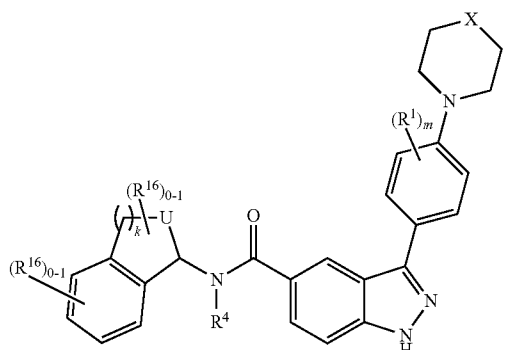
(III-E3)



(III-E4)

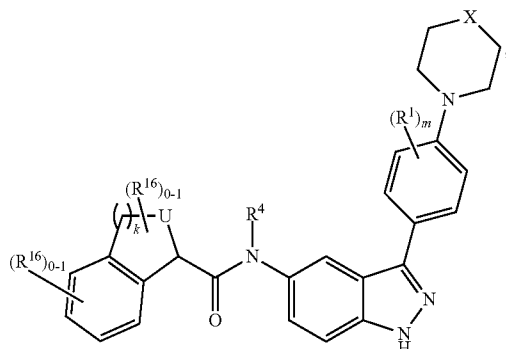


(III-D3)



and

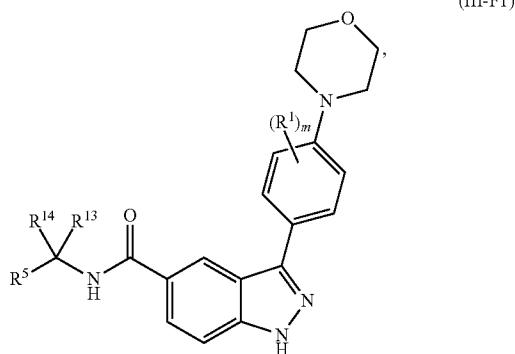
(III-D4)



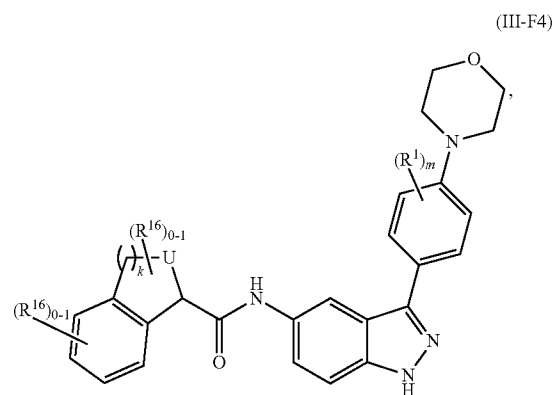
or a pharmaceutically acceptable salt thereof; and values and alternative values for the remainder of the variables are as described for Structural Formula (I) or in the first or second embodiment.

or a pharmaceutically acceptable salt thereof; and values and alternative values for the remainder of the variables are as described for Structural Formula (I) or in the first or second embodiment.

[0089] In a twenty-fourth embodiment, the compound is represented by a structural formula selected from:

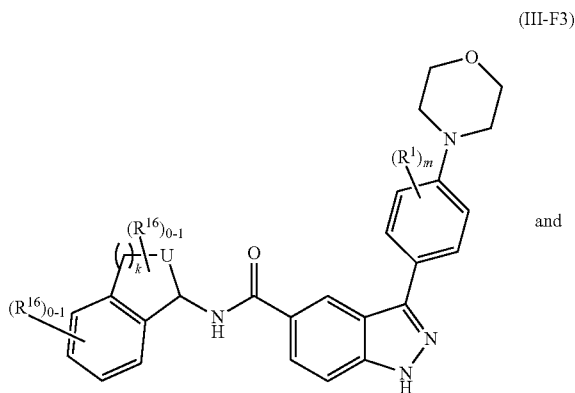
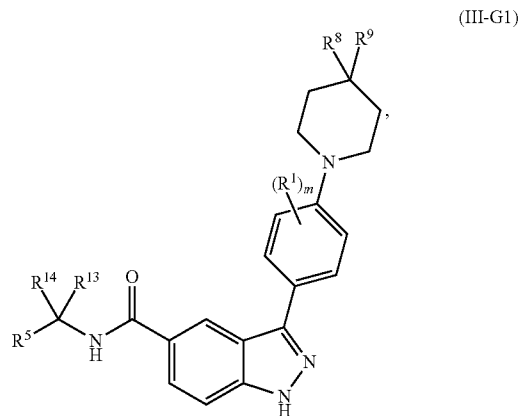
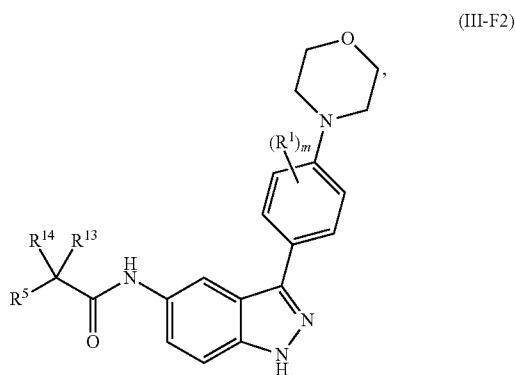


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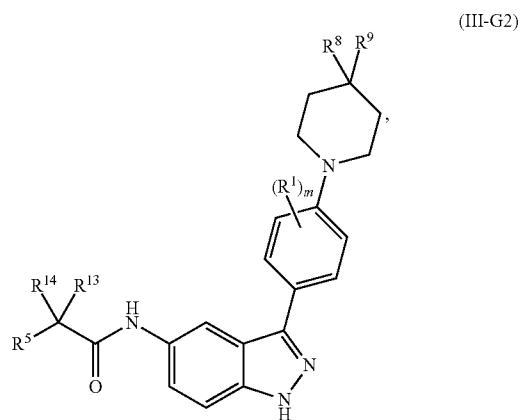


or a pharmaceutically acceptable salt thereof; and values and alternative values for the remainder of the variables are as described for Structural Formula (I) or in the first or second embodiment.

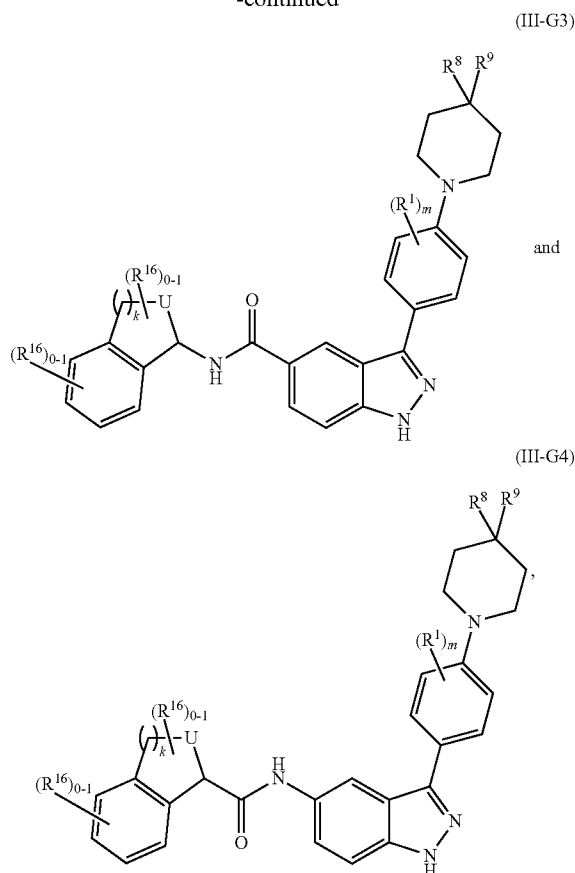
[0090] In a twenty-fifth embodiment, the compound is represented by a structural formula selected from:



and



-continued



[0091] or a pharmaceutically acceptable salt thereof, wherein R^8 is $-H$ or (C_1-C_4) alkyl; R^9 is $-OR^c$ or hydroxy (C_1-C_4) alkyl; R^c is $-H$ or (C_1-C_4) alkyl; and values and alternative values for the remainder of the variables are as described for Structural Formula (I) or in the first or second embodiment.

[0092] In a twenty-sixth embodiment, for compounds represented by any one of structural formulas (I), (III) or (III-A1)-(II-G4), the group represented by X is $-O-$, $-CR^8R^9-$ or $-NR^{11}-$;

[0093] R^4 is $-H$ or an alkyl group optionally substituted with a substituent selected from halogen, hydroxy and (C_1-C_3) alkoxy;

[0094] R^8 and R^9 are each independently selected from $-H$, $-OR^c$, and (C_1-C_6) alkyl, wherein the (C_1-C_6) alkyl group is optionally substituted with a substituent selected from halogen, hydroxy and (C_1-C_3) alkoxy;

[0095] R^{11} is $-H$, (C_1-C_6) alkyl, wherein the (C_1-C_6) alkyl is optionally substituted with a substituent selected from halogen, hydroxy, (C_1-C_3) alkoxy and $-C(=O)NR^cR^f$;

[0096] R^{13} and R^{14} are each independently selected from $-H$, alkyl, $-OR^c$, $-(C_1-C_3)$ alkylene- OR^c , $-(C_1-C_3)$ alkylene-OH, (C_3-C_8) cycloalkyl, $-O-(C_3-C_8)$ cycloalkyl and 3 to 8 membered heterocycloalkyl, provided that R^{13} and R^{14} are not both $-OR^c$, wherein each of the cycloalkyl or heterocycloalkyl groups is optionally substituted with a (C_1-C_3) alkyl;

[0097] n is an integer from 1 to 2;

[0098] m is an integer from 1 to 2;

[0099] each p is 1 or 2; and values and alternative values for the remainder of the variables are as described for Structural Formula (I) or in the first or second embodiment.

[0100] In a twenty-seventh embodiment, for compounds represented by any one of structural formulas (I), (III) or (III-A1)-(II-G4), each R^1 is independently selected from $-H$, -halogen, $-CN$, $-NO_2$, $-OR^c$, $-NR^aR^b$, $-S(O)_iR^c$, $-C(=O)OR^c$, $-OC(=O)OR^c$, $-C(=O)NR^cR^f$, $-NR^cC(=O)R^c$, $-C(=O)R^c$ or alkyl, wherein the alkyl is optionally substituted with a substituent selected from -halogen, $-OR^c$, $-NR^aR^b$, and $-S(O)_iR^c$;

[0101] R^5 is (a) cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, morpholinyl, thiomorpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, piperazinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, azetidiny, dihydroimidazole, dihydrofuranyl, dihydropyranly, dihydropyridinyl, dihydropyrimidinyl, dihydrothienyl, dihydrothiophenyl, dihydrothiopyranly, tetrahydroimidazole, tetrahydrofuranyl, tetrahydropyranly, tetrahydrothienyl, tetrahydropyridinyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranly, phenyl, furanyl, imidazolyl, oxazolyl, isoxazolyl, oxadiazolyl, pyrazolyl, pyrrolyl, pyridyl, pyrimidinyl, pyridazinyl, thiazolyl, isothiazolyl, triazolyl, tetrazolyl or thienyl, each of which is optionally substituted with 1 to 3 groups represented by R^{15} or (b) (b) bicyclooctanyl, decahydronaphthyl, octahydroindeny, dihydronaphthalenyl, tetrahydronaphthalenyl, dihydroindolyl, dihydroisindolyl, dihydrobenzimidazolyl, dihydrobenzothienyl, dihydrobenzofuranyl, dihydroisobenzofuranyl, dihydrobenzotriazolyl, dihydrobenzothiazolyl, dihydrobenzoxazolyl, dihydrobenzisoxazolyl, dihydroquinolinyl, tetrahydroquinolinyl, dihydroisoquinolinyl, tetrahydroisoquinolinyl, dihydroindazolyl, dihydroacridinyl, tetrahydroacridinyl, chromanyl, isochromanyl, chromenyl, isochromenyl, naphthyl, anthracenyl, fluorenyl, indanyl, indenyl, carbazolyl, benzimidazolyl, benzothienyl, benzofuranyl, isobenzofuranyl, indolyl, isindolyl, benzotriazolyl, benzothiazolyl, benzoxazolyl, benzisoxazolyl, quinolinyl, isoquinolinyl, indazolyl or acridinyl, each of which is optionally substituted with 1 to 3 groups represented by R^{16} ;

[0102] R^{13} is H and R^{14} is $-H$, (C_1-C_6) alkyl, $-OR^c$, $-(C_1-C_3)$ alkylene- OR^c , $-(C_1-C_3)$ alkylene-OH, a cycloalkyl selected from cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl, a $-O$ -cycloalkyl selected from $-O$ -cyclopropyl, $-O$ -cyclobutyl, and $-O$ -cyclopentyl, $-O$ -cyclohexyl, or a heterocycloalkyl selected from morpholinyl, thiomorpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, piperazinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, azetidiny, dihydroimidazole, dihydrofuranyl, dihydropyranly, dihydropyridinyl, dihydropyrimidinyl, dihydrothienyl, dihydrothiophenyl, dihydrothiopyranly, tetrahydroimidazole, tetrahydrofuranyl, tetrahydropyranly, tetrahydrothienyl, tetrahydropyridinyl, tetrahydropyrimidinyl, tetrahydrothiophenyl and tetrahydrothiopyranly, provided that R^{13} and R^{14} are not both $-OR^c$, wherein each of the $-O$ -cycloalkyl, cycloalkyl or heterocycloalkyl groups is optionally substituted with a (C_1-C_3) alkyl; and R^c is $-H$, or (C_1-C_6) alkyl

[0103] each R^{15} is independently selected from halogen, $-CN$, $-NO_2$, $=O$, $-OR^c$, $-NR^aR^b$, $-C(=O)OR^c$, $-OC(=O)OR^c$, $-C(=O)NR^cR^f$, $-NR^cC(=O)R^c$, $-NR^cC(=O)OR^c$, $-O(C=O)NR^cR^f$, $-NR^cC(=O)NR^cR^f$, $-C(=O)R^c$, (C_1-C_6) alkyl, morpholinyl, thiomorpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, piperazinyl,

hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, azetidiny, dihydroimidazole, dihydrofuranyl, dihydropyranyl, dihydropyridinyl, dihydropyrimidinyl, dihydrothienyl, dihydrothiophenyl, dihydrothiopyranyl, tetrahydroimidazole, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothienyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, phenyl, benzyl, furanyl, imidazolyl, oxazolyl, isoxazolyl, oxadiazolyl, pyrazolyl, pyrrolyl, pyridyl, pyrimidinyl, pyridazinyl, thiazolyl, isothiazolyl, triazolyl, tetrazolyl, and thienyl; wherein the (C₁-C₆) alkyl represented by R¹⁵ is optionally substituted with a substituent selected from -halogen, —OR^c, (C₁-C₆)alkyl, (C₁-C₃)alkoxy, morpholinyl, thiomorpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, piperazinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, azetidiny, dihydroimidazole, dihydrofuranyl, dihydropyranyl, dihydropyridinyl, dihydropyrimidinyl, dihydrothienyl, dihydrothiophenyl, dihydrothiopyranyl, tetrahydroimidazole, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothienyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, furanyl, imidazolyl, oxazolyl, isoxazolyl, oxadiazolyl, pyrazolyl, pyrrolyl, pyridyl, pyrimidinyl, pyridazinyl, thiazolyl, isothiazolyl, triazolyl, tetrazolyl, and thienyl;

[0104] each R¹⁶ is independently selected from halogen, —OR^c, —NR^aR^b, —C(=O)OR^c, —C(=O)NR^aR^b, —NR^aC(=O)R^c, —C(=O)R^c, (C₁-C₆)alkyl, phenyl, phenyl(C₁-C₃)alkyl, morpholinyl, thiomorpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, piperazinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, azetidiny, dihydroimidazole, dihydrofuranyl, dihydropyranyl, dihydropyridinyl, dihydropyrimidinyl, dihydrothienyl, dihydrothiophenyl, dihydrothiopyranyl, tetrahydroimidazole, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothienyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, furanyl, imidazolyl, oxazolyl, isoxazolyl, oxadiazolyl, pyrazolyl, pyrrolyl, pyridyl, pyrimidinyl, pyridazinyl, thiazolyl, isothiazolyl, triazolyl, tetrazolyl, and thienyl; and values and alternative values for the remainder of the variables are as described for Structural Formula (I) or in the first, second or twenty-sixth embodiment.

[0105] In a twenty-eighth embodiment, for compounds represented by any one of structural formulas (I), (III) or (III-A1)-(II-G4), R¹ is selected from —H, -halogen, —OCH₃, —N(CH₃)₂, —S(O)₂CH₃, or methyl;

[0106] R⁵ is cyclopentyl, cyclohexyl, morpholinyl, pyrrolidinyl, piperidinyl, dihydropyridinyl, tetrahydropyridinyl, dihydropyrimidinyl, tetrahydropyrimidinyl, phenyl, furanyl, imidazolyl, pyrrolyl, pyridyl, pyrimidinyl or thienyl, each of which is optionally substituted with 1 to 3 groups represented by R¹⁵ or (b) chromanyl, chromenyl, dihydroindolyl, dihydroisoindolyl, dihydrobenzothienyl, dihydrobenzofuranyl, dihydroisobenzofuranyl, dihydrobenzotriazolyl, dihydroquinolinyl, tetrahydroquinolinyl, dihydroisoquinolinyl, tetrahydroisoquinolinyl, dihydrobenzisoaxazolyl, naphthyl, anthracenyl, fluorenyl, indanyl, indenyl, dihydronaphthalene, tetrahydronaphthalene, carbazolyl, benzimidazolyl, benzothienyl, benzofuranyl, isobenzofuranyl, indolyl, quinolinyl, isoquinolinyl or isoindolyl, each of which is optionally substituted with 1 to 3 groups represented by R¹⁶;

[0107] R¹³ is —H and R¹⁴ is —H, (C₁-C₆)alkyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, —O-cyclopropyl, —O-cyclobutyl, —O-cyclopentyl, —O-cyclohexyl, morpholinyl, thiomorpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, piperazinyl, hydantoinyl, valerolactamyl, oxiranyl,

oxetanyl, azetidiny, dihydroimidazole, dihydrofuranyl, dihydropyranyl, dihydropyridinyl, dihydropyrimidinyl, dihydrothienyl, dihydrothiophenyl, dihydrothiopyranyl, tetrahydroimidazole, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothienyl, tetrahydrothiophenyl or tetrahydrothiopyranyl;

[0108] R¹⁵ is independently selected from halogen, —OR^c, —NR^aR^b, and (C₁-C₆)alkyl;

[0109] each R¹⁶ is independently selected from (C₁-C₆)alkyl;

[0110] m is 1; and values and alternative values for the remainder of the variables are as described for Structural Formula (I) or in the first, second, twenty-sixth or twenty-seventh embodiment.

[0111] In a twenty-ninth embodiment, for compounds represented by any one of structural formulas (III-C1)-(II-G4), U is —CH₂—, —NH—, or —O—; each (R¹⁶)₀₋₁ is absent.

[0112] In a thirtieth embodiment, for compounds represented by any one of structural formulas (I), (III) or (III-A1)-(II-E4), X is —NR¹¹—; R¹¹ is (C₁-C₄)alkyl; and values and alternative values for the remainder of the variables are as described for Structural Formula (I) or in the first, second, twenty-sixth, twenty-seventh, twenty-eighth or twenty-ninth embodiment.

[0113] In a thirty-first embodiment, for compounds represented by any one of structural formulas (I)-(III), (II-A1)-(II-I4) or (III-A1)-(II-G4), R⁵ is cyclohexyl, phenyl, pyridyl, or thienyl, each of which is optionally substituted with 1 to 3 groups selected from methyl, ethyl, propyl, halogen, hydroxymethyl, hydroxyethyl, methoxy, ethoxy, and —(CH₂)₀₋₂-morpholinyl; and values and alternative values for the remainder of the variables are as described for Structural Formula (I) or in the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, twelfth, thirteenth, fourteenth, fifteenth, sixteenth, seventeenth, eighteenth, nineteenth, twentieth, twenty-first, twenty-second, twenty-third, twenty-fourth, twenty-fifth, twenty-sixth, twenty-seventh, twenty-eighth, twenty-ninth or thirtieth embodiment.

[0114] Alternatively, in a thirty-second embodiment, for compounds represented by any one of structural formulas (I)-(III), (II-A1)-(II-I4) or (III-A1)-(II-G4), R⁵ is cyclohexyl, phenyl, pyridyl, or thienyl, each of which is optionally substituted with 1 to 3 groups selected from methyl, ethyl, propyl and halogen; and values and alternative values for the remainder of the variables are as described for Structural Formula (I) or in the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, twelfth, thirteenth, fourteenth, fifteenth, sixteenth, seventeenth, eighteenth, nineteenth, twentieth, twenty-first, twenty-second, twenty-third, twenty-fourth, twenty-fifth, twenty-sixth, twenty-seventh, twenty-eighth, twenty-ninth or thirtieth embodiment.

[0115] In a thirty-third embodiment, for compounds represented by any one of structural formulas (I)-(III), (II-A1)-(II-I4) or (III-A1)-(II-G4), R¹⁴ is —H, methyl, ethyl, propyl, hydroxymethyl, hydroxyethyl, hydroxypropyl, methoxy, ethoxy, propoxy, methoxymethyl, methoxyethyl, methoxypropyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, —O-cyclopropyl, —O-cyclobutyl, —O-cyclopentyl, —O-cyclohexyl, morpholinyl, oxetanyl, tetrahydrofuryl, tetrahydropyranyl, azetidiny, pyrrolidinyl, piperidinyl, wherein the morpholinyl, tetrahydrofuryl, tetrahydropyranyl, pyrrolidinyl or piperidinyl are optionally substituted with methyl; and values and alternative values for the remainder of the

variables are as described for Structural Formula (I) or in the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, twelfth, thirteenth, fourteenth, fifteenth, sixteenth, seventeenth, eighteenth, nineteenth, twentieth, twenty-first, twenty-second, twenty-third, twenty-fourth, twenty-fifth, twenty-sixth, twenty-seventh, twenty-eighth, twenty-ninth, thirtieth, thirty-first or thirty-second embodiment.

[0116] In a thirty-fourth embodiment, for compounds represented by any one of structural formulas (I)-(III), (II-A1)-(II-I4) or (III-A1)-(II-G4), R^3 is piperidyloxy, N-methylpiperidyloxy, morpholinyl or hydroxypiperidyl; and values and alternative values for the remainder of the variables are as described for Structural Formula (I) or in the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, twelfth, thirteenth, fourteenth, fifteenth, sixteenth, seventeenth, eighteenth, nineteenth, twentieth, twenty-first, twenty-second, twenty-third, twenty-fourth, twenty-fifth, twenty-sixth, twenty-seventh, twenty-eighth, twenty-ninth, thirtieth, thirty-first, thirty-second or thirty-third embodiment.

[0117] In certain embodiments, the present teachings provide the compounds depicted and/or described by name in the Exemplification, as well as neutral forms and pharmaceutically acceptable salts thereof.

[0118] The term “alkyl” used alone or as part of a larger moiety, such as “alkoxy”, “haloalkyl”, “cycloalkylalkyl”, “heterocycloalkylalkyl”, “aralkyl”, “heteroaralkyl” and the like, means saturated aliphatic straight-chain or branched monovalent hydrocarbon radical. Unless otherwise specified, an alkyl group typically has 1-6 carbon atoms, i.e. (C_1 - C_6) alkyl. As used herein, a “(C_1 - C_6)alkyl” group is means a radical having from 1 to 6 carbon atoms in a linear or branched arrangement.

[0119] An “alkylene group” is a saturated aliphatic branched or straight-chain divalent hydrocarbon radical. Unless otherwise specified, an alkylene group typically has 1-6 carbon atoms, i.e. (C_1 - C_6)alkylene.

[0120] An “alkenyl” means branched or straight-chain monovalent hydrocarbon radical containing at least one double bond. Alkenyl may be mono or polyunsaturated, and may exist in the E or Z configuration. Unless otherwise specified, an alkenyl group typically has 2-6 carbon atoms, i.e. (C_2 - C_6)alkenyl. For example, “(C_2 - C_6)alkenyl” means a radical having from 2-6 carbon atoms in a linear or branched arrangement.

[0121] “Alkynyl” means branched or straight-chain monovalent hydrocarbon radical containing at least one triple bond. Unless otherwise specified, an alkynyl group typically has 2-6 carbon atoms, i.e. (C_2 - C_6)alkynyl. For example, “(C_2 - C_6)alkynyl” means a radical having from 2-6 carbon atoms in a linear or branched arrangement.

[0122] “Alkoxy” means an alkyl radical attached through an oxygen linking atom, represented by —O-alkyl. For example, “(C_1 - C_4)alkoxy” includes methoxy, ethoxy, propoxy, and butoxy.

[0123] The terms “haloalkyl” and “haloalkoxy” means alkyl or alkoxy, as the case may be, substituted with one or more halogen atoms. The term “halogen” means F, Cl, Br or I. Preferably the halogen in a haloalkyl or haloalkoxy is F.

[0124] The term “aryl group” used alone or as part of a larger moiety as in “aralkyl”, “aralkoxy”, or “aryloxyalkyl”, means an aromatic hydrocarbon ring system. The term “aryl” may be used interchangeably with the terms “aryl ring” “aro-

matic ring”, “aryl group” and “aromatic group”. An aryl group typically has six to fourteen ring atoms. Examples includes phenyl, naphthyl, anthracenyl, 1,2-dihydronaphthyl, 1,2,3,4-tetrahydronaphthyl, fluorenyl, indanyl, indenyl and the like. A “substituted aryl group” is substituted at any one or more substitutable ring atom, which is a ring carbon atom bonded to a hydrogen.

[0125] “Cycloalkyl” means a saturated aliphatic cyclic hydrocarbon radical optionally containing one or more double bonds. It can be monocyclic, bicyclic, polycyclic (e.g., tricyclic), or fused. For example, monocyclic (C_3 - C_8)cycloalkyl means a radical having from 3-8 carbon atoms arranged in a monocyclic ring. A (C_3 - C_8)cycloalkyl includes, but is not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

[0126] “Heterocycloalkyl” means a saturated or unsaturated non-aromatic 4-12 membered ring radical optionally containing one or more double bonds. It can be monocyclic, bicyclic, tricyclic, or fused. The heterocycloalkyl contains 1 to 4 heteroatoms, which may be the same or different, selected from N, O or S. The heterocycloalkyl ring optionally contains one or more double bonds and/or is optionally fused with one or more aromatic rings (e.g., phenyl ring). The term “heterocycloalkyl” is intended to include all the possible isomeric forms. Examples of heterocycloalkyl include, but are not limited to, morpholinyl, thiomorpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, piperazinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, dihydroimidazole, dihydrofuranyl, dihydropyranyl, dihydropyridinyl, dihydropyrimidinyl, dihydrothienyl, dihydrothiophenyl, dihydrothiopyranyl, tetrahydroimidazole, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothienyl, tetrahydropyridinyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, and tetrahydrothiopyranyl. Examples of polycyclic heterocycloalkyl groups include dihydroindolyl, dihydroisoindolyl, dihydrobenzimidazolyl, dihydrobenzothienyl, dihydrobenzofuranyl, dihydroisobenzofuranyl, dihydrobenzotriazolyl, dihydrobenzothiazolyl, dihydrobenzoxazolyl, dihydroquinolinyl, tetrahydroquinolinyl, dihydroisoquinolinyl, tetrahydroisoquinolinyl, dihydroindazolyl, dihydroacridinyl, tetrahydroacridinyl, dihydrobenzisoxazolyl, chroman, chromene, isochroman and isochromene.

[0127] The term “heteroaryl”, “heteroaromatic”, “heteroaryl ring”, “heteroaryl group”, “heteroaromatic ring”, and “heteroaromatic group”, are used interchangeably herein. “Heteroaryl” when used alone or as part of a larger moiety as in “heteroaralkyl” or “heteroarylalkoxy”, refers to aromatic ring groups having five to fourteen ring atoms selected from carbon and at least one (typically 1 to 4, more typically 1 or 2) heteroatoms (e.g., oxygen, nitrogen or sulfur). “Heteroaryl” includes monocyclic rings and polycyclic rings in which a monocyclic heteroaromatic ring is fused to one or more other aromatic or heteroaromatic rings. As such, “5-14 membered heteroaryl” includes monocyclic, bicyclic or tricyclic ring systems.

[0128] Examples of monocyclic 5-6 membered heteroaryl groups include furanyl (e.g., 2-furanyl, 3-furanyl), imidazolyl (e.g., N-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl), isoxazolyl (e.g., 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl), oxadiazolyl (e.g., 2-oxadiazolyl, 5-oxadiazolyl), oxazolyl (e.g., 2-oxazolyl, 4-oxazolyl, 5-oxazolyl), pyrazolyl (e.g., 3-pyrazolyl, 4-pyrazolyl), pyrrolyl (e.g., 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl), pyridyl (e.g., 2-pyridyl, 3-pyridyl, 4-pyridyl), pyrimidinyl (e.g., 2-pyrimidinyl, 4-pyrimidinyl,

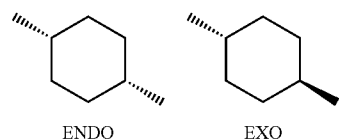
5-pyrimidinyl), pyridazinyl (e.g., 3-pyridazinyl), thiazolyl (e.g., 2-thiazolyl, 4-thiazolyl, 5-thiazolyl), isothiazolyl, triazolyl (e.g., 2-triazolyl, 5-triazolyl), tetrazolyl (e.g., tetrazolyl), and thienyl (e.g., 2-thienyl, 3-thienyl). Examples of polycyclic aromatic heteroaryl groups include carbazoyl, benzimidazolyl, benzothienyl, benzofuranyl, isobenzofuranyl, indolyl, benzotriazolyl, benzothiazolyl, benzoxazolyl, quinolinyl, isoquinolinyl, indazolyl, isoindolyl, acridinyl, or benzisoxazolyl. A “substituted heteroaryl group” is substituted at any one or more substitutable ring atom, which is a ring carbon or ring nitrogen atom bonded to a hydrogen.

[0129] Unless otherwise indicated, suitable substituents for a substituted alkyl, cycloalkyl, heterocycloalkyl, aryl group and heteroaryl group include the groups represented by halogen, $-\text{OR}^c$, $-\text{NR}^a\text{R}^b$, $-\text{S}(\text{O})_i\text{R}^c$, $-\text{NR}^d\text{S}(\text{O})_i\text{R}^c$, $-\text{S}(\text{O})_i\text{NR}^e\text{R}^f$, $-\text{C}(=\text{O})\text{OR}^c$, $-\text{OC}(=\text{O})\text{OR}^c$, $-\text{C}(=\text{S})\text{OR}^c$, $-\text{O}(\text{C}=\text{S})\text{R}^c$, $-\text{C}(=\text{O})\text{NR}^e\text{R}^f$, $-\text{NR}^d\text{C}(=\text{O})\text{R}^c$, $-\text{C}(=\text{S})\text{NR}^e\text{R}^f$, $-\text{NR}^d\text{C}(=\text{S})\text{R}^c$, $-\text{NR}^d(\text{C}=\text{O})\text{OR}^c$, $-\text{O}(\text{C}=\text{O})\text{NR}^e\text{R}^f$, $-\text{NR}^d(\text{C}=\text{S})\text{OR}^c$, $-\text{O}(\text{C}=\text{S})\text{NR}^e\text{R}^f$, $-\text{NR}^d(\text{C}=\text{O})\text{NR}^e\text{R}^f$, $-\text{NR}^d(\text{C}=\text{S})\text{NR}^e\text{R}^f$, $-\text{C}(=\text{S})\text{R}^c$, $-\text{C}(=\text{O})\text{R}^c$, $(\text{C}_1\text{--}\text{C}_6)\text{alkyl}$, cycloalkyl, cycloalkyl $(\text{C}_1\text{--}\text{C}_3)$ alkyl, heterocycloalkyl, heterocycloalkyl $(\text{C}_1\text{--}\text{C}_3)$ alkyl, aryl, aryl $(\text{C}_1\text{--}\text{C}_3)$ alkyl, heteroaryl and heteroaryl $(\text{C}_1\text{--}\text{C}_3)$ alkyl, wherein R^a , R^b , R^c , R^d , R^e and R^f are described above for Structural Formula (I). Each of the $(\text{C}_1\text{--}\text{C}_6)\text{alkyl}$, cycloalkyl, cycloalkyl $(\text{C}_1\text{--}\text{C}_3)$ alkyl, heterocycloalkyl, heterocycloalkyl $(\text{C}_1\text{--}\text{C}_3)$ alkyl, aryl, aryl $(\text{C}_1\text{--}\text{C}_3)$ alkyl, heteroaryl and heteroaryl $(\text{C}_1\text{--}\text{C}_3)$ alkyl substituents is optionally substituted with halogen, $-\text{NO}_2$, $-\text{CN}$, $-\text{NR}^g\text{C}(=\text{O})\text{R}^c$, $-\text{NR}^g\text{R}^h$, $(\text{C}_1\text{--}\text{C}_3)\text{alkyl}$, halo $(\text{C}_1\text{--}\text{C}_3)\text{alkyl}$, $(\text{C}_1\text{--}\text{C}_3)\text{alkoxy}$, $(\text{C}_1\text{--}\text{C}_3)\text{alkyl}$, $(\text{C}_1\text{--}\text{C}_3)\text{alkoxy}$ and halo $(\text{C}_1\text{--}\text{C}_3)\text{alkoxy}$, wherein R^g and R^h are as described above for Structural Formula (I). Suitable substituents for a substituted alkyl, cycloalkyl, heterocycloalkyl can also include $=\text{O}$. In certain embodiments, suitable substituents include alkyl, haloalkyl, alkoxy, haloalkoxy, cyano, nitro and halogen.

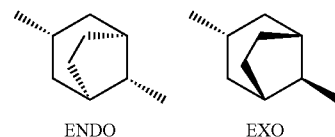
[0130] Regarding connectivity, an “arylalkyl” moiety, for example, refers to an alkyl group substituted with an aryl group (e.g., phenylmethyl (i.e., benzyl)). Similarly, a “heteroarylalkyl” moiety refers to an alkyl group substituted with a heteroaryl group.

[0131] As used herein, the term “bridged bicyclic group” refers to a ring system which includes two rings that share at least three adjacent ring atoms.

[0132] As used herein, the term “endo”, when used in connection with saturated (or partially saturated) ring substitution, refers to two substituents being present on the same face of the ring. Similarly, the term “exo”, when used in connection with saturated (or partially saturated) ring substitution, refers to two substituents being present on opposing faces of the ring. For example, endo and exo adducts of dimethylcyclohexane are as follows:



Similarly, exemplary endo and exo adducts of a bridged bicyclic compound are as follows:



[0133] The present teachings also include various isomers and mixtures thereof. “Isomer” refers to compounds that have the same composition and molecular weight but differ in physical and/or chemical properties. The structural difference may be in constitution (geometric isomers) or in the ability to rotate the plane of polarized light (stereoisomers).

[0134] Certain of the compounds described herein may exist in various stereoisomeric or tautomeric forms. Stereoisomers are compounds which differ only in their spatial arrangement. The present teachings encompass all such forms, including compounds in the form of essentially pure enantiomers, racemic mixtures and tautomers, which includes forms not depicted structurally. When a disclosed compound is named or depicted by structure without indicating stereochemistry, it is understood that the name or structure encompasses all possible stereoisomers, tautomers, geometric isomers or a combination thereof.

[0135] When a geometric isomer is depicted by name or structure, it is to be understood that the geometric isomeric purity of the named or depicted geometric isomer is at least 60%, 70%, 80%, 90%, 99% or 99.9% pure by weight. Geometric isomeric purity is determined by dividing the weight of the named or depicted geometric isomer in the mixture by the total weight of all of the geometric isomers in the mixture.

[0136] Racemic mixture means 50% of one enantiomer and 50% of its corresponding enantiomer. The present teachings encompass all enantiomerically-pure, enantiomerically-enriched, diastereomerically pure, diastereomerically enriched, and racemic mixtures, and diastereomeric mixtures of the compounds described herein.

[0137] Enantiomeric and diastereomeric mixtures can be resolved into their component enantiomers or stereoisomers by well known methods, such as chiral-phase gas chromatography, chiral-phase high performance liquid chromatography, crystallizing the compound as a chiral salt complex, or crystallizing the compound in a chiral solvent. Enantiomers and diastereomers can also be obtained from diastereomerically- or enantiomerically-pure intermediates, reagents, and catalysts by well known asymmetric synthetic methods.

[0138] When a compound is designated by a name or structure that indicates a single enantiomer, unless indicated otherwise, the compound is at least 60%, 70%, 80%, 90%, 99% or 99.9% optically pure (also referred to as “enantiomerically pure”). Optical purity is the weight in the mixture of the named or depicted enantiomer divided by the total weight in the mixture of both enantiomers.

[0139] When the stereochemistry of a disclosed compound is named or depicted by structure, and the named or depicted structure encompasses more than one stereoisomer (e.g., as in a diastereomeric pair), it is to be understood that one of the encompassed stereoisomers or any mixture of the encompassed stereoisomers are included. It is to be further understood that the stereoisomeric purity of the named or depicted stereoisomers at least 60%, 70%, 80%, 90%, 99% or 99.9% by weight. The stereoisomeric purity in this case is determined by dividing the total weight in the mixture of the

stereoisomers encompassed by the name or structure by the total weight in the mixture of all of the stereoisomers.

[0140] Included in the present teachings are pharmaceutically acceptable salts of the compounds disclosed herein. The disclosed compounds have basic amine groups and therefore can form pharmaceutically acceptable salts with pharmaceutically acceptable acid(s). Suitable pharmaceutically acceptable acid addition salts of the compounds described herein include salts of inorganic acids (such as hydrochloric acid, hydrobromic, phosphoric, metaphosphoric, nitric, and sulfuric acids) and of organic acids (such as, acetic acid, benzenesulfonic, benzoic, citric, ethanesulfonic, fumaric, gluconic, glycolic, isethionic, lactic, lactobionic, maleic, malic, methanesulfonic, succinic, p-toluenesulfonic, and tartaric acids). Compounds of the present teachings with acidic groups such as carboxylic acids can form pharmaceutically acceptable salts with pharmaceutically acceptable base(s). Suitable pharmaceutically acceptable basic salts include ammonium salts, alkali metal salts (such as sodium and potassium salts) and alkaline earth metal salts (such as magnesium and calcium salts). Compounds with a quaternary ammonium group also contain a counteranion such as chloride, bromide, iodide, acetate, perchlorate and the like. Other examples of such salts include hydrochlorides, hydrobromides, sulfates, methanesulfonates, nitrates, maleates, acetates, citrates, fumarates, tartrates [e.g. (+)-tartrates, (–)-tartrates or mixtures thereof including racemic mixtures], succinates, benzoates and salts with amino acids such as glutamic acid.

[0141] Compounds described herein can inhibit various kinases, including the TTK, PLK (such as PLK4), Aurora A, Aurora B and CHK (such as CHK2). Thus, generally, compounds described herein are useful in the treatment of diseases or conditions associated with such kinases. In some embodiments, compounds described herein can inhibit TTK, PLK (such as PLK4), and/or Aurora B kinases.

[0142] In one embodiment, the compounds described herein are TTK, PLK, Aurora A, Aurora B and/or CHK inhibitors, and are useful for treating diseases, such as cancer, associated with such kinase(s). Alternatively, the compounds described herein are TTK inhibitors and are useful for treating diseases associated with TTK, such as cancer. In another alternative embodiment, the compounds described herein are Aurora A and/or B inhibitors and are useful in inhibiting Aurora A and/or B activity for the treatment of various conditions such as cancers. In yet another specific embodiment, the compounds described herein are PLK inhibitors and are useful in inhibiting PLK activity for the treatment of various conditions such as cancers. Typically, the PLK is PLK4, PLK2 and/or PLK1. In one example, the PLK is PLK1 and/or PLK4. In another example, the PLK is PLK4. In another alternative embodiment, the compounds described herein are CHK inhibitors and are useful in inhibiting CHK activity for the treatment of various conditions such as cancers.

[0143] Another aspect of the present teachings relates to a method of treating a subject with cancer comprising administering to the subject an effective amount of a compound described herein. In one embodiment, the compounds described herein inhibit the growth of a tumor. For example, the compounds described herein inhibit the growth of a tumor that overexpresses at least one of TTK, PLK, Aurora A, Aurora B, and CHK. In one embodiment, the compounds described herein inhibit the growth of a tumor that overexpresses TTK.

[0144] Cancers that can be treated (including reduction in the likelihood of recurrence) by the methods of the present teachings include lung cancer, breast cancer, colon cancer, brain cancer, neuroblastoma, prostate cancer, melanoma, glioblastoma multiform, ovarian cancer, lymphoma, leukemia, melanoma, sarcoma, paraneoplasia, osteosarcoma, germinoma, glioma and mesothelioma. In one embodiment, the cancer is selected from leukemia, acute myeloid leukemia, chronic myelogenous leukemia, breast cancer, brain cancer, colon cancer, colorectal cancer, head and neck cancer, hepatocellular carcinoma, lung adenocarcinoma, metastatic melanoma, pancreatic cancer, prostate cancer, ovarian cancer and renal cancer. In one embodiment, the cancer is lung cancer, colon cancer, brain cancer, neuroblastoma, prostate cancer, melanoma, glioblastoma multiform or ovarian cancer. In another embodiment, the cancer is lung cancer, breast cancer, colon cancer, brain cancer, neuroblastoma, prostate cancer, melanoma, glioblastoma multiform or ovarian cancer. In yet another embodiment, the cancer is breast cancer, colon cancer and lung cancer. In yet another embodiment, the cancer is a breast cancer. In yet another embodiment, the cancer is a basal sub-type breast cancer or a luminal B sub-type breast cancer. In yet another embodiment, the cancer is a basal sub-type breast cancer that overexpresses TTK. In yet another embodiment, the basal sub-type breast cancer is ER (estrogen receptor), HER2 and PR (progesterone receptor) negative breast cancer. In yet another embodiment, the cancer is a soft tissue cancer. A “soft tissue cancer” is an art-recognized term that encompasses tumors derived from any soft tissue of the body. Such soft tissue connects, supports, or surrounds various structures and organs of the body, including, but not limited to, smooth muscle, skeletal muscle, tendons, fibrous tissues, fatty tissue, blood and lymph vessels, perivascular tissue, nerves, mesenchymal cells and synovial tissues. Thus, soft tissue cancers can be of fat tissue, muscle tissue, nerve tissue, joint tissue, blood vessels, lymph vessels, and fibrous tissues. Soft tissue cancers can be benign or malignant. Generally, malignant soft tissue cancers are referred to as sarcomas, or soft tissue sarcomas. There are many types of soft tissue tumors, including lipoma, lipoblastoma, hibernoma, liposarcoma, leiomyoma, leiomyosarcoma, rhabdomyoma, rhabdomyosarcoma, neurofibroma, schwannoma (neurilemoma), neuroma, malignant schwannoma, neurofibrosarcoma, neurogenic sarcoma, nodular tenosynovitis, synovial sarcoma, hemangioma, glomus tumor, hemangiopericytoma, hemangioendothelioma, angiosarcoma, Kaposi sarcoma, lymphangioma, fibroma, elastofibroma, superficial fibromatosis, fibrous histiocytoma, fibrosarcoma, fibromatosis, dermatofibrosarcoma protuberans (DFSP), malignant fibrous histiocytoma (MFH), myxoma, granular cell tumor, malignant mesenchymomas, alveolar soft-part sarcoma, epithelioid sarcoma, clear cell sarcoma, and desmoplastic small cell tumor. In a particular embodiment, the soft tissue cancer is a sarcoma selected from the group consisting of a fibrosarcoma, a gastrointestinal sarcoma, a leiomyosarcoma, a dedifferentiated liposarcoma, a pleomorphic liposarcoma, a malignant fibrous histiocytoma, a round cell sarcoma, and a synovial sarcoma.

[0145] In some embodiments, the present teachings provide methods of inhibiting the growth of tumor-initiating cells or reducing the likelihood of recurrence of a cancer in a subject who is undergoing an anti-cancer therapy. The method comprises the steps of:

[0146] a) assessing the subject to determine whether the cancer is in remission; and

[0147] b) if the cancer is in remission; then administering to the subject an effective amount of a TTK inhibitor (e.g., a compound represented by Structural Formula (I)). If the cancer is not in remission, the method optionally further comprises the step of continuing the anti-cancer therapy until the cancer goes into remission and then the step b) of administering an effective amount of a TTK inhibitor (e.g., a compound represented by Structural Formula (I)).

[0148] As used herein, the term “tumor-initiating cells” or “TICs” refer to cells present within some tumors that possess the ability to self-renew and proliferate. These cells are sometimes called cancer stem cells (CSCs) and may be observed to share certain characteristics with normal stem cells, including a stem cell-like phenotype and function. In some embodiments, TICs are characterized by their ability to form tumors after xenotransplantation in immunodeficient mice.

[0149] In some embodiments, the present teachings provide methods of inhibiting the growth of tumor-initiating cells or reducing the likelihood of recurrence of a cancer in a subject whose cancer is in remission comprising administering to the subject an effective amount of a TTK inhibitor (e.g., a compound represented by Structural Formula (I)).

[0150] In some embodiments, e.g., where the subject is being treated to reduce the likelihood of recurrence of a cancer, the subject has already been treated with an anti-cancer therapy. Alternatively, the subject has already been treated with an anti-cancer therapy and the subject is in remission.

[0151] In some embodiments, the present teachings provide methods of treating a subject with a cancer comprising administering to the subject an effective amount of a compound represented by Structural Formula (I) in combination with an effective anti-cancer therapy. In one embodiment, the cancer is a metastatic cancer. A “metastatic cancer” is a cancer that has spread from its primary site to other parts of the body.

[0152] In another embodiment, the present teachings are directed to a method of treating a subject with a drug-resistant cancer. A “drug-resistant cancer” is a cancer that is not responsive to one, two, three, four, five or more drugs that are typically used for the treatment of the cancer. In one embodiment, the drug-resistant cancer is mediated by the growth of tumor-initiating cells.

[0153] The term “inhibiting the growth of tumor-initiating cells” refers to preventing or decreasing the rate of the proliferation and/or survival of the tumor-initiating cells.

[0154] As used herein, the term “reducing the likelihood of recurrence of a cancer” means partially or totally inhibiting, preventing or delaying the return of a cancer at or near a primary site and/or at a secondary site after a period of remission. It also means that the cancer is less likely to return with treatment described herein than in its absence.

[0155] As used herein, the term “remission” refers to a state of cancer, wherein the clinical symptoms or indicators associated with a cancer have disappeared or cannot be detected, typically after the subject has been successfully treated with an anti-cancer therapy.

[0156] As used herein, “treating a subject with a cancer” includes achieving, partially or substantially, one or more of the following: arresting the growth, reducing the extent of the cancer (e.g., reducing size of a tumor), inhibiting the growth rate of the cancer, ameliorating or improving a clinical symp-

tom or indicator associated with the cancer (such as tissue or serum components) or increasing longevity of the subject; and reducing the likelihood of recurrence of the cancer.

[0157] Suitable methods known in the art can be used for assessing a subject to determine whether the cancer is in remission. For example, the size of the tumor and/or tumor markers, usually proteins associated with tumors, can be monitored to determine the state of the cancer. Size of the tumor can be monitored with imaging devices, such as X-ray, MRI, CAT scans, ultrasound, mammography, PET and the like or via biopsy.

[0158] For methods described herein, e.g., coadministration methods, the anti-cancer therapy is selected from the group consisting of surgery, radiation therapy, immunotherapy, endocrine therapy, gene therapy and administration of an anti-cancer agent. Alternatively, the anti-cancer therapy is radiation therapy. In another alternative, the anti-cancer therapy is immunotherapy. In another alternative, the anti-cancer therapy is administration of an anti-cancer agent. In yet another alternative, the anti-cancer therapy is surgery.

[0159] Radiation therapy is the use of radiation to kill, destroy or treat the cancers. Exemplary radiation therapy includes, but is not limited to, gamma-radiation, neutron beam radiotherapy, electron beam radiotherapy, proton therapy, brachytherapy, and radioisotope therapy (i.e., systemic radioactive isotopes therapy).

[0160] An endocrine therapy is a treatment that adds, blocks or removes hormones. For example, chemotherapeutic agents that can block the production or activity of estrogen have been used for treating breast cancer. In addition, hormonal stimulation of the immune system has been used to treat specific cancers, such as renal cell carcinoma and melanoma. In one embodiment, the endocrine therapy comprises administration of natural hormones, synthetic hormones or other synthetic molecules that may block or increase the production of the body’s natural hormones. In another embodiment, the endocrine therapy includes removal of a gland that makes a certain hormone.

[0161] As use herein, a gene therapy is the insertion of genes into a subject’s cell and biological tissues to treat diseases, such as cancer. Exemplary gene therapy includes, but is not limited to, a germ line gene therapy and a somatic gene therapy.

[0162] Immunotherapy (also called biological response modifier therapy, biologic therapy, biotherapy, immune therapy, or biological therapy) is treatment that uses parts of the immune system to fight disease. Immunotherapy can help the immune system recognize cancer cells, or enhance a response against cancer cells. Immunotherapies include active and passive immunotherapies. Active immunotherapies stimulate the body’s own immune system while passive immunotherapies generally use immune system components created outside of the body.

[0163] Examples of active immunotherapies include, but are not limited to vaccines including cancer vaccines, tumor cell vaccines (autologous or allogeneic), dendritic cell vaccines, antigen vaccines, anti-idiotypic vaccines, DNA vaccines, viral vaccines, or Tumor-Infiltrating Lymphocyte (TIL) Vaccine with Interleukin-2 (IL-2) or Lymphokine-Activated Killer (LAK) Cell Therapy.

[0164] Examples of passive immunotherapies include but are not limited to monoclonal antibodies and targeted therapies containing toxins. Monoclonal antibodies include naked antibodies and conjugated monoclonal antibodies (also called

tagged, labeled, or loaded antibodies). Naked monoclonal antibodies do not have a drug or radioactive material attached whereas conjugated monoclonal antibodies are joined to, for example, a chemotherapy drug (chemolabeled), a radioactive particle (radiolabeled), or a toxin (immunotoxin). Examples of these naked monoclonal antibody drugs include, but are not limited to Rituximab (Rituxan), an antibody against the CD20 antigen used to treat, for example, B cell non-Hodgkin lymphoma; Trastuzumab (Herceptin), an antibody against the HER2 protein used to treat, for example, advanced breast cancer; Alemtuzumab (Campath), an antibody against the CD52 antigen used to treat, for example, B cell chronic lymphocytic leukemia (B-CLL); Cetuximab (Erbix), an antibody against the EGFR protein used, for example, in combination with irinotecan to treat, for example, advanced colorectal cancer and head and neck cancers; and Bevacizumab (Avastin) which is an antiangiogenesis therapy that works against the VEGF protein and is used, for example, in combination with chemotherapy to treat, for example, metastatic colorectal cancer. Examples of the conjugated monoclonal antibodies include, but are not limited to Radiolabeled antibody Ibritumomab tiuxetan (Zevalin) which delivers radioactivity directly to cancerous B lymphocytes and is used to treat, for example, B cell non-Hodgkin lymphoma; radiolabeled antibody Tositumomab (Bexxar) which is used to treat, for example, certain types of non-Hodgkin lymphoma; and immunotoxin Gemtuzumab ozogamicin (Mylotarg) which contains calicheamicin and is used to treat, for example, acute myelogenous leukemia (AML). BL22 is a conjugated monoclonal antibody for treating, for example, hairy cell leukemia, immunotoxins for treating, for example, leukemias, lymphomas, and brain tumors, and radiolabeled antibodies such as OncoScint for example, for colorectal and ovarian cancers and ProstaScint for example, for prostate cancers.

[0165] Further examples of therapeutic antibodies that can be used include, but are not limited to, HERCEPTIN® (Trastuzumab) (Genentech, CA) which is a humanized anti-HER2 monoclonal antibody for the treatment of patients with metastatic breast cancer; REOPRO® (abciximab) (Centocor) which is an anti-glycoprotein IIb/IIIa receptor on the platelets for the prevention of clot formation; ZENAPAX® (dacizumab) (Roche Pharmaceuticals, Switzerland) which is an immunosuppressive, humanized anti-CD25 monoclonal antibody for the prevention of acute renal allograft rejection; PANOREX™ which is a murine anti-17-1A cell surface antigen IgG2a antibody (Glaxo Wellcome/Centocor); BEC2 which is a murine anti-idiotypic (GD3 epitope) IgG antibody (ImClone System); IMC-C225 which is a chimeric anti-EGFR IgG antibody (ImClone System); VITAXIN™ which is a humanized anti- $\alpha V\beta 3$ integrin antibody (Applied Molecular Evolution/MedImmune); Campath 1H/LDP-03 which is a humanized anti CD52 IgG1 antibody (Leukosite); Smart M195 which is a humanized anti-CD33 IgG antibody (Protein Design Lab/Kanobo); RITUXAN™ which is a chimeric anti-CD20 IgG1 antibody (IDEC Pharm/Genentech, Roche/Zetayaku); LYMPHOCIDE™ which is a humanized anti-CD22 IgG antibody (Immunomedics); LYMPHOCIDE™ Y-90 (Immunomedics); Lymphoscan (Tc-99m-labeled; radioimaging; Immunomedics); Nuvion (against CD3; Protein Design Labs); CM3 is a humanized anti-ICAM3 antibody (ICOS Pharm); IDEC-114 is a primatized anti-CD80 antibody (IDEC Pharm/Mitsubishi); ZEVALIN™ is a radiolabelled murine anti-CD20 antibody (IDEC/Schering AG);

IDEC-131 is a humanized anti-CD40L antibody (IDEC/Eisai); IDEC-151 is a primatized anti-CD4 antibody (IDEC); IDEC-152 is a primatized anti-CD23 antibody (IDEC/Seikagaku); SMART anti-CD3 is a humanized anti-CD3 IgG (Protein Design Lab); 5G1.1 is a humanized anti-complement factor 5 (C5) antibody (Alexion Pharm); D2E7 is a humanized anti-TNF- α antibody (CAT/BASF); CDP870 is a humanized anti-TNF- α Fab fragment (Celltech); IDEC-151 is a primatized anti-CD4 IgG1 antibody (IDEC Pharm/Smith-Kline Beecham); MDX-CD4 is a human anti-CD4 IgG antibody (Medarex/Eisai/Genmab); CD20-sreptavidin (+biotin-yttrium 90; NeoRx); CDP571 is a humanized anti-TNF- α IgG4 antibody (Celltech); LDP-02 is a humanized anti- $\alpha 487$ antibody (LeukoSite/Genentech); OrthoClone OKT4A is a humanized anti-CD4 IgG antibody (Ortho Biotech); ANTOVA™ is a humanized anti-CD40L IgG antibody (Biogen); ANTEGREN™ is a humanized anti-VLA-4 IgG antibody (Elan); and CAT-152 is a human anti-TGF- β_2 antibody (Cambridge Ab Tech).

[0166] Immunotherapies that can be used in the present teachings include adjuvant immunotherapies. Examples include cytokines, such as granulocyte-macrophage colony-stimulating factor (GM-CSF), granulocyte-colony stimulating factor (G-CSF), macrophage inflammatory protein (MIP)-1-alpha, interleukins (including IL-1, IL-2, IL-4, IL-6, IL-7, IL-12, IL-15, IL-18, IL-21, and IL-27), tumor necrosis factors (including TNF-alpha), and interferons (including IFN-alpha, IFN-beta, and IFN-gamma); aluminum hydroxide (alum); Bacille Calmette-Guérin (BCG); Keyhole limpet hemocyanin (KLH); Incomplete Freund's adjuvant (IFA); QS-21; DETOX; Levamisole; and Dinitrophenyl (DNP), and combinations thereof, such as, for example, combinations of, interleukins, for example, IL-2 with other cytokines, such as IFN-alpha.

[0167] Alternatively, the anti-cancer therapy described herein includes administration of an anti-cancer agent. An "anti-cancer agent" is a compound, which when administered in an effective amount to a subject with cancer, can achieve, partially or substantially, one or more of the following: arresting the growth, reducing the extent of a cancer (e.g., reducing size of a tumor), inhibiting the growth rate of a cancer, and ameliorating or improving a clinical symptom or indicator associated with a cancer (such as tissue or serum components) or increasing longevity of the subject.

[0168] The anti-cancer agent suitable for use in the methods described herein include any anti-cancer agents that have been approved for the treatment of cancer. In one embodiment, the anti-cancer agent includes, but is not limited to, a targeted antibody, an angiogenesis inhibitor, an alkylating agent, an antimetabolite, a vinca alkaloid, a taxane, a podophyllotoxin, a topoisomerase inhibitor, a hormonal antineoplastic agent and other antineoplastic agents.

[0169] Examples of alkylating agents useful in the methods of the present teachings include but are not limited to, nitrogen mustards (e.g., mechlorethamine, cyclophosphamide, chlorambucil, melphalan, etc.), ethylenimine and methylmelamines (e.g., hexamethylmelamine, thiotepa), alkyl sulfonates (e.g., busulfan), nitrosoureas (e.g., carmustine, lomustine, semustine, streptozocin, etc.), or triazines (decarbazine, etc.). Examples of antimetabolites useful in the methods of the present teachings include but are not limited to folic acid analog (e.g., methotrexate), or pyrimidine analogs (e.g., fluorouracil, floxuridine, Cytarabine), purine analogs (e.g., mercaptopurine, thioguanine, pentostatin). Examples of plant

alkaloids and terpenoids or derivatives thereof include, but are not limited to, vinca alkaloids (e.g., vincristine, vinblastine, vinorelbine, vindesine), podophyllotoxin, and taxanes (e.g., paclitaxel, docetaxel). Examples of a topoisomerase inhibitor includes, but is not limited to, irinotecan, topotecan, amsacrine, etoposide, etoposide phosphate and teniposide. Examples of antineoplastic agents include, but are not limited to, actinomycin, anthracyclines (e.g., doxorubicin, daunorubicin, valrubicin, idarubicin, epirubicin), bleomycin, plicamycin and mitomycin.

[0170] In one embodiment, the anti-cancer agents that can be used in the present teachings include Adriamycin, Dactinomycin, Bleomycin, Vinblastine, Cisplatin, acivicin; aclarubicin; acodazole hydrochloride; acronine; adozelesin; aldesleukin; altretamine; ambomycin; ametantrone acetate; aminoglutethimide; amsacrine; anastrozole; anthramycin; asparaginase; asperlin; azacitidine; azetepa; azotomycin; batimastat; benzodepa; bicalutamide; bisantrene hydrochloride; bismafide dimethylate; bizelesin; bleomycin sulfate; brequinar sodium; broprimine; busulfan; cactinomycin; calusterone; caracemide; carbetimer; carboplatin; carmustine; carubicin hydrochloride; carzelesin; cedefingol; chlorambucil; cirolemycin; cladribine; crisnatol mesylate; cyclophosphamide; cytarabine; dacarbazine; daunorubicin hydrochloride; decitabine; dexormaplatin; dezaguanine; dezaguanine mesylate; diaziquone; doxorubicin; doxorubicin hydrochloride; droloxifene; droloxifene citrate; dromostanolone propionate; duazomycin; edatrexate; eflornithine hydrochloride; elsamitrucin; enloplatin; enpromate; epipropidine; epirubicin hydrochloride; erbulozole; esorubicin hydrochloride; estramustine; estramustine phosphate sodium; etanidazole; etoposide; etoposide phosphate; etoprine; fadrozole hydrochloride; fazarabine; fenretinide; floxuridine; fludarabine phosphate; fluorouracil; fluorocitabine; fosquidone; fostriecin sodium; gemcitabine; gemcitabine hydrochloride; hydroxyurea; idarubicin hydrochloride; ifosfamide; ilmofofene; interleukin II (including recombinant interleukin II, or rIL2), interferon alfa-2a; interferon alfa-2b; interferon alfa-n1; interferon alfa-n3; interferon beta-1a; interferon gamma-1b; iproplatin; irinotecan hydrochloride; lanreotide acetate; letrozole; leuprolide acetate; liarozole hydrochloride; lometrexol sodium; lomustine; losoxantrone hydrochloride; masoprocol; maytansine; mechlorethamine hydrochloride; megestrol acetate; melengestrol acetate; melphalan; menogaril; mercaptopurine; methotrexate; methotrexate sodium; metoprine; meturedpa; mitindomide; mitocarcin; mitocromin; mitogillin; mitomalcin; mitomycin; mitosper; mitotane; mitoxantrone hydrochloride; mycophenolic acid; nocodazole; nogalamycin; ormaplatin; oxisuran; pegaspargase; peliomycin; pentamustine; peplomycin sulfate; perfosfamide; pipobroman; pipsulfan; piroxantrone hydrochloride; plicamycin; plomestane; porfimer sodium; porfiromycin; prednimustine; procabazine hydrochloride; puromycin; puromycin hydrochloride; pyrazofurin; riboprine; rogletimide; safingol; safingol hydrochloride; semustine; simtrazene; sparfosate sodium; sparsomycin; spirogermanium hydrochloride; spiromustine; spiroplatin; streptonigrin; streptozocin; sulofenur; talisomycin; tecogalan sodium; tegafur; teloxantrone hydrochloride; temoporfin; teniposide; teroxirone; testolactone; thiamiprine; thioguanine; thiotepa; tiazofurin; tirapazamine; toremifene citrate; trestolone acetate; tricitriline phosphate; trimetrexate; trimetrexate glucuronate; triporelin; tubulozole hydrochloride; uracil mustard; uredepa; vapreotide; verteporfin; vinblastine sulfate; vincristine sul-

fate; vindesine; vindesine sulfate; vinepidine sulfate; vinglycininate sulfate; vinleurosine sulfate; vinorelbine tartrate; vinrosidine sulfate; vinzolidine sulfate; vorozole; zeniplatin; zinostatin; zorubicin hydrochloride.

[0171] Yet other anti-cancer agents/drugs that can be used in the present teachings include, but are not limited to: 20-epi-1,25 dihydroxyvitamin D3; 5-ethynyluracil; abiraterone; aclarubicin; acylfulvene; adecypenol; adozelesin; aldesleukin; ALL-TK antagonists; altretamine; ambamustine; amidox; amifostine; aminolevulinic acid; amrubicin; amsacrine; anagrelide; anastrozole; andrographolide; angiogenesis inhibitors; antagonist D; antagonist G; antarelix; anti-dorsalizing morphogenetic protein-1; antiandrogen, prostatic carcinoma; antiestrogen; antineoplaston; antisense oligonucleotides; aphidicolin glycinate; apoptosis gene modulators; apoptosis regulators; apurinic acid; ara-CDP-DL-PTBA; arginine deaminase; asulacrine; atamestane; atrimustine; axinastatin 1; axinastatin 2; axinastatin 3; azasetron; azatoxin; azatyrosine; baccatin III derivatives; balanol; batimastat; BCR/ABL antagonists; benzochlorins; benzoylstauroporphine; beta lactam derivatives; beta-alethine; betaclamycin B; betulinic acid; bFGF inhibitor; bicalutamide; bisantrene; bisaziridinylspermine; bismafide; bistratene A; bizelesin; breflate; broprimine; budotitane; buthionine sulfoximine; calcipotriol; calphostin C; camptothecin derivatives; canarypox IL-2; capecitabine; carboxamide-amino-triazole; carboxyamidotriazole; CaRest M3; CARN 700; cartilage derived inhibitor; carzelesin; casein kinase inhibitors (ICOS); castanospermine; cecropin B; cetorelix; chlorlins; chloroquinolaxaline sulfonamide; cicaprost; cis-porphyrin; cladribine; clomifene analogues; clotrimazole; collismycin A; collismycin B; combretastatin A4; combretastatin analogue; conagein; crambescidin 816; crisnatol; cryptophycin 8; cryptophycin A derivatives; curacin A; cyclopentantraquinones; cycloplatin; cypemycin; cytarabine ocfosfate; cytolytic factor; cytostatin; dacliximab; decitabine; dehydrididemnin B; deslorelin; dexamethasone; dexifosfamide; dextrazoxane; dexverapamil; diaziquone; didemnin B; didox; diethylnorspermine; dihydro-5-azacytidine; 9-dioxamycin; diphenyl spiromustine; docosanol; dolasetron; doxifluridine; droloxifene; dronabinol; duocarmycin SA; ebselen; ecomustine; edelfosine; edrecolomab; eflornithine; elemene; emitefur; epirubicin; epristeride; estramustine analogue; estrogen agonists; estrogen antagonists; etanidazole; etoposide phosphate; exemestane; fadrozole; fazarabine; fenretinide; filgrastim; finasteride; flavopiridol; flezelastine; fluasterone; fludarabine; fluorodaunorubicin hydrochloride; forfenimex; formestane; fostriecin; fotemustine; gadolinium texaphyrin; gallium nitrate; galocitabine; ganirelix; gelatinase inhibitors; gemcitabine; glutathione inhibitors; hepsulfam; heregulin; hexamethylene bisacetamide; hypericin; ibandronic acid; idarubicin; idoxifene; idramantone; ilmofofene; ilomastat; imidazoacridones; imiquimod; immunostimulant peptides; insulin-like growth factor-1 receptor inhibitor; interferon agonists; interferons; interleukins; iobenguane; iodoxoxorubicin; ipomeanol, 4-; iroplact; irsogladine; isobengazole; isohomohalicondrin B; itasetron; jaspilakinolide; kahalalide F; lamellarin-N triacetate; lanreotide; leinamycin; lenograstim; lentinan sulfate; leptolstatin; letrozole; leukemia inhibiting factor; leukocyte alpha interferon; leuprolide+estrogen+progesterone; leuporelin; levamisole; liarozole; linear polyamine analogue; lipophilic disaccharide peptide; lipophilic platinum compounds; lissoclinamide 7; lobaplatin; lombricine; lometrexol; lonidamine; losoxantrone; lovasta-

tin; loxoribine; lurtotecan; lutetium texaphyrin; lysosylline; lytic peptides; maitansine; mannosatin A; marimastat; masoproc; maspin; matrilysin inhibitors; matrix metalloproteinase inhibitors; menogaril; merbarone; meterelin; methioninase; metoclopramide; MIF inhibitor; mifepristone; miltefosine; mirimostim; mismatched double stranded RNA; mitoguazone; mitolactol; mitomycin analogues; mitonafide; mitotoxin fibroblast growth factor-saporin; mitoxantrone; mofarotene; molgramostim; monoclonal antibody, human chorionic gonadotrophin; monophosphoryl lipid A+myobacterium cell wall sk; mopidamol; multiple drug resistance gene inhibitor; multiple tumor suppressor 1-based therapy; mustard anticancer agent; mycaperoxide B; mycobacterial cell wall extract; myriaporone; N-acetyldinaline; N-substituted benzamides; nafarelin; nagrestip; naloxone+pentazocine; napavin; naphterpin; nartogastim; nedaplatin; nemorubicin; neridronic acid; neutral endopeptidase; nilutamide; nisamyacin; nitric oxide modulators; nitroxide antioxidant; nitrullin; O6-benzylguanine; octreotide; okicenone; oligonucleotides; onapristone; ondansetron; ondansetron; oracin; oral cytokine inducer; ormaplatin; osaterone; oxaliplatin; oxaunomycin; palauamine; palmitoylrhizoxin; pamidronic acid; panaxytriol; panomifene; parabactin; pazelliptine; pegaspargase; peldesine; pentosan polysulfate sodium; pentostatin; pentrozole; perflubron; perfosfamide; perillyl alcohol; phenazinomycin; phenylacetate; phosphatase inhibitors; picibanil; pilocarpine hydrochloride; pirarubicin; piritrexim; placetin A; placetin B; plasminogen activator inhibitor; platinum complex; platinum compounds; platinum-triamine complex; porfimer sodium; porfiormycin; prednisone; propyl bis-acridone; prostaglandin J2; proteasome inhibitors; protein A-based immune modulator; protein kinase C inhibitor; protein kinase C inhibitors, microalgal; protein tyrosine phosphatase inhibitors; purine nucleoside phosphorylase inhibitors; purpurins; pyrazoloacridine; pyridoxylated hemoglobin polyoxyethylene conjugate; raf antagonists; raltitrexed; ramosectron; ras farnesyl protein transferase inhibitors; ras inhibitors; ras-GAP inhibitor; retelliptine demethylated; rhodium Re 186 etidronate; rhizoxin; ribozymes; RII retinamide; rogletimide; rohitukine; romurtide; roquinimex; rubiginone B1; ruboxyl; safingol; saintopin; SarCNU; sarcophytol A; sargramostim; Sdi 1 mimetics; semustine; senescence derived inhibitor 1; sense oligonucleotides; signal transduction inhibitors; signal transduction modulators; single chain antigen-binding protein; sizofuran; sobuzoxane; sodium borocaptate; sodium phenylacetate; solverol; somatomedin binding protein; sonermin; sparfosic acid; spicamycin D; spiromustine; splenopentin; spongistatin 1; squalamine; stem cell inhibitor; stem-cell division inhibitors; stipiamide; stromelysin inhibitors; sulfinosine; superactive vasoactive intestinal peptide antagonist; suradista; suramin; swainsonine; synthetic glycosaminoglycans; tallimustine; tamoxifen methiodide; taumustine; tazarotene; tecogalan sodium; tegafur; tellurapyrylium; telomerase inhibitors; temoporfin; temozolomide; teniposide; tetrachlorodecaoxide; tetrazomine; thaliblastine; thiocoraline; thrombopoietin; thrombopoietin mimetic; thymalfasin; thymopoietin receptor agonist; thymotrinan; thyroid stimulating hormone; tin ethyl etiopurpurin; tirapazamine; titanocene bichloride; topsentin; toremifene; totipotent stem cell factor; translation inhibitors; tretinoin; triacetyluridine; tricribine; trimetrexate; triptorelin; tropisetron; turosteride; tyrosine kinase inhibitors; typhostins; UBC inhibitors; ubenimex; urogenital sinus-derived growth inhibitory factor; urokinase receptor

antagonists; vapreotide; variolin B; vector system, erythrocyte gene therapy; velaresol; veramine; verdins; verteporfin; vinorelbine; vinxaltine; vitaxin; vorozole; zanoterone; zeniplatin; zilascorb; and zinostatin stimalamer. Preferred additional anti-cancer drugs are 5-fluorouracil and leucovorin.

[0172] In one embodiment, the anti-cancer agents that can be used in methods described herein are selected from the group consisting of paclitaxel, docetaxel, 5-fluorouracil, trastuzumab, lapatinib, bevacizumab, letrozole, goserelin, tamoxifen, cetuximab, panitumumab, gemcitabine, capecitabine, irinotecan, oxaliplatin, carboplatin, cisplatin, doxorubicin, epirubicin, cyclophosphamide, methotrexate, vinblastine, vincristine, melphalan and a combination thereof.

[0173] In one embodiment, the anti-cancer agent and the compound represented by Structural Formula (I) are administered contemporaneously. When administered contemporaneously, the anti-cancer agent and the compound can be administered in the same formulation or in different formulations. Alternatively, the compound and the additional anti-cancer agent are administered separately.

[0174] In one embodiment, the subject in the methods described herein has not been previously treated with a TTK inhibitor (e.g., the compound represented by Structural Formula (I)).

[0175] The term an “effective amount” means an amount when administered to the subject which results in beneficial or desired results, including clinical results, e.g., inhibits, suppresses or reduces the cancer (e.g., as determined by clinical symptoms or the amount of cancer cells) in a subject as compared to a control. Specifically, “treating a subject with a cancer” includes achieving, partially or substantially, one or more of the following: arresting the growth, reducing the extent of a cancer (e.g., reducing size of a tumor), inhibiting the growth rate of a cancer, and ameliorating or improving a clinical symptom or indicator associated with a cancer (such as tissue or serum components) or increasing longevity of the subject.

[0176] Generally, an effective amount of a compound taught herein varies depending upon various factors, such as the given drug or compound, the pharmaceutical formulation, the route of administration, the type of disease or disorder, the identity of the subject or host being treated, and the like, but can nevertheless be routinely determined by one skilled in the art. An effective amount of a compound of the present teachings may be readily determined by one of ordinary skill by routine methods known in the art.

[0177] In an embodiment, an effective amount of a compound taught herein ranges from about 0.1 to about 1000 mg/kg body weight, alternatively about 1 to about 500 mg/kg body weight, and in another alternative, from about 20 to about 300 mg/kg body weight. In another embodiment, an effective amount of a compound taught herein ranges from about 0.5 to about 5000 mg/m², alternatively about from 5 to about 2500 mg/m², and in another alternative from about 50 to about 1000 mg/m². The skilled artisan will appreciate that certain factors may influence the dosage required to effectively treat a subject suffering from cancer or reduce the likelihood of recurrence of a cancer. These factors include, but are not limited to, the severity of the disease or disorder, previous treatments, the general health and/or age of the subject and other diseases present.

[0178] Moreover, for methods described herein (including treating a subject with a cancer or reducing the likelihood of recurrence of a cancer), a “treatment” or dosing regime of a

subject with an effective amount of the compound of the present teachings may consist of a single administration, or alternatively comprise a series of applications. For example, the compound of the present teachings may be administered at least once a week. However, in another embodiment, the compound may be administered to the subject from about one time per week to once daily for a given treatment. The length of the treatment period depends on a variety of factors, such as the severity of the disease, the age of the patient, the concentration and the activity of the compounds of the present teachings, or a combination thereof. It will also be appreciated that the effective dosage of the compound used for the treatment may increase or decrease over the course of a particular treatment regime. Changes in dosage may result and become apparent by standard diagnostic assays known in the art. In some instances, chronic administration may be required.

[0179] As used herein, “treatment” is an approach for obtaining beneficial or desired results, including clinical results. Beneficial or desired clinical results can include, but are not limited to, alleviation or amelioration of one or more symptoms or conditions, diminishment of extent of disease, stabilized (i.e. not worsening) state of disease, delay or slowing of disease progression, amelioration or palliation of the disease state, and remission (whether partial or total), whether detectable or undetectable. “Treatment” can also mean prolonging survival as compared to expected survival if not receiving treatment.

[0180] A “subject” is a mammal, preferably a human, but can also be an animal in need of veterinary treatment, e.g., companion animals (e.g., dogs, cats, and the like), farm animals (e.g., cows, sheep, pigs, horses, and the like) and laboratory animals (e.g., rats, mice, guinea pigs, and the like).

[0181] The compounds taught herein can be administered to a patient in a variety of forms depending on the selected route of administration, as will be understood by those skilled in the art. The compounds of the present teachings may be administered, for example, by oral, parenteral, buccal, sublingual, nasal, rectal, patch, pump or transdermal administration and the pharmaceutical compositions formulated accordingly. Parenteral administration includes intravenous, intraperitoneal, subcutaneous, intramuscular, transepithelial, nasal, intrapulmonary, intrathecal, rectal and topical modes of administration. Parenteral administration can be by continuous infusion over a selected period of time.

[0182] The compounds taught herein can be suitably formulated into pharmaceutical compositions for administration to a subject. The pharmaceutical compositions of the present teachings optionally include one or more pharmaceutically acceptable carriers and/or diluents therefor, such as lactose, starch, cellulose and dextrose. Other excipients, such as flavoring agents; sweeteners; and preservatives, such as methyl, ethyl, propyl and butyl parabens, can also be included. More complete listings of suitable excipients can be found in the Handbook of Pharmaceutical Excipients (5th Ed., Pharmaceutical Press (2005)). A person skilled in the art would know how to prepare formulations suitable for various types of administration routes. Conventional procedures and ingredients for the selection and preparation of suitable formulations are described, for example, in Remington’s Pharmaceutical Sciences (2003-20th edition) and in The United States Pharmacopeia: The National Formulary (USP 24 NF19) published in 1999. The carriers, diluents and/or excipients are “acceptable” in the sense of being compatible with the other

ingredients of the pharmaceutical composition and not deleterious to the recipient thereof.

[0183] Typically, for oral therapeutic administration, a compound of the present teachings may be incorporated with excipient and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like.

[0184] Typically for parenteral administration, solutions of a compound of the present teachings can generally be prepared in water suitably mixed with a surfactant such as hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, DMSO and mixtures thereof with or without alcohol, and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

[0185] Typically, for injectable use, sterile aqueous solutions or dispersion of, and sterile powders of, a compound described herein for the extemporaneous preparation of sterile injectable solutions or dispersions are appropriate.

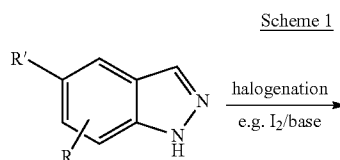
[0186] For nasal administration, the compounds of the present teachings can be formulated as aerosols, drops, gels and powders. Aerosol formulations typically comprise a solution or fine suspension of the active substance in a physiologically acceptable aqueous or non-aqueous solvent and are usually presented in single or multidose quantities in sterile form in a sealed container, which can take the form of a cartridge or refill for use with an atomizing device. Alternatively, the sealed container may be a unitary dispensing device such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve which is intended for disposal after use. Where the dosage form comprises an aerosol dispenser, it will contain a propellant which can be a compressed gas such as compressed air or an organic propellant such as fluorochlorohydrocarbon. The aerosol dosage forms can also take the form of a pump-atomizer.

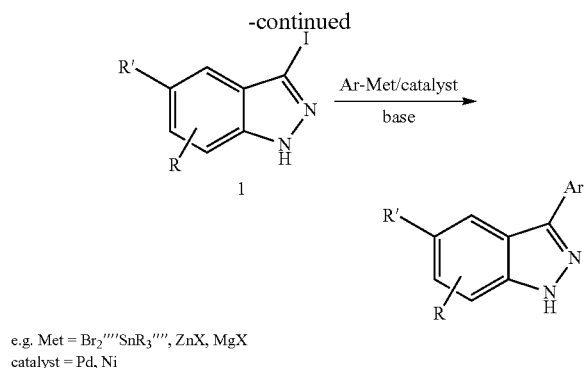
[0187] For buccal or sublingual administration, the compounds of the present teachings can be formulated with a carrier such as sugar, acacia, tragacanth, or gelatin and glycerine, as tablets, lozenges or pastilles.

[0188] For rectal administration, the compounds described herein can be formulated in the form of suppositories containing a conventional suppository base such as cocoa butter.

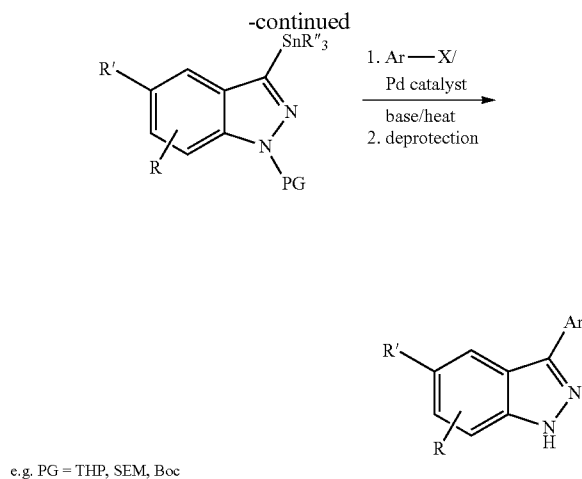
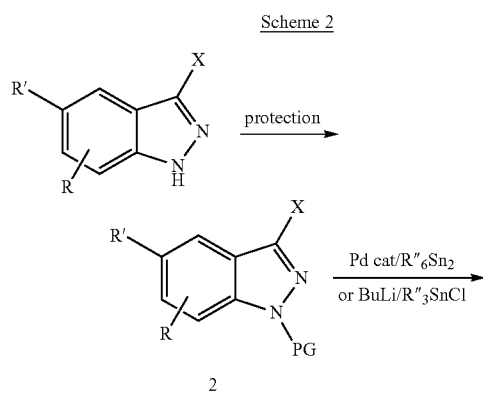
[0189] Compounds described herein may be prepared using the reaction routes and syntheses described below, employing the techniques available in the art using starting materials that are readily available.

[0190] In one general synthetic process, compounds described herein can be prepared according to the following reaction Scheme 1. Halogenation of an appropriately substituted indazole wherein the indazole is substituted as defined herein provides intermediate 1 that can be reacted with a suitable cross coupling partner, ArMet (e.g. ArBpin), in the presence of a metal catalyst (e.g. PdCl₂(dppf) or Pd(PPh₃)₄).



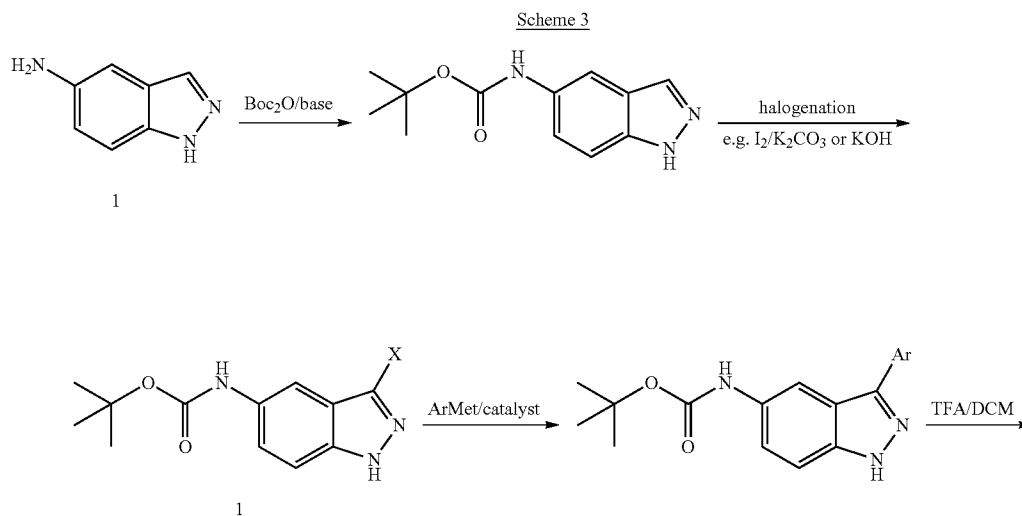


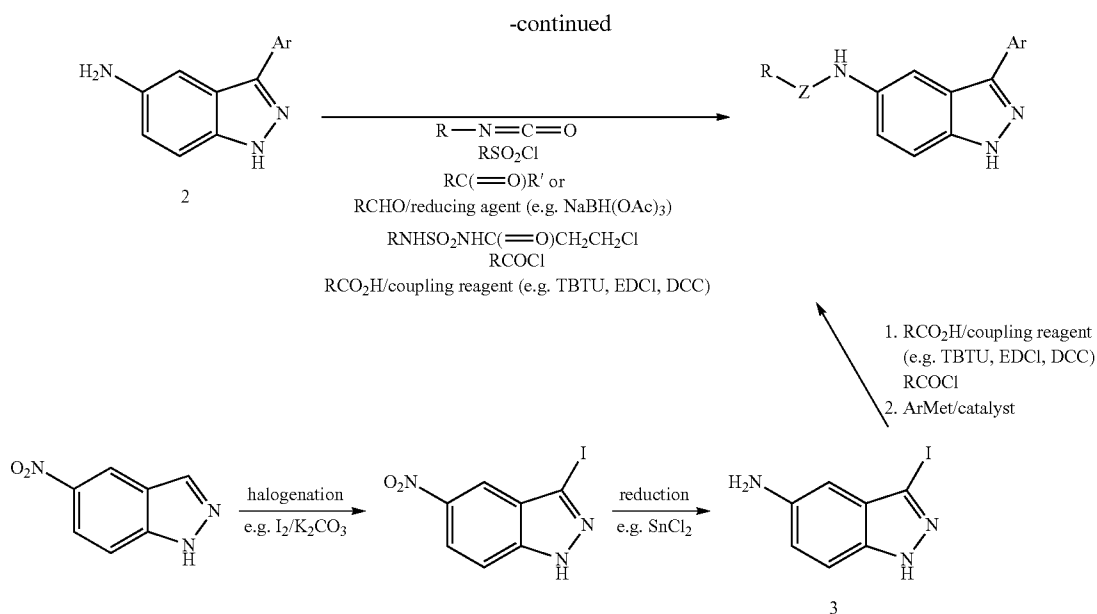
[0191] Alternatively, haloindazole 2 can be converted into a 3-(trialkylstannyl)-1H-indazole that can be subjected to Stille-type cross-coupling reaction as shown in Scheme 2 (e.g. 1. Me₃Sn₂/Pd(PPh₃)₄/PhMe 2. ArI/Pd(PPh₃)₄/CuI/THF ref. WO200102369).



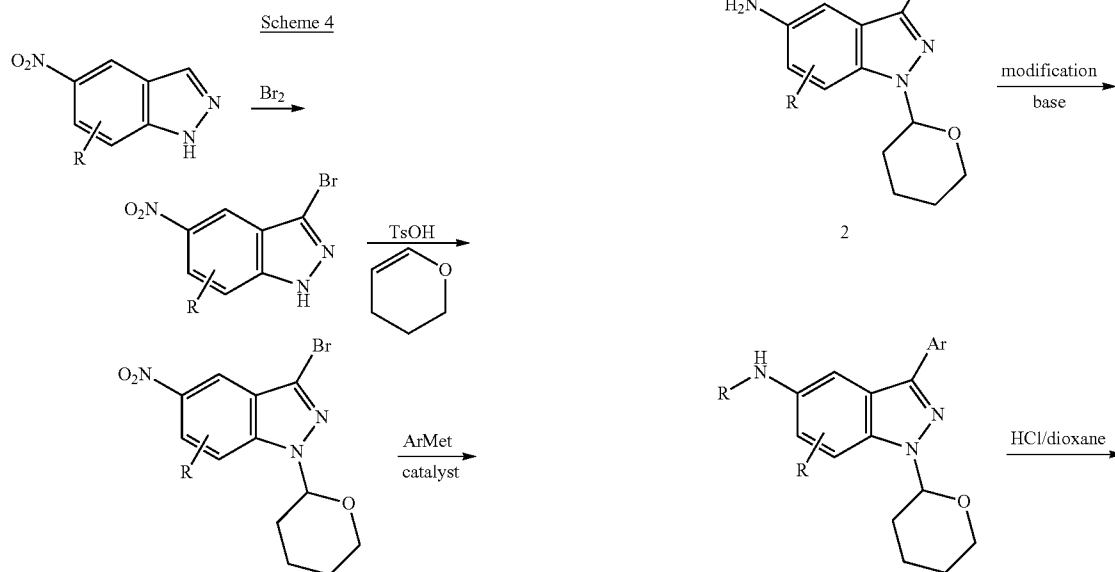
[0192] Compounds described herein can also be prepared according to the general procedures shown in the Scheme 3. 5-Aminoindazole is protected by a suitable aniline protecting group such as a Boc group followed by halogenations (e.g. I₂/K₂CO₃). A sequence of Suzuki-Miyaura cross coupling and removal of the protecting group yields anilines 2 that can be reacted with a variety of electrophilic reagents (e.g. R—NCO, R'R''NH/phosgene or triphosgene, ROH/triphosgene, RNHSO₂NHC(=O)CH₂CH₂Cl, RSO₂Cl, RC(=O)R'/reducing agent, RCOCl or RCO₂H/coupling reagent: TBTU, EDC, DCC, HATU, pyBOP, COMU) leading to preparation of substituted ureas, carbamates, sulfamides, sulfonamides, anilines and amides.

[0193] Alternatively, 5-nitro-1H-indazole can be halogenated and reduced to provide 3-halo-5-amino indazoles 3 that can be subjected to an amide formation followed by Pd-catalyzed cross-coupling.

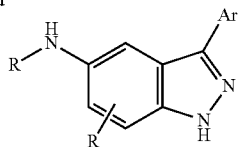




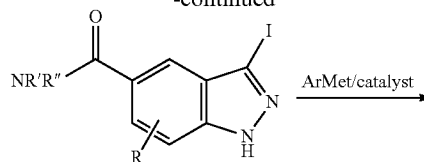
[0194] Alternatively, compounds described herein, containing trisubstituted indazoles can be prepared as outlined in Scheme 4. 5-Nitro-1H-indazole is halogenated with Br_2 , protected with a suitable indazole protecting group such as tetrahydropyranyl, and subjected to Miyaura-Suzuki cross coupling conditions (e.g. $\text{ArBpin}/\text{dioxane}/\text{H}_2\text{O}/\text{PdCl}_2(\text{dppf})/\text{Na}_2\text{CO}_3$). Hydrogenation of the intermediate 1 yields 1H-indazol-5-amine 2 that can be modified in a reaction with electrophilic reagents (e.g. $\text{R}-\text{NCO}$, $\text{R}'\text{R}''\text{NH}/\text{triphosgene}$, $\text{ROH}/\text{triphosgene}$, $\text{RNHSO}_2\text{NHC}(=\text{O})\text{CH}_2\text{CH}_2\text{Cl}$, RSO_2Cl , $\text{RC}(=\text{O})\text{R}'/\text{reducing agent}$, RCOCl or $\text{RCO}_2\text{H}/\text{coupling reagent}$: TBTU, EDC, DCC, HATU, pyBOP, COMU) before deprotection of the THP protecting group with HCl.



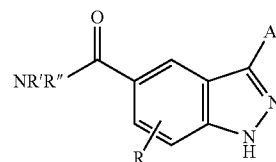
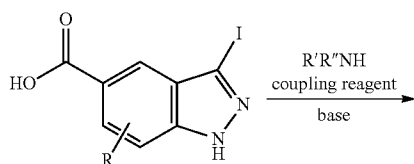
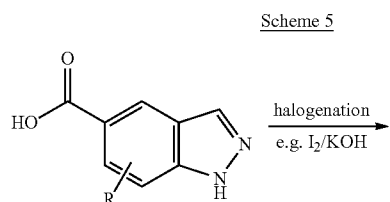
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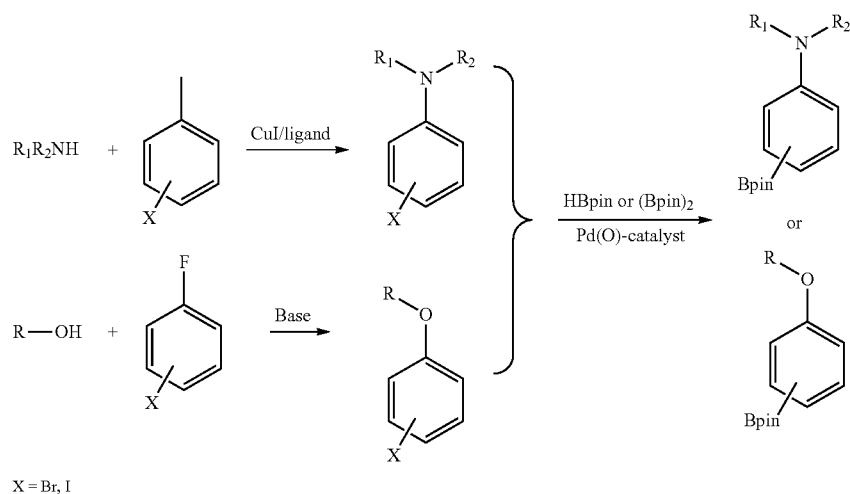
[0195] Compounds described herein having an carboxamide group can be synthesized from 3-halo-1H-indazole-5-carboxylic acid in a two-step sequence outlined below (Scheme 5).



coupling reagent e.g.
DCC, EDC, DIC, HBTU, HATU, HCTU, pyBOP, TBTU
SOCl₂ or (COCl)₂

[0196] The intermediate boronic esters described herein can be prepared as outlined in Scheme 6. Aniline-based boronic esters can be prepared via Cu(I) catalyzed amination of an appropriately substituted dihalobenzene followed by borylation with a suitable borylating agent (HBpin or (Bpin)₂) in the presence of a Pd-catalyst (e.g. Cl₂Pd(CH₃CN)₂ or Cl₂Pdppf). Aryloxy-based boronic esters can be prepared via reaction of an alcohol with an appropriately substituted halofluorobenzene in the presence of base (e.g. NaH) followed by borylation (Pd-catalyzed or metal-halogenexchange followed by a quench with B(OR)₃).

Scheme 6



[0197] Compounds described herein can be prepared in a manner analogous to the general procedures described above or the detailed procedures described in the examples herein. [0198] The invention is illustrated by the following examples which are not intended to be limiting in any way.

EXEMPLIFICATION

Example A

Synthesis

General Methods

[0199] Commercially available starting materials, reagents, and solvents were used as received. In general, anhydrous reactions were performed under an inert atmosphere such as nitrogen or Argon. PoraPak® Rxn CX refers to a commercial cation-exchange resin available from Waters. [0200] Microwave reactions were performed with a Biotage Initiator microwave reactor. Reaction progress was generally monitored by TLC using Merck silica gel plates with visualization by UV at 254 nm, by analytical HPLC or by LCMS (Bruker Exquire 4000). Flash column chromatographic purification of intermediates or final products was performed using 230-400 mesh silica gel 60 from EMD chemicals or Silicycle, or purified using a Biotage Isolera with KP-SIL or HP-SIL silica cartridges, or KP-NH basic modified silica and corresponding samplelets. RPReverse-phase RPHPLC purification was performed on a Varian Prep-Star model SD-1 HPLC system with a Varian Monochrom 10u C-18 reverse-phase column using a of about 5-30% MeCN or MeOH/0.05% TFA-H₂O to 70-90% MeCN or MeOH/0.05% TFA-H₂O over a 20-40-min period at a flow rate of 30-50 mL/min. RPpurification was also performed using a Biotage Isolera equipped with a KP-C18-H column using a between 10-95% MeOH/0.1% TFA in H₂O. Proton NMRs were recorded on a Bruker 400 MHz spectrometer, and mass spectra were obtained using a Bruker Esquire 4000 spectrometer. Optical rotations were measured at the sodium D-line (589.44 nm) using an AA-55 polarimeter from Optical Activity Ltd with a 2.5×100 mm unjacketed stainless steel tube at given sample concentrations (c, units of g/100 mL). [0201] Compound names were generated using the software built into ChemBioDraw Ultra version 11.0 or 12.0.

ABBREVIATIONS

[0202] aq aqueous
[0203] anh anhydrous
[0204] Ar Argon
[0205] br. Broad
[0206] BINOL 1,1'-binaphthalene-2,2'-diol
[0207] calcd calculated
[0208] COMU (1-cyano-2-ethoxy-2-oxoethylidenaminoxy)dimethylamino-morpholino-carbenium hexafluorophosphate
[0209] d doublet (only when used within 1H NMR spectra)
[0210] d day
[0211] DCE 1,2-dichloroethane
[0212] DCM dichloromethane
[0213] DIPEA diisopropylethylamine
[0214] DME 1,2-dimethoxyethane
[0215] DMF N,N-dimethylformamide
[0216] DMSO dimethylsulfoxide
[0217] dppf 1,1'-bis(diphenylphosphino) ferrocene

[0218] e.e. enantiomeric excess
[0219] h hour
[0220] HPLC high performance liquid chromatography
[0221] HATU 2-(1H-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
[0222] LC-MS liquid chromatography coupled to mass spectrometry
[0223] min minute
[0224] m multiplet
[0225] MS ESI mass spectra, electrospray ionization
[0226] NBS N-Bromosuccinimide
[0227] NMR nuclear magnetic resonance
[0228] O/N overnight
[0229] PCC pyridinium chlorochromate
[0230] pin pinacol
[0231] prep preparative
[0232] RBF round bottomed flask
[0233] rt room temperature
[0234] Rt retention time
[0235] s singlet
[0236] satd saturated
[0237] SPE solid phase extraction
[0238] S-Phos 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl
[0239] t triplet
[0240] TBTU O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate
[0241] temp. temperature
[0242] TEA triethylamine
[0243] TFA trifluoroacetic acid
[0244] TLC thin layer chromatography
[0245] THF tetrahydrofuran
[0246] xs excess

Preparation of Starting Materials

Method A (Amide Coupling)

[0247] A DMF solution of 3-iodo-1H-indazol-5-amine 2,2,2-trifluoroacetate (1.0 equiv), DIPEA (3 equiv) and RCO₂H (1.05 equiv) at 0° C. was treated with TBTU (1.05 equiv) added in one portion. The reaction was stirred allowing slowly to warm to rt. After several h or overnight stirring the crude reaction was subsequently diluted with H₂O. In the majority of examples a filtration and washing (H₂O) of the precipitate provided the desired material with the required purity or alternatively the material was purified directly by prepHPLC or/and flash chromatography. [0248] Alternatively, a DMF solution of 3-iodo-1H-indazole-5-carboxylic acid (1.0 equiv), DIPEA (3 equiv) and RR'NH (1.05 equiv) at 0° C. or rt was treated with TBTU (1.05 equiv) added in one portion. The reaction was stirred allowing slowly to warm to rt. After several h or overnight stirring the crude reaction was subsequently diluted with H₂O. In the majority of examples a filtration and washing (H₂O) of the precipitate provided the desired material with the required purity or alternatively the material was purified directly by prepHPLC or/and flash chromatography.

Method B (Iodination)

[0249] To a cooled (0° C.) DMF solution indazole (1.0 equiv) and K₂CO₃ or KOH (~3 equiv) was added I₂ (2-4 equiv) in one portion. The reaction was stirred with cooling or rt for several h and then was treated with xs 10% aq NaHSO₃

and subsequently diluted with H₂O. In the majority of examples a filtration and washing (H₂O) of the precipitate provided the desired material with the required purity.

Method C (Suzuki-Miyaura Cross Coupling)

[0250] A mixture of 3-iodo-1H-indazole (1.0 equiv), aryl boronic acid or boronate ester (1.2 equiv), base and palladium catalyst (0.05 equiv e.g. and PdCl₂dppf.DCM, Pd(PPh₃)₄) in solvents was degassed with Ar and heated sealed in a Biotage microwave reactor. The crude material was filtered through Celite using MeOH to rinse the pad. In the majority of examples, purification by RPHPLC provided the target material.

Method C2 (Suzuki-Miyaura Cross Coupling with PdCl₂dppf.DCM-Na₂CO₃)

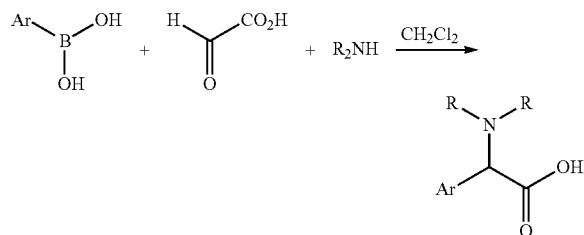
[0251] Aq Na₂CO₃ (2 M, 3-4 mmol) was added to a mixture of 5-substituted-3-iodo-1H-indazole (1.0 mmol), aryl boronic acid or boronate ester (1.0-1.4 mmol), and PdCl₂dppf.DCM (0.1 mmol) in PhMe:EtOH (1:1, 20 mL) was heated under Ar in a Biotage microwave reactor, an oil bath or a reaction block at temperatures from 100-130° C. The crude material was filtered through Celite using MeOH (alternatively, acetone/MeOH or EtOAc) to rinse the pad or partitioned between EtOAc and H₂O followed by drying (Na₂SO₄ or MgSO₄), and evaporated and purified by chromatography.

Method C3 (Suzuki-Miyaura Cross Coupling with Pd(PPh₃)₄-LiCl-Na₂CO₃)

[0252] Aq Na₂CO₃ (2 M, 5 mmol) was added to a mixture of 5-substituted-3-iodo-1H-indazole (1.0 mmol), aryl boronic acid or boronate ester (1.0-1.4 mmol), LiCl (3 mmol) and Pd(PPh₃)₄ (0.1 mmol) in dioxane (12 mL) was heated under Ar in a Biotage microwave reactor, an oil bath or a reaction block at temperatures from 120-130° C. The crude material was filtered through Celite using MeOH or acetone/MeOH to rinse the pad or partitioned between EtOAc and H₂O followed by drying (Na₂SO₄ or MgSO₄), evaporated and purified by chromatography.

Method D (Petasis Reaction)

[0253]



[0254] To a mixture of arylboronic acid (1 mmol) and glyoxylic acid monohydrate (1 mmol) in CH₂Cl₂ (5 mL) was added dialkylamine (1 mmol). The resulting mixture was stirred overnight at rt. After evaporation of solvents, it was used crude or purified by column chromatography.

Method E (Borylation of Aryl Halides): Using B₂pin₂/Pd

[0255] A mixture of aryl iodide or aryl bromide (1 equiv.), bis(pinacolato)diboron (1.2 to 1.5 equiv.), KOAc (3 equiv.) and DMF or DMSO was purged with Ar for 10 min. [1,1'-PdCl₂dppf*CH₂Cl₂ (3-5 mol %)] was added, the vial sealed and heated at 85° C. for 2 h. The product was partitioned

between EtOAc and satd aqNaHCO₃ solution, washed with brine, dried over Na₂SO₄ or MgSO₄, filtered, and concentrated to dryness. The crude product was purified by flash chromatography to give the title compound.

Method F (Boronation of Aryl Halides): Using HBpin/Pd

[0256] To a solution of aryl iodide or aryl bromide (1.0 mmol) in NEt₃ (3.0 mmol) and dioxane (1.0 mL) was added under Ar and 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.5 mmol), S-Phos (0.040 mmol) and Cl₂Pd(CH₃CN)₂ (0.010 mmol) and the reaction heated to 110° C. for 3 h. The mixture was then transferred to a separatory funnel with EtOAc (10 mL) and washed with NaHCO₃ (satd) (2×10 mL), H₂O (10 mL), and brine (10 mL). The organic layer was dried over MgSO₄, filtered and the solvent removed to yield pinacol boronic esters which were used directly for subsequent steps.

Method G (Reductive Amination)

[0257] NaBH₃CN (4 mmol) was added to a solution of aryl alkyl ketone (1 mmol) and NH₄OAc (12 mmol) in MeOH (4-5 mL) under Ar, and the reaction mixture was heated at 60° C. for 14-24 h. Aq. NaOH (2 M, 15 mL) was added and the product was extracted into Et₂O (3×40 mL). The combined Et₂O layer was washed with H₂O (10 mL) and brine (10 mL), dried (Na₂SO₄), filtered, concentrated to dryness and used crude or purified by chromatography.

Method H (Nucleophilic Substitution on 1,4-hal-C₆H₄-F)

[0258] NaH (60% in mineral oil, 1.2 mmol) was added portion-wise to a solution of the alcohol (1 mmol) and 1-fluoro-4-iodobenzene (1 mmol) in DMF (1.5 mL) at 0° C. After 15 min, the reaction mixture was allowed to warm to rt, then heated at 80-85° C. for 6-14 h in an oil bath. The mixture was quenched by adding H₂O (10 mL) and the product was extracted with EtOAc (30 mL). The organic layer was washed with brine (10 mL), dried (Na₂SO₄ or MgSO₄), concentrated to dryness and purified by chromatography.

Method I (Copper Catalyzed Amination of aryl-hal)

[0259] A microwave vial was charged with 1,4-diiodobenzene or 1-bromo-4-iodobenzene (1.0 equiv), CuI (20 mol %), BINOL (20 mol %), and K₃PO₄ (2 equiv.). The vial was capped and then evacuated and backfilled with Ar. Dialkylamine (1.2 equiv) and DMF were then added. The resulting mixture was stirred at rt for 2 to 4 d. The mixture was diluted with EtOAc, filtered through a cake of Celite and the filtrate was concentrated to give the crude product. Crude product was purified by flash chromatography to give the title compound.

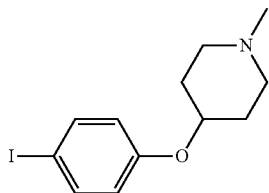
Method J (Urea Formation)

[0260] A solution of 3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazol-5-amine bis(2,2,2-trifluoroacetate) (0.0731 mmol), DIPEA (5 mmol), and DMF (70 mL) was cooled to 0° C. and then 1,3-diethyl-2-isocyanatobenzene (2 mmol) was added dropwise. The reaction was stirred for 2 h while warming to rt. A mixture of mono- and di-urea products were obtained which was treated directly with NaOMe (80 uL of a 25% wt solution in MeOH) and the mixture stirred for 15 min and then transferred to a separatory funnel with EtOAc (15 mL). The mixture was then washed with satd aq NaHCO₃ (2×10 mL), H₂O (1×10 mL), and brine (1×10 mL). The organic layer was dried over MgSO₄, filtered, and the solvent removed and the residue was purified by chromatography (prep-HPLC).

Intermediates:

Synthesis of 4-(4-iodophenoxy)-1-methylpiperidine

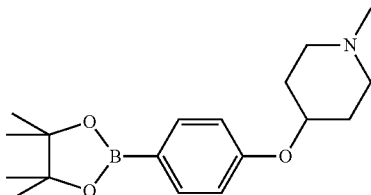
[0261]



[0262] A solution of 1-methylpiperidin-4-ol (20.01 g, 174 mmol) in DMF (30 mL) was added via pipet to a cold (ice-bath) flask containing NaH (60% in mineral oil, 8.11 g, 203 mmol) suspended in DMF (100 mL) under Ar, and additional DMF (3×10 mL) was used to rinse the vial and pipet. After the mixture was stirred in ice bath for 30 min, 1-fluoro-4-iodobenzene (20.0 mL, 174 mmol) was added to the mixture and the reaction mixture was allowed to stir at rt for 30 min, then placed in an 85° C. oil bath. After a few min, due to excessive foaming, the flask was removed from the oil bath and allowed to stir at rt for 10 min. This was repeated 3 times until no longer foaming excessively on introduction to the oil bath, then the reaction flask was heated at 85° C. in oil bath for 24 h. After cooling to rt, H₂O (50 mL) was added dropwise at first, then rapidly when little gas evolution occurred. The reaction mass was then poured into H₂O (450 mL) and the resulting aq. suspension was cooled in ice bath, then the precipitate was collected by vacuum filtration, rinsing with H₂O (2×50 mL). The resulting solid was dissolved in MeOH and the solvent was removed in vacuo, then EtOH was added and the solution was evaporated in vacuo to yield the title compound as a tan solid (36.9 g, 67%). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.55 (d, J=8.9 Hz, 2H), 6.69 (d, J=8.9 Hz, 2H), 4.24-4.32 (m, 1H), 2.68 (br. s., 2H), 2.31 (s, 3H), 2.23-2.29 (m, 2H), 1.94-2.03 (m, 2H), 1.78-1.88 (m, 2H).

Synthesis of 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine

[0263]



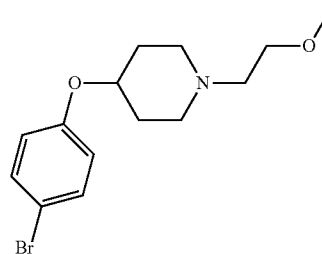
[0264] The title compound was prepared in a manner similar to general Method F using 4-(4-iodophenoxy)-1-methylpiperidine (9.5794 g, 30.2 mmol) with S-Phos (378.8 mg, 0.92 mmol) and Cl₂Pd(CH₃CN)₂ (59.8 mg, 0.23 mmol) at 110° C. for 6.5 h. MeOH (2 mL) was slowly added to quench excess borane, followed by DCM (200 mL) and NaHCO₃ (50 mL). After vacuum filtration through a pad of Celite and rinsing with DCM (150 mL) and NaHCO₃ (50 mL), the layers were separated and the aq. layer was extracted with DCM

(100 mL). The combined DCM layers were washed with H₂O (50 mL), and brine (50 mL), and dried (Na₂SO₄), filtered and the solvent removed to yield the crude product. Purification by flash chromatography (SiO₂, 0-15% MeOH/DCM) gave 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine (white solid, 7.79 g, 90% pure, 73%). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.79 (d, J=8.3 Hz, 2H), 6.90 (d, J=8.5 Hz, 2H), 4.81 (br. s., 1H), 3.42 (d, J=12.0 Hz, 1H), 3.23 (t, J=12.0 Hz, 2H), 2.79 (s, 3H), 2.72 (t, J=14.3 Hz, 2H), 2.25 (d, J=14.3 Hz, 2H), 1.34 (s, 12H). MS ESI 318.1 [M+H]⁺, calcd for [C₁₈H₂₈BNO₃+H]⁺ 318.22.

Synthesis of

4-(4-bromophenoxy)-1-(2-methoxyethyl)piperidine

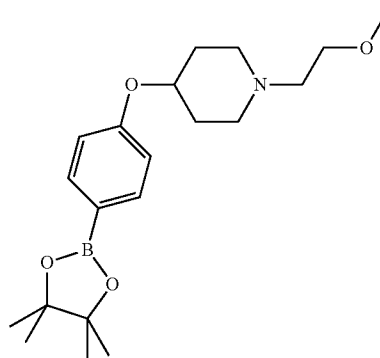
[0265]



[0266] A mixture of 4-(4-bromophenoxy)piperidine hydrochloride (1.5 g, 5.13 mmol), 1-bromo-2-methoxyethane (0.48 mL, 5.13 mmol), K₂CO₃ (2.13 g, 15.4 mmol) and DMF (15 mL) was heated to 40° C. and stirred for 18 h at which time the mixture was transferred to a separatory funnel with EtOAc (250 mL) and the organic layer washed with satd aqNaHCO₃ (1×100 mL) and brine (1×100 mL). The organic layer was dried over MgSO₄, filtered and the solvent removed to give the alkylated material which was used for the next step.

Synthesis of 1-(2-methoxyethyl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine

[0267]

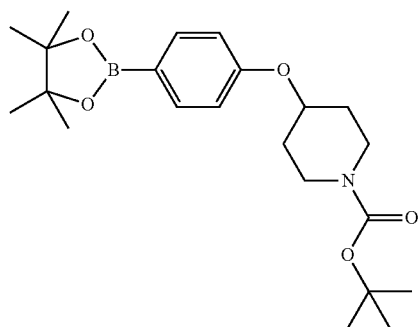


[0268] To a solution of 4-(4-bromophenoxy)-1-(2-methoxyethyl)piperidine (5.13 mmol from step A), NEt₃ (2.1 mL, 15.4 mmol), and dioxane (15 mL) under Ar was added 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.1 mL, 7.70 mmol),

SPhos (86 mg, 0.210 mmol), and $\text{PdCl}_2(\text{CH}_3\text{CN})_2$ (13 mg, 0.051 mmol) and the reaction heated to 110°C . for 2 h. The mixture was then transferred to a separatory funnel with EtOAc (100 mL) and washed successively with satd aq NaHCO_3 (2×50 mL), H_2O (2×50 mL), and brine (1×50 mL). The organic layer was dried over MgSO_4 , filtered, and the solvent removed to give the product as a yellow oil. ^1H NMR (400 MHz, CDCl_3) δ ppm 7.72 (d, $J=8.4$ Hz, 2H), 6.88 (d, $J=8.4$ Hz, 2H), 4.41-4.36 (m, 1H), 3.51 (t, $J=5.6$ Hz, 2H), 3.36 (s, 3H), 2.77-2.74 (m, 2H), 2.59 (t, $J=5.6$ Hz, 2H), 2.36-2.33 (m, 2H), 2.03-1.98 (m, 2H), 1.88-1.81 (m, 2H), 1.32 (s, 12H); MS ESI 362.1 $[\text{M}+\text{H}]^+$, calcd for $[\text{C}_{20}\text{H}_{32}\text{BNO}_4+\text{H}]^+$ 362.25.

Synthesis of tert-butyl 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine-1-carboxylate

[0269]

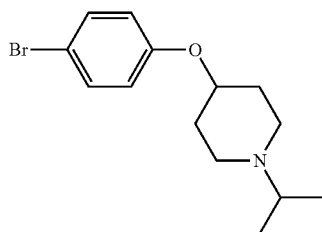


[0270] Using Method E with 3% catalyst in DMSO, tert-butyl 4-(4-iodophenoxy)piperidine-1-carboxylate (258.6 g, 96% pure, 0.61 mmol) gave the title compound (152.7 mg, 61%) after aq. work-up and purification by flash chromatography (SiO_2 , 5-25% EtOAc in hexane). ^1H NMR (400 MHz, CDCl_3) δ ppm 7.75 (d, $J=8.8$ Hz, 2H), 6.91 (d, $J=8.5$ Hz, 2H), 4.55 (tt, $J=7.0$, 3.4 Hz, 1H), 3.69 (ddd, $J=12.9$, 8.2, 4.1 Hz, 2H), 3.36 (ddd, $J=13.0$, 8.1, 4.3 Hz, 2H), 1.92 (br. s., 2H), 1.77 (br. s., 2H), 1.34 (s, 12H).

[0271] In a separate experiment, using Method E in DMF, tert-butyl 4-(4-iodophenoxy)piperidine-1-carboxylate gave the title compound as a white solid (112 mg, 28% yield). ^1H NMR was identical to the previous sample; MS ESI $[\text{M}-\text{C}_4\text{H}_9+\text{H}]^+$ 348.1, calcd for $[\text{C}_{18}\text{H}_{26}\text{BNO}_5+\text{H}]^+$ 348.20.

Synthesis of
4-(4-bromophenoxy)-1-isopropylpiperidine

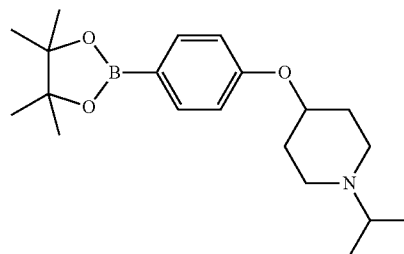
[0272]



[0273] AcOH (1 drop) was added to a mixture of acetone (0.12 mL, 1.65 mmol), $\text{NaBH}(\text{OAc})_3$ (161.5 mg, 0.76 mmol) and 4-(4-bromophenoxy)piperidine (97 mg, 0.38 mmol) in THF (1 mL) and DCE (2 mL), and the mixture was stirred at rt under Ar for 20 h, when second portions of AcOH (1 drop), acetone (0.12 mL, 1.65 mmol) and $\text{NaBH}(\text{OAc})_3$ (161.5 mg, 0.76 mmol) were added and the mixture was heated at 40°C . for 24 h. The mixture was partitioned between EtOAc (150 mL) and half satd aq NaHCO_3 (25 mL). The organic layer was washed with H_2O (25 mL) and brine (25 mL), dried, filtered and concentrated to dryness. Purification by flash chromatography (SiO_2 , 2-5% 2 M NH_3 -MeOH/DCM) gave the title compound (white solid, 80.4 mg, 71% yield). ^1H NMR (400 MHz, CDCl_3) δ ppm 7.37 (d, $J=9.0$ Hz, 6H), 6.80 (d, $J=9.0$ Hz, 6H), 4.27 (br. s., 1H), 2.74-2.84 (m, 3H), 2.35-2.47 (m, 2H), 2.01 (br. s., 2H), 1.76-1.87 (m, 2H), 1.08 (d, $J=6.5$ Hz, 6H). MS ESI 298.0 $[\text{M}+\text{H}]^+$, calcd for $[\text{C}_{14}\text{H}_{22}\text{BrNO}+\text{H}]^+$ 298.08.

Synthesis of 1-isopropyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine

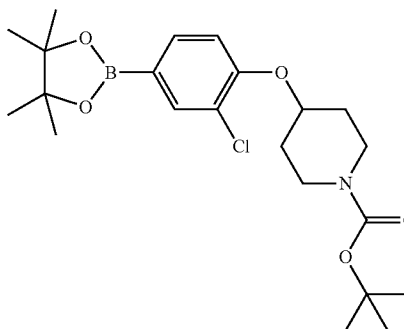
[0274]



[0275] Using Method E with 3.4% catalyst in DMSO, 4-(4-bromophenoxy)-1-isopropylpiperidine (80 mg, 0.27 mmol) gave the title compound (47.5 mg, 77% pure, 40% yield) after aq. work-up with EtOAc and purification by flash chromatography (SiO_2 , 2-20% MeOH in DCM). ^1H NMR (400 MHz, CDCl_3) δ ppm 7.74 (d, $J=8.5$ Hz, 2H), 6.90 (d, $J=8.5$ Hz, 2H), 4.40 (br. s., 1H), 2.80 (d, $J=4.0$ Hz, 3H), 2.45 (m, $J=7.8$ Hz, 2H), 2.04 (br. s., 2H), 1.85 (d, $J=8.5$ Hz, 2H), 1.34 (s, 12H), 1.09 (d, $J=6.3$ Hz, 6H). MS ESI 346.2 $[\text{M}+\text{H}]^+$, calcd for $[\text{C}_{20}\text{H}_{32}\text{BNO}_3+\text{H}]^+$ 346.26.

Synthesis of tert-butyl 4-(2-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine-1-carboxylate

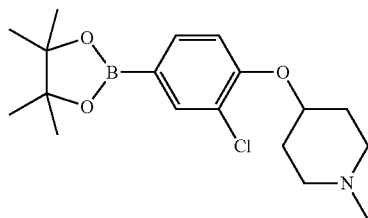
[0276]



[0277] DIAD (0.24 mL, 1.22 mmol) was added drop-wise to a solution of PPh_3 (308.9 mg, 1.18 mmol), 2-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (199.8 mg, 0.785 mmol) and tert-butyl 4-hydroxypiperidine-1-carboxylate (236.7 mg, 1.18 mmol) in DCM (5 mL) under Ar and the reaction was stirred at rt for 14 d. Purification on the Biotage without work-up or evaporation (SiO_2 , 0-100% EtOAc in DCM) gave the title compound (244.8 mg, 90% pure, 64%). ^1H NMR (400 MHz, CDCl_3) δ ppm 7.82 (d, $J=1.5$ Hz, 1H), 7.63 (dd, $J=8.2, 1.6$ Hz, 1H), 6.93 (d, $J=8.3$ Hz, 1H), 4.59-4.65 (m, 1H), 3.63 (ddd, $J=13.2, 8.4, 4.3$ Hz, 2H), 3.42-3.54 (m, 2H), 1.78-1.95 (m, 4H), 1.47 (s, 9H), 1.33 (s, 12H).

Synthesis of 4-(2-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)-1-methylpiperidine

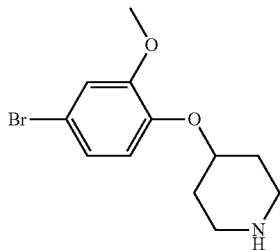
[0278]



[0279] DIAD (0.48 mL, 2.4 mmol) was added drop-wise to a solution of PPh_3 (610 mg, 2.3 mmol), 2-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (296 mg, 1.2 mmol) and 1-methylpiperidin-4-ol (270 mg, 2.3 mmol) in DCM (14 mL) under Ar and the reaction was stirred at rt for 4 d. Evaporation and purification on the Biotage (SiO_2 , 5-30% MeOH in DCM) gave the title compound (403 mg, 80% pure, 79%). ^1H NMR (400 MHz, CDCl_3) δ ppm 7.83 (d, $J=1.5$ Hz, 1H), 7.64 (dd, $J=8.3, 1.5$ Hz, 1H), 6.93 (d, $J=8.3$ Hz, 1H), 4.53 (br. s., 1H), 2.68-2.81 (m, 2H), 2.39 (m+s, 5H), 2.02-2.15 (m, 2H), 1.94-2.02 (m, 2H), 1.34 (s, 12H). MS ESI 352.2 $[\text{M}+\text{H}]^+$, calcd for $[\text{C}_{18}\text{H}_{27}\text{BClNO}_3+\text{H}]^+$ 352.19.

Synthesis of
4-(4-bromo-2-methoxyphenoxy)piperidine

[0280]

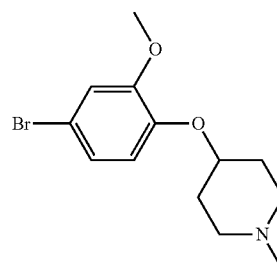


[0281] tert-Butyl 4-(4-bromo-2-methoxyphenoxy)piperidine-1-carboxylate (400 mg, 1.04 mmol) was dissolved in DCM (10 mL), and cooled to 0°C . TFA (3 mL) was added and the mixture was allowed to slowly warm to RT. After 1 h, solvent was removed under reduced pressure and dissolved in EtOAc (10 mL). The reaction was washed with NaHCO_3 (15 mL) and brine (15 mL), and dried with MgSO_4 . Solvent was

removed under reduced pressure to give the title compound (yellow oil, 287 mg, 96%). ^1H NMR (400 MHz, CDCl_3) δ ppm 6.98-7.04 (m, 2H), 6.80 (d, $J=9.3$ Hz, 1H), 4.41-4.48 (br. m, 1H), 3.84 (s, 3H), 3.28-3.39 (m, 2H), 2.97-3.07 (m, 2H), 2.06-2.17 (m, 2H), 1.97 (m, $J=3.5$ Hz, 2H); MS ESI 285.9, 287.9 $[\text{M}+\text{H}]^+$, calcd for $[\text{C}_{12}\text{H}_{16}\text{BrNO}_2+\text{H}]^+$ 286.0, 288.0.

Synthesis of
4-(4-bromo-2-methoxyphenoxy)-1-methylpiperidine

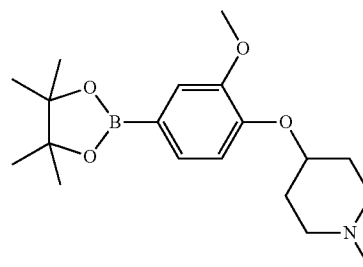
[0282]



[0283] In a microwave vial 4-(4-bromo-2-methoxyphenoxy)piperidine (430 mg, 1.5 mmol) was combined with formic acid (4.5 mL) and formalin (0.5 mL). The reaction was heated at 150°C in the microwave reactor for 5 min. The mixture was concentrated under reduced pressure and partitioned between 0.5 M NaOH (20 mL) and EtOAc (10 mL). Reaction was washed with brine and dried with MgSO_4 . Removal of solvent under reduced pressure gave the title compound (clear oil, 412 mg, 92%). ^1H NMR (400 MHz, CDCl_3) δ ppm 6.98-7.03 (m, 2H), 6.80 (d, $J=9.0$ Hz, 1H), 4.27 (br. s, 1H), 3.84 (s, 3H), 2.77-2.89 (br. m, 2H), 2.35-2.48 (br. m, 5H), 2.00-2.10 (br. m, 2H), 1.86-1.97 (br. m, 2H); MS ESI 300.0, 302.0 $[\text{M}+\text{H}]^+$, calcd for $[\text{C}_{13}\text{H}_{18}\text{BrNO}_2+\text{H}]^+$ 300.1, 302.2.

Synthesis of 4-(2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)-1-methylpiperidine

[0284]

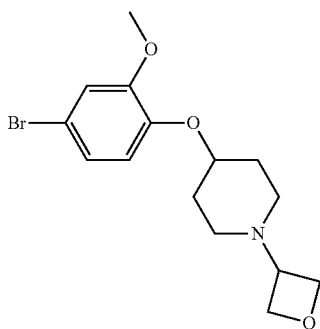


[0285] The title compound was synthesized according to the General Method E utilizing 4-(4-bromo-2-methoxyphenoxy)-1-methylpiperidine (400 mg, 1.33 mmol), bis(pinacolato)diboron (509 mg, 2 mmol), PdCl_2dppf (68 mg, 0.084 mmol), KOAc (655 mg, 6.68 mmol), and DMF (10 mL). The mixture was charged with Ar and heated at 100°C in the microwave reactor for 2 h. Purification by RPcolumn chromatography (Biotage C_{18} , 60 g, 90:10-10:90% 0.1% TFA- H_2O :MeOH) gave the title compound (off-white solid, 145

mg, 31%). $^1\text{H NMR}$ (400 MHz, CD_3OD) δ ppm 7.27-7.34 (m, 2H), 6.99 (d, $J=8.3$ Hz, 1H), 4.46 (br. s, 1H), 3.84 (s, 3H), 2.86-2.95 (br. m, 2H), 2.50-2.62 (br. m, 2H), 2.43 (s, 3H), 1.97-2.07 (br. m, 2H), 1.82-1.93 (br. m, 2H), 1.33 (s, 12H); MS ESI 348.2 $[\text{M}+\text{H}]^+$, calcd for $[\text{C}_{19}\text{H}_{30}\text{BNO}_4+\text{H}]^+$ 348.2.

Synthesis of 4-(4-bromo-2-methoxyphenoxy)-1-(oxetan-3-yl)piperidine

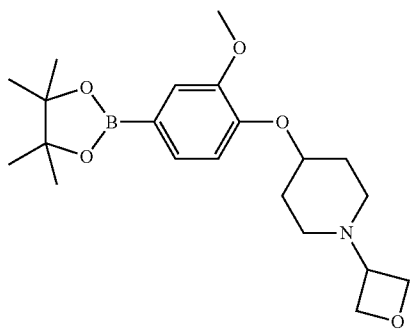
[0286]



[0287] The title compound was synthesized according to the General Method G, utilizing 4-(4-bromo-2-methoxyphenoxy)piperidine (287 mg, 1 mmol), 3-oxetan 1 (86 mg, 1.2 mmol), $\text{NaBH}(\text{OAc})_3$ (318 mg, 1.5 mmol), DCE (10 mL), and 4 drops of acetic acid. Purification by flash chromatography (SiO_2 , Biotage 25 g, 0-20% MeOH in CH_2Cl_2) gave the title compound (off-white solid, 230 mg, 67%). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ ppm 6.96-7.02 (m, 2H), 6.79 (d, $J=8.5$ Hz, 1H), 4.58-4.69 (m, 3H), 4.20-4.30 (m, 1H), 3.84 (s, 3H), 3.45-3.54 (m, 2H), 2.54-2.64 (m, 2H), 2.07-2.20 (m, 2H), 1.93-2.03 (m, 2H), 1.80-1.93 (m, 2H); MS ESI 342.2, 344.0 $[\text{M}+\text{H}]^+$, calcd for $[\text{C}_{15}\text{H}_{20}\text{BrNO}_3+\text{H}]^+$ 342.1, 344.1.

Synthesis of 4-(2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)-1-(oxetan-3-yl)piperidine

[0288]

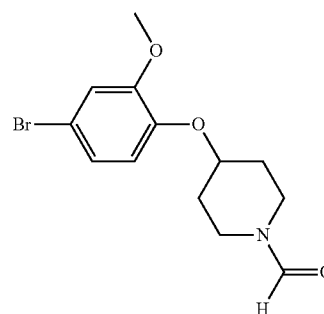


[0289] The title compound was synthesized according to the General Method E, utilizing 4-(4-bromo-2-methoxyphenoxy)-1-(oxetan-3-yl)piperidine (220 mg, 0.54 mmol), Bpin_2 (195 mg, 0.77 mmol), KOAc (188 mg, 1.92 mmol), PdCl_2dppf (26 mg, 0.032 mmol) and DMF. The mixture was heated in the microwave reactor for 2 h at 85°C . Purification

by flash chromatography (SiO_2 , Biotage 25 g, 0-25% MeOH in CH_2Cl_2) gave the title compound (brown oil, 95 mg, 38%). $^1\text{H NMR}$ (400 MHz, CD_3OD) δ ppm 7.28-7.34 (m, 2H), 6.97 (d, $J=8.0$ Hz, 1H), 4.69 (t, $J=6.8$ Hz, 2H), 4.60 (t, $J=6.3$ Hz, 2H), 4.39-4.48 (m, 1H), 3.83 (s, 3H), 3.48-3.55 (m, 1H), 2.56-2.67 (m, 2H), 2.16-2.26 (m, 2H), 1.94-2.04 (m, 2H), 1.76-1.89 (m, 2H), 1.33 (s, 12H); MS ESI 390.1 $[\text{M}+\text{H}]^+$, calcd for $[\text{C}_{21}\text{H}_{32}\text{BNO}_5+\text{H}]^+$ 390.2.

Synthesis of 4-(4-bromo-2-methoxyphenoxy)piperidine-1-carbaldehyde

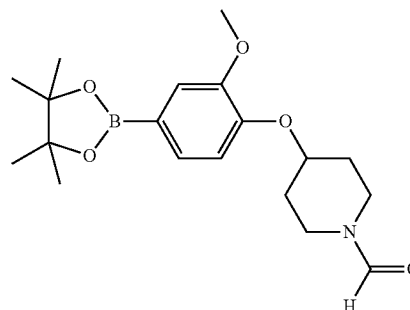
[0290]



[0291] The title compound was synthesized according to the General Method A utilizing 4-(4-bromo-2-methoxyphenoxy)piperidine (400 mg, 1.39 mmol), formic acid (64 mg, 1.39 mmol), TBTU (446 mg, 1.39 mmol), DIPEA (0.73 mL, 4.18 mmol), and DMF (4 mL) to give the title compound (yellow solid, 372 mg, 85%). $^1\text{H NMR}$ (400 MHz, CD_3OD) δ ppm 8.02 (s, 1H), 7.12 (d, $J=2.3$ Hz, 1H), 7.02 (dd, $J=8.5$, 2.3 Hz, 1H), 6.94 (d, $J=8.5$ Hz, 1H), 4.52-4.59 (m, 1H), 3.83 (s, 3H), 3.65-3.77 (m, 2H), 3.45-3.53 (m, 1H), 3.34-3.41 (m, 1H), 1.68-1.99 (m, 4H); MS ESI 314.2, 316.0 $[\text{M}+\text{H}]^+$, calcd for $[\text{C}_{13}\text{H}_{16}\text{BrNO}_3+\text{H}]^+$ 314.0, 316.0.

Synthesis of 4-(2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine-1-carbaldehyde

[0292]

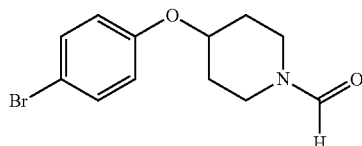


[0293] The title compound was synthesized according to the General Method E, utilizing 4-(4-bromo-2-methoxyphenoxy)piperidine-1-carbaldehyde (370 mg, 1.17 mmol), bis(pinacolato)diboron (356 mg, 1.40 mmol), KOAc (344 mg, 3.51 mmol), PdCl_2dppf (48 mg, 0.06 mmol) and DMF (10

mL). The mixture was heated in the microwave reactor for 2 h at 85° C. Purification by flash chromatography (SiO₂, Biotage 25 g, 0-15% MeOH in CH₂Cl₂) gave the title compound (brown oil, 266 mg, 82%). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.02 (s, 1H), 7.29-7.35 (m, 2H), 7.03 (d, J=8.3 Hz, 1H), 4.63-4.71 (m, 1H), 3.84 (s, 3H), 3.65-3.79 (m, 2H), 3.45-3.54 (m, 1H), 3.35-3.43 (m, 1H), 1.86-2.02 (m, 2H), 1.70-1.86 (m, 2H), 1.34 (s, 12H); MS ESI 362.3 [M+H]⁺, calcd for [C₁₉H₂₈BNO₅+H]⁺ 362.2.

Synthesis of
4-(4-bromophenoxy)piperidine-1-carbaldehyde

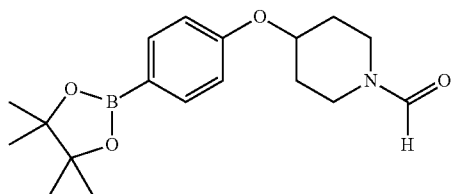
[0294]



[0295] The title compound was synthesized according to Method A utilizing 4-(4-bromophenoxy)piperidine HCl salt and formic acid and obtained as a yellow solid (885 mg, 91% yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 8.07 (s, 1H), 7.58 (d, J=8.78 Hz, 2H), 6.71 (d, J=9.03 Hz, 2H), 4.54-4.61 (m, 1H), 3.56-3.68 (m, 3H), 3.29-3.40 (m, 1H), 1.76-1.98 (m, 4H); MS ESI [M+H]⁺ 284.0, calcd for [C₁₂H₁₄BrNO₂+H]⁺ 284.03.

Synthesis of 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine-1-carbaldehyde

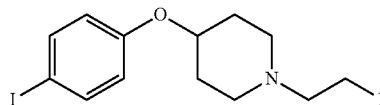
[0296]



[0297] A microwave oven vial was charged with 4-(4-bromophenoxy)piperidine-1-carbaldehyde (480 mg, 1.68 mmols), bis(pinacolato)diboron (513 mg, 2.02 mmols), KOAc (495 mg, 5.05 mmols) and DMF (8 mL). The mixture was purged with Ar for 2 min, then PdCl₂(dppf).DCM (69 mg, 0.05 mmol) was added and the vial was sealed. The resulting mixture was stirred at 85° C. for 2 h with microwave irradiation and then was filtered through Celite. The filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/hexanes 0% to 100%) to give the title compound as a light yellow solid (473 mg, 85%). ¹H NMR (400 MHz, CDCl₃) δ ppm 8.06 (s, 1H), 7.77 (d, J=8.53 Hz, 2H), 6.88-6.94 (d, J=8.53 Hz, 2H), 4.65-4.72 (m, 1H), 3.55-3.69 (m, 3H), 3.29-3.39 (m, 1H), 1.90 (m, 4H), 1.34 (s, 12H); MS ESI [M-C₄H₉+H]⁺ 332.3, calcd for [C₁₈H₂₆BNO₄+H]⁺ 332.20.

Synthesis of
1-(2-fluoroethyl)-4-(4-iodophenoxy)piperidine

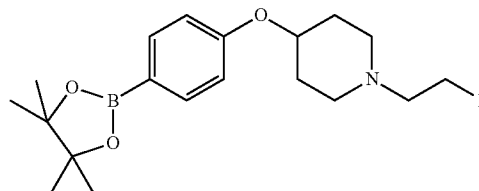
[0298]



[0299] To the solution of 1-(2-fluoroethyl)piperidin-4-ol (500 mg, 3.4 mmols), 1-fluoro-4-iodobenzene (0.39 mL, 3.4 mmols) in anhydrous DMF (6 mL) was added 60% NaH (272 mg, 6.8 mmols) in portions at rt. The resulting reaction mixture was stirred at 85° C. for 3 d under Ar. After cooled down to rt, the mixture was poured into ice/H₂O (5 mL/mmol) and stirred for 10 min before filtration to give the title compound as a light yellow solid (746 mg, 63% yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.50-7.59 (m, 2H), 6.65-6.73 (m, 2H), 4.65 (t, J=5.02 Hz, 1H), 4.49-4.56 (m, 1H), 4.26-4.35 (m, 1H), 2.74-2.84 (m, 2H), 2.70 (t, J=5.02 Hz, 1H), 2.43 (t, J=8.28 Hz, 2H), 1.95-2.05 (m, 2H), 1.79-1.90 (m, 2H), 0.88 (d, J=11.04 Hz, 1H); MS ESI [M+H]⁺ 350.0, calcd for [C₁₉H₂₉BFNO₃+H]⁺ 350.04.

Synthesis of 1-(2-fluoroethyl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine

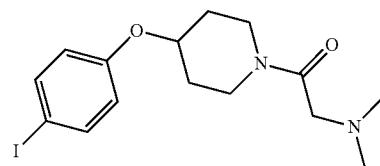
[0300]



[0301] The title compound was synthesized according to Method E utilizing 1-(2-fluoroethyl)-4-(4-iodophenoxy)piperidine and obtained as a yellow solid (33 mg, 30% yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.75 (d, J=8.53 Hz, 2H), 6.90 (d, J=8.53 Hz, 2H), 4.73 (t, J=4.77 Hz, 1H), 4.61 (t, J=4.77 Hz, 1H), 4.43-4.52 (m, 1H), 2.84-2.91 (m, 3H), 2.77-2.83 (m, 1H), 2.55-2.67 (m, 2H), 2.07-2.18 (m, 2H), 1.86-1.99 (m, 2H), 1.34 (s, 12H); MS ESI [M+H]⁺ 350.1, calcd for [C₁₉H₂₉BFNO₃+H]⁺ 350.23.

Synthesis of 2-(dimethylamino)-1-(4-(4-iodophenoxy)piperidin-1-yl)ethanone

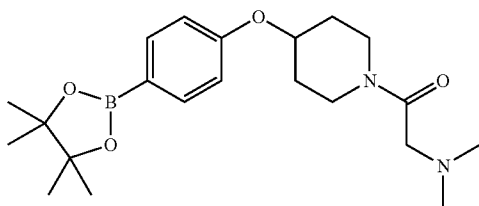
[0302]



[0303] The title compound was synthesized according to the Method A utilizing 4-(4-iodophenoxy)piperidine HCl salt and 2-(dimethylamino)acetic acid and obtained as a yellow solid (739 mg, 95% yield). ^1H NMR (400 MHz, CDCl_3) δ ppm 7.52-7.60 (m, 2H), 6.66-6.73 (m, 2H), 4.50 (tt, $J=6.6, 3.5$ Hz, 1H), 3.79 (dd, $J=8.8, 4.0$ Hz, 2H), 3.57-3.66 (m, 1H), 3.48-3.57 (m, 1H), 3.13 (s, 2H), 2.29 (s, 6H), 1.73-2.00 (m, 4H); MS ESI $[\text{M}+\text{H}]^+$ 389.1, calcd for $[\text{C}_{15}\text{H}_{21}\text{N}_2\text{O}_2+\text{H}]^+$ 389.07.

Synthesis of 2-(dimethylamino)-1-(4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidin-1-yl)ethanone

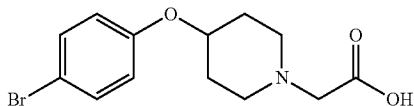
[0304]



[0305] The title compound was synthesized according to General Method F utilizing 2-(dimethylamino)-1-(4-(4-iodophenoxy)piperidin-1-yl)ethanone and obtained as a pale solid (380 mg, 91% yield). ^1H NMR (400 MHz, CDCl_3) δ ppm 7.76 (d, $J=8.53$ Hz, 2H), 6.90 (d, $J=8.53$ Hz, 2H), 4.62 (br. s., 1H), 3.61-3.82 (m, 3H), 3.47-3.57 (m, 1H), 3.30 (m, 2H), 2.31-2.47 (m, 6H), 1.74-2.02 (m, 4H), 1.34 (s, 9H); MS ESI $[\text{M}+\text{H}]^+$ 389.1, calcd for $[\text{C}_{21}\text{H}_{33}\text{BN}_2\text{O}_4+\text{H}]^+$ 389.26.

Synthesis of
2-(4-(4-bromophenoxy)piperidin-1-yl)acetic acid

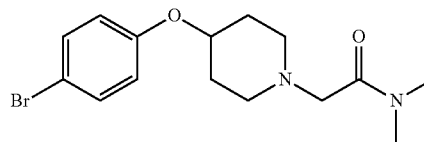
[0306]



[0307] The solution of ethyl 2-(4-(4-bromophenoxy)piperidin-1-yl)acetate (680 mg, 2 mmols), 2N NaOH (8 mL) in MeOH (8 mL) was stirred at rt for 30 min before solvent was removed under reduced pressure. The residue was suspended in H_2O and adjusted pH to 1 with 5% HCl. The resulting solution was concentrated under reduced pressure. The residue was purified with RP column to give a TFA salt of the title compound as a white solid (392 mg, 46% yield). ^1H NMR (400 MHz, CD_3OD) δ ppm 7.41-7.46 (m, 2H), 6.96 (d, $J=8.8$ Hz, 2H), 4.67-4.73 (m, 1H), 3.93 (s, 2H), 3.35-3.57 (m, 4H), 2.08-2.29 (m, 4H); MS ESI $[\text{M}+\text{H}]^+$ 314.2, calcd for $[\text{C}_{13}\text{H}_{16}\text{BrNO}_3+\text{H}]^+$ 314.04.

Synthesis of 2-(4-(4-iodophenoxy)piperidin-1-yl)-N,N-dimethylacetamide

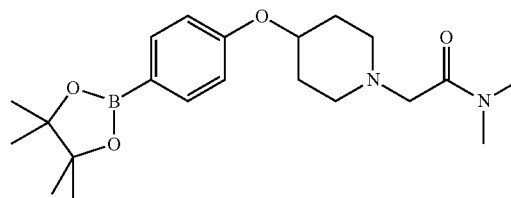
[0308]



[0309] The title compound was synthesized according to Method A utilizing 2-(4-(4-bromophenoxy)piperidin-1-yl)acetic acid TFA salt and dimethylamine and obtained as a yellow solid (171 mg, 100% yield). ^1H NMR (400 MHz, CDCl_3) δ ppm 7.22-7.29 (m, 2H), 6.66-6.73 (m, 2H), 4.19 (dt, $J=7.7, 3.8$ Hz, 1H), 3.11 (s, 2H), 3.00 (s, 3H), 2.86 (s, 3H), 2.64-2.74 (m, 2H), 2.28-2.38 (m, 2H), 1.86-1.97 (m, 2H), 1.67-1.78 (m, 2H); MS ESI $[\text{M}+\text{H}]^+$ 341.2, calcd for $[\text{C}_{15}\text{H}_{21}\text{BrN}_2\text{O}_2+\text{H}]^+$ 341.09.

Synthesis of N,N-dimethyl-2-(4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidin-1-yl)acetamide

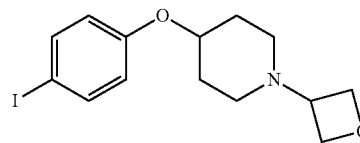
[0310]



[0311] The title compound was synthesized according to Method E utilizing 2-(4-(4-iodophenoxy)piperidin-1-yl)-N,N-dimethylacetamide and obtained as a white solid (74 mg, 41% yield). ^1H NMR (400 MHz, CDCl_3) δ ppm 7.74 (d, $J=8.5$ Hz, 2H), 6.89 (d, $J=8.5$ Hz, 2H), 4.36-4.45 (m, 1H), 3.22 (s, 2H), 3.09 (s, 3H), 2.96 (s, 3H), 2.79 (br. s., 2H), 2.48 (br. s., 2H), 1.97-2.08 (m, 2H), 1.85 (m, 2H), 1.33 (s, 12H); MS ESI $[\text{M}+\text{H}]^+$ 389.2, calcd for $[\text{C}_{21}\text{H}_{33}\text{BN}_2\text{O}_4+\text{H}]^+$ 389.26.

Synthesis of
4-(4-iodophenoxy)-1-(oxetan-3-yl)piperidine

[0312]

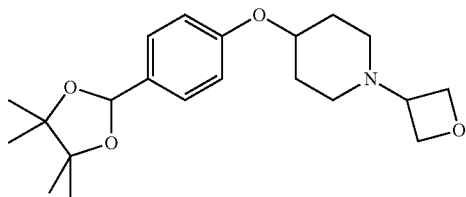


[0313] The suspension of 4-(4-iodophenoxy)piperidine HCl salt (528 mg, 1.55 mmols) in EtOAc was washed with satd aq NaHCO_3 . The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was dissolved in DCE (4 mL) followed by adding of $\text{NaBH}(\text{OAc})_3$ (493 mg, 2.33 mmols), 3-octane (112 mg, 1.55 mmols), and

HOAc (3 drops). The resulting suspension was stirred at rt for 2 h before the solvent was removed under reduced pressure. The residue was washed with satd aqNaHCO₃ and extracted with EtOAc. The combined organic layer was dried over Na₂SO₄ and concentrated under reduced pressure to give the title compound as a yellow solid (460 mg, 83% yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.51-7.59 (m, 2H), 6.65-6.72 (m, 2H), 4.60-4.70 (m, 4H), 4.28-4.38 (m, 1H), 3.51 (quin, J=6.5 Hz, 1H), 2.54 (br. s., 2H), 2.20 (br. s., 2H), 1.93-2.04 (m, 2H), 1.79-1.92 (m, 2H); MS ESI [M+H]⁺ 360.0, calcd for [C₁₄H₁₈INO₂+H]⁺ 360.05.

Synthesis of 1-(oxetan-3-yl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine

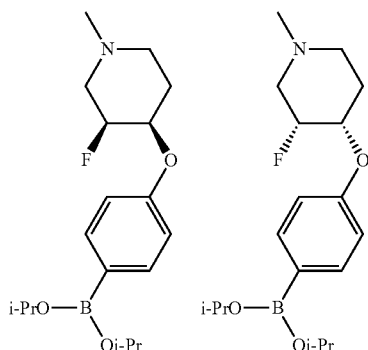
[0314]



[0315] The title compound was synthesized according to Method E utilizing 4-(4-iodophenoxy)-1-(oxetan-3-yl)piperidine and obtained as a pale solid (468 mg, 62% yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.70 (d, J=8.5 Hz, 2H), 6.84 (d, J=8.5 Hz, 2H), 4.55-4.65 (m, 4H), 4.37-4.43 (m, 1H), 3.47 (t, J=6.5 Hz, 1H), 2.50 (d, J=7.8 Hz, 2H), 2.19 (br. s., 2H), 1.91-2.01 (m, 2H), 1.84 (td, J=6.7, 3.4 Hz, 2H), 1.28 (s, 12H); MS ESI [M+H]⁺ 360.1, calcd for [C₂₀H₃₀BNO₄+H]⁺ 360.23.

Synthesis of diisopropyl 4-((3R,4S)-3-fluoro-1-methylpiperidin-4-yl)oxyphenylboronate compound with diisopropyl 4-(((3S,4R)-3-fluoro-1-methylpiperidin-4-yl)oxy)phenylboronate, a 1:1 mixture

[0316]



[0317] A. (3R,4S)-tert-butyl 3-fluoro-4-(4-iodophenoxy)piperidine-1-carboxylate compound with (3S,4R)-tert-butyl 3-fluoro-4-(4-iodophenoxy)piperidine-1-carboxylate (1:1 mixture) was synthesized according to General Method H utilizing 1-fluoro-4-iodobenzene (0.80 g, 3.6 mmol), (3R,4S)-tert-butyl 3-fluoro-4-hydroxypiperidine-1-carboxylate/(3S,4R)-tert-butyl 3-fluoro-4-hydroxypiperidine-1-carboxylate (1:1 mixture) (0.73 g, 3.3 mmol) and NaH (60% in mineral oil, 0.17, 4.3 mmol) in anh DMF (20

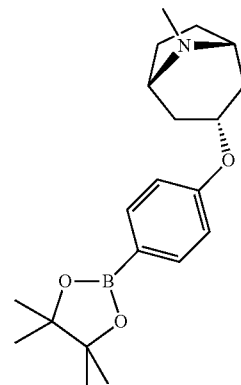
mL) under Ar. After 2 d of heating at 80° C. the reaction was quenched with H₂O/MeOH, concentrated under reduced pressure. The residue was taken into DCM (70 mL) and stirred with TFA (8 mL) at 0° C. for 3 h. The reaction was then concentrated under reduced pressure and purified by RP HPLC (Biotage C18 100 g, 5-9% MeOH/H₂O+0.1% TFA) to afford cis-3-fluoro-4-(4-iodophenoxy)piperidine 2,2,2-trifluoroacetate as a tan solid. MS ESI [M+H]⁺ 321.9, calcd for [C₁₁H₁₃FINO: +H]⁺ 322.0

[0318] B. The material (0.47 g, 1.1 mmol) in MeCN (70 mL) was treated with HCHO (30% in H₂O, 0.72 mL, 9.7 mmol) followed by NaBH(OAc)₃ (0.69 g, 3.2 mmol) at rt. After overnight stirring, the reaction was concentrated under reduced pressure and filtered through PoraPak CX columns (2x2 g, Waters) using MeOH to load and rinse and 2 M NH₃/MeOH to elute. The crude material was subsequently purified by flash chromatography (SiO₂, 0-40% 2 M NH₃/MeOH in DCM) to afford cis-3-fluoro-4-(4-iodophenoxy)-1-methylpiperidine as a clear gum (0.23 g, 64%). ¹H NMR (400 MHz, CD₃OD) δ ppm 7.59 (d, J=8.80 Hz, 2H), 6.82 (d, J=8.80 Hz, 2H), 4.78-4.84 (m, 1H), 4.44-4.60 (m, 1H), 3.09 (br. s., 1H), 2.82 (br. s., 1H), 2.50-2.73 (m, 1H), 2.45 (m, 1H), 2.39 (s, 3H), 2.03-2.17 (m, 1H), 1.88-2.00 (m, 1H); MS ESI 336.0 [M+H]⁺ calcd for [C₁₂H₁₅FINO: +H]⁺ 336.0.

[0319] C. To a stirred solution of cis-3-fluoro-4-(4-iodophenoxy)-1-methylpiperidine (0.12 g, 0.33 mmol) in anh THF (5 mL) under Ar was added n-BuLi (1.6 M in hexanes, 0.45 mL, 0.72 mmol) dropwise at -78° C. The reaction was stirred for 15 min at the temperature before B(Oi-Pr)₃ (1.2 mL, 5.2 mmol) was added rapidly. After additional 30 min at -78° C. the reaction was removed from the cooling bath and stirred for 1 h before it was concentrated under reduced pressure to afford a crude mixture of cis-4-((3-fluoro-1-methylpiperidin-4-yl)oxy)phenylboronic acid and diisopropyl 4-((cis-3-fluoro-1-methylpiperidin-4-yl)oxy)phenylboronate as an off-white solid (0.34 g) that was used without further purification. MS ESI [M+H]⁺ 254.1, calcd for [C₁₂H₁₇BFNO₃: +H]⁺ 254.1.

Synthesis of (1R,3r,5S)-8-methyl-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)-8-azabicyclo[3.2.1]octane

[0320]



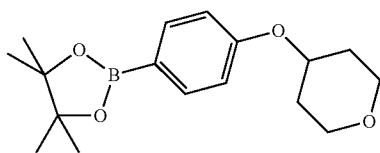
[0321] A. (1R,3r,5S)-3-(4-iodophenoxy)-8-methyl-8-azabicyclo[3.2.1]octane was synthesized according to

method H utilizing 1-fluoro-4-iodobenzene (2.99 g, 13.5 mmol), (1R,3r,5S)-8-methyl-8-azabicyclo[3.2.1]octan-3-ol (1.9 g, 13.5 mmol) and NaH (60% in oil, 0.64 g, 16.1 mmol) in DMF (40 mL). After 1 d of heating at 85° C., the reaction was quenched with MeOH and concentrated under reduced pressure. The residue was partitioned between satd aq NaHCO₃ and EtOAc. The aq layer was extracted with EtOAc (2×). The organic fractions were combined, dried (Na₂SO₄) and concentrated under reduced pressure. The crude material was purified by RP HPLC (Biotage C18 100 g, 5-90% MeOH/H₂O+0.1% TFA) to TFA salt of (1R,3r,5S)-3-(4-iodophenoxy)-8-methyl-8-azabicyclo[3.2.1]octane as an off-white solid (2.0 g, 33%). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.60 (d, J=8.78 Hz, 2H), 6.62 (d, J=8.78 Hz, 2H), 4.65 (t, J=4.89 Hz, 1H), 3.79 (br. s., 2H), 2.71-2.83 (m, 5H), 2.55-2.47 (m, 2H), 2.15-2.32 (m, 4H); MS ESI 344.0 [M+H]⁺, calcd for [C₁₄H₁₈INO: +H]⁺ 344.0;

[0322] B. (1R,3r,5S)-8-methyl-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)-8-azabicyclo[3.2.1]octane was synthesized according to General Method E utilizing (1R,3r,5S)-3-(4-iodophenoxy)-8-methyl-8-azabicyclo[3.2.1]octane 2,2,2-trifluoroacetate (0.50 g, 1.1 mmol). The to afford, after aq workup (satd aq NaHCO₃/DCM) followed by a flash chromatography (25 g SiO₂, 0-30% MeOH-DCM), the desired compound as an off-white solid (14 mg, 13%). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.79 (d, J=8.53 Hz, 2H), 6.84 (d, J=8.78 Hz, 2H), 4.81 (br. s., 1H), 3.82 (br. s., 2H), 3.38-3.18 (m, 2H), 2.77 (s, 3H), 2.63-2.54 (m, 2H), 2.21-2.36 (m, 4H), 134 (s, 12H); MS ESI 344.2 [M+H]⁺, calcd for [C₂₀H₃₀BN₂O₃: +H]⁺ 344.2;

Synthesis of 4,4,5,5-tetramethyl-2-(4-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)-1,3,2-dioxaborolane

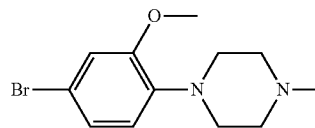
[0323]



[0324] The title compound was synthesized according to general Method E by using a solution of 4-(4-bromophenoxy) tetrahydro-2H-pyran (800 mg, 3.11 Mmmol) in DMF (12 mL) was added bis(pinacolato)diboron (948 mg, 3.73 mmol), KOAc (916 mg, 9.33 mmol) and PdCl₂dppf (254 mg, 0.311 mmol) under Ar. The degassed suspension under Ar was sealed and heated in an oil bath at 125° C. for 5 h. The reaction mixture was diluted using EtOAc (60 mL) and H₂O (36 mL). The organic layer was separated and aq. layer extracted with EtOAc (36 mL). The combined EtOAc layer was washed with H₂O and brine, dried (Na₂SO₄) and concentrated under vacuum at 40° C./100 mbar to give crude brown thick oil. The crude oily product purified by Biotage (50 g SiO₂, 0-30% EtOAc in Hexane) to give title compound (cream color solid, 728 mg, 77%). ¹H NMR (400 MHz, CDCl₃) δ 7.76-7.74 (d, J=2.8 Hz, 2H), 6.92 (d, J=2.8 Hz, 2H), 4.59-4.53 (m, 1H), 4.01-3.96 (m, 2H), 3.62-3.57 (m, 2H), 2.05-2.0 (m, 2H), 1.84-1.77 (m, 2H), 1.34 (s, 12H); MS ESI 305.1 [M+H]⁺, calcd for [C₁₇H₂₅BO₄+H]⁺ 305.1.

Synthesis of
1-(4-bromo-2-methoxyphenyl)-4-methylpiperazine

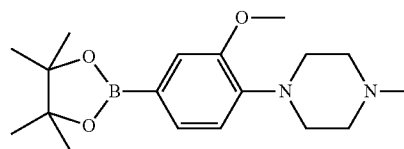
[0325]



[0326] The title compound was synthesized according to the General Method C, utilizing 5-bromo-2-iodoanisole (683 mg, 2.18 mmol), 1-methylpiperazine (262 mg, 2.62 mmol), CuI (83 mg, 0.44 mmol), BINOL (125 mg, 0.44 mmol), K₃PO₄ (924 mg, 4.36 mmol), and DMF (4 mL) and purified using flash chromatography (SiO₂, Biotage 25 g, 5-25% MeOH in CH₂Cl₂) to give the title compound (light yellow solid, 213 mg, 34%). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.01 (d, J=8.3 Hz, 1H), 6.94 (s, 1H), 6.76 (d, J=8.3 Hz, 1H), 3.83 (s, 3H), 3.27 (br. s., 4H), 2.99 (br. s., 4H), 2.59 (s, 3H).

Synthesis of 1-(2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-4-methylpiperazine

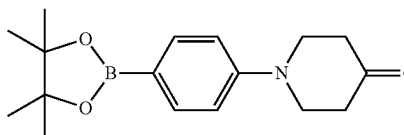
[0327]



[0328] The title compound was synthesized according to the General Method E utilizing 1-(4-bromo-2-methoxyphenyl)-4-methylpiperazine (200 mg, 0.70 mmol), Bis(pinacolato)diboron (213 mg, 0.84 mmol), PdCl₂dppf (17 mg, 0.021 mmol), KOAc (206 mg, 2.1 mmol), and DMSO (10 mL). The mixture was charged with Ar and heated at 85° C. in the microwave reactor for 2 h. Purification by flash chromatography (SiO₂, Biotage 25 g, 5-25% MeOH in CH₂Cl₂) gave the title compound (brown solid, 63 mg, 27%). MS ESI 333.3 [M+H]⁺, calcd for [C₁₈H₂₉BN₂O₃+H]⁺ 333.2.

Synthesis of 1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidin-4-one

[0329]

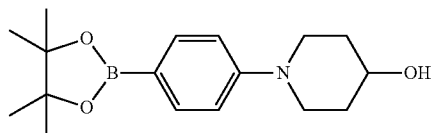


[0330] The title compound was synthesized according to general Method E by using a mixture of 1-(4-Bromophenyl) piperidin-4-one (1.5 g, 5.9 mmol), Bis(pinacolato)diboron (2.62 g, 10.3 mmol), KOAc (1.73 g, 17.7 mmol) and DMF (15 mL) was purged with Ar for 10 min. PdCl₂dppf (0.32 g, 0.44 mmol) was added in round bottom flask and heated at 125° C.

for 4 h in oil bath under Ar. The reaction mixture was diluted using 10% sodium chloride solution (100 mL) and the product extracted with EtOAc (2×100 mL) and the combined EtOAc layer was washed with brine (2×25 mL), dried (Na_2SO_4), and concentrated under vacuum at 40° C./100 mbar to give crude brown thick oil. The crude oily mass purified by flash chromatography (50 g SiO_2 , 0-40% EtOAc in Hexane) to give the title compound (pale yellow solid, 584 mg, 33%). ^1H NMR (400 MHz, CDCl_3) δ ppm 7.77 (d, J=8.8 Hz, 2H), 6.97 (d, J=8.8 Hz, 2H), 3.71 (t, J=6.0 Hz, 4H), 2.56 (t, J=6.0 Hz, 4H), 1.34 (s, 12H); MS ESI 302 $[\text{M}+\text{H}]^+$, calcd for $[\text{C}_{17}\text{H}_{24}\text{BNO}_3+\text{H}]^+$ 302.1

Synthesis of 1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidin-4-ol

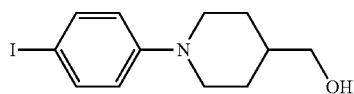
[0331]



[0332] Using Method F with excess HBpin (3 equiv) at 100° C. for 17 h, from 1-(4-bromophenyl)piperidin-4-one (1.4885 g, 5.86 mmol), after aq. work-up with EtOAc, purification by flash chromatography (SiO_2 , 50-60% EtOAc in hexane) gave the title compound (1.59 g, 80% pure, 72%). ^1H NMR (400 MHz, CDCl_3) δ ppm 7.70 (d, J=8.8 Hz, 2H), 6.91 (d, J=8.8 Hz, 2H), 3.88 (tt, J=8.6, 4.2 Hz, 1H), 3.68 (dt, J=13.1, 4.1 Hz, 2H), 3.00 (ddd, J=12.7, 10.1, 3.0 Hz, 2H), 1.92-2.04 (m, 2H), 1.60-1.73 (m, 2H), 1.33 (s, 12H).

Synthesis of (1-(4-iodophenyl)piperidin-4-yl)methanol

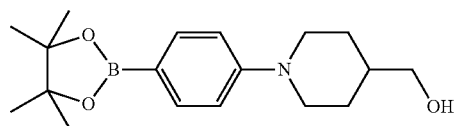
[0333]



[0334] The title compound was synthesized according to the General Method I utilizing piperidin-4-ylMeOHEtOH and obtained as a white solid (989 mg, 31% yield). ^1H NMR (400 MHz, CDCl_3) δ ppm 7.50 (d, J=9.03 Hz, 2H), 6.71 (d, J=9.03 Hz, 2H), 3.65-3.72 (m, 2H), 3.53-3.58 (m, 2H), 2.72 (td, J=12.55, 2.51 Hz, 2H), 1.82-1.89 (m, 2H), 1.62-1.73 (m, 1H), 1.35-1.45 (m, 2H), 1.32 (t, J=5.40 Hz, 1H); MS ESI $[\text{M}+\text{H}]^+$ 318.0, calcd for $[\text{C}_{12}\text{H}_{16}\text{INO}+\text{H}]^+$ 318.04.

Synthesis of 1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidin-4-yl)methanol

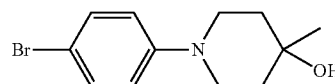
[0335]



[0336] The title compound was synthesized according to Method E utilizing (1-(4-iodophenyl)piperidin-4-yl)methanol and obtained as a bright brown solid (272 mg, 70% yield). ^1H NMR (400 MHz, CDCl_3) δ ppm 7.70 (d, J=8.78 Hz, 2H), 6.91 (d, J=8.78 Hz, 2H), 3.85 (d, J=12.55 Hz, 2H), 3.55 (d, J=6.53 Hz, 2H), 2.79 (td, J=12.36, 2.64 Hz, 2H), 1.85 (d, J=13.05 Hz, 2H), 1.64-1.77 (m, 1H), 1.51-1.63 (m, 2H), 1.39 (br. s., 1H), 1.33 (s, 12H); MS ESI $[\text{M}+\text{H}]^+$ 318.1, calcd for $[\text{C}_{12}\text{H}_{16}\text{INO}+\text{H}]^+$ 318.22.

Synthesis of 1-(4-bromophenyl)-4-methylpiperidin-4-ol

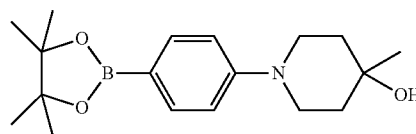
[0337]



[0338] The mixture of 1-(4-bromophenyl)piperidin-4-one (254 mg, 1 mmol) in anhydrous THF (10 mL) was cooled down to -78° C. MeMgCl (3M in THF, 1.7 mL, 5 mmols) was added dropwise and stirred at -78° C. for 0.5 h then at 0° C. for 2 h. The reaction was quenched with satd aq NH_4Cl solution dropwise at 0° C. The mixture was poured into brine and extracted with EtOAc. The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to provide the title compound as a yellow solid (262 mg, 97% yield). ^1H NMR (400 MHz, CDCl_3) δ ppm 7.33 (d, J=8.78 Hz, 2H), 6.83 (d, J=8.78 Hz, 2H), 3.33 (dt, J=12.49, 4.17 Hz, 2H), 3.11-3.22 (m, 2H), 1.65-1.83 (m, 4H), 1.31 (s, 3H); MS ESI $[\text{M}+\text{H}]^+$ 270.2, calcd for $[\text{C}_{12}\text{H}_{16}\text{BrNO}+\text{H}]^+$ 270.05.

Synthesis of 4-methyl-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidin-4-ol

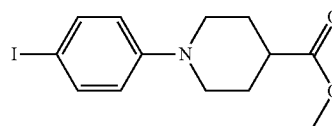
[0339]



[0340] The title compound was synthesized according to Method E utilizing 1-(4-bromophenyl)-4-methylpiperidin-4-ol and obtained as a white solid (42 mg, 27% yield). ^1H NMR (400 MHz, CDCl_3) δ ppm 7.71 (d, J=8.78 Hz, 2H), 6.92 (d, J=8.78 Hz, 2H), 3.49 (dt, J=12.80, 4.39 Hz, 2H), 3.27 (br. s., 2H), 1.63-1.81 (m, 4H), 1.56 (s, 3H), 1.33 (s, 12H); MS ESI $[\text{M}+\text{H}]^+$ 318.3, calcd for $[\text{C}_{18}\text{H}_{28}\text{BNO}_3+\text{H}]^+$ 318.22.

Synthesis of methyl 1-(4-iodophenyl)piperidine-4-carboxylate

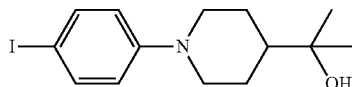
[0341]



[0342] The title compound was synthesized according to the General Method I utilizing methyl piperidine-4-carboxylate and obtained as a yellow solid (471 mg, 14% yield). ^1H NMR (400 MHz, CDCl_3) δ ppm 7.48-7.54 (m, 2H), 6.70 (d, $J=9.03$ Hz, 2H), 3.72 (s, 3H), 3.61 (d, $J=12.80$ Hz, 2H), 2.79 (td, $J=12.05$, 2.76 Hz, 2H), 2.47 (s, 1H), 2.03 (d, $J=13.30$ Hz, 2H), 1.82-1.92 (m, 2H); MS ESI $[\text{M}+\text{H}]^+$ 346.0, calcd for $[\text{C}_{13}\text{H}_{16}\text{INO}_2+\text{H}]^+$ 346.03.

Synthesis of 2-(1-(4-iodophenyl)piperidin-4-yl)propan-2-ol

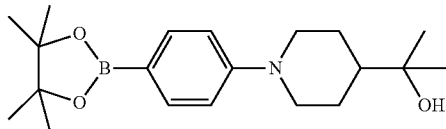
[0343]



[0344] The title compound was synthesized according to the Method of 1-(4-bromophenyl)-4-methylpiperidin-4-ol utilizing 1-(4-iodophenyl)piperidine-4-carboxylate and obtained as a white solid (81 mg, 81% yield). ^1H NMR (400 MHz, CDCl_3) δ ppm 7.50 (d, $J=9.0$ Hz, 2H), 6.71 (d, $J=9.0$ Hz, 2H), 3.74 (d, $J=12.3$ Hz, 2H), 2.65 (t, $J=11.4$ Hz, 2H), 1.87 (m, $J=9.8$ Hz, 2H), 1.40-1.54 (m, 3H), 1.17-1.26 (m, 6H); MS ESI $[\text{M}+\text{H}]^+$ 346.1, calcd for $[\text{C}_{14}\text{H}_{20}\text{INO}+\text{H}]^+$ 346.07.

Synthesis of 2-(1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidin-4-yl)propan-2-ol

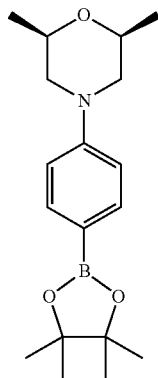
[0345]



[0346] The title compound was synthesized according to General Method F utilizing 2-(1-(4-iodophenyl)piperidin-4-yl)propan-2-ol and obtained as a white solid (74 mg, 91% yield). ^1H NMR (400 MHz, CDCl_3) δ ppm 7.70 (d, $J=8.78$ Hz, 2H), 6.92 (d, $J=8.78$ Hz, 2H), 3.90 (d, $J=12.30$ Hz, 2H), 2.72 (t, $J=12.42$ Hz, 2H), 1.85 (br s., 2H), 1.47 (br s., 3H), 1.29-1.37 (m, 12H), 1.18-1.25 (m, 6H); MS ESI $[\text{M}+\text{H}]^+$ 346.1, calcd for $[\text{C}_{20}\text{H}_{32}\text{BNO}_3+\text{H}]^+$ 346.26.

Synthesis of (2S,6R)-2,6-dimethyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)morpholine

[0347]

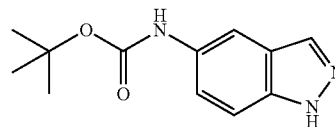


[0348] A. (2S,6R)-4-(4-iodophenyl)-2,6-dimethylmorpholine was synthesized according to the General Method I utilizing 1,4-diiodobenzene (2.4 g, 7.3 mmol) and (2R,6S)-2,6-dimethylmorpholine (1.0 g, 8.8 mmol). After heating for 2 d, the crude reaction mixture was cooled to rt, diluted with EtOAc (100 mL) and filtered through Celite. The filtrate was then washed (H_2O , brine), dried (Na_2SO_4) and concentrated under reduced pressure to provide as a light yellow solid (2.2 g) which was purified by flash chromatography (SiO_2 , 0-20% MeOH-DCM) affording (2S,6R)-4-(4-iodophenyl)-2,6-dimethylmorpholine as a light yellow solid (0.68 g, 30%). MS ESI $[\text{M}+\text{H}]^{+318.0}$, calcd for $[\text{C}_{12}\text{H}_{16}\text{INO}+\text{H}]^+$ 318.0;

[0349] B. (2S,6R)-2,6-Dimethyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)morpholine was synthesized according to the General Method F utilizing (2S,6R)-4-(4-iodophenyl)-2,6-dimethylmorpholine (0.20 g, 0.63 mmol). The crude reaction mixture was concentrated under reduced pressure, taken in DCM and filtered through a column made of two layers (Celite (10 g) and silica gel (10 g)) using hexanes-EtOAc as the eluent (1:1 then 1:3) to afford a pale yellow solid (0.25 g, 125%) which was used without further purification. MS ESI 318.2 $[\text{M}+\text{H}]^+$, calcd for $[\text{C}_{18}\text{H}_{28}\text{BNO}_3+\text{H}]^+$ 318.2.

Synthesis of tert-butyl 1H-indazol-5-ylcarbamate

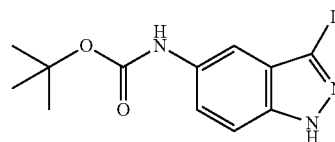
[0350]



[0351] A DMF (15 mL) solution of aminoindazole (1.0 g, 7.5 mmol) and DIPEA (2.0 mL, 11 mmol) was treated with Boc_2O (1.7 g, 7.7 mmol) (50% added in one portion as a solid, and 50% as a solution in anhyd DMF (1 mL)) at 0°C . The reaction was stirred with the cooling for 1.5 h and then allowed to warm slowly to rt overnight. Later it was diluted with H_2O to ~ 100 mL. A tan precipitate was collected by filtration, washed with H_2O and dried to afford the product as a light tan solid (1.7 g, 94%). ^1H NMR (400 MHz, DMSO- d_6) δ ppm 12.90 (s., 1H), 9.27 (s, 1H), 7.94 (s, 1H), 7.87 (br.s, 1H), 7.41 (d, $J=8.80$ Hz, 1H), 7.33 (d, $J=9.2$ Hz, 1H), 1.47 (s, 9H). MS ESI 233.9 $[\text{M}+\text{H}]^+$, calcd for $[\text{C}_{12}\text{H}_{15}\text{N}_3\text{O}_2+\text{H}]^+$ 234.0.

B. tert-butyl 3-iodo-1H-indazol-5-ylcarbamate

[0352]

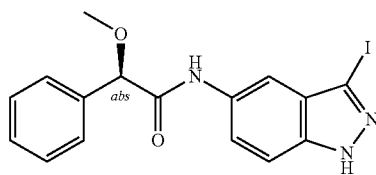


[0353] To a cooled (0°C .) DMF (30 mL) solution t-butyl 1H-indazol-5-ylcarbamate (1.6 g, 6.9 mmol) and K_2CO_3 (3.8 g, 27.6 mmol) was added I_2 (1.8 g, 7.1 mmol) in one portion. The reaction was stirred with cooling for 3 h and then treated

with 10% aq NaHSO₃ (50 mL) and subsequently with H₂O (150 mL). A filtration and washing (H₂O) of the ppt provided crude material which after purification by flash chromatography (SiO₂, 70 g, 0 to 6% MeOH in DCM) and recrystallization from EtOAc/hexanes yielded tert-butyl 3-iodo-1H-indazol-5-ylcarbamate (3) as an off-white solid (1.9 g, 78%). ¹H NMR (400 MHz, Acetone-d₆) δ ppm 12.54 (br. s., 1H), 8.51 (br. s., 1H), 7.87 (br. s., 1H), 7.24-7.66 (m, 2H), 1.51 (s, 9H); MS ESI [M+H]⁺ 359.9 (100)⁺, calcd for [C₁₂H₁₄IN₃O₂+H]⁺ 360.0.

Synthesis of (R)—N-(3-iodo-1H-indazol-5-yl)-2-methoxy-2-phenylacetamide

[0354]

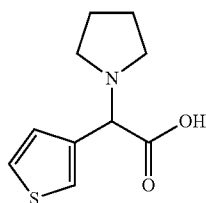


[0355] A. (R)—N-(1H-indazol-5-yl)-2-methoxy-2-phenylacetamide was synthesized according to the General Method A utilizing 1H-indazol-5-amine (0.50 g, 3.76 mmol), (R)-2-methoxy-2-phenylacetic acid (0.65 g, 3.9 mmol), N-ethyl-N-isopropylpropan-2-amine (1.3 mL, 7.5 mmol) and TBTU (1.27 g, 3.9 mmol) in DMF (10 mL). The (R)—N-(1H-indazol-5-yl)-2-methoxy-2-phenylacetamide was precipitated by addition of H₂O, filtered and dried to provide a tan solid (0.81 g) which was used without further purification. MS ESI 282.1 [M+H]⁺, calcd for [C₁₆H₁₅N₃O₂: +H]⁺ 281.1;

[0356] B. (R)—N-(3-iodo-1H-indazol-5-yl)-2-methoxy-2-phenylacetamide was prepared according to the General method B using (0.81 g, 2.8 mmol), 12 (1.4 g, 5.7 mmol) and KOH (0.48 g, 8.5 mmol) in DMF (8 mL) to provide the desired compound as a white solid (0.58 g, 50%). MS ESI 408.1 [M+H]⁺, calcd for [C₁₆H₁₄IN₃O₂+H]⁺ 408.1;

Synthesis of 2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetic acid

[0357]

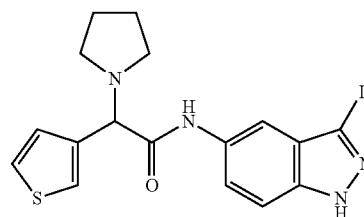


[0358] The title compound was synthesized according to general Method D by using a glyoxylic acid monohydrate (10.79 g, 0.11 mol) and pyrrolidine (9.69 mL, 0.11 mol) was combined with DCM (375 mL) and sonicated for 15 minutes. Thiophene-3-boronic acid (15 g, 0.11 mol) was added and the mixture was stirred at room temperature for 24 h. the solid was filtered and washed with little DCM to gave 38 g crude product as crop-1. The mother liquor concentrated under

reduced pressure to give an additional 4 g as crop-2. The combined crude product purified by Biotage SNAP 100 g silica column (gradient 0-50% MeOH in DCM) gave the title compound as a cream solid (21.7 g, 70%). ¹H NMR (400 MHz, CD₃OD) δ 7.66 (dd, J=2.8 Hz, J=1.2 Hz, 1H), 7.53 (dd, J=5.2 Hz, J=2.8 Hz, 1H), 7.28 (dd, J=5.2 Hz, J=1.2 Hz, 1H), 4.65 (s, 1H), 3.06 (br.s, 2H), 2.04-1.95 (br.s, 4H), 2H merged with solvent peak; MS ESI 212 [M+H]⁺, calcd for [C₁₀H₁₃NO₂S+H]⁺ 212.07.

Synthesis of N-(3-iodo-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide

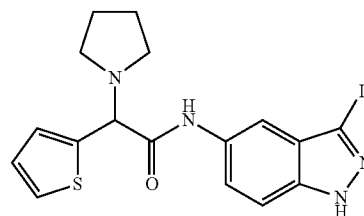
[0359]



[0360] Using method A, 3-iodo-1H-indazol-5-amine (2.53 g, 9.76 mmol) and 2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetic acid (1.69 g, 8.0 mmol) in DMF (57.5 mL) were stirred at rt for 29 h. The reaction mixture was added dropwise into 400 mL H₂O and the precipitate was collected by filtration, transferred using a mixture of acetone and EtOH, and concentrated to dryness. Purification on Biotage Isolera (silica, 60-90% EtOAc/Hexane) gave the title compound (1.61 g, 44%) which was used without further purification. ¹H NMR (400 MHz, CD₃OD) δ ppm 7.83 (s, 1H), 7.49-7.56 (m, 2H), 7.44-7.48 (m, 1H), 7.39-7.44 (m, 1H), 7.33 (d, J=5.0 Hz, 1H), 4.11 (s, 1H), 2.67 (d, J=6.0 Hz, 2H), 2.51 (d, J=5.8 Hz, 2H), 1.81-1.87 (m, 5H).

Synthesis of N-(3-iodo-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-2-yl)acetamide

[0361]



A. 2-(pyrrolidin-1-yl)-2-(thiophen-2-yl)acetic acid

[0362] The title compound was synthesized according to general Method D by using a glyoxylic acid monohydrate (1.08 g, 11.7 mmol) and pyrrolidine (0.97 mL, 11.7 mol) was combined with DCM (45 mL) and sonicated for 15 minutes. Thiophene-2-boronic acid (1.5 g, 11.7 mmol) was added and the mixture was stirred at room temperature for 24 h. the solid was filtered and washed with little DCM to gave 2.2 g crude product. The crude product purified by Biotage SNAP 50 g

silica column (0-30% MeOH in DCM) gave the title compound as an off white solid (1.97 g, 79%). ¹H NMR (400 MHz, CD₃OD) δ 7.54-7.53 (br.s, 1H), 7.35 (s, 1H), 7.07 (s, 1H), 3.42-3.35 (br.s, 2H), 3.13 (br.s, 2H), 2.02 (br.s, 4H), 1H merged with solvent peak; MS ESI 212 [M+H]⁺, calcd for [C₁₀H₁₃NO₂S+H]⁺ 212.07.

B. N-(1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-2-yl)acetamide

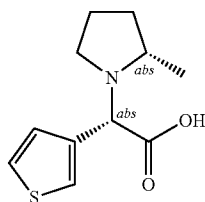
[0363] To a cooled (0-5° C.) solution of 2-(pyrrolidin-1-yl)-2-(thiophen-2-yl)acetic acid (200 mg, 0.946 mmol) in DCM (8 mL) was added DMAP (10 mg) followed by TEA (0.53 mL, 3.79 mmol) and (CH₃)₃COCl (0.14 mL, 1.14 mmol) added slowly at the same temperature. After 1 h stirring at 0° C. 5-amino-1H-indazole (145 mg, 1.09 mmol) added to the reaction mass in one lot and stirred the reaction mass at rt for 24 h. The reaction mass diluted with DCM (20 mL) washed with H₂O and dried (Na₂SO₄) and concentrated under reduced pressure to give the title compound as a brown oil. The crude product purified by Biotage SNAP 25 g silica column (0-10% MeOH in DCM) gave the title compound as a brown solid (210 mg, 68%). ¹H NMR (400 MHz, DMSO-d₆) δ ppm 12.96 (s, 1H), 10.08 (s, 1H), 8.07 (s, 1H), 7.98 (s, 1H), 7.46-7.41 (m, 3H), 7.12 (s, 1H), 6.95 (s, 1H), 4.33 (s, 1H), 1.69 (br.s, 4H), 4H merged with solvent peak; MS ESI 327 [M+H]⁺, calcd for [C₁₇H₁₈N₄OS+H]⁺ 327.1.

C. N-(3-iodo-1H-indazol-5-yl)-2-(piperidin-1-yl)-2-thiophen-3-yl)acetamide

[0364] The title compound was synthesized according to general Method B by using a solution of N-(1H-indazol-5-yl)-2-(piperidin-1-yl)-2-(thiophen-2-yl)acetamide (143 mg, 0.438 mmol) in DMF (2.14 mL) and K₂CO₃ (242 mg, 1.75 mmol) was added I₂ (122 mg, 0.481 mmol) in one portion. The reaction was stirred at rt for 24 h and then treated with 5% aq Na₂S₂O₃·5H₂O (20 mL). The product was extracted using EtOAc (25 mL) and washed with of H₂O (5 mL) followed by brine (5 mL), dried (Na₂SO₄) and concentrated under vacuum to give brown oily residue. The crude product was purified by Biotage SNAP 25 g silica column (0-80% EtOAc in hexanes) to give a yellow solid (78 mg, 39%). ¹H NMR (400 MHz, CDCl₃) δ ppm 11.06-10.88 (br.s, 1H), 9.14 (s, 1H), 7.74 (s, 1H), 7.62-7.60 (m, 1H), 7.42-7.40 (m, 1H), 7.26 (s, 1H), 7.12 (s, 1H), 6.97 (s, 1H), 4.31 (s, 1H), 2.70 (br.s, 2H), 2.62 (br.s, 2H), 1.86 (br.s, 4H); MS ESI 453.1 [M+H]⁺, calcd for [C₁₇H₁₇IN₄OS+H]⁺ 453.02

Synthesis of (S)-2-((S)-2-methylpyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide

[0365]

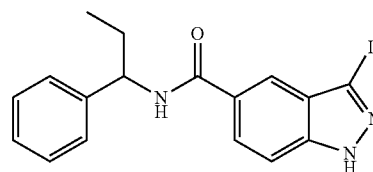


[0366] To a mixture of (S)-2-methylpyrrolidine (1.07 g, 12.6 mmol), glyoxylic acid hydrate (1.16 g, 12.6 mmol) in

DCM (50 mL) was added thiophen-3-ylboronic acid (1.59 g, 12.6 mmol). The resulting mixture was stirred for 3 h at rt. Oil formed on the sides of flask and MeOH (5 mL) was added to make a clear solution. Reaction was stirred overnight at rt. After removing all the solvents, the residue was purified by Biotage column system (gradient: MeOH/DCM 0 to 30%) to give (S)-2-((S)-2-methylpyrrolidin-1-yl)-2-(thiophen-3-yl)acetic acid as a beige solid (1.294 g, 46%). ¹H NMR (400 MHz, CD₃OD) δ 7.68 (dd, J=2.8, 1.2 Hz, 1H), 7.52 (dd, J=5.0, 3.0 Hz, 1H), 7.29 (dd, J=5.0, 0.8 Hz, 1H), 4.71 (s, 1H), 3.71-3.60 (m, 1H), 3.25-3.16 (m, 1H), 3.06-2.88 (s, br, 1H), 2.37-2.25 (m, 1H), 2.07-1.89 (m, 2H), 1.84-1.74 (m, 1H), 1.50 (pseudo s, 3H).

Synthesis of 3-iodo-N-(1-phenylpropyl)-1H-indazole-5-carboxamide

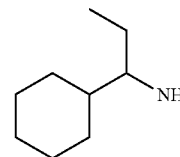
[0367]



[0368] The title compound was synthesized according to Method A utilizing 1-phenylpropan-1-amine and obtained as a yellow solid (583 mg, 72% yield). ¹H NMR (400 MHz, CDCl₃) δ=8.08 (d, J=0.8 Hz, 1H), 7.97-7.91 (m, 1H), 7.57 (d, J=8.8 Hz, 1H), 7.45-7.39 (m, 2H), 7.35 (s, 2H), 7.26 (d, J=7.3 Hz, 1H), 5.05-4.98 (m, 1H), 2.05-1.89 (m, 2H), 1.02 (t, J=7.3 Hz, 3H); MS ESI [M+H]⁺ 406.1, calcd for [C₁₇H₁₆IN₃O+H]⁺ 406.04.

Synthesis of 1-cyclohexylpropan-1-amine

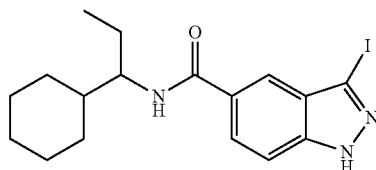
[0369]



[0370] The mixture of 1-cyclohexylpropan-1-one (1402.2 mg, 10 mmols), NH₄OAc (9249.6 mg, 120 mmols), NaC-NBH₃ (2513.6 mg, 40 mmols) in MeOH (80 mL) was refluxed overnight. The resulting reaction mixture was cooled down to rt and concentrated under reduced pressure. The residue was added 1 M NaOH (100 mL) and stirred for 20 min. The mixture was extracted with Et₂O. The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure to provide the title compound as white crystals (380 mg, 27% yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 2.55-2.41 (dt, J=8.2, 4.1 Hz, 1H), 1.81-1.46 (m, 7H), 1.33-1.08 (m, 4H), 1.08-0.96 (m, 2H), 0.93 (t, J=8.2 Hz, 3H); MS ESI [M+H]⁺ 142.1, calcd for [C₉H₁₉N+H]⁺ 142.16.

Synthesis of N-(1-cyclohexylpropyl)-3-iodo-1H-indazole-5-carboxamide

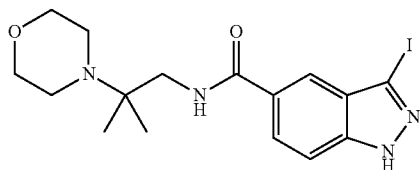
[0371]



[0372] The mixture of 1-cyclohexylpropan-1-amine (380 mg, 2.69 mmols), 3-iodo-1H-indazole-5-carboxylic acid (774.9 mg, 2.69 mmols), DIPEA (1.33 mL, 8.07 mmols) in DMF (8 mL) was cooled down to 0° C. and added TBTU (863.8 mg, 2.69 mmols). After stirring at 0° C. for 1 h, H₂O was added followed by EtOAc. The organic layer was separated and washed with H₂O for three times and then with brine followed by dried over Na₂SO₄ and concentrated under reduced pressure to provide the title compound as a light yellow solid (418 mg, 38% yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 10.65 (s, 1H), 7.92 (m, 2H), 7.54 (d, J=8.8 Hz, 1H), 5.89 (d, J=4.1 Hz, 1H), 4.02 (m, 1H), 1.86-1.67 (m, 6H), 1.56-1.44 (m, 2H), 1.31-1.06 (m, 4H), 0.99 (t, J=8.2 Hz, 3H); MS ESI [M+H]⁺ 412.3, calcd for [C₁₇H₂₂IN₃O+H]⁺ 412.09.

Synthesis of 3-iodo-N-(2-methyl-2-morpholinopropyl)-1H-indazole-5-carboxamide

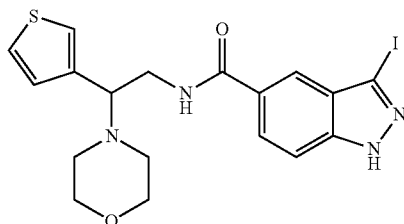
[0373]



[0374] The title compound was synthesized according to Method A utilizing 2-methyl-2-morpholinopropan-1-amine and obtained as a white solid (65 mg, 15% yield). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.02 (s, 1H), 7.93 (d, J=8.78 Hz, 1H), 7.62 (d, J=8.28 Hz, 1H), 3.72-3.78 (m, 4H), 2.70 (br. s., 4H), 1.15 (s, 6H); MS ESI [M+H]⁺ 429.0, calcd for [C₁₆H₂₁N₄O₂+H]⁺ 429.08.

Synthesis of 3-iodo-N-(2-morpholino-2-(thiophen-3-yl)ethyl)-1H-indazole-5-carboxamide

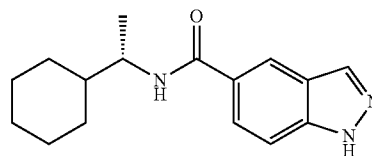
[0375]



[0376] The title compound was synthesized according to Method A utilizing 2-morpholino-2-(thiophen-3-yl)ethanamine and obtained as an off-white solid (180 mg, 37% yield). ¹H NMR (400 MHz, CD₃OD) δ ppm 7.88 (s, 1H), 7.83 (d, J=8.78 Hz, 1H), 7.56 (d, J=8.78 Hz, 1H), 7.43-7.48 (m, 1H), 7.32 (m, J=2.50 Hz, 1H), 7.15 (d, J=5.02 Hz, 1H), 3.96-4.05 (m, 2H), 3.64-3.76 (m, 5H), 2.54-2.64 (m, 2H), 2.51 (br. s., 2H); MS ESI [M+H]⁺ 483.1, calcd for [C₁₈H₁₉IN₄O₂S+H]⁺ 483.04.

Synthesis of (S)—N-(1-cyclohexylethyl)-1H-indazole-5-carboxamide

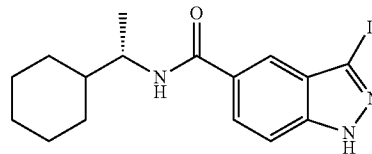
[0377]



[0378] The title compound was synthesized according to the General Method A utilizing 1H-indazole-5 carboxylic acid (500 mg, 3.1 mmol), (S)-(+)-1-cyclohexylethyl amine (349 mg, 3.1 mmol), TBTU (992 mg, 3.1 mmol), DIPEA (1.1 mL, 6.2 mmol), and DMF (15 mL) to give the title compound (off-white solid, 850 mg, 100%). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.29 (s, 1H), 8.16 (s, 1H), 7.85 (d, J=8.8 Hz, 1H), 7.59 (d, J=9.0 Hz, 1H), 3.92-4.01 (m, 1H), 1.74-1.92 (m, 4H), 1.64-1.71 (m, 1H), 1.44-1.55 (m, 1H), 1.22 (d, J=6.8 Hz, 6H), 0.99-1.13 (m, 2H); MS ESI 272.1 [M+H]⁺, calcd for [C₁₆H₂₁N₃O+H]⁺ 272.2.

Synthesis of (S)—N-(1-cyclohexylethyl)-3-iodo-1H-indazole-5-carboxamide

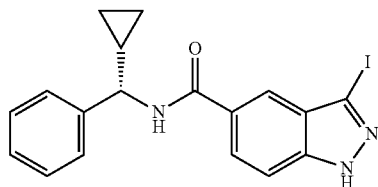
[0379]



[0380] The title compound was synthesized according to the General Method B utilizing (S)—N-(1-cyclohexylethyl)-1H-indazole-5-carboxamide (850 mg, 3.2 mmol), I₂ (1.59 g, 6.4 mmol), K₂CO₃ (1.32 g, 9.6 mmol), and DMF (15 mL) to give the title compound (light orange solid, 846 mg, 67%). ¹H NMR (400 MHz, CD₃OD) δ ppm 7.99-8.03 (m, 1H), 7.86 (d, J=8.8 Hz, 1H), 7.56 (d, J=8.0 Hz, 1H), 3.91-4.02 (m, 1H), 1.72-1.91 (m, 4H), 1.61-1.72 (m, 1H), 1.44-1.56 (m, 1H), 1.13-1.34 (m, 6H), 0.98-1.11 (m, 2H); MS ESI 398.2 [M+H]⁺, calcd for [C₁₆H₂₀IN₃O+H]⁺ 398.1.

Synthesis of (S)—N-(cyclopropyl(phenyl)methyl)-3-iodo-1H-indazole-5-carboxamide

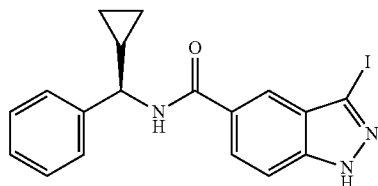
[0381]



[0382] The title compound was synthesized according to the General Method A utilizing 3-iodo-1H-indazole-5-carboxylic acid (79 mg, 0.79 mmol), (s)-cyclopropylphenylmethylamine ·HCl (50 mg, 0.27 mmol), TBTU (87 mg, 0.27 mmol), DIPEA (0.14 mL, 0.81 mmol), and DMF (4 mL) to give the title compound (orange solid, 110 mg, 98%). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.09 (s, 1H), 7.95 (dd, J=8.9, 1.6 Hz, 1H), 7.56 (d, J=8.8 Hz, 1H), 7.43-7.50 (m, 2H), 7.33 (t, J=7.6 Hz, 2H), 7.24 (t, J=7.3 Hz, 1H), 4.46 (d, J=9.5 Hz, 1H), 1.34-1.46 (m, 1H), 0.66 (d, J=8.0 Hz, 2H), 0.48 (m, 2H); MS ESI 418.1 [M+H]⁺, calcd for [C₁₈H₁₆IN₃O+H]⁺ 418.0.

Synthesis of (R)—N-(cyclopropyl(phenyl)methyl)-3-iodo-1H-indazole-5-carboxamide

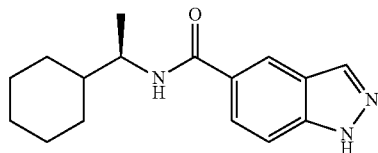
[0383]



[0384] The title compound was synthesized according to the General Method A utilizing 3-iodo-1H-indazole-5-carboxylic acid (160 mg, 0.55 mmol), (R)-cyclopropylphenylmethylamine ·HCl (100 mg, 0.55 mmol), TBTU (177 mg, 0.55 mmol), DIPEA (0.29 mL, 1.65 mmol), and DMF (8 mL) to give the title compound (orange solid, 232 mg, 100%). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.09 (s, 1H), 7.95 (dd, J=8.8, 1.51 Hz, 1H), 7.55 (d, J=8.8 Hz, 1H), 7.44-7.50 (m, 2H), 7.32 (t, J=7.5 Hz, 2H), 7.22 (t, J=7.3 Hz, 1H), 4.46 (d, J=9.5 Hz, 1H), 1.39 (br. s, 1H), 0.61-0.68 (m, 2H), 0.39-0.52 (m, 2H); MS ESI 418.1 [M+H]⁺, calcd for [C₁₈H₁₆IN₃O+H]⁺ 418.0.

Synthesis of (R)—N-(1-cyclohexylethyl)-1H-indazole-5-carboxamide

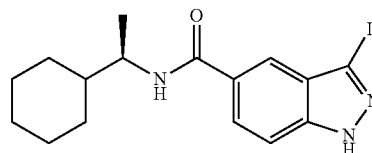
[0385]



[0386] The title compound was synthesized according to the General Method A utilizing 1H-indazole-5-carboxylic acid (500 mg, 3.1 mmol), (R)-(–)-1-cyclohexylethylamine (392 mg, 3.1 mmol), TBTU (992 mg, 3.1 mmol), DIPEA (1.1 mL, 6.2 mmol), and DMF (15 mL) to give the title compound (off-white solid, 800 mg, 96%). MS ESI 272.2 [M+H]⁺, calcd for [C₁₆H₂₁N₃O+H]⁺ 272.2.

Synthesis of (R)—N-(1-cyclohexylethyl)-3-iodo-1H-indazole-5-carboxamide

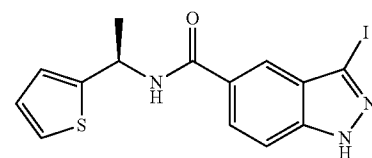
[0387]



[0388] The title compound was synthesized according to the General Method B utilizing (R)—N-(1-cyclohexylethyl)-1H-indazole-5-carboxamide (800 mg, 3.0 mmol), I₂ (1.5 g, 5.9 mmol), K₂CO₃ (1.22 g, 8.9 mmol), and DMF (15 mL) to give the title compound (pale yellow solid, 825 mg, 70%). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.02 (s, 1H), 7.91 (dd, J=8.8, 1.5 Hz, 1H), 7.56 (d, J=8.8 Hz, 1H), 3.91-4.02 (m, 1H), 1.73-1.91 (m, 4H), 1.61-1.72 (m, 1H), 1.45-1.56 (m, 1H), 1.13-1.34 (m, 6H), 0.98-1.12 (m, 2H); MS ESI 398.2 [M+H]⁺, calcd for [C₁₆H₂₀IN₃O+H]⁺ 398.1.

Synthesis of (R)-3-iodo-N-(1-(thiophen-2-yl)ethyl)-1H-indazole-5-carboxamide

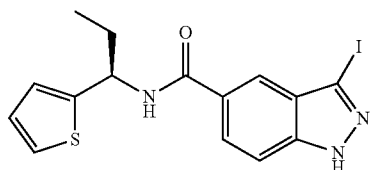
[0389]



[0390] The title compound was synthesized according to the General Method A utilizing 3-iodo-1H-indazole-5-carboxylic acid (86 mg, 0.30 mmol), (R)-1-(2-thienyl)ethylamine (50 mg, 0.30 mmol), TBTU (96 mg, 0.30 mmol), DIPEA (0.15 mL, 0.90 mmol), and DMF (5 mL). Purification by flash chromatography (SiO₂, Biotage 25 g, 5-25% MeOH in CH₂Cl₂) gave the title compound (yellow solid, 70 mg, 59%). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.06 (s, 1H), 7.94 (dd, J=8.8, 1.5 Hz, 1H), 7.56 (dd, J=8.8, 0.8 Hz, 1H), 7.27 (dd, J=5.1, 1.1 Hz, 1H), 7.05 (dt, J=3.5, 1.0 Hz, 1H), 6.96 (dd, J=5.0, 3.5 Hz, 1H), 5.57 (q, J=6.9 Hz, 1H), 1.69 (d, J=7.0 Hz, 3H); MS ESI 398.1 [M+H]⁺, calcd for [C₁₄H₁₂IN₃OS+H]⁺ 398.0.

Synthesis of (R)-3-iodo-N-(1-(thiophen-2-yl)propyl)-1H-indazole-5-carboxamide

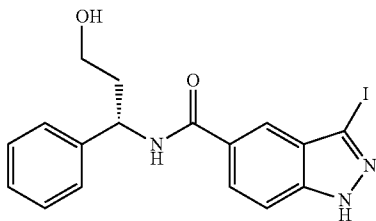
[0391]



[0392] The title compound was synthesized according to the General Method A utilizing 3-iodo-1H-indazole-5-carboxylic acid (75 mg, 0.26 mmol), (R)-1-(2-thienyl)propylamine (50 mg, 0.26 mmol), TBTU (83 mg, 0.26 mmol), DIPEA (0.14 mL, 0.78 mmol), and DMF (4 mL) to give the title compound (yellow oil, 90 mg, 84%). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.07 (dd, J=1.8, 0.8 Hz, 1H), 7.94 (dd, J=8.9, 1.6 Hz, 1H), 7.57 (dd, J=8.9, 0.6 Hz, 1H), 7.27 (dd, J=5.1, 1.1 Hz, 1H), 7.06 (dt, J=2.4, 1.1 Hz, 1H), 6.97 (dd, J=5.3, 3.5 Hz, 1H), 5.34 (t, J=7.5 Hz, 1H), 2.01-2.12 (m, 2H), 1.05 (t, J=7.3 Hz, 3H); MS ESI 412.0 [M+H]⁺, calcd for [C₁₅H₁₄IN₃OS+H]⁺ 412.0.

Synthesis of (S)-N-(3-hydroxy-1-phenylpropyl)-3-iodo-1H-indazole-5-carboxamide

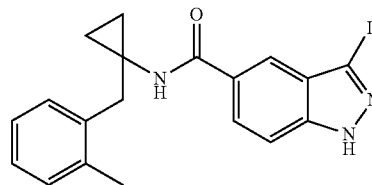
[0393]



[0394] The title compound was synthesized according to the General Method A utilizing 3-iodo-1H-indazole-5-carboxylic acid (288 mg, 1 mmol), (S)-3-phenyl-beta-alaninol (151 mg, 1 mmol), TBTU (321 mg, 1 mmol), DIPEA (0.52 mL, 3 mmol), and DMF (15 mL). Purification by flash chromatography (SiO₂, Biotage 25 g, 0-25% MeOH in CH₂Cl₂) gave the title compound (white solid, 203 mg, 48%). ¹H NMR (400 MHz, DMSO-d₆) δ ppm 13.70 (s, 1H), 8.93 (d, J=8.0 Hz, 1H), 8.07 (s, 1H), 7.94 (d, J=8.3 Hz, 1H), 7.59 (d, J=8.5 Hz, 1H), 7.40 (d, J=7.5 Hz, 2H), 7.33 (t, J=7.5 Hz, 2H), 7.22 (t, J=7.0 Hz, 1H), 5.15-5.23 (m, 1H), 4.56-4.61 (m, 1H), 3.39-3.52 (m, 2H), 2.02-2.14 (m, 1H), 1.86-1.98 (m, 1H), 1.19-1.29 (m, 1H); MS ESI 422.1 [M+H]⁺, calcd for [C₁₇H₁₆IN₃O₂+H]⁺ 422.0.

Synthesis of 3-iodo-N-(1-(2-methylbenzyl)cyclopropyl)-1H-indazole-5-carboxamide

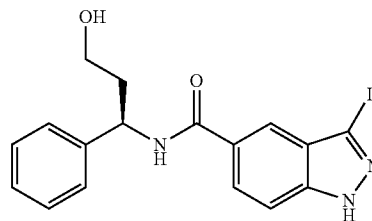
[0395]



[0396] The title compound was synthesized according to the General Method A utilizing 3-iodo-1H-indazole-5-carboxylic acid (288 mg, 1 mmol), 1-(2-methylbenzyl)cyclopropylamine ·HCl (197 mg, 1 mmol), TBTU (321 mg, 1 mmol), DIPEA (0.52 mL, 3 mmol), and DMF (15 mL). Purification by flash chromatography (SiO₂, Biotage 25 g, 0-25% MeOH in CH₂Cl₂) gave the title compound (off-white solid, 193 mg, 45%); MS ESI 432.1 [M+H]⁺, calcd for [C₁₉H₁₈IN₃O+H]⁺ 432.1.

Synthesis of (R)-N-(3-hydroxy-1-phenylpropyl)-3-iodo-1H-indazole-5-carboxamide

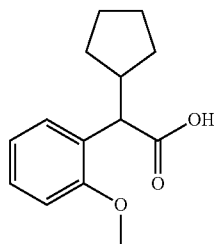
[0397]



[0398] The title compound was synthesized according to the General Method A utilizing 3-iodo-1H-indazole-5-carboxylic acid (288 mg, 1 mmol), (R)-3-phenyl-beta-alaninol (151 mg, 1 mmol), TBTU (321 mg, 1 mmol), DIPEA (0.52 mL, 3 mmol), and DMF (15 mL). Purification by flash chromatography (SiO₂, Biotage 25 g, 0-25% MeOH in CH₂Cl₂) gave the title compound (white solid, 247 mg, 59%). ¹H NMR (400 MHz, DMSO-d₆) δ ppm 13.70 (s, 1H), 8.93 (d, J=8.3 Hz, 1H), 8.06 (s, 1H), 7.94 (d, J=9.0 Hz, 1H), 7.59 (d, J=8.5 Hz, 1H), 7.40 (d, J=7.5 Hz, 2H), 7.33 (t, J=7.5 Hz, 2H), 7.22 (t, J=7.5 Hz, 1H), 5.15-5.24 (m, 1H), 4.59 (br. s., 1H), 3.45 (br. s., 2H), 2.02-2.15 (m, 1H), 1.86-1.98 (m, 1H), 1.22-1.29 (m, 1H); MS ESI 422.1 [M+H]⁺, calcd for [C₁₇H₁₆IN₃O₂+H]⁺ 422.0.

Synthesis of
2-cyclopentyl-2-(2-methoxyphenyl)acetic acid

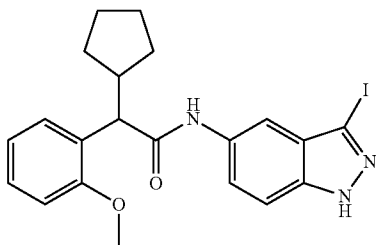
[0399]



[0400] Methyl 2-(2-methoxyphenyl)acetate (900 mg, 5 mmol) and 60% NaH (240 mg, 6 mmol) were dissolved in DMF (25 mL) and cooled to 0° C. Cyclopentyl bromide (745 mg, 5 mmol) was added and the reaction was gradually warmed to RT. The reaction was stirred at RT for 16 h and then partitioned between EtOAc (100 mL) and NaHCO₃ (150 mL). The mixture was washed with brine (150 mL), dried over MgSO₄ and the solvent was removed under reduced pressure. Saponification was conducted by addition of 2 M NaOH (20 mL) and heating at 60° C. for 16 h. The mixture was then acidified with 2 M HCl and then extracted with EtOAc. The solution was dried over MgSO₄ and concentrated to give the title compound (yellow solid, 760 mg, 65%). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.39 (dd, J=7.6, 1.6 Hz, 1H), 7.24 (td, J=7.8, 1.3 Hz, 1H), 6.95 (m, 1H), 6.89 (d, J=8.3 Hz, 1H), 3.94 (d, J=11.0 Hz, 1H), 3.84 (s, 3H), 2.48-2.60 (m, 1H), 1.93-2.04 (m, 1H), 1.51-1.76 (m, 3H), 1.39-1.51 (m, 2H), 1.32-1.39 (m, 1H), 0.97-1.07 (m, 1H); MS ESI 235.1 [M+H]⁺, calcd for [C₁₄H₁₈O₃+H]⁺ 235.1.

Synthesis of 2-cyclopentyl-N-(3-iodo-1H-indazol-5-yl)-2-(2-methoxyphenyl)acetamide

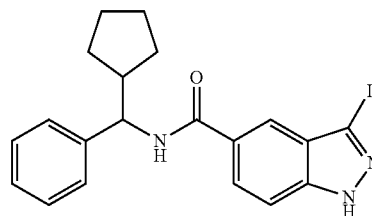
[0401]



[0402] The title compound was synthesized according to the General Method A utilizing 3-iodo-1H-indazol-5-amine (221 mg, 0.85 mmol), 2-cyclopentyl-2-(2-methoxyphenyl)acetic acid (200 mg, 0.85 mmol), TBTU (273 mg, 0.85 mmol), DIPEA (0.44 mL, 2.55 mmol), and DMF (10 mL). Purification by flash chromatography (SiO₂, Biotage 25 g, 0-25% MeOH in CH₂Cl₂) gave the title compound (orange solid, 81 mg, 20%). MS ESI 476.2 [M+H]⁺, calcd for [C₂₁H₂₂IN₃O₂+H]⁺ 476.1.

Synthesis of N-(cyclopentyl(phenyl)methyl)-3-iodo-1H-indazole-5-carboxamide

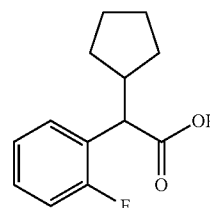
[0403]



[0404] The title compound was synthesized according to the General Method A utilizing 3-iodo-1H-indazole-5-carboxylic acid (288 mg, 1 mmol), cyclopentyl(phenyl)methanamine (204 mg, 1 mmol), TBTU (321 mg, 1 mmol), DIPEA (0.52 mL, 3 mmol), and DMF (7 mL) to give the title compound (yellow solid, 445 mg, 97%). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.03 (s, 1H), 7.90 (dd, J=8.7, 1.6 Hz, 1H), 7.56 (d, J=8.8 Hz, 1H), 7.44 (d, J=7.3 Hz, 2H), 7.33 (t, J=7.5 Hz, 2H), 7.24 (t, J=7.5 Hz, 1H), 4.83 (d, J=11.0 Hz, 1H), 2.48-2.61 (m, 1H), 1.95-2.07 (m, 1H), 1.35-1.79 (m, 6H), 1.14-1.26 (m, 1H).

Synthesis of 2-cyclopentyl-2-(2-fluorophenyl)acetic acid

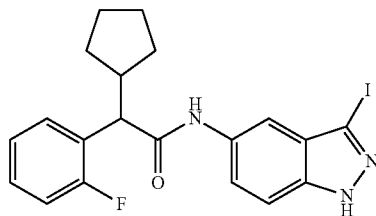
[0405]



[0406] Ethyl (2-fluorophenyl)acetate (900 mg, 5 mmol) and 60% NaH (240 mg, 6 mmol) were dissolved in DMF (25 mL) and cooled to 0° C. Cyclopentyl bromide (745 mg, 5 mmol) was added and the reaction was gradually warmed to RT. Reaction was stirred at RT for 16 h and then partitioned between EtOAc (100 mL) and NaHCO₃ (150 mL). The reaction was washed with brine (150 mL), dried over MgSO₄ and solvent was removed under reduced pressure. Saponification was conducted by addition of 2 M NaOH (20 mL) and heating at 60° C. for 16 h. The mixture was then acidified with 2 M HCl and then extracted with EtOAc. The solution was dried over MgSO₄ and concentrated to give the title compound (yellow solid, 800 mg, 72%). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.46 (t, J=6.6 Hz, 1H), 7.20-7.26 (m, 1H), 7.12 (t, J=7.5 Hz, 1H), 7.05 (t, J=9.2 Hz, 1H), 3.78 (d, J=11.0 Hz, 1H), 2.47-2.60 (m, 1H), 1.93-2.04 (m, 1H), 1.54-1.75 (m, 3H), 1.41-1.54 (m, 2H), 1.29-1.41 (m, 1H), 0.98-1.12 (m, 1H).

Synthesis of 2-cyclopentyl-2-(2-fluorophenyl)-N-(3-iodo-1H-indazol-5-yl)acetamide

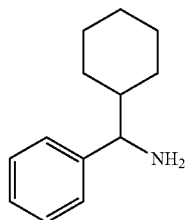
[0407]



[0408] The title compound was synthesized according to the General Method A utilizing 3-iodo-1H-indazol-5-amine (518 mg, 2 mmol), 2-cyclopentyl-2-(2-fluorophenyl)acetic acid (444 mg, 2 mmol), TBTU (642 mg, 2 mmol), DIPEA (1 mL, 6 mmol), and DMF (10 mL). Purification by flash chromatography (SiO₂, Biotage 25 g, 0-25% MeOH in CH₂Cl₂) gave the title compound (yellow oil, 217 mg, 23%). Some di-acetate by product was also collected as a yellow solid (201 mg, 15%). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.08 (d, J=9.0 Hz, 1H), 7.54 (td, J=7.5, 1.6 Hz, 1H), 7.20-7.27 (m, 1H), 7.01-7.14 (m, 3H), 6.66 (d, J=2.3 Hz, 1H), 5.24 (d, J=11.3 Hz, 1H), 2.68-2.82 (m, 1H), 1.87-2.00 (m, 1H), 1.59-1.78 (m, 3H), 1.43-1.59 (m, 2H), 1.20-1.36 (m, 2H).

Synthesis of cyclohexyl(phenyl)methanamine

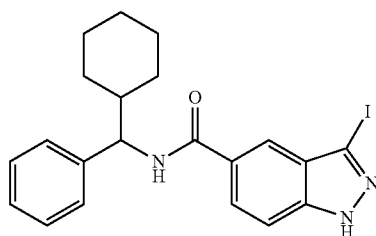
[0409]



[0410] The title compound was synthesized according to the General Method G, utilizing cyclohexylphenyl ketone (1.5 g, 8.0 mmol), NH₄OAc (7.4 g, 96 mmol), NaCNBH₃ (2 g, 32 mmol), and MeOH (30 mL) to give the title compound (clear oil, 1.41 g, 93%). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.27-7.39 (m, 3H), 7.23 (d, J=7.3 Hz, 2H), 4.24 (br. s., 2H), 3.58 (d, J=8.3 Hz, 1H), 1.83-1.98 (m, 1H), 1.72-1.83 (m, 1H), 1.63 (br. d, J=8.5 Hz, 3H), 1.19-1.38 (m, 2H), 1.11 (d, J=8.5 Hz, 2H), 0.91-1.05 (m, 1H), 0.71-0.87 (m, 1H).

Synthesis of N-(cyclohexyl(phenyl)methyl)-3-iodo-1H-indazole-5-carboxamide

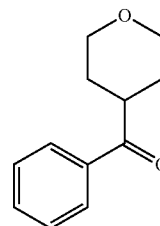
[0411]



[0412] The title compound was synthesized according to the General Method A utilizing 3-iodo-1H-indazole-5-carboxylic acid (576 mg, 2 mmol), cyclohexyl(phenyl)methanamine (378 mg, 2 mmol), TBTU (642 mg, 2 mmol), DIPEA (1 mL, 6 mmol), and DMF (6 mL) to give the title compound (yellow solid, 917 mg, 100%). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.03 (s, 1H), 7.90 (d, J=8.8 Hz, 1H), 7.55 (d, J=9.0 Hz, 1H), 7.40 (d, J=7.3 Hz, 2H), 7.33 (s, 3H), 4.79 (d, J=10.0 Hz, 1H), 2.04-2.16 (m, 1H), 1.59-2.01 (m, 4H), 1.12-1.41 (m, 6H), 0.86-1.02 (m, 1H).

Synthesis of phenyl(tetrahydro-2H-pyran-4-yl)methanone

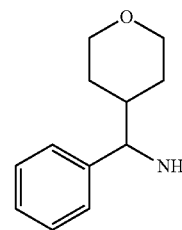
[0413]



[0414] SOCl₂ (8 mL) was added to tetrahydro-2H-pyran-4-carboxylic acid (3.0 g, 23.1 mmol) and the resulting mixture was heated at 85° C. (oil temp.) for 1 h and cooled to rt. Removal of volatile materials gave crude acid chloride as pale yellow liquid. It was diluted with benzene (12 mL) and added slowly to a suspension of AlCl₃ (5.84 g, 43.8 mmol) in benzene (12 mL). After addition, the resulting mixture was heated at 75° C. for 1 h, cooled to rt, poured onto ice/H₂O, extracted with DCM and purified by flash chromatography (EtOAc/hex 20%) to give phenyl(tetrahydro-2H-pyran-4-yl)methanone (light yellow solid, 3.154 g, 72%). ¹H NMR (400 MHz, CDCl₃) δ 7.64 (d, J=7.6 Hz, 2H), 7.58 (t, J=7.4 Hz, 1H), 7.49 (t, J=7.6 Hz, 2H), 4.07 (tt, J=11.6 Hz, 2.8 Hz, 2H), 3.58 (dt, J=11.6 Hz, 2.5 Hz, 2H), 3.54-3.48 (m, 1H), 1.96-1.84 (m, 2H), 1.83-1.77 (m, 2H).

Synthesis of phenyl(tetrahydro-2H-pyran-4-yl)methanamine

[0415]

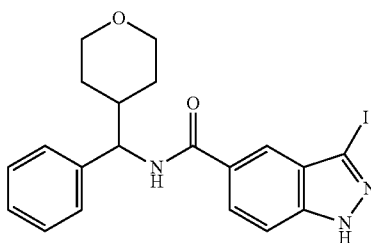


[0416] A mixture of phenyl(tetrahydro-2H-pyran-4-yl)methanone (950 mg, 5 mmol), NH₄OAc (4.62 g, 60 mmol) and NaCNBH₃ (1.26 g, 20 mmol) in MeOH (30 mL) was heated O/N at 60° C. It was diluted with H₂O, extracted with DCM and purified by flash chromatography (MeOH/DCM 0-20%) to give phenyl(tetrahydro-2H-pyran-4-yl)metha-

namine (white solid, 262 mg, 42%). ^1H NMR (400 MHz, CD_3OD) δ 7.42-7.28 (m, 5H), 3.98 (dd, $J=11.2$ Hz, 3.6 Hz, 1H), 3.81 (dd, $J=11.6$ Hz, 2.8 Hz, 1H), 3.68 (d, $J=8.8$ Hz, 1H), 3.42 (dt, $J=12.0$ Hz, 2.0 Hz, 1H), 3.26 (dt, $J=11.6$ Hz, 2.8 Hz, 1H), 1.96-1.85 (m, 2H), 1.46-1.34 (m, 1H), 1.26-1.10 (m, 2H); MS ESI 175.0 $[\text{M}+\text{H}]^+$, calcd for $[\text{C}_{12}\text{H}_{17}\text{NO}-\text{NH}_3+\text{H}]^+$ 175.1.

Synthesis of 3-iodo-N-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1H-indazole-5-carboxamide

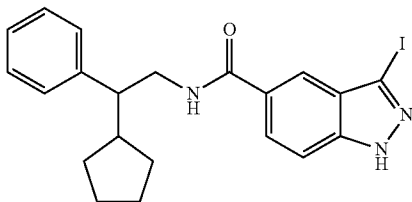
[0417]



[0418] To a solution of phenyl(tetrahydro-2H-pyran-4-yl)methanamine (262 mg, 1.37 mmol), 3-iodo-1H-indazole-5-carboxamide (395 mg, 1.37 mmol) in DMF (5 mL) at 0°C . was added TBTU (440 mg, 1.37 mmol), followed by $^i\text{Pr}_2\text{NEt}$ (0.48 mL, 2.74 mmol). The resulting mixture was stirred at 0°C . for 30 min, quenched with H_2O and stirred for 10 min at rt. Suction filtration gave crude 3-iodo-N-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1H-indazole-5-carboxamide (off white solid, 589 mg). MS ESI 462.1 $[\text{M}+\text{H}]^+$, calcd for $[\text{C}_{20}\text{H}_{21}\text{N}_3\text{O}+\text{H}]^+$ 462.1.

Synthesis of N-(2-cyclopentyl-2-phenylethyl)-3-iodo-1H-indazole-5-carboxamide

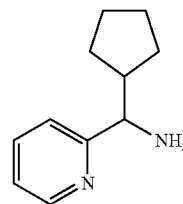
[0419]



The title compound was synthesized according to the General Method A utilizing 3-iodo-1H-indazole-5-carboxylic acid (500 mg, 1.74 mmol), 2-cyclopentyl-2-phenylethanamine (329 mg, 1.74 mmol), TBTU (559 mg, 1.74 mmol), DIPEA (0.90 mL, 5.21 mmol), and DMF (6 mL) to give the title compound (yellow solid, 602 mg, 75%). ^1H NMR (400 MHz, CD_3OD) δ ppm 7.65-7.70 (m, 2H), 7.49 (d, $J=9.0$ Hz, 1H), 7.17-7.34 (m, 5H), 3.80-3.91 (m, 1H), 3.45-3.56 (m, 1H), 2.80-2.85 (m, 1H), 2.12-2.23 (m, 1H), 2.00-2.12 (m, 1H), 1.38-1.77 (m, 6H), 0.99-1.11 (m, 1H); MS ESI 460.2 $[\text{M}+\text{H}]^+$, calcd for $[\text{C}_{21}\text{H}_{22}\text{N}_3\text{O}+\text{H}]^+$ 460.1.

Synthesis of cyclopentyl(pyridin-2-yl)methanamine

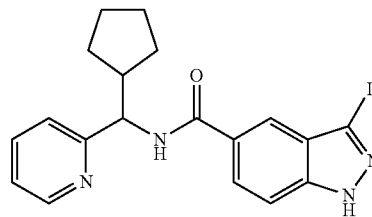
[0420]



[0421] The title compound was synthesized according to the General Method G, utilizing cyclopentyl-2-pyridyl ketone (1 g, 5.7 mmol), NH_4OAc (5.3 g, 69 mmol), NaC-NBH_3 (1.4 g, 23 mmol), and MeOH (20 mL) to give the title compound (clear oil, 931 g, 93%). ^1H NMR (400 MHz, CD_3OD) δ ppm 8.50 (d, $J=4.0$ Hz, 1H), 7.80 (t, $J=7.9$ Hz, 1H), 7.41 (d, $J=8.0$ Hz, 1H), 7.31 (t, $J=5.0$ Hz, 1H), 3.76 (d, $J=8.8$ Hz, 1H), 2.14-2.27 (m, 1H), 1.88-1.99 (m, 1H), 1.36-1.75 (m, 5H), 1.25-1.35 (m, 1H), 1.12-1.24 (m, 1H).

Synthesis of N-(cyclopentyl(pyridin-2-yl)methyl)-3-iodo-1H-indazole-5-carboxamide

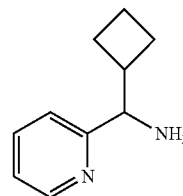
[0422]



[0423] The title compound was synthesized according to the General Method A utilizing 3-iodo-1H-indazole-5-carboxylic acid (1.52 g, 5.28 mmol), cyclopentyl(pyridin-2-yl)methanamine (930 mg, 5.28 mmol), TBTU (1.69 mg, 5.28 mmol), DIPEA (2.75 mL, 15.8 mmol), and DMF (10 mL) to give the title compound (pale yellow solid, 1.76 g, 75%). ^1H NMR (400 MHz, CD_3OD) δ ppm 8.50-8.57 (m, 1H), 8.07 (s, 1H), 7.93 (d, $J=9.3$ Hz, 1H), 7.82 (t, $J=7.4$ Hz, 1H), 7.57 (d, $J=8.8$ Hz, 1H), 7.51 (d, $J=7.5$ Hz, 1H), 7.32 (dd, $J=6.6$, 5.4 Hz, 1H), 5.01 (d, $J=9.8$ Hz, 1H), 2.48-2.62 (m, 1H), 1.94-2.05 (m, 1H), 1.48-1.78 (m, 5H), 1.23-1.42 (m, 2H); MS ESI 447.1 $[\text{M}+\text{H}]^+$, calcd for $[\text{C}_{19}\text{H}_{19}\text{IN}_4\text{O}+\text{H}]^+$ 447.1.

Synthesis of cyclobutyl(pyridin-2-yl)methanamine

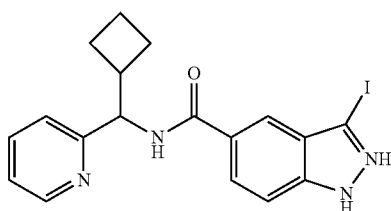
[0424]



[0425] The title compound was synthesized according to the General Method G, utilizing cyclobutyl-2-pyridyl ketone (1 g, 6.2 mmol), NH_4OAc (5.8 g, 74 mmol), NaCNBH_3 (1.6 g, 25 mmol), and MeOH (20 mL) to give the title compound (clear oil, 991 mg, 98%). ^1H NMR (400 MHz, CD_3OD) δ ppm 8.49 (d, $J=4.3$ Hz, 1H), 7.78 (td, $J=7.6, 1.8$ Hz, 1H), 7.39 (d, $J=7.8$ Hz, 1H), 7.26-7.32 (m, 1H), 3.88 (d, $J=9.3$ Hz, 1H), 2.55-2.65 (m, 1H), 2.09-2.20 (m, 1H), 1.64-2.01 (m, 6H).

Synthesis of N-(cyclobutyl(pyridin-2-yl)methyl)-3-iodo-1H-indazole-5-carboxamide

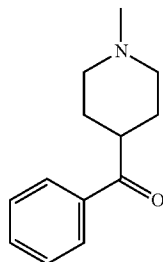
[0426]



[0427] The title compound was synthesized according to the General Method A utilizing 3-iodo-1H-indazole-5-carboxylic acid (1.76 g, 6.1 mmol), cyclobutyl(pyridin-2-yl)methanamine (990 mg, 6.1 mmol), TBTU (1.96 mg, 6.1 mmol), DIPEA (3.2 mL, 18 mmol), and DMF (10 mL) to give the title compound (pale yellow solid, 1.83 g, 69%). ^1H NMR (400 MHz, CD_3OD) δ ppm 8.51 (d, $J=4.8$ Hz, 1H), 8.08 (s, 1H), 7.94 (dd, $J=8.7, 0.9$ Hz, 1H), 7.80 (td, $J=7.6, 1.4$ Hz, 2H), 7.57 (d, $J=8.8$ Hz, 1H), 7.48 (d, $J=8.0$ Hz, 1H), 7.27-7.32 (m, 1H), 5.19 (d, $J=10.3$ Hz, 1H), 2.86-2.97 (m, 1H), 2.16-2.26 (m, 1H), 1.77-2.05 (m, 5H); MS ESI 433.1 $[\text{M}+\text{H}]^+$, calcd for $[\text{C}_{18}\text{H}_{17}\text{IN}_4\text{O}+\text{H}]^+$ 433.0.

Synthesis of
(1-methylpiperidin-4-yl)(phenyl)methanone

[0428]

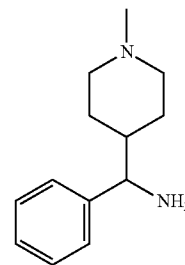


[0429] In a microwave vial, 4-benzylpiperidine $\cdot\text{HCl}$ (650 mg, 2.89 mmol) was dissolved in formic acid (3 mL) and formalin (937 μL , 11.6 mmol) was added. The vial was sealed and placed in microwave reactor and heated at 150°C . for 5 min. LC-MS was checked and then concentrated. The residue was partitioned between EtOAc (20 mL) and 0.5 M NaOH (30 mL), washed with brine and then dried using MgSO_4 and under reduced pressure to give the title compound (clear oil, 520 mg, 89%). ^1H NMR (400 MHz, CD_3OD) δ ppm 7.97-8.06 (m, 2H), 7.65 (t, $J=7.5$ Hz, 1H), 7.54 (t, $J=7.3$ Hz, 2H),

3.69-3.81 (m, 1H), 3.61 (d, $J=11.5$ Hz, 2H), 3.18 (t, $J=13.6$ Hz, 2H), 2.92 (s, 3H), 2.16 (d, $J=14.8$ Hz, 2H), 1.92 (q, $J=13.6$ Hz, 2H).

Synthesis of
(1-methylpiperidin-4-yl)(phenyl)methanamine

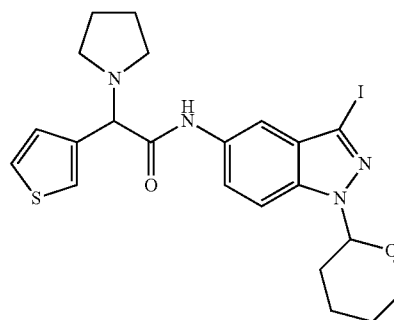
[0430]



[0431] Using Method G, (1-methylpiperidin-4-yl)(phenyl)methanone (520 mg, 2.56 mmol), MeOH (15 mL), NH_4OAc (2.37 g, 30 mmol), and NaCNBH_3 (645 mg, 10.2 mmol) gave the title compound (clear oil, 503 mg, 96%). MS ESI $[\text{M}+\text{H}]^+$ 205.1, calcd for $[\text{C}_{13}\text{H}_{20}\text{N}_2+\text{H}]^+$ 205.2.

Synthesis of N-(3-iodo-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide

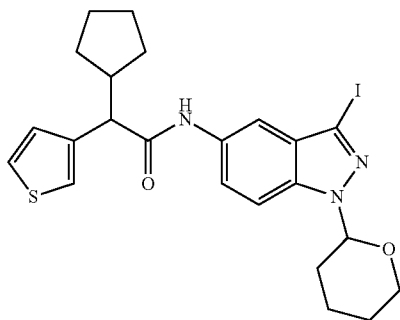
[0432]



[0433] The title compound was synthesized according to the Method A utilizing 3-iodo-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-amine (686 mg, 2 mmol), 2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetic acid (422 mg, 2 mmol), TBTU (642 mg, 2 mmol), DIPEA (1 mL, 6 mmol), and DMF (10 mL). Purification by flash chromatography (SiO_2 , Biotage 25 g, 0-30% MeOH in CH_2Cl_2) gave the title compound (yellow solid, 921 mg, 86%). ^1H NMR (400 MHz, CD_3OD) δ ppm 7.83 (s, 1H), 7.62 (d, $J=8.8$ Hz, 1H), 7.56 (d, $J=8.5$ Hz, 1H), 7.50 (br. s, 1H), 7.38-7.45 (m, 1H), 7.30-7.36 (m, 1H), 5.76 (d, $J=7.3$ Hz, 1H), 4.11 (s, 1H), 3.92-4.00 (m, 1H), 3.72-3.82 (m, 1H), 2.62-2.71 (m, 2H), 2.38-2.55 (m, 3H), 2.06-2.16 (m, 1H), 1.95-2.05 (m, 1H), 1.56-1.90 (m, 7H), 1.24-1.35 (m, 1H); MS ESI 537.2 $[\text{M}+\text{H}]^+$, calcd for $[\text{C}_{22}\text{H}_{25}\text{N}_4\text{O}_2\text{S}+\text{H}]^+$ 537.1.

Synthesis of 2-cyclopentyl-N-(3-iodo-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-yl)-2-(thiophen-3-yl)acetamide

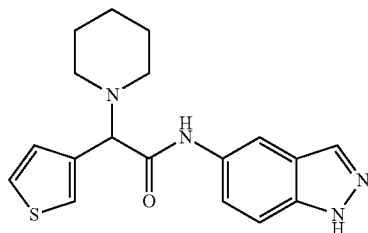
[0434]



[0435] The title compound was synthesized according to the General Method A utilizing 3-iodo-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-amine (172 mg, 0.5 mmol), 2-(cyclopentyl)-2-(thiophen-3-yl)acetic acid (105 mg, 0.5 mmol), TBTU (160 mg, 0.5 mmol), DIPEA (0.26 mL, 1.5 mmol), and DMF (10 mL). Purification by flash chromatography (SiO₂, Biotage 25 g, 0-30% MeOH in CH₂Cl₂) gave the title compound (white solid, 260 mg, 97%). ¹H NMR (400 MHz, CD₃OD) δ ppm 7.98 (s, 1H), 7.84 (s, 1H), 7.61 (d, J=9.0 Hz, 1H), 7.49-7.54 (m, 1H), 7.34-7.39 (m, 1H), 7.28-7.31 (m, 1H), 7.21 (d, J=5.0 Hz, 1H), 5.73-5.78 (m, 1H), 3.93-4.00 (m, 1H), 3.74-3.82 (m, 1H), 3.54 (d, J=11.0 Hz, 1H), 2.61-2.70 (m, 1H), 2.39-2.51 (m, 1H), 2.07-2.15 (m, 1H), 1.88-2.05 (m, 2H), 1.77-1.86 (m, 1H), 1.60-1.77 (m, 5H), 1.50-1.59 (m, 2H), 1.30-1.41 (m, 1H), 1.09-1.22 (m, 1H).

Synthesis of N-(1H-indazol-5-yl)-2-(piperidin-1-yl)-2-(thiophen-3-yl)acetamide

[0436]



A. 2-(Piperidin-1-yl)-2-(thiophen-3-yl)acetic acid

[0437] The title compound was synthesized according to general Method D by using glyoxylic acid monohydrate (1.8 g, 19 mmol) and piperidine (1.93 mL, 19 mmol) in CH₂Cl₂ (75 mL) and sonicating for 15 min. Thiophene-3-boronic acid (2.5 g, 19 mmol) was added and the mixture was stirred at rt for 24 h. Purification by Biotage (50 g SiO₂, 0-30% MeOH in DCM) gave the title compound (cream solid, 3.4 g, 77%). ¹H NMR (400 MHz, CD₃OD) δ 7.58 (s, 1H), 7.33 (s, 2H), 4.70 (s, 1H), 3.71-3.63 (br.m, 2H), 3.17 (br.s, 2H), 1.94-1.93 (br.m,

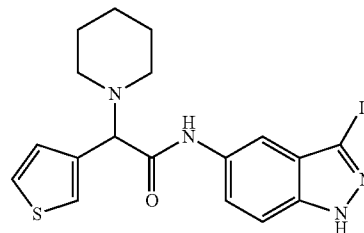
2H), 1.83-1.80 (br.m, 2H), 1.55-1.53 (br.s, 2H); MS ESI 226.1 [M+H]⁺, calcd for [C₁₁H₁₅NO₂S+H]⁺ 226.1.

B. N-(1H-indazol-5-yl)-2-(piperidin-1-yl)-2-(thiophen-3-yl)acetamide

[0438] (CH₃)₃COCl (1.82 mL, 0.014 mol) was added slowly to a cooled (0-5° C.) solution of 2-(piperidin-1-yl)-2-(thiophen-3-yl)acetic acid (3.0 g, 13 mmol), DMAP (81 mg) and TEA (7.5 mL, 53 mmol) in DCM (150 mL). After 1 h stirring at 0° C. 5-amino-1H-indazole (1.95 g, 14 mmol) added and the mixture was stirred at rt for 24 h. The reaction mixture was washed with H₂O, dried (Na₂SO₄) and concentrated under vacuum. The crude product was heated in 1:1 hexane-isopropyl alcohol (40 mL) at 75° C. for 30 min and the product filtered at rt to give the first crop of title compound (off white solid, 2.65 g). The filtrate concentrated under reduced pressure and purified by flash chromatography (SiO₂, 0-15% MeOH in DCM) to give the second crop (360 mg, combined yield 3.01 g, 66%). ¹H NMR (400 MHz, CDCl₃) δ ppm 10.1 (br.s., 1H), 8.51 (br. s., 1H), 9.57 (s, 1H), 8.14 (s, 1H), 8.04 (d, J=0.8 Hz, 1H), 7.51-7.45 (m, 2H), 7.32-7.31 (m, 1H), 7.06 (dd, J=5.2 Hz, J=1.2 Hz, 1H), 4.22 (s, 1H), 2.49-2.40 (br.m, 4H), 1.67-1.61 (br.m, 6H); MS ESI 341.1 [M+H]⁺, calcd for [C₁₈H₂₀N₄OS+H]⁺ 341.4.

Synthesis of N-(3-iodo-1H-indazol-5-yl)-2-(piperidin-1-yl)-2-(thiophen-3-yl)acetamide

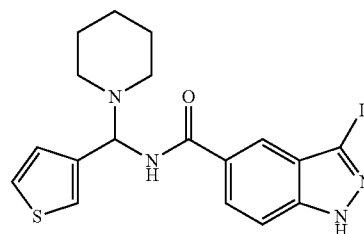
[0439]



[0440] The title compound was synthesized according to general Method B from N-(1H-indazol-5-yl)-2-(piperidin-1-yl)-2-(thiophen-3-yl)acetamide (3.0 g, 8.8 mmol), K₂CO₃ (4.87 g, 8.8 mmol) and 12 (2.45 g, 9.6 mmol) in DMF (24 mL). The reaction was stirred at rt for 24 h and then treated with 5% aq. Na₂S₂O₃·5H₂O (200 mL). The solid was filtered and washed with H₂O (4x25 mL) to give crude brown solid. The crude product was purified by flash chromatography (SiO₂, 0-80% EtOAc in Hexane) to give the title compound (pale yellow solid, 1.8 g, 44%). ¹H NMR (400 MHz, CDCl₃) δ ppm 10.4 (s, 1H), 9.62 (s, 1H), 7.83 (d, J=1.2 Hz, 1H), 7.62 (dd, J=8.8 Hz, J=3.2 Hz, 1H), 7.44 (d, J=8.8 Hz, 1H), 7.34-7.32 (m, 1H), 7.07 (d, J=4 Hz, 1H), 4.25 (s, 1H), 2.49 (br.m, 4H), 1.69 (br.m, 4H), 1.48 (br.s., 2H); MS ESI 467.1 [M+H]⁺, calcd for [C₁₈H₁₉IN₄OS+H]⁺ 467.

Synthesis of N-(cyclopentyl(thiophen-3-yl)methyl)-3-iodo-1H-indazole-5-carboxamide

[0441]



A. cyclopentyl(thiophen-3-yl)methanamine

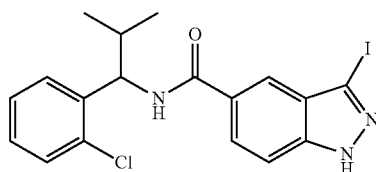
[0442] The title compound was prepared using Method G from cyclopentyl-3-thienyl ketone (3.5 g, 19.4 mmol) at 60° C. for 24 h. Evaporation of MeOH and addition of 2 M NaOH (50 mL), extraction using EtOAc (2×100 mL), and purification by flash chromatography (SiO₂, 0-20% MeOH in DCM) gave the title compound (colorless oil, 3.25 g, 92.5%). ¹H NMR (400 MHz, DMSO-d₆) δ ppm 7.44-7.42 (m, 1H), 7.27 (t, J=2 Hz, 1H), 7.412-7.10 (m, 1H), 3.74 (t, J=8.4 Hz, 1H), 2.09-1.99 (m, 1H), 1.76-1.68 (m, 1H), 1.58-1.29 (m, 6H), 1.16-1.14 (m, 1H).

B. N-(cyclopentyl(thiophen-3-yl)methyl)-3-iodo-1H-indazole-5-carboxamide

[0443] The title compound was prepared using Method A by from cyclopentyl(thiophen-3-yl)methanamine (3.25 g, 17.9 mmol), 3-iodo-1H-indazol-5-carboxylic acid (5.16 g, 17.9 mmol), DIPEA (12.49 mL, 71.6 mmol) and TBTU (5.74 g, 17.9 mmol) in DMF (49 mL) at 20° C. for 4 h. The mixture was poured into H₂O (1.3 L) and the solid was collected by filtration and washed with H₂O to provide the title compound (cream color solid, 7.95 g, 98%). ¹H NMR (400 MHz, DMSO-d₆) δ ppm 13.72 (br.s, 1H), 8.86 (t, J=8.8 Hz, 1H), 7.92-7.9 (m, 1H), 7.58 (t, J=8.8 Hz, 1H), 7.46-7.44 (m, 1H), 7.39-7.38 (m, 1H), 7.22 (d, J=4.8 Hz, 1H), 4.98 (t, J=9.6 Hz, 1H), 1.81-1.78 (m, 1H), 1.61-1.32 (m, 7H), 1.2-1.17 (m, 1H); MS ESI 452 [M+H]⁺, calcd for [C₁₈H₁₈IN₃OS+H]⁺ 452.

Synthesis of N-(1-(2-chlorophenyl)-2-methylpropyl)-3-iodo-1H-indazole-5-carboxamide

[0444]



A. 1-(2-chlorophenyl)-2-methylpropan-1-ol

[0445] A solution of 2-chlorobenzaldehyde (2.75 g) in Et₂O (30 mL) was slowly added to a solution of isopropyl magnesium bromide (obtained from 0.98 g of magnesium and 4.85 g 2-bromopropane in 70 mL anhydrous Et₂O) at 0° C. The reaction mixture was stirred for 1 h at 0° C., and then quenched with aq. 25% NH₄Cl (100 mL). The organic layer was separated and the aq. layer was extracted with EtOAc (50 mL). The combined organic layer was washed with H₂O and brine, dried (Na₂SO₄) and concentrated under vacuum. Purification by flash chromatography (SiO₂, 0-25% EtOAc in Hexane) gave the title compound (clear colorless oil, 1.5 g, 41%). ¹H NMR (400 MHz, DMSO-d₆) δ 7.52 (d, J=7.2 Hz, 1H), 7.37-7.31 (m, 2H), 7.25-7.21 (m, 1H), 5.27 (d, J=4.4 Hz, 1H), 4.68 (dd, J=5.2 Hz, 1H), 1.88-1.80 (m, 1H), 0.86 (dd, J=17.2 Hz, J=6.8 Hz, 6H).

B. 1-(2-chlorophenyl)-2-methyl-propan-1-one

[0446] A solution of 1-(2-chlorophenyl)-2-methylpropan-1-ol (1.5 g in 15 mL DCM) was added to a suspension of PCC

(2.62 g in 30 mL DCM) at 25° C., monitoring the reaction by TLC. The reaction was complete in 2 h. Et₂O (120 mL) was added and the reaction mixture was stirred for 15 min. The supernatant was decanted, dried (Na₂SO₄) and concentrated under vacuum. Purification by flash chromatography (SiO₂, 0-10% EtOAc in Hexane) gave the title compound (clear colorless oil, 1.24 g, 82%). ¹H NMR (400 MHz, CDCl₃) δ 7.41-7.27 (m, 4H), 3.37-3.30 (m, 1H), 1.19 (d, J=6.8 Hz, 6H).

C. 1-(2-chlorophenyl)-2-methylpropan-1-amine

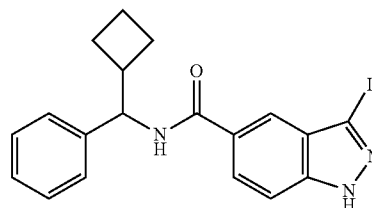
[0447] The title compound was prepared using Method G from 1-(2-chlorophenyl)-2-methyl-propan-1-one (1.5 g, 8.2 mmol) at 65° C. for 24 h. Evaporation of MeOH and addition of 3M NaOH (100 mL), extraction using EtOAc (2×100 mL), and purification by flash chromatography (SiO₂, 0-25% DCM in MeOH) to give the title compound (colorless oil, 348 mg, 23%). ¹H NMR (400 MHz, DMSO-d₆) δ ppm 7.38-7.21 (m, 4H), 4.87 (br.s, 2H), 4.16 (d, J=8.0 Hz, 1H), 2.12-2.04 (m, 1H), 1.02 (d, J=6.4 Hz, 3H), 0.82 (d, J=6.8 Hz, 3H); MS ESI 184.08. [M+H]⁺, calcd for [C₁₀H₁₄ClN+H]⁺ 184.08.

D. N-(1-(2-chlorophenyl)-2-methylpropyl)-3-iodo-1H-indazole-5-carboxamide

[0448] The title compound was synthesized according to general Method A by using 1-(2-chlorophenyl)-2-methylpropan-1-amine (0.55 g, 2.99 mmol), DMF (11 mL), 3-iodo-1H-indazole-5-carboxylic acid (863 mg, 2.99 mmol), DIPEA (2.09 mL, 11.98 mmol) and TBTU (960 mg, 2.99 mmol). The resultant reaction mass stirred at 25° C. for 12 h and then quenched it in H₂O (440 mL). The solid collected by filtration and was washed with H₂O to provide the title compound (cream color solid, 1.29 g, 95%). ¹H NMR (400 MHz, DMSO-d₆) δ 13.76 (s, 1H), 8.91 (d, J=8.8 Hz, 1H), 7.91 (d, J=9.2 Hz, 1H), 7.74-7.66 (m, 1H), 7.59 (d, J=8.8 Hz, 1H), 7.46-7.22 (m, 4H), 5.27 (t, J=9.2 Hz, 1H), 2.20-2.15 (m, 1H), 1.08 (d, J=6.0 Hz, 3H), 0.79 (d, J=6.8 Hz, 3H); MS ESI 454 [M+H]⁺, calcd for [C₁₈H₁₇ClIN₃O+H]⁺ 454.

Synthesis of N-(cyclobutyl(phenyl)methyl)-3-iodo-1H-indazole-5-carboxamide

[0449]



A. cyclobutyl(phenyl)methanamine

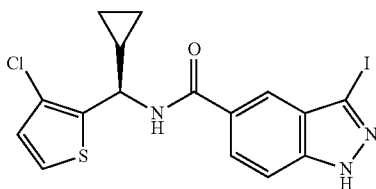
[0450] Using Method G, cyclobutyl(phenyl)methanone (1.06 mL, 13.9 mmol) gave the title compound (1.12 g, 100%) which was used crude. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.28-7.35 (m, 4H), 7.21-7.27 (m, 1H), 3.80 (d, J=9.3 Hz, 1H), 2.46-2.56 (m, 1H), 2.10-2.21 (m, 1H), 1.67-1.93 (m, 5H).

B. N-(cyclobutyl(phenyl)methyl)-3-iodo-1H-indazole-5-carboxamide

[0451] Using Method A, 3-iodo-1H-indazole-5-carboxylic acid (285.4 mg, 0.99 mmol) and cyclobutyl(phenyl)methanamine (177.2 mg, 1.10 mmol) gave the title compound (brown solid, 334 mg, 78%) after purification on the Biotage (RPC18, 10-95% MeOH in 0.1% TFA-H₂O). ¹H NMR (400 MHz, Acetone-d₆) δ ppm 12.89 (m, 0H), 8.24 (d, J=7.8 Hz, 1H), 8.09 (s, 1H), 8.04 (dd, J=8.8, 1.3 Hz, 1H), 7.64 (d, J=8.8 Hz, 1H), 7.47 (d, J=7.5 Hz, 2H), 7.33 (t, J=7.5 Hz, 2H), 7.23 (t, J=7.5 Hz, 1H), 5.21 (dd, J=10.2, 8.9 Hz, 1H), 2.18 (d, J=5.3 Hz, 1H), 1.94-2.03 (m, 1H), 1.80-1.93 (m, 4H). MS ESI 432.1 [M+H]⁺, calcd for [C₁₉H₁₈IN₃O+H]⁺ 432.06.

Synthesis of (R)—N-((3-chlorothiophen-2-yl)(cyclopropyl)methyl)-3-iodo-1H-indazole-5-carboxamide

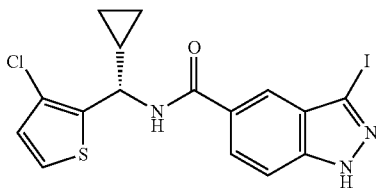
[0452]



[0453] Using Method A, 3-iodo-1H-indazole-5-carboxylic acid (161.0 mg, 0.56 mmol) and (R)-(3-chlorothiophen-2-yl)(cyclopropyl)methanamine hydrochloride (125.2 mg, 0.56 mmol) in DMF (6 mL) were stirred at rt for 29 h. The reaction mixture was added dropwise into 70 mL H₂O and the precipitate was collected by filtration, transferred using a mixture of acetone and EtOH, and concentrated to dryness. Purification by flash chromatography (SiO₂, 0-40% EtOAc/DCM) gave the title compound (light tan solid, 209.3 mg, 85% pure, 70%) which was used without further purification. ¹H NMR (400 MHz, CD₃OD) δ ppm 8.08 (s, 1H), 7.94 (dd, J=8.8, 1.5 Hz, 1H), 7.58 (d, J=9.0 Hz, 1H), 7.39 (d, J=5.5 Hz, 1H), 6.94 (d, J=5.3 Hz, 1H), 4.97 (d, J=9.0 Hz, 1H), 1.51 (td, J=8.4, 3.8 Hz, 1H), 0.62-0.74 (m, 2H), 0.50-0.62 (m, 2H).

Synthesis of (S)—N-((3-chlorothiophen-2-yl)(cyclopropyl)methyl)-3-iodo-1H-indazole-5-carboxamide

[0454]

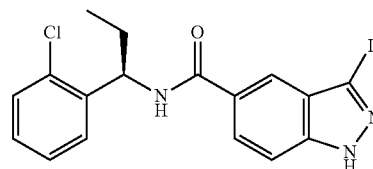


[0455] Using Method A following the work-up Method for the corresponding (R) enantiomer, 3-iodo-1H-indazole-5-carboxylic acid (161.5 mg, 0.56 mmol) and (S)-(3-chlorothiophen-2-yl)(cyclopropyl)methanamine hydrochloride (125.2 mg, 0.56 mmol) gave the title compound (beige solid, 218 mg, 85% pure, 72%) which was used without further purification. ¹H NMR (400 MHz, CD₃OD) δ ppm 8.08 (s,

1H), 7.94 (dd, J=8.8, 1.5 Hz, 1H), 7.58 (d, J=9.0 Hz, 1H), 7.39 (d, J=5.5 Hz, 1H), 6.94 (d, J=5.3 Hz, 1H), 4.97 (d, J=9.0 Hz, 1H), 1.51 (td, J=8.4, 3.8 Hz, 1H), 0.62-0.74 (m, 2H), 0.50-0.62 (m, 2H).

Synthesis of (R)—N-(1-(2-chlorophenyl)propyl)-3-iodo-1H-indazole-5-carboxamide

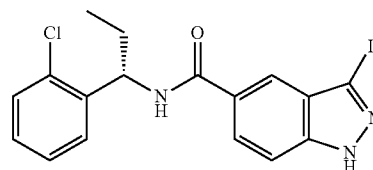
[0456]



[0457] Using Method A, 3-iodo-1H-indazole-5-carboxylic acid (488.7 mg, 1.7 mmol) and (R)-1-(2-chlorophenyl)propan-1-amine hydrochloride (349.7 mg, 1.7 mmol) gave the title compound (white solid, 650.3 mg, 95% pure, 83%) after aq. work-up with EtOAc and purification by flash chromatography (SiO₂, 5-30% EtOAc in DCM). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.11 (s, 1H), 7.95 (dd, J=8.9, 1.6 Hz, 1H), 7.59 (d, J=8.5 Hz, 1H), 7.51 (dd, J=7.7, 1.4 Hz, 1H), 7.41 (dd, J=7.8, 1.4 Hz, 1H), 7.31 (td, J=7.5, 1.5 Hz, 1H), 7.21-7.27 (m, 1H), 5.46 (dd, J=8.9, 5.9 Hz, 1H), 1.87-2.01 (m, 2H), 1.09 (t, J=7.3 Hz, 3H). MS ESI 440.2 [M+H]⁺, calcd for [C₁₇H₁₅ClIN₃O+H]⁺ 440.0.

Synthesis of (S)—N-(1-(2-chlorophenyl)propyl)-3-iodo-1H-indazole-5-carboxamide

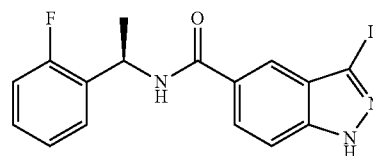
[0458]



[0459] Using Method A, 3-iodo-1H-indazole-5-carboxylic acid (490.2 mg, 1.7 mmol) and (S)-1-(2-chlorophenyl)propan-1-amine hydrochloride (348.6 mg, 1.69 mmol) gave the title compound (white solid, 525.5 mg, 70.7%) after aq. work-up with EtOAc and purification by flash chromatography (SiO₂, 5-30% EtOAc in DCM). ¹H NMR (400 MHz, Acetone-d₆) δ ppm 12.89 (s, 1H), 8.39 (d, J=8.5 Hz, 1H), 8.16 (s, 1H), 8.07 (dd, J=8.8, 1.5 Hz, 1H), 7.67 (s, 1H), 7.65 (td, J=3.8, 1.6 Hz, 1H), 7.43 (dd, J=7.5, 1.6 Hz, 1H), 7.33 (td, J=7.5, 1.6 Hz, 1H), 7.27 (td, J=7.5, 1.6 Hz, 1H), 5.55 (td, J=8.2, 6.3 Hz, 1H), 1.88-1.96 (m, 2H), 1.08 (t, J=7.4 Hz, 3H). MS ESI 440.2 [M+H]⁺, calcd for [C₁₇H₁₅ClIN₃O+H]⁺ 440.0.

Synthesis of (R)—N-(1-(2-fluorophenyl)ethyl)-3-iodo-1H-indazole-5-carboxamide

[0460]



A. (R)-1-(2-fluorophenyl)ethanamine hydrochloride

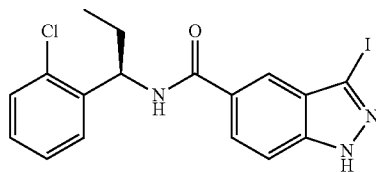
[0461] To (R)-2-methylpropane-2-sulfinamide (121 mg, 1.0 mmol), $\text{Ti}(\text{OEt})_4$ (0.41 mL, 2.0 mmol) in THF (2.0 mL) was added 1-(2-fluorophenyl)ethanone (0.15 mL, 1.2 mmol) and the mixture heated to 70° C. for 18 h. The reaction was then cooled to -48° C. and NaBH_4 (151 mg, 4.0 mmol) was added and the reaction was allowed to warm to rt and stir for 4 h at which time it was quenched with MeOH, brine was added (5 mL), and the resulting slurry was filtered through Celite washing with EtOAc. The resulting filtrate was extracted with EtOAc washing with brine and the material purified by column chromatography (silica gel, 98:2 $\text{CH}_2\text{Cl}_2/\text{MeOH}$) which gave 189 mg, 78% of (R)-N-((R)-1-(2-fluorophenyl)ethyl)-2-methylpropane-2-sulfinamide which was 58% de by NMR. This material was taken up in MeOH (3.5 mL) and HCl (1.6 mL of a 1.0M solution in Et_2O) was added and the reaction stirred for 1.5 h. The solvent was then removed and the product precipitated with Et_2O (10 mL) and filtered to give 109 mg, 62% (over the 2 steps) of a white solid (58% ee).

B. (R)-N-(1-(2-fluorophenyl)ethyl)-3-iodo-1H-indazole-5-carboxamide

[0462] General Method A was used except using (R)-1-(2-fluorophenyl)ethanamine hydrochloride (109 mg, 0.621 mmol), 3-iodo-1H-indazole-5-carboxylic acid (179 mg, 0.621 mmol), TBTU (209 mg, 0.652 mmol), DIPEA (0.44 mL, 2.5 mmol), and DMF (3.5 mL). Obtained 120 mg of product, 47%. ^1H NMR (400 MHz, CD_3OD) δ ppm 8.09 (s, 1H), 7.94 (d, $J=9.2$ Hz, 1H), 7.57 (d, $J=9.2$ Hz, 1H), 7.45 (t, $J=7.2$ Hz, 1H), 7.30-7.25 (m, 1H), 7.16-7.07 (m, 2H), 5.51 (q, $J=7.2$ Hz, 1H), 1.60 (d, $J=7.2$ Hz, 3H); MS ESI 410.1 $[\text{M}+\text{H}]^+$, calcd for $[\text{C}_{16}\text{H}_{13}\text{FIN}_3\text{O}+\text{H}]^+$ 410.02.

Synthesis of (R)-N-(1-(2-chlorophenyl)propyl)-3-iodo-1H-indazole-5-carboxamide

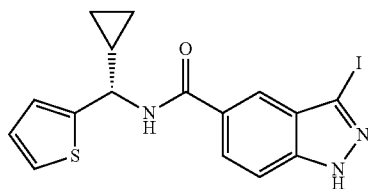
[0463]



[0464] Prepared in the same way as (R)-N-(1-(2-fluorophenyl)ethyl)-3-iodo-1H-indazole-5-carboxamide except substituting 1-(2-chlorophenyl)propan-1-one. The ee was determined to be 36% using the Method described for (R)-N-(1-(2-fluorophenyl)ethyl)-3-iodo-1H-indazole-5-carboxamide. MS ESI 440.0 $[\text{M}+\text{H}]^+$, calcd for $[\text{C}_{17}\text{H}_{15}\text{ClIN}_3\text{O}+\text{H}]^+$ 440.00.

Synthesis of (S)-N-(cyclopropyl(thiophen-2-yl)methyl)-3-iodo-1H-indazole-5-carboxamide

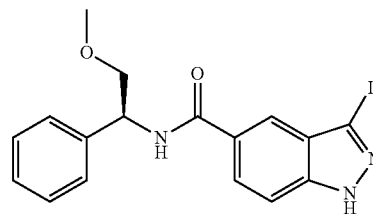
[0465]



[0466] Prepared in the same way as (R)-N-(1-(2-fluorophenyl)ethyl)-3-iodo-1H-indazole-5-carboxamide except substituting cyclopropyl(thiophen-2-yl)methanone. The ee was determined to be 50% using the Method described for (R)-N-(1-(2-fluorophenyl)ethyl)-3-iodo-1H-indazole-5-carboxamide. MS ESI 424.0 $[\text{M}+\text{H}]^+$, calcd for $[\text{C}_{16}\text{H}_{14}\text{IN}_3\text{OS}+\text{H}]^+$ 424.00.

Synthesis of (S)-3-iodo-N-(2-methoxy-1-phenylethyl)-1H-indazole-5-carboxamide

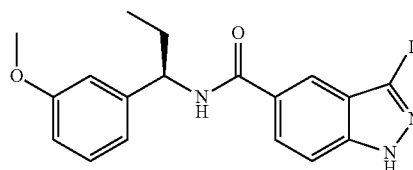
[0467]



[0468] General Method A was used except using (S)-2-methoxy-1-phenylethanamine (0.30 mL, 2.0 mmol), 3-iodo-1H-indazole-5-carboxylic acid (576 mg, 2.0 mmol), TBTU (640 mg, 2.0 mmol), DIPEA (1.4 mL, 8.0 mmol), and DMF (13 mL). Obtained 575 mg, 68% of the product as a white solid. MS ESI 422.0 $[\text{M}+\text{H}]^+$, calcd for $[\text{C}_{17}\text{H}_{16}\text{IN}_3\text{O}_2+\text{H}]^+$ 422.04.

Synthesis of (R)-3-iodo-N-(1-(3-methoxyphenyl)propyl)-1H-indazole-5-carboxamide

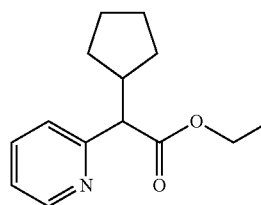
[0469]



[0470] General Method A was used except using (R)-1-(3-methoxyphenyl)propan-1-amine hydrochloride (202 mg, 1.0 mmol), 3-iodo-1H-indazole-5-carboxylic acid (288 mg, 1.0 mmol), TBTU (320 mg, 1.0 mmol), DIPEA (0.70 mL, 4.0 mmol), and DMF (6.0 mL). Obtained 336 mg, 77% of the product as a white solid. MS ESI 436.0 $[\text{M}+\text{H}]^+$, calcd for $[\text{C}_{18}\text{H}_{18}\text{IN}_3\text{O}_2+\text{H}]^+$ 436.05.

Synthesis of ethyl 2-cyclopropyl-2-(pyridin-2-yl)acetate

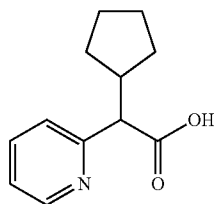
[0471]



[0472] The solution of ethyl 2-(pyridin-2-yl)acetate (2 g, 12.1 mmols) in anhydrous DMF (20 mL) was cooled down to 0° C. followed by adding of 60% NaH (581 mg, 14.5 mmols) in portions and bromocyclopentane (1.98 g, 13.3 mmols) dropwise. The resulting suspension was stirred at rt for 2 h before H₂O was added. The mixture was extracted with EtOAc. The organic layer was washed with H₂O for three times and brine for one time before dried over Na₂SO₄ and concentrated under reduced pressure to give the title compound as a yellow oil (370 mg, 52% yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 8.55 (d, J=4.8 Hz, 1H), 7.65 (td, J=7.7, 1.8 Hz, 1H), 7.40 (d, J=8.0 Hz, 1H), 7.17 (ddd, J=7.4, 5.0, 0.9 Hz, 1H), 4.04-4.23 (m, 2H), 3.58 (d, J=11.0 Hz, 1H), 2.58-2.75 (m, 1H), 1.88-2.01 (m, 1H), 1.24-1.54 (m, 5H), 1.22 (t, J=7.2 Hz, 3H), 1.07 (dq, J=12.4, 8.2 Hz, 1H), 0.79-0.92 (m, 1H); MS ESI [M+H]⁺ 234.0, calcd for [C₁₄H₁₉NO₂+H]⁺ 234.15.

Synthesis of 2-cyclopentyl-2-(pyridin-2-yl)acetic acid

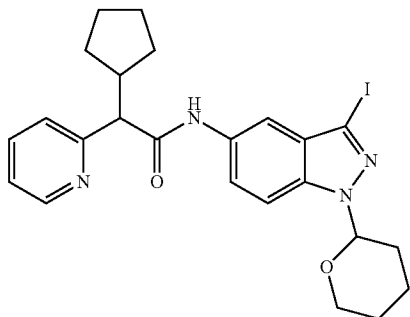
[0473]



[0474] The title compound was synthesized according to the Method of 2-(4-(4-bromophenoxy)piperidin-1-yl)acetic acid utilizing ethyl 2-cyclopentyl-2-(pyridin-2-yl)acetate and obtained as a colourless gel (216 mg, 43% yield). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.75 (d, J=5.3 Hz, 1H), 8.45-8.53 (m, 1H), 8.08 (d, J=7.8 Hz, 1H), 7.86-7.95 (m, 1H), 3.85 (d, J=11.0 Hz, 1H), 2.66 (m, J=10.5, 9.0, 9.0 Hz, 1H), 1.99-2.10 (m, 1H), 1.39-1.82 (m, 6H), 1.04-1.16 (m, 1H); MS ESI [M+H]⁺ 206.1, calcd for [C₁₂H₁₅NO₂+H]⁺ 206.12.

Synthesis of 2-cyclopentyl-N-(3-iodo-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-yl)-2-(pyridin-2-yl)acetamide

[0475]

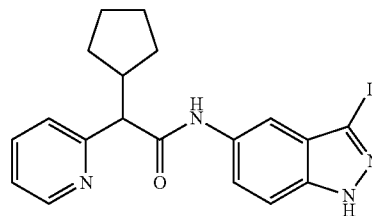


[0476] The title compound was synthesized according to Method A utilizing 2-cyclopentyl-2-(pyridin-2-yl)acetic acid

and 3-iodo-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-amine and obtained as a brown solid (178 mg, 23% yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 10.06 (br. s., 1H), 8.63 (d, J=4.0 Hz, 1H), 7.64-7.80 (m, 2H), 7.43-7.58 (m, 2H), 7.20-7.38 (m, 3H), 5.64 (d, J=8.0 Hz, 1H), 3.98 (d, J=10.5 Hz, 1H), 3.70 (t, J=9.3 Hz, 1H), 3.42-3.56 (m, 1H), 2.60-2.75 (m, 1H), 2.51 (d, J=9.5 Hz, 1H), 1.88-2.21 (m, 3H), 1.33-1.82 (m, 9H), 1.00-1.15 (m, 1H); MS ESI [M+H]⁺ 531.2, calcd for [C₂₄H₂₇N₄O₂+H]⁺ 531.13.

Synthesis of 2-cyclopentyl-N-(3-iodo-1H-indazol-5-yl)-2-(pyridin-2-yl)acetamide

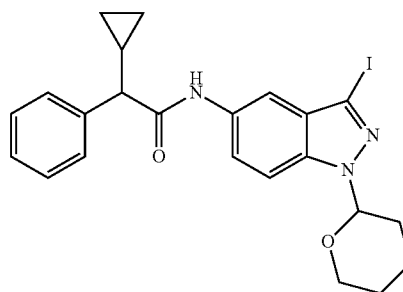
[0477]



[0478] The solution of 2-cyclopentyl-N-(3-iodo-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-yl)-2-(pyridin-2-yl)acetamide (178 mg, 0.34 mmol) and TsOH.H₂O (288 mg, 1.51 mmols) in MeOH (3 mL) was stirred at 125° C. for 3 h with microwave irradiation in a sealed vial before concentrated under reduced pressure. The residue was purified by flash chromatography (MeOH/DCM 0%-10%) to give the title compound as a light yellow solid (104 mg, 69% yield). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.48 (dd, J=4.9, 0.9 Hz, 1H), 7.85 (d, J=1.3 Hz, 1H), 7.76 (td, J=7.7, 1.8 Hz, 1H), 7.60 (d, J=7.8 Hz, 1H), 7.40-7.51 (m, 2H), 7.27 (ddd, J=7.5, 5.0, 1.0 Hz, 1H), 3.59 (d, J=11.0 Hz, 1H), 2.68-2.84 (m, 1H), 1.94 (dd, J=11.7, 4.6 Hz, 1H), 1.35-1.76 (m, 6H), 0.99-1.12 (m, 1H); MS ESI [M+H]⁺ 447.1, calcd for [C₁₉H₁₉IN₂O₄+H]⁺ 447.07.

Synthesis of 2-cyclopropyl-N-(3-iodo-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-yl)-2-phenylacetamide

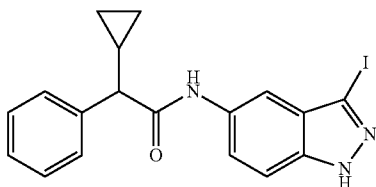
[0479]



[0480] The title compound was synthesized according to Method A utilizing 2-cyclopropyl-2-phenylacetic acid and 3-iodo-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-amine and obtained as a pale solid (120 mg, 70% yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.88 (s, 1H), 7.70 (d, J=5.5 Hz, 1H), 7.25-7.44 (m, 6H), 5.59 (dd, J=9.3, 2.0 Hz, 1H), 3.97 (d, J=11.5 Hz, 1H), 3.64-3.74 (m, 1H), 2.88 (d, J=9.8 Hz, 1H), 2.40-2.54 (m, 1H), 2.07-2.17 (m, 1H), 1.95-2.04 (m, 1H), 1.58-1.79 (m, 3H), 1.48-1.58 (m, 1H), 0.74-0.85 (m, 1H), 0.56-0.69 (m, 1H), 0.44-0.54 (m, 1H), 0.24 (dq, J=9.5, 4.9 Hz, 1H); MS ESI [M+H]⁺ 502.2, calcd for [C₂₃H₂₄IN₃O₂+H]⁺ 502.10.

Synthesis of 2-cyclopropyl-N-(3-iodo-1H-indazol-5-yl)-2-phenylacetamide

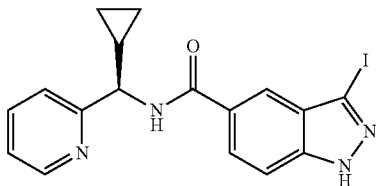
[0481]



[0482] The title compound was synthesized according to the Method of 2-cyclopentyl-N-(3-iodo-1H-indazol-5-yl)-2-(pyridin-2-yl)acetamide utilizing 2-cyclopropyl-N-(3-iodo-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-yl)-2-phenylacetamide and obtained as a white solid (87 mg, 87% yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.80 (s, 1H), 7.38-7.49 (m, 6H), 7.33-7.37 (m, 1H), 2.91 (d, J=9.3 Hz, 1H), 0.82-0.91 (m, 1H), 1.20-1.27 (m, 1H), 0.63-0.71 (m, 1H), 0.50-0.61 (m, 1H), 0.27-0.34 (m, 1H); MS ESI [M+H]⁺ 418.1, calcd for [C₁₈H₁₆IN₃O+H]⁺ 418.04.

Synthesis of (R)-2-cyclopropyl-N-(3-iodo-1H-indazol-5-yl)-2-(pyridin-2-yl)acetamide

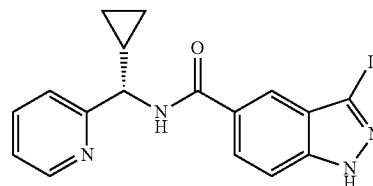
[0483]



[0484] The title compound was synthesized according to Method A utilizing (R)-cyclopropyl(pyridin-2-yl)methanamine and obtained as a light yellow solid (334 mg, 80% yield). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.51-8.55 (m, 1H), 8.13-8.16 (m, 1H), 7.95-8.00 (m, 1H), 7.81-7.86 (m, 1H), 7.53-7.61 (m, 2H), 7.30-7.36 (m, 1H), 4.49-4.53 (m, 1H), 1.38-1.48 (m, 1H), 0.68-0.75 (m, 1H), 0.51-0.64 (m, 3H); MS ESI [M+H]⁺ 419.0, calcd for [C₁₇H₁₅INO₄+H]⁺ 419.04.

Synthesis of (S)-2-cyclopropyl-N-(3-iodo-1H-indazol-5-yl)-2-(pyridin-2-yl)acetamide

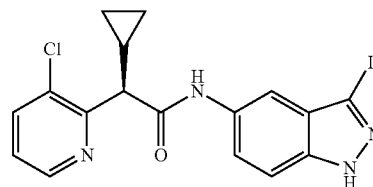
[0485]



[0486] The title compound was synthesized according to Method A utilizing (S)-cyclopropyl(pyridin-2-yl)methanamine and obtained as a yellow solid (874 mg, 77% yield). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.51-8.55 (m, 1H), 8.13-8.16 (m, 1H), 7.95-8.00 (m, 1H), 7.81-7.86 (m, 1H), 7.53-7.61 (m, 2H), 7.30-7.36 (m, 1H), 4.49-4.53 (m, 1H), 1.38-1.48 (m, 1H), 0.68-0.75 (m, 1H), 0.51-0.64 (m, 3H); MS ESI [M+H]⁺ 419.0, calcd for [C₁₇H₁₅INO₄+H]⁺ 419.04.

Synthesis of (R)-2-(3-chloropyridin-2-yl)-2-cyclopropyl-N-(3-iodo-1H-indazol-5-yl)acetamide

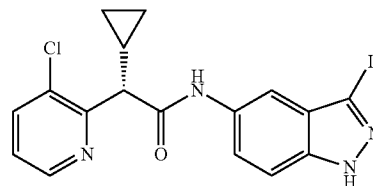
[0487]



[0488] The title compound was synthesized according to Method A utilizing (R)-(3-chloropyridin-2-yl)(cyclopropyl)methanamine and obtained as a white solid (322 mg, 78% yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 13.10 (s, 1H), 8.49-8.50 (m, 1H), 8.00-8.02 (d, J=9.6 Hz, 1H), 7.95 (s, 1H), 7.84-7.86 (dd, J=8.8, 0.8 Hz, 1H), 7.67-7.69 (m, 1H), 7.40-7.42 (d, J=8.8 Hz, 1H), 7.16-7.19 (m, 1H), 5.46-5.50 (t, J=8.0 Hz, 1H), 1.37-1.45 (m, 1H), 0.61-0.66 (m, 1H), 0.47-0.58 (m, 3H); MS ESI [M+H]⁺ 453.2, calcd for [C₁₇H₁₄ClINO₄+H]⁺ 453.00.

Synthesis of (S)-2-(3-chloropyridin-2-yl)-2-cyclopropyl-N-(3-iodo-1H-indazol-5-yl)acetamide

[0489]

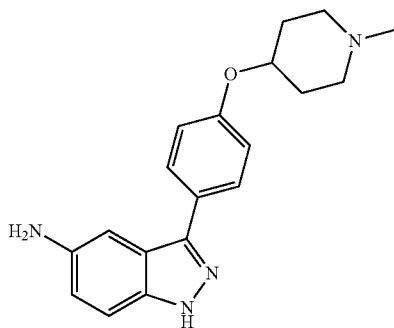


[0490] The title compound was synthesized according to Method A utilizing (S)-(3-chloropyridin-2-yl)(cyclopropyl)methanamine and obtained as a yellow solid (863 mg, 83%

yield). ^1H NMR (400 MHz, CDCl_3) δ ppm 13.10 (s, 1H), 8.49-8.50 (m, 1H), 8.00-8.02 (d, $J=9.6$ Hz, 1H), 7.95 (s, 1H), 7.84-7.86 (dd, $J=8.8$, 0.8 Hz, 1H), 7.67-7.69 (m, 1H), 7.40-7.42 (d, $J=8.8$ Hz, 1H), 7.16-7.19 (m, 1H), 5.46-5.50 (t, $J=8.0$ Hz, 1H), 1.37-1.45 (m, 1H), 0.61-0.66 (m, 1H), 0.47-0.58 (m, 3H); MS ESI $[\text{M}+\text{H}]^{+453.2}$, calcd for $[\text{C}_{17}\text{H}_{14}\text{Cl}_1\text{NO}_4+\text{H}]^{+}$ 453.00.

Synthesis of 3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazol-5-amine

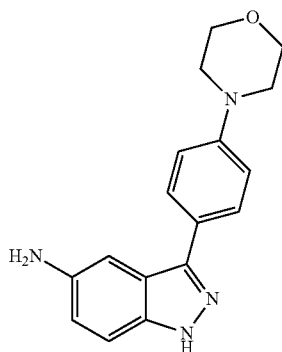
[0491]



[0492] Tert-butyl (3-iodo-1H-indazol-5-yl)carbamate (398 mg, 1.11 mmol), 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine (530 mg, 1.67 mmol), and LiCl (141 mg, 3.33 mmol) were dissolved into dioxane (7.0 mL) and 2 M aq Na_2CO_3 (2.8 mL) in a microwave vial. The mixture was purged with Ar for 15 min at which time $\text{Pd}(\text{PPh}_3)_4$ (96 mg, 0.083 mmol) was added. The vial was sealed and heated in the microwave at 120°C . for 3 h. The reaction was cooled, the solvent removed and the residue purified by column chromatography (silica gel, 90:10 $\text{CH}_2\text{Cl}_2/\text{MeOH}$) which gave 230 mg of BOC protected material which was dissolved into CH_2Cl_2 (5 mL) and TFA (0.5 mL) was added. The reaction was stirred for 3 h. The solvent was removed and product precipitated with Et_2O which gave after drying 235 mg, 38% of a brown solid as the di-TFA salt. ^1H NMR (400 MHz, CD_3OD) δ ppm 8.01 (s, 1H), 7.90-7.86 (m, 2H), 7.73 (d, $J=8.8$ Hz, 1H), 7.42 (d, $J=9.0$, 1H), 7.23-7.16 (m, 2H), 4.88 (bs, 1H), 3.66-3.39 (m, 2H), 3.39-3.00 (m, 2H), 2.95-2.89 (m, 3H), 2.46-2.29 (m, 2H), 2.17-1.90 (m, 2H); MS ESI 323.1 $[\text{M}+\text{H}]^{+}$, calcd for $[\text{C}_{19}\text{H}_{22}\text{N}_4\text{O}+\text{H}]^{+}$ 323.19.

Synthesis of 3-(4-morpholinophenyl)-1H-indazol-5-amine

[0493]



[0494] The same procedure was followed as for 3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazol-5-amine bis

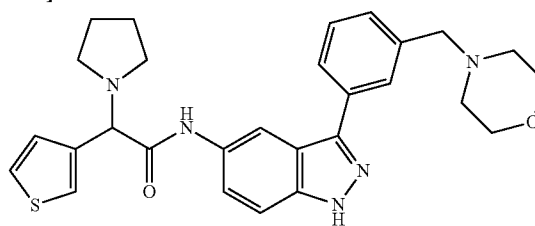
(2,2,2-trifluoroacetate) using tert-butyl (3-iodo-1H-indazol-5-yl)carbamate (359 mg, 1.0 mmol) and 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)morpholine (434 mg, 1.5 mmol). Obtained 210 mg of an impure brown solid as the di-TFA salt which was used for subsequent synthetic steps; MS ESI 295.1 $[\text{M}+\text{H}]^{+}$, calcd for $[\text{C}_{17}\text{H}_{18}\text{N}_4\text{O}+\text{H}]^{+}$ 295.16.

Preparation of Exemplary Compounds of the Invention

Example A1

N-(3-(3-(morpholinomethyl)phenyl)-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide

[0495]

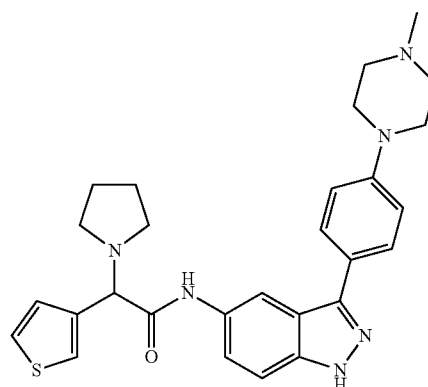


[0496] To a mixture of N-(3-iodo-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide (56.6 mg, 0.125 mmol) and 4-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)morpholine (33.3 mg, 0.11 mmol) in $\text{PhCH}_3/\text{EtOH}$ (1.5 mL/3 mL) was added 1 M aq Na_2CO_3 (0.3 mL, 0.3 mmol), followed by $\text{Pd}(\text{PPh}_3)_4$ (5.8 mg, 0.005 mmol). The resulting mixture was purged with Ar and microwaved 30 min at 125°C . After removal of solvents, it was purified by flash chromatography (EtOAc/hex 0 to 100%, then MeOH/DCM 5-15%) and then triturated with Et_2O to give the title compound as beige solid (15 mg, 27%). ^1H NMR (400 MHz, CD_3OD) δ 8.37 (s, 1H), 7.91 (s, 1H), 7.83 (d, $J=6.8$ Hz, 1H), 7.55-7.47 (m, 4H), 7.45-7.39 (m, 2H), 7.35 (dd, $J=4.8$ Hz, 1H), 4.15 (s, 1H), 3.72 (t, $J=4.6$ Hz, 4H), 3.65 (s, 2H), 2.75-2.65 (m, 2H), 2.60-2.50 (m, 6H), 1.90-1.85 (m, 4H); MS ESI 502.2 $[\text{M}+\text{H}]^{+}$, calcd for $[\text{C}_{28}\text{H}_{31}\text{N}_5\text{O}_2\text{S}+\text{H}]^{+}$ 502.2.

Example A2

N-(3-(4-(4-methylpiperazin-1-yl)phenyl)-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide

[0497]

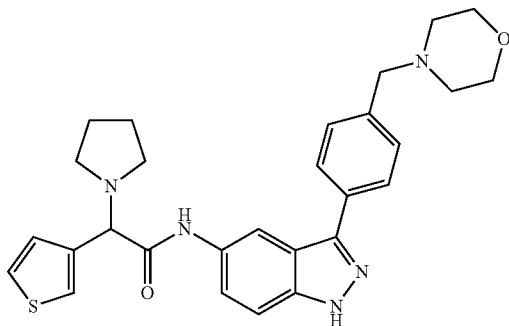


[0498] The title compound was synthesized according to general Method C by using a mixture of N-(3-iodo-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide (50 mg, 0.11 mmol), 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazine (40 mg, 0.13 mmol), Pd(PPh₃)₄ (6.35 mg, 0.005 mmol) and 1 M aq Na₂CO₃ (0.22 mL) in PhMe/EtOH (2.25 mL, 2:1 mixture) in vial under Ar was heated under microwave irradiation at 125° C. for 2 h. The reaction mixture was diluted with EtOAc (10 mL) and washed with H₂O (5 mL) followed by brine (5 mL), dried (Na₂SO₄) and concentrated under vacuum to give brown oily residue. The crude product was purified by flash chromatography (100 g SiO₂ column, 0-10% 2 M NH₃-MeOH in DCM; then by RP HPLC C18 60 g column, 10-80% MeOH in 0.1% TFA-H₂O) to give the title compound as a TFA salt (pale yellow solid, 21 mg, 26%). ¹H NMR (400 MHz, CD₃OD) δ 8.35 (s, 1H), 7.85-7.83 (m, 3H), 7.64 (br.s, 1H), 7.54-7.49 (m, 2H), 7.38 (dd, J=4.4 Hz, 1H), 7.19 (d, J=8.4 Hz, 2H), 5.26 (s, 1H), 3.98-3.86 (br.m, 3H), 3.67-3.60 (m, 2H), 3.17-3.11 (br. m, 4H), 3.00 (s, 3H), 2.26-2.14 (br.m, 3H), 2.02-2.01 (br.s, 1H), 2H merged with solvent peak, MS ESI 501.1[M+H]⁺, calcd for [C₂₈H₃₂N₆OS+H]⁺ 501.2.

Example A3

N-(3-(4-(morpholinomethyl)phenyl)-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide

[0499]

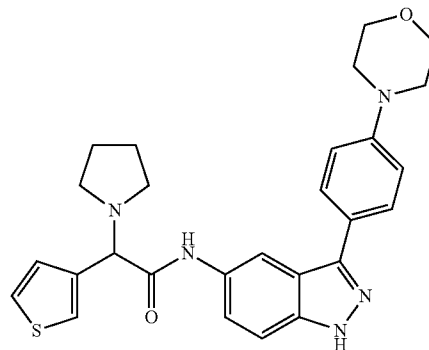


[0500] To a mixture of N-(3-iodo-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide (181 mg, 0.4 mmol) and 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)morpholine (121 mg, 0.4 mmol) in EtOH (10 mL) was added 1 M aq Na₂CO₃ (0.8 mL, 0.8 mmol), followed by Pd(PPh₃)₄ (23 mg, 0.02 mmol). The resulting mixture was purged with Ar and microwaved 1 h at 125° C. After removal of solvents, it was redissolved in DMF/MeOH/TFA (4 mL/1 mL/0.5 mL), filtered thru microfilter and purified by PREP-HPLC twice to give the title compound as a di-TFA salt (off white solid, 52 mg, 18%). ¹H NMR (400 MHz, CD₃OD) δ 8.40 (s, 1H), 8.05 (d, J=8.0 Hz, 2H), 7.89-7.85 (m, 1H), 7.68 (d, J=8.0 Hz, 2H), 7.63 (dd, J=4.8 Hz, 2.8 Hz, 1H), 7.60-7.52 (m, 2H), 7.38 (dd, J=4.8 Hz, 0.8 Hz, 1H), 5.32 (s, 1H), 4.44 (s, 2H), 4.10-3.05 (m, 12H), 2.30-1.95 (m, 4H); MS ESI 502.1 [M+H]⁺, calcd for [C₂₈H₃₁N₅O₂S+H]⁺ 502.2.

Example A4

N-(3-(4-(morpholinophenyl)-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide

[0501]

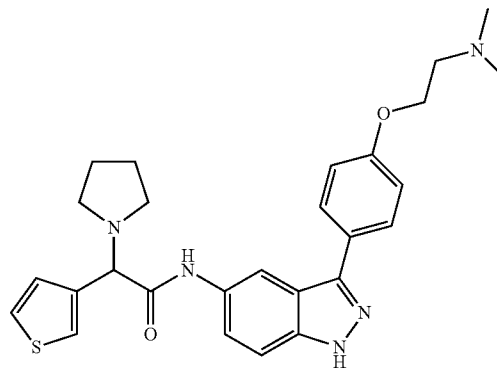


[0502] Aq. Na₂CO₃ (2 M, 1.0 mL, 2.0 mmol) was added to a solution of N-(3-iodo-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide (300.2 mg, 0.66 mmol), (4-morpholinophenyl)boronic acid (191.2 mg, 0.93 mmol) and PdCl₂(dppf).DCM (52.0 mg, 0.064 mmol) in 1:1 PhMe: EtOH (14 mL), and the mixture was heated in microwave for 3 h at 120° C. The product was partitioned between EtOAc (250 mL) and H₂O (25 mL), and the aq. layer was extracted with EtOAc (4x100 mL). The combined organic layers were washed sequentially with H₂O (25 mL) and brine (25 mL), dried (Na₂SO₄), filtered and evaporated in vacuo. Purification by flash chromatography (SiO₂, 0-10% MeOH in DCM; followed by RPC18, 10-80% MeOH in 0.1% TFA-H₂O) gave the title compound as the TFA salt (yellow powder, 265.1 mg, 56%). ¹H NMR (400 MHz, CDOD) δ ppm 8.38 (d, J=1.25 Hz, 1H), 7.87 (dd, J=3.01, 1.25 Hz, 1H), 7.82 (d, J=8.78 Hz, 2H), 7.67 (dd, J=5.02, 3.01 Hz, 1H), 7.53 (d_{AB}, J=9.00 Hz, 1H), 7.48 (d_{AB}d, J=9.00, 1.70 Hz, 1H), 7.38 (dd, J=5.02, 1.25 Hz, 1H), 7.16 (d, J=8.78 Hz, 2H), 5.20 (s, 1H), 3.87-3.92 (m, 4H), 3.25-3.30 (m, 4H), 3.13-3.24 (m, 1H), 3.10 (br. s., 1H), 2.20-2.29 (m, 1H), 2.10-2.20 (m, 2H), 2.01 (br. s., 1H). MS ESI 488.3 [M+H]⁺, calcd for [C₂₇H₂₉N₅O₂S+H]⁺ 488.21.

Example A5

N-(3-(4-(2-(dimethylamino)ethoxy)phenyl)-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide

[0503]

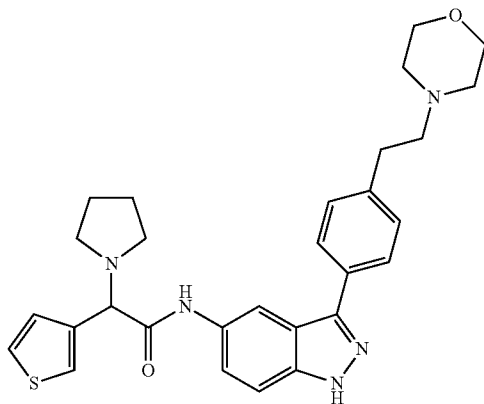


[0504] To a mixture of N-(3-iodo-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide (226 mg, 0.5 mmol) and N,N-dimethyl-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)ethanamine (146 mg, 0.5 mmol) in EtOH (10 mL) was added 1 M aq Na₂CO₃ (1 mL, 1 mmol), followed by Pd(PPh₃)₄ (23 mg, 0.02 mmol). The resulting mixture was purged with Ar and microwaved 1 h at 125° C. Additional Pd(PPh₃)₄ (11.6 mg, 0.01 mmol) was added and the reaction mixture was purged with Ar and microwaved 2 h at 125° C. After removal of solvents, it was purified by flash chromatography (MeOH/DCM 5-15%, then pure MeOH) and prep-HPLC to give the title compound as a di-TFA salt (white solid, 114 mg, 32%). ¹H NMR (400 MHz, CD₃OD) δ 8.34 (s, 1H), 7.88-7.83 (m, 3H), 7.59 (dd, J=4.8 Hz, 3.2 Hz, 1H), 7.53 (s, 2H), 7.38 (d, J=5.2 Hz, 1H), 7.13 (d, J=8.8 Hz, 2H), 5.35 (s, 1H), 4.38 (t, J=4.6 Hz, 2H), 3.83 (brs, 1H), 3.60 (t, J=4.6 Hz, 2H), 3.35-3.05 (m, 3H), 2.98 (s, 6H), 2.25-1.90 (m, 4H); MS ESI 490.2 [M+H]⁺, calcd for [C₂₇H₃₁N₅O₂S+H]⁺ 490.2.

Example A6

N-(3-(4-(2-morpholinoethyl)phenyl)-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide

[0505]

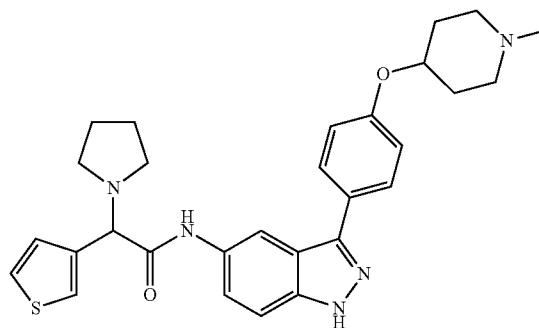


[0506] To a mixture of N-(3-iodo-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide (181 mg, 0.4 mmol) and 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenethyl)morpholine (127 mg, 0.4 mmol) in EtOH (10 mL) was added 1 M aq Na₂CO₃ (0.8 mL, 0.8 mmol), followed by Pd(PPh₃)₄ (23 mg, 0.02 mmol). The resulting mixture was purged with Ar and microwaved 2 h at 125° C. Additional Pd(PPh₃)₄ (11.6 mg, 0.01 mmol) was added and the reaction mixture was purged with Ar and microwaved 1 h at 125° C. After removal of solvents, it was purified by flash chromatography (MeOH/DCM 5-15%, then pure MeOH) and prep-HPLC to give the title compound as a di-TFA salt (white solid, 85 mg, 29%). ¹H NMR (400 MHz, CD₃OD) δ 8.38 (s, 1H), 7.92-7.85 (m, 3H), 7.64-7.59 (m, 1H), 7.54 (s, 2H), 7.44 (d, J=8.0 Hz, 2H), 7.38 (d, J=4.4 Hz, 1H), 5.32 (s, 1H), 4.12-4.03 (m, 2H), 3.90-3.77 (m, 3H), 3.63-3.55 (m, 2H), 3.47-3.40 (m, 2H), 3.26-3.06 (m, 7H), 2.30-1.90 (m, 4H); MS ESI 516.2 [M+H]⁺, calcd for [C₂₉H₃₃N₅O₂S+H]⁺ 516.2.

Example A7

N-(3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide

[0507]

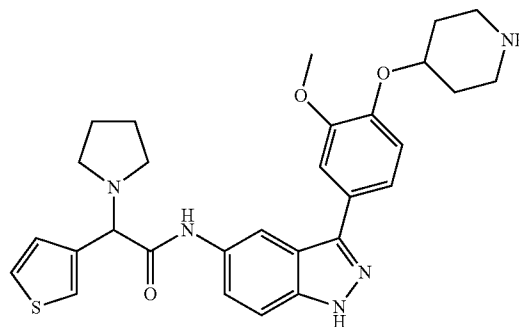


[0508] Using Method C2, three vials each containing N-(3-iodo-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide (400 mg, 0.882 mmol) and 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine (368 mg, 1.05 mmol) with 15% catalyst in PhMe:EtOH (8 mL:4 mL) were heated for 5 h at 125° C. in the microwave. The combined reactions were extracted with EtOAc, and purified by flash chromatography (SiO₂, 0-80% MeOH in DCM); followed by purification with prep HPLC and Biotage RPC18, 10-90% MeOH in 0.1% TFA-H₂O, the title compound was obtained as the TFA salt (off-white solid, 545 mg, 27.6%). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.36 (s, 1H), 7.82-7.91 (m, 3H), 7.64 (dd, J=5.0, 3.0 Hz, 1H), 7.49-7.57 (m, 2H), 7.38 (dd, J=5.1, 1.1 Hz, 1H), 7.11-7.22 (m, 2H), 5.29 (s, 1H), 4.62-4.73 (m, 0.33 H), 3.87 (br. s., 1H), 3.60-3.69 (m, 0.67 H), 3.49-3.34 (m, 3.33 H), 3.02-3.27 (m, 3H), 2.94, 2.93 (2-s, 3H), 2.43 (d, J=14.3 Hz, 0.67 H), 1.86-2.34 (m, 8H). MS ESI 516.2 [M+H]⁺, calcd for [C₂₉H₃₃N₅O₂S+H]⁺ 516.24.

Example A8

N-(3-(3-methoxy-4-(piperidin-4-yloxy)phenyl)-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide

[0509]

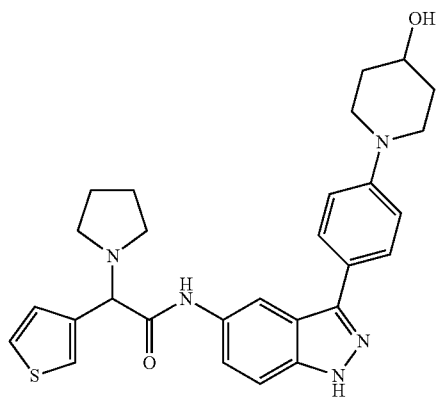


[0510] The title compound was synthesized according to the General Method C, utilizing N-(3-iodo-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide (50 mg, 0.11 mmol), 4-(1-boc-piperidin-4-yloxy)-3-methoxyphenyl boronic acid (46 mg, 0.13 mmol), PdCl₂dppf (4.5 mg, 0.0055 mmol), satd. aq Na₂CO₃ (0.5 mL), and 1.5 mL of PhMe:EtOH (1:1). The vial was charged with Ar and heated in the microwave reactor at 125° C. for 2 h. The mixture was purified by RPHPLC, treated with using DCM/TFA for 1 h, followed by trituration with Et₂O to give the title compound as a TFA salt (beige solid, 54 mg, 65%). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.45 (s, 1H), 7.86 (br. s, 1H), 7.62-7.68 (m, 1H), 7.44-7.59 (m, 4H), 7.37 (d, J=5.0 Hz, 1H), 7.21 (d, J=8.3 Hz, 1H), 5.24 (s, 1H), 4.71 (br. s, 1H), 3.98 (s, 3H), 3.80-3.92 (m, 1H), 3.44-3.56 (m, 3H), 3.02-3.28 (m, 5H), 2.13 (br. s, 7H), 1.90-2.05 (m, 1H); MS ESI 532.2 [M+H]⁺, calcd for [C₂₉H₃₃N₅O₃S+H]⁺ 532.2.

Example A9

N-(3-(4-(4-hydroxypiperidin-1-yl)phenyl)-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide

[0511]



A. N-(3-(4-(4-oxopiperidin-1-yl)phenyl)-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide

[0512] The title compound was synthesized according to general Method C by using a sealed degassed mixture of N-(3-iodo-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide (700 mg, 1.54 mmol), 1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidin-4-one (466 mg, 1.54 mmol), Pd(PPh₃)₄ (139 mg, 0.12 mmol), 1 M aq Na₂CO₃ (3.1 mL) in PhMe/EtOH (14 mL, 2:1 mixture) under Ar was heated under microwave irradiation at 125° C. for 3 h. The reaction mixture was diluted with EtOAc (42 mL) and washed it with H₂O (2×15 mL) followed by brine (20 mL), dried (Na₂SO₄), and concentrated under vacuum. Purification by flash chromatography (100 g SiO₂, 0-10% MeOH in DCM; then 25 g SiO₂ column; 0-40% MeOH in DCM) gave the title compound (light brown solid, 300 mg, 39%). MS ESI 500.2 [M+H]⁺, calcd for [C₂₈H₃₀N₄O₃S+H]⁺ 500.6.

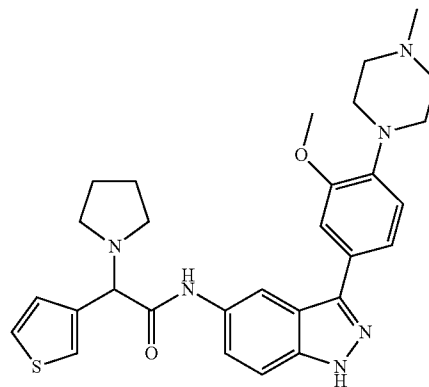
B. N-(3-(4-(4-hydroxypiperidin-1-yl)phenyl)-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide

[0513] To a solution of N-(3-(4-(4-oxopiperidin-1-yl)phenyl)-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide (340 mg, 0.68 mmol) in a mixture of DCM (3.4 mL) and MeOH (6.8 mL) was added NaBH₄ (52 mg, 1.36 mmol) in two lots at rt. The reaction mixture was stirred at rt for 5 h, and then concentrated under reduced pressure. The residue treated with 25% aq NH₄Cl solution (10 mL) and the product was extracted with EtOAc (100 mL, 25 mL), washed with H₂O followed by brine, dried (Na₂SO₄), and concentrated under vacuum. Purification by RP HPLC provided the title compound as a TFA salt (yellow solid, 230 g, 46%). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.42 (m, 1H), 8.13 (dd, J=6.8 Hz, J=2 Hz, 2H), 7.89 (dd, J=2.8 Hz, J=1.2 Hz, 1H), 7.79 (s, 1H), 7.77 (s, 1H), 7.64-7.62 (m, 1H), 7.59-7.53 (m, 2H), 7.39 (dd, J=4.8 Hz, J=1.2 Hz, 1H), 5.36 (s, 1H), 4.12-4.1 (m, 1H), 3.90-3.85 (m, 3H), 3.66-3.61 (m, 2H), 3.30-3.05 (br.m, 2H), 2.29-2.01 (br.m, 8H), 1H merged with solvent peak; MS ESI 502.1 [M+H]⁺, calcd for [C₂₈H₃₁N₅O₂S+H]⁺ 502.2.

Example A10

N-(3-(3-methoxy-4-(4-methylpiperazin-1-yl)phenyl)-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide

[0514]

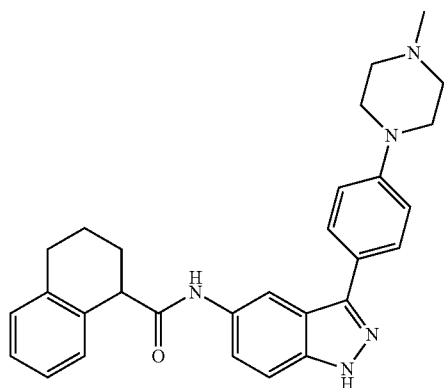


[0515] The title compound was synthesized according to the General Method C, utilizing N-(3-iodo-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide (50 mg, 0.11 mmol), 1-(2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-4-methylpiperazine (43 mg, 0.13 mmol), PdCl₂dppf (4.5 mg, 0.0055 mmol), satd. aq Na₂CO₃ (0.5 mL), and 1.5 mL of PhMe:EtOH (1:1). The vial was charged with Ar and heated in the microwave reactor at 125° C. for 2 h. Purification by RP HPLC, followed by flash chromatography (SiO₂, Biotage 25 g, 5-25% MeOH in CH₂Cl₂) to give the title compound (white solid, 11 mg, 19%). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.40 (s, 1H), 7.44-7.55 (m, 5H), 7.39-7.44 (m, 1H), 7.33 (d, J=5.3 Hz, 1H), 7.09 (d, J=7.8 Hz, 1H), 4.18 (s, 1H), 3.97 (s, 3H), 3.08-3.24 (m, 4H), 2.73 (br. s, 6H), 2.49-2.59 (m, 2H), 2.42 (s, 3H), 1.86 (br. s, 4H); MS ESI 531.4 [M+H]⁺, calcd for [C₂₉H₃₄N₆O₂S+H]⁺ 531.3.

Example A11

N-(3-(4-(4-methylpiperazin-1-yl)phenyl)-1H-indazol-5-yl)-1,2,3,4-tetrahydronaphthalene-1-carboxamide

[0516]

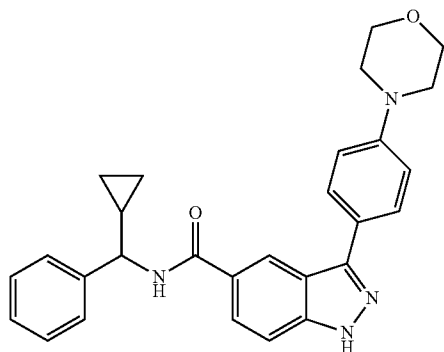


[0517] To a mixture of N-(3-iodo-1H-indazol-5-yl)-1,2,3,4-tetrahydronaphthalene-1-carboxamide (167 mg, 0.4 mmol) and 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazine (121 mg, 0.4 mmol) in EtOH (12 mL) was added 1 M aq Na₂CO₃ (0.8 mL, 0.8 mmol), followed by Pd(PPh₃)₄ (23 mg, 0.02 mmol). The resulting mixture was purged with Ar and microwaved 3 h at 125° C. After removal of solvents, it was redissolved in DMF (5 mL), filtered and purified by prep-HPLC to give the title compound as white solid (135 mg, 59%) in TFA salt. ¹H NMR (400 MHz, CD₃OD) δ 8.50 (s, 1H), 7.54 (d, J=8.0 Hz, 2H), 7.48 (s, 2H), 7.10 (d, J=7.2 Hz, 1H), 7.07-6.97 (m, 3H), 6.86 (d, J=8.4 Hz, 2H), 3.88 (t, J=6.6 Hz, 1H), 3.61 (d, J=11.2 Hz, 2H), 3.37 (d, J=10.0 Hz, 2H), 2.94 (quint, J=12.4 Hz, 4H), 2.80-2.63 (m, 5H; s, 3H at 2.75), 2.12-1.95 (m, 3H), 1.71-1.59 (m, 1H); MS ESI 466.3 [M+H]⁺, calcd for [C₂₉H₃₁N₅O+H]⁺ 466.3.

Example A12

N-(cyclopropyl(phenyl)methyl)-3-(4-morpholinophenyl)-1H-indazole-5-carboxamide

[0518]

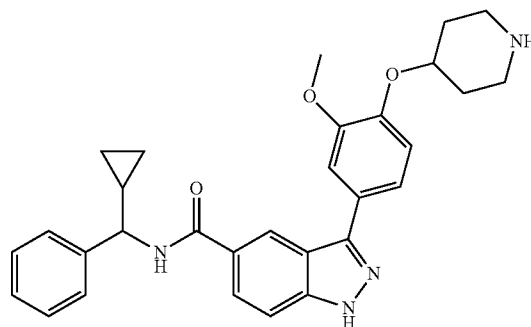


[0519] The title compound was synthesized according to the General Method C, utilizing N-(cyclopropyl(phenyl)methyl)-3-iodo-1H-indazole-5-carboxamide (50 mg, 0.12 mmol), 4-morpholinophenylboronic acid pinacol ester (40 mg, 0.14 mmol), PdCl₂dppf (4.9 mg, 0.006 mmol), satd. Na₂CO₃ (0.5 mL), and 1.5 mL of PhMe:EtOH (1:1). The vial was charged with Ar and heated in the microwave reactor at 125° C. for 2 h. Purification by RP HPLC, followed by trituration with Et₂O gave the title compound as a TFA salt (beige solid, 11 mg, 16%). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.60 (s, 1H), 7.87-7.98 (m, 3H), 7.58 (d, J=8.8 Hz, 1H), 7.47 (d, J=7.0 Hz, 2H), 7.31 (t, J=7.2 Hz, 2H), 7.22 (t, J=6.8 Hz, 1H), 7.15 (d, J=7.8 Hz, 2H), 4.48 (d, J=9.5 Hz, 1H), 3.86 (br. s, 4H), 3.25 (br. s, 4H), 1.34-1.44 (m, 1H), 0.64 (m, 2H), 0.46 (m, 2H); MS ESI 453.3 [M+H]⁺, calcd for [C₂₈H₂₈N₄O₂+H]⁺ 453.2.

Example A13

N-(cyclopropyl(phenyl)methyl)-3-(3-methoxy-4-(piperidin-4-yloxy)phenyl)-1H-indazole-5-carboxamide

[0520]

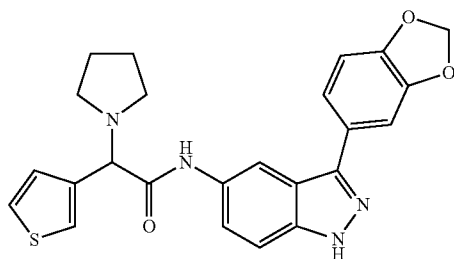


[0521] The title compound was synthesized according to the General Method C, utilizing N-(cyclopropyl(phenyl)methyl)-3-iodo-1H-indazole-5-carboxamide (50 mg, 0.12 mmol), 4-(1-boc-piperidin-4-yloxy)-3-methoxyphenyl boronic acid (49 mg, 0.14 mmol), PdCl₂dppf (4.9 mg, 0.006 mmol), satd. Na₂CO₃ (0.5 mL), and 1.5 mL of PhMe:EtOH (1:1). The vial was charged with Ar and heated in the microwave reactor at 125° C. for 2 h. The mixture was purified by RPHPLC, treated with DCM/TFA for 1 h, followed by trituration with Et₂O to give the title compound as a TFA salt (white solid, 25 mg, 34%). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.59 (s, 1H), 7.95 (d, J=8.5 Hz, 1H), 7.54-7.66 (m, 3H), 7.48 (d, J=7.3 Hz, 2H), 7.33 (t, J=7.7 Hz, 2H), 7.17-7.27 (m, 2H), 4.69 (br. s, 1H), 4.48 (d, J=9.5 Hz, 1H), 3.96 (s, 3H), 3.44-3.55 (m, 2H), 3.18-3.27 (m, 2H), 2.11 (m, 4H), 1.34-1.46 (m, 1H), 0.66 (d, J=8.3 Hz, 2H), 0.41-0.54 (m, 2H); MS ESI 497.4 [M+H]⁺, calcd for [C₃₀H₃₂N₄O₃+H]⁺ 497.3.

Example A14

N-(3-(benzo[d][1,3]dioxol-5-yl)-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide

[0522]

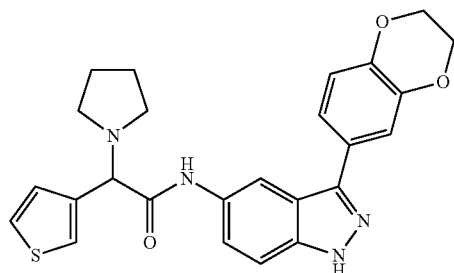


[0523] To a mixture of N-(3-iodo-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide (90 mg, 0.2 mmol) and 2-(benzo[d][1,3]dioxol-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (50 mg, 0.2 mmol) in EtOH (4.5 mL) was added 1 M aq Na₂CO₃ (0.4 mL, 0.4 mmol), followed by Pd(PPh₃)₄ (11.6 mg, 0.01 mmol). The resulting mixture was purged with Ar and microwaved 2.5 h at 125° C. After removal of solvents, it was redissolved in DMF (5 mL), filtered and purified by prep-HPLC twice to give the title compound as light brown solid (49.3 mg, 44%) in TFA salt. ¹H NMR (400 MHz, CD₃OD) δ 8.35 (t, J=1.2 Hz, 1H), 7.87 (dd, J=2.8 Hz, 1.2 Hz, 1H), 7.63 (dd, J=5.0 Hz, 3.0 Hz, 1H), 7.54-7.47 (m, 2H), 7.39-7.36 (m, 2H), 7.34 (d, J=1.6 Hz, 1H), 6.95 (d, J=8.0 Hz, 1H), 6.01 (s, 2H), 5.28 (s, 1H), 3.87 (brs, 1H), 3.35-3.05 (m, 3H), 2.30-1.90 (m, 4H); MS ESI 447.2 [M+H]⁺, calcd for [C₂₄H₂₂N₄O₃+H]⁺ 447.1

Example A15

N-(3-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide

[0524]



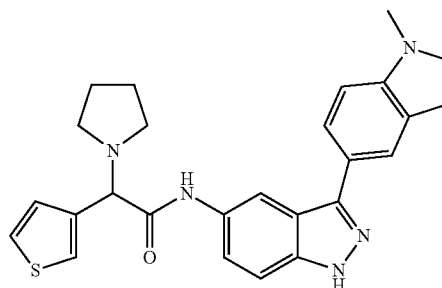
[0525] To a mixture of N-(3-iodo-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide (90 mg, 0.2 mmol) and 2-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (54 mg, 0.2 mmol) in EtOH (4.5 mL) was added 1 M aq Na₂CO₃ (0.4 mL, 0.4 mmol), followed by Pd(PPh₃)₄ (11.6 mg, 0.01 mmol). The resulting mixture was purged with Ar and microwaved 2.5 h at 125° C. After removal of solvents, it was redissolved in DMF (5 mL), filtered and purified by prep-HPLC to give the title compound

as a TFA salt (light brown solid, 58.8 mg, 51%). ¹H NMR (400 MHz, CD₃OD) δ 8.35 (t, J=0.8 Hz, 1H), 7.86 (dd, J=2.8 Hz, 1.2 Hz, 1H), 7.62 (dd, J=5.0 Hz, 3.0 Hz, 1H), 7.50 (s, 2H), 7.39-7.34 (m, 3H), 6.94 (d, J=8.8 Hz, 1H), 5.27 (s, 1H), 4.28 (s, 4H), 3.86 (brs, 1H), 3.35-3.05 (m, 3H), 2.30-1.90 (m, 4H); MS ESI 461.2 [M+H]⁺, calcd for [C₂₅H₂₄N₄O₃S+H]⁺ 461.2

Example A16

N-(3-(1-methylindolin-5-yl)-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide

[0526]

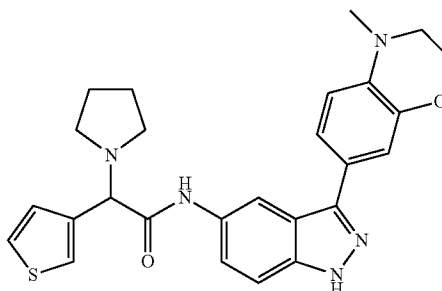


[0527] To a mixture of N-(3-iodo-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide (90 mg, 0.2 mmol) and 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indoline (52 mg, 0.2 mmol) in EtOH (4.5 mL) was added 1 M aq Na₂CO₃ (0.4 mL, 0.4 mmol), followed by Pd(PPh₃)₄ (11.6 mg, 0.01 mmol). The resulting mixture was purged with Ar and microwaved 2.5 h at 125° C. After removal of solvents, it was redissolved in DMF (5 mL), filtered and purified by prep-HPLC to give the title compound as a TFA salt (brown solid, 27.2 mg, 24%). ¹H NMR (400 MHz, CD₃OD) δ 8.36 (t, J=1.2 Hz, 1H), 7.88 (dd, J=2.8 Hz, 1.2 Hz, 1H), 7.83-7.79 (m, 2H), 7.64 (dd, J=5.2 Hz, 2.8 Hz, 1H), 7.55 (pseudo s, 2H), 7.38 (dd, J=4.8 Hz, 1.2 Hz, 1H), 7.18 (d, J=8.4 Hz, 1H), 5.28 (s, 1H), 3.88 (brs, 1H), 3.70 (t, J=7.6 Hz, 2H), 3.27-3.04 (m, 8H; s, 3H at 2.86), 2.30-1.90 (m, 4H); MS ESI 458.1 [M+H]⁺, calcd for [C₂₆H₂₇N₅OS+H]⁺ 458.2.

Example A17

N-(3-(4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide

[0528]

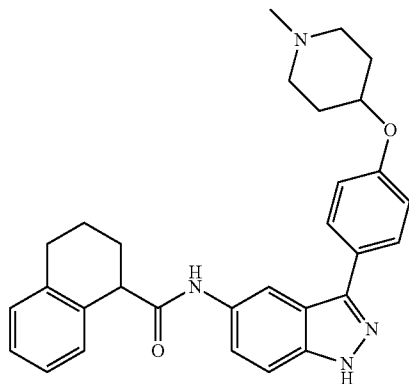


[0529] To a mixture of N-(3-iodo-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide (90 mg, 0.2 mmol) and 4-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydro-2H-benzo[b][1,4]oxazine (55 mg, 0.2 mmol) in EtOH (4.5 mL) was added 1 M aq Na₂CO₃ (0.4 mL, 0.4 mmol), followed by Pd(PPh₃)₄ (11.6 mg, 0.01 mmol). The resulting mixture was purged with Ar and microwaved 2.5 h at 125° C. After removal of solvents, it was redissolved in DMF (5 mL), filtered and purified by prep-HPLC to give the title compound as a TFA salt (dark yellow solid, 37.4 mg, 32%) in TFA salt. ¹H NMR (400 MHz, CD₃OD) δ 8.36 (s, 1H), 7.86 (d, J=2.0 Hz, 1H), 7.64 (dd, J=4.8 Hz, 2.8 Hz, 1H), 7.50 (s, 2H), 7.39-7.33 (m, 2H), 7.25 (d, J=1.6 Hz, 1H), 6.83 (d, J=8.4 Hz, 1H), 5.24 (s, 1H), 4.31 (t, J=4.2 Hz, 1H), 3.87 (brs, 1H), 3.35-3.05 (m, 5H), 2.95 (s, 3H), 2.27-1.92 (m, 4H); MS ESI 474.2 [M+H]⁺, calcd for [C₂₆H₂₇N₅O₂S+H]⁺ 474.2.

Example A18

N-(3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazol-5-yl)-1,2,3,4-tetrahydronaphthalene-1-carboxamide

[0530]

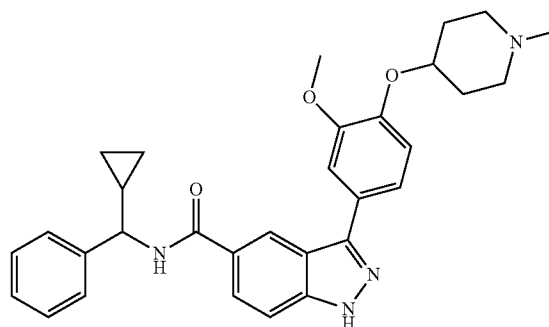


[0531] To a mixture of N-(3-iodo-1H-indazol-5-yl)-1,2,3,4-tetrahydronaphthalene-1-carboxamide (167 mg, 0.4 mmol) and 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine (130 mg, 0.44 mmol) in EtOH (10 mL) was added 1 M aq Na₂CO₃ (0.8 mL, 0.8 mmol), followed by Pd(PPh₃)₄ (23 mg, 0.02 mmol). The resulting mixture was purged with Ar and microwaved 2 h at 130° C. After removal of solvents, it was redissolved in DMF/TFA (5 mL/0.5 mL), filtered and purified by prep-HPLC to give the title compound as a TFA salt (white solid, 130 mg, 55%). ¹H NMR (400 MHz, CD₃OD) δ 8.49 (s, 1H), 7.85-7.77 (m, 2H), 7.54-7.46 (m, 2H), 7.16-6.97 (m, 6H), 4.65-4.61 (m, 0.7H), 4.50-4.42 (m, 0.3H), 3.91 (t, J=7.0 Hz, 1H), 3.50-3.44 (m, 0.7H), 3.30-3.17 (m, 2.8H; partially overlapped with CD₃OD solvent residue), 3.07-2.98 (m, 0.7H), 2.86-2.70 (m, 5.3H), 2.27-1.65 (m, 8H); MS ESI 481.3 [M+H]⁺, calcd for [C₃₀H₃₂N₄O₂+H]⁺ 481.3.

Example A19

N-(cyclopropyl(phenyl)methyl)-3-(3-methoxy-4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazole-5-carboxamide

[0532]

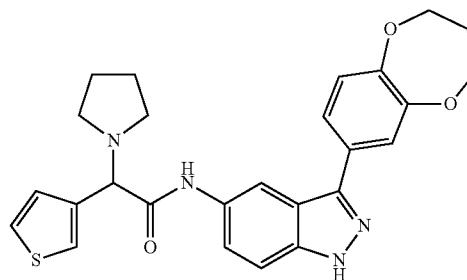


[0533] The title compound was synthesized according to the General Method C, utilizing N-(cyclopropyl(phenyl)methyl)-3-iodo-1H-indazole-5-carboxamide (70 mg, 0.17 mmol), 4-(2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)-1-methylpiperidine (70 mg, 0.20 mmol), PdCl₂dppf (6.9 mg, 0.0085 mmol), satd. Na₂CO₃ (0.5 mL), and 1.5 mL of PhMe:EtOH (1:1). The vial was charged with Ar and heated in the microwave reactor at 125° C. for 2 h. Purification by RPHPLC, followed by trituration with Et₂O gave the title compound as a TFA salt (white solid, 26 mg, 25%). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.59 (s, 1H), 7.95 (d, J=8.3 Hz, 1H), 7.52-7.67 (m, 3H), 7.48 (d, J=7.0 Hz, 2H), 7.33 (t, J=7.0 Hz, 2H), 7.13-7.28 (m, 2H), 4.71 (br s., 1H), 4.51-4.59 (m, 0.3 H), 4.48 (br t., J=8.2 Hz, 1H), 3.90-4.02 (m, 3H), 3.56-3.67 (m, 0.7H), 3.37-3.52 (m, 1.3H), 3.07-3.19 (m, 0.7H), 2.84-2.97 (m, 3H), 1.87-2.43 (m, 5H), 1.35-1.45 (m, 1H), 0.65 (d, J=7.8 Hz, 2H), 0.37-0.54 (m, 2H); MS ESI 511.6 [M+H]⁺, calcd for [C₃₁H₃₄N₄O₃+H]⁺ 511.3.

Example A20

N-(3-(3,4-dihydro-2H-benzo[b][1,4]dioxepin-7-yl)-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide

[0534]

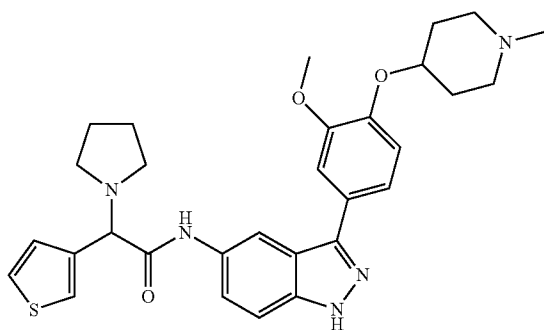


[0535] To a mixture of N-(3-iodo-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide (90 mg, 0.2 mmol) and (3,4-dihydro-2H-benzo[b][1,4]dioxepin-7-yl)boronic acid (39 mg, 0.2 mmol) in EtOH (4.5 mL) was added 1 M aq Na_2CO_3 (0.4 mL, 0.4 mmol), followed by $\text{Pd}(\text{PPh}_3)_4$ (11.6 mg, 0.01 mmol). The resulting mixture was purged with Ar and microwaved 2.5 h at 125° C. After removal of solvents, it was redissolved in DMF (5 mL), filtered, purified by prep-HPLC twice and triturated with Et_2O to give the title compound as a TFA salt (light brown solid, 33.5 mg, 28%). ^1H NMR (400 MHz, CD_3OD) δ 8.36 (s, 1H), 7.87 (dd, $J=2.8$ Hz, $J=1.2$ Hz, 1H), 7.64 (dd, $J=5.0$ Hz, 3.0 Hz, 1H), 7.52 (d, $J=1.2$ Hz, 2H), 7.49 (d, $J=2.0$ Hz, 1H), 7.46 (dd, $J=8.2$ Hz, 2.2 Hz, 1H), 7.38 (dd, $J=4.8$ Hz, 1.2 Hz, 1H), 7.08 (d, $J=8.4$ Hz, 1H), 5.26 (s, 1H), 4.27-4.18 (m, 4H), 3.87 (brs, 1H), 3.35-3.05 (m, 3H), 2.25-1.93 (m, 6H); MS ESI 475.3 $[\text{M}+\text{H}]^+$, calcd for $[\text{C}_{26}\text{H}_{26}\text{N}_4\text{O}_3\text{S}+\text{H}]^+$ 475.2.

Example A21

N-(3-(3-methoxy-4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide

[0536]

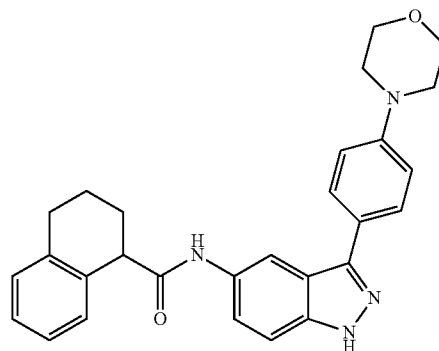


[0537] The title compound was synthesized according to the General Method C, utilizing N-(3-iodo-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide (76 mg, 0.17 mmol), 4-(2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)-1-methylpiperidine (70 mg, 0.20 mmol), PdCl_2dppf (6.9 mg, 0.0085 mmol), satd. aq Na_2CO_3 (0.5 mL), and 1.5 mL of PhMe:EtOH (1:1). The vial was charged with Ar and heated in the microwave reactor at 125° C. for 2 h. Purification by RPHPLC, followed by trituration with Et_2O gave the title compound as a bis-TFA salt (light brown solid, 41 mg, 31%). ^1H NMR (400 MHz, CD_3OD) δ ppm 8.45 (s, 1H), 7.87 (s, 1H), 7.63 (br. s., 1H), 7.42-7.59 (m, 4H), 7.37 (d, $J=4.8$ Hz, 1H), 7.20 (d, $J=8.0$ Hz, 1H), 5.29 (s, 1H), 4.65-4.76 (m, 1H), 4.50-4.61 (m, 0.3 H), 3.98 (s, 3H), 3.55-3.69 (m, 0.7H), 3.37-3.54 (m, 4H), 3.06-3.27 (m, 3H), 2.93 (s, 3H), 1.89-2.50 (m, 8H); MS ESI 546.1 $[\text{M}+\text{H}]^+$, calcd for $[\text{C}_{30}\text{H}_{35}\text{N}_5\text{O}_3\text{S}+\text{H}]^+$ 546.3.

Example A22

N-(3-(4-morpholinophenyl)-1H-indazol-5-yl)-1,2,3,4-tetrahydronaphthalene-1-carboxamide

[0538]

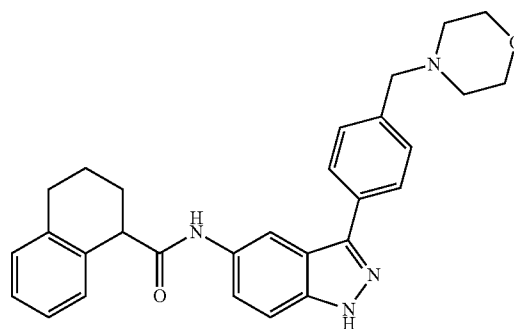


[0539] To a mixture of N-(3-iodo-1H-indazol-5-yl)-1,2,3,4-tetrahydronaphthalene-1-carboxamide (167 mg, 0.4 mmol) and (4-morpholinophenyl)boronic acid (91 mg, 0.44 mmol) in EtOH (12 mL) was added 1 M aq Na_2CO_3 (0.8 mL, 0.8 mmol), followed by $\text{Pd}(\text{PPh}_3)_4$ (23 mg, 0.02 mmol). The resulting mixture was purged with Ar and microwaved 2 h at 125° C. After removal of solvents, it was purified by flash chromatography (MeOH/DCM 0-10%) and prep-HPLC to give the title compound as a TFA salt (light yellow solid, 59.8 mg, 26%). ^1H NMR (400 MHz, CD_3OD) δ 8.49 (s, 1H), 8.43 (d, $J=8.8$ Hz, 2H), 7.49 (s, 2H), 7.16-7.02 (m, 6H), 3.90 (t, $J=7.0$ Hz, 1H), 3.81 (t, $J=4.6$ Hz, 4H), 3.19 (brs, 4H), 2.89-2.70 (m, 2H), 2.18-2.02 (m, 3H), 1.77-1.67 (m, 1H); MS ESI 453.3 $[\text{M}+\text{H}]^+$, calcd for $[\text{C}_{28}\text{H}_{28}\text{N}_4\text{O}_2+\text{H}]^+$ 453.2.

Example A23

N-(3-(4-(morpholinomethyl)phenyl)-1H-indazol-5-yl)-1,2,3,4-tetrahydronaphthalene-1-carboxamide

[0540]

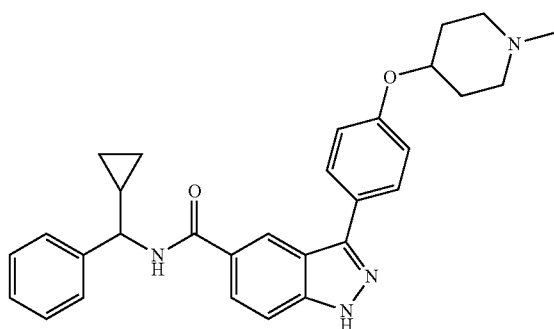


[0541] To a mixture of N-(3-iodo-1H-indazol-5-yl)-1,2,3,4-tetrahydronaphthalene-1-carboxamide (167 mg, 0.4 mmol) and 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)morpholine (121 mg, 0.4 mmol) in EtOH (12 mL) was added 1 M aq Na₂CO₃ (0.8 mL, 0.8 mmol), followed by Pd(PPh₃)₄ (23 mg, 0.02 mmol). The resulting mixture was purged with Ar and microwaved 2 h at 125° C. After removal of solvents, it was redissolved in DMF/TFA (6 mL/0.5 mL) and purified by prep-HPLC to give the title compound as a TFA salt (white solid, 135 mg, 58%). ¹H NMR (400 MHz, CD₃OD) δ 8.50 (s, 1H), 7.98 (d, J=8.0 Hz, 2H), 7.56-7.47 (m, 4H), 7.15 (d, J=7.2 Hz, 1H), 7.12-7.03 (m, 3H), 4.26 (s, 2H), 3.98-3.88 (m, 3H), 3.67 (t, J=12.0 Hz, 2H), 3.28 (d, J=11.6 Hz, 2H), 3.08 (t, J=10.8 Hz, 2H), 2.86-2.69 (m, 2H), 2.20-2.02 (m, 3H), 1.77-1.67 (m, 1H); MS ESI 467.3 [M+H]⁺, calcd for [C₂₉H₃₀N₄O₂+H]⁺ 467.2.

Example A24

N-(cyclopropyl(phenyl)methyl)-3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazole-5-carboxamide

[0542]

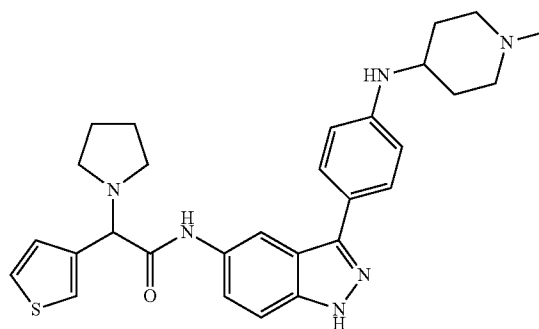


[0543] The title compound was synthesized according to the General Method C, utilizing N-(cyclopropyl(phenyl)methyl)-3-iodo-1H-indazole-5-carboxamide (200 mg, 0.48 mmol), 4-((1-methylpiperidin-4-yl)oxy)phenylboronic acid pinacol ester (152 mg, 0.48 mmol), PdCl₂dppf (20 mg, 0.024 mmol), satd. Na₂CO₃ (1.25 mL), and 3.75 mL of PhMe:EtOH (1:1). The vial was charged with Ar and heated in the microwave reactor at 125° C. for 2 h. Purification by RP HPLC, followed by flash chromatography (SiO₂, Biotage 25 g, 0-30% MeOH in CH₂Cl₂) gave the title compound (white solid, 80 mg, 35%). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.60 (s, 1H), 7.95 (d, J=9.0 Hz, 1H), 7.90 (d, J=8.8 Hz, 2H), 7.59 (d, J=8.8 Hz, 1H), 7.47 (d, J=7.5 Hz, 2H), 7.31 (t, J=7.5 Hz, 2H), 7.22 (t, J=7.5 Hz, 1H), 7.08 (d, J=8.8 Hz, 2H), 4.55 (br. s, 1H), 4.47 (d, J=9.3 Hz, 1H), 2.91-3.03 (m, 2H), 2.63-2.76 (m, 2H), 2.50 (s, 3H), 2.02-2.14 (m, 2H), 1.85-1.98 (m, 2H), 1.34-1.44 (m, 1H), 0.64 (d, J=8.3 Hz, 2H), 0.45 (dd, J=9.5, 4.52 Hz, 2H); MS ESI 481.4 [M+H]⁺, calcd for [C₃₀H₃₂N₄O₂+H]⁺ 481.3

Example A25

N-(3-(4-((1-methylpiperidin-4-yl)amino) phenyl)-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-thiophen-3-yl)acetamide

[0544]



A. 1-methyl-N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidin-4-amine

[0545] NaBH(OAc)₃ (290 mg, 1.36 mmol) was added to a solution of N-methyl-4-piperidone (155 mg, 1.36 mmol) in 1,2-dichloroethane (10 mL) at rt. Then 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (200 mg, 0.912 mmol) and 2-3 drop of acetic acid under N₂ were added to the mixture at rt and stirring was continued for 18 h. Satd aqNaHCO₃ (10 mL) was added in one lot at the same temperature and the mixture was stirred for 15 min. DCM (10 mL) was then added and the layers were separated. The aq. layer was extracted using DCM (10 mL), and the combined organic layer was washed with brine and dried (Na₂SO₄). Then solvent was removed under vacuum. The resultant oily residue purified by Biotage (25 g SiO₂ column, 0-50% MeOH in DCM) to give the title compound (cream solid, 84 mg, 29%). ¹H NMR (400 MHz, CDCl₃) δ 7.63 (d, J=8.8 Hz, 2H), 6.58 (d, J=8.8 Hz, 2H), 3.77 (d, J=7.6 Hz, 1H), 3.35 (br.s, 1H), 2.82-2.79 (br.d, 1H), 2.30 (s, 3H), 2.14 (t, J=1.2 Hz, 2H), 2.07-2.03 (m, 2H), 1.66 (br.s, 1H), 1.54-1.45 (m, 2H), 1.32 (s, 12H); MS ESI 317.1[M+H]⁺, calcd for [C₁₈H₂₉BN₂O₂+H]⁺ 317.2.

B. N-(3-(4-((1-methylpiperidin-4-yl)amino) phenyl)-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-thiophen-3-yl)acetamide

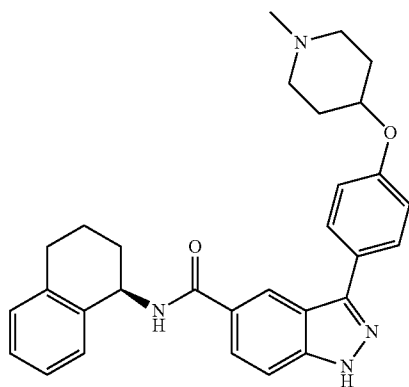
[0546] The title compound was synthesized according to general Method C by using a sealed degassed mixture of N-(3-iodo-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide (50 mg, 0.11 mmol), 1-methyl-N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidin-4-amine (42 mg, 0.13 mmol), Pd (PPh₃)₄ (7 mg, 0.005 mmol), 1 M aq Na₂CO₃ (0.22 mL) in PhMe/EtOH (2.25 mL, 1:0.5 mixture) under Ar was heated under microwave irradiation at 125° C. for 2 h. The reaction mixture was diluted with EtOAc (10 mL) and washed with H₂O and brine (5 mL each), dried (Na₂SO₄), and concentrated under vacuum to give brown oily residue. The crude product was purified by Biotage (100 g SiO₂, 0-10% 2 M NH₃-MeOH in DCM; then RP column C18 60 g, 10-80% MeOH in 0.1% TFA-H₂O) to

give the title compound as a TFA salt (pale yellow solid, 9 mg, 11%). ¹H NMR (400 MHz, CD₃OD) δ 8.34 (s, 1H), 7.87 (t, J=1.6 Hz, 1H), 7.72 (d, J=8.4 Hz, 2H), 7.66 (dd, J=3.2 Hz, J=5.2 Hz, 1H), 7.53-7.50 (m, 2H), 7.38 (dd, J=4.8 Hz, J=1.2 Hz, 2H), 6.89-6.85 (m, 2H), 5.23 (s, 1H), 4.44 (t, J=4.8 Hz, 1H), 3.88-3.60 (br.m, 4H), 3.26-3.09 (br.m, 4H), 2.92 (s, 3H), 2.38-2.34 (br.m, 2H), 2.24-2.15 (br.m, 4H), 2.01-1.97 (br.m, 1H), 1.79-1.70 (br.m, 1H); MS ESI 515.1 [M+H]⁺, calcd for [C₂₉H₃₄N₆OS+H]⁺ 515.2.

Example A26

(R)-3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-N-(1,2,3,4-tetrahydronaphthalen-1-yl)-1H-indazole-5-carboxamide

[0547]



[0548] To a solution of (R)-1,2,3,4-tetrahydronaphthalen-1-amine (735 mg, 5 mmol), 1H-indazole-5-carboxylic acid (810 g, 5 mmol) in DMF (30 mL) was added ^tPr₂NEt (2.61 mL, 15 mmol), followed by TBTU (1.605 g, 5 mmol). The resulting mixture was stirred for 2 h at 0° C. Attempted iodination failed so was quenched with Na₂S₂O₃/H₂O to give (R)-N-(1,2,3,4-tetrahydronaphthalen-1-yl)-1H-indazole-5-carboxamide (orange solid, 1.64 g, may contain H₂O). ¹H NMR (400 MHz, DMSO-d₆) δ 0.79 (s, 1H), 8.76 (d, J=8.4 Hz, 1H), 8.39 (s, 1H), 8.18 (s, 1H), 7.92 (dd, J=8.6 Hz, 1.4 Hz, 1H), 7.56 (d, J=8.8 Hz, 1H), 7.23-7.10 (m, 4H), 5.30-5.20 (m, 1H), 2.85-2.70 (m, 2H), 2.05-1.90 (m, 2H), 1.90-1.70 (m, 2H); MS ESI 292.1 [M+H]⁺, calcd for [C₁₈H₁₇N₃O+H]⁺ 292.1.

[0549] A solution of (R)-N-(1,2,3,4-tetrahydronaphthalen-1-yl)-1H-indazole-5-carboxamide (29.1 mg, 0.1 mmol), NBS (19.6 mg, 0.11 mmol) in EtOH (5 mL) was refluxed for 1 h. Additional (R)-N-(1,2,3,4-tetrahydronaphthalen-1-yl)-1H-indazole-5-carboxamide (582 mg, 2 mmol), NBS (392 mg, 2.2 mmol) and EtOH (30 mL) were added and it was refluxed for 4 h. After removal of solvents, it was purified by flash chromatography (MeOH/DCM 0-10%) to give crude (R)-3-bromo-N-(1,2,3,4-tetrahydronaphthalen-1-yl)-1H-indazole-5-carboxamide (dark beige solid, 0.77 g). ¹H NMR (400 MHz, CDCl₃) δ 6 MS ESI 370.0 [M+H]⁺, calcd for [C₁₈H₁₆BrN₃O+H]⁺ 370.0.

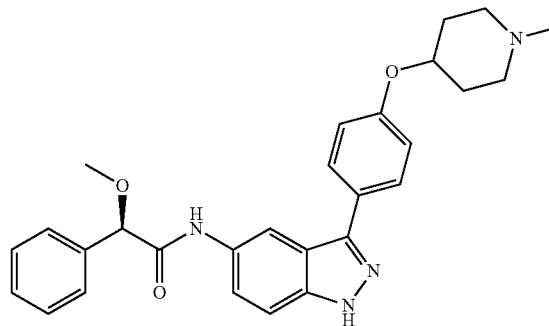
[0550] To a mixture of (R)-3-bromo-N-(1,2,3,4-tetrahydronaphthalen-1-yl)-1H-indazole-5-carboxamide (163 mg, 0.44 mmol) and 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine (127 mg, 0.4 mmol) in

EtOH (12 mL) was added 1 M aq Na₂CO₃ (0.8 mL, 0.8 mmol), followed by Pd(PPh₃)₄ (23 mg, 0.02 mmol). The resulting mixture was purged with Ar and microwaved 2 h at 130° C. After removal of solvents, it was redissolved in DMF/TFA (6 mL/0.5 mL) and purified by prep-HPLC to give the title compound as a TFA salt (white solid, 85 mg, 36%). ¹H NMR (400 MHz, CD₃OD) δ 8.59 (s, 1H), 7.97-7.88 (m, 3H), 7.58 (d, J=8.0 Hz, 1H), 7.27-7.23 (m, 1H), 7.14-7.05 (m, 5H), 5.35 (t, J=6.6 Hz, 1H), 4.80-4.76 (m, 0.7H), 4.65-4.56 (m, 0.3H), 3.64-3.57 (m, 0.7H), 3.43-3.28 (m, 2.6H; partially overlapped with CD₃OD solvent residue), 3.21-3.13 (m, 0.7H), 2.91 (s, 3H), 2.90-2.72 (m, 2H), 2.42-1.76 (m, 8H); MS ESI 481.4 [M+H]⁺, calcd for [C₃₀H₃₂N₄O₂+H]⁺ 481.3.

Example A27

(R)-2-methoxy-N-(3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazol-5-yl)-2-phenylacetamide

[0551]

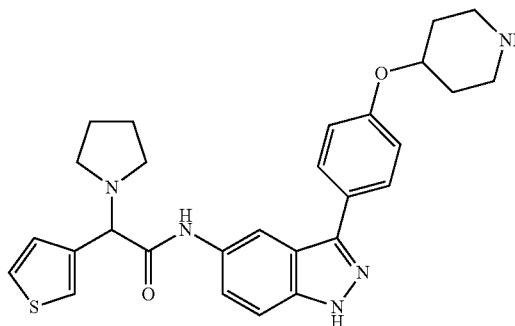


The title compound was synthesized according to the General Method C utilizing ((R)-N-(3-iodo-1H-indazol-5-yl)-2-methoxy-2-phenylacetamide (0.060 g, 0.15 mmol), 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine (71 mg, 0.22 mmol), PdCl₂dppf/CH₂Cl₂ (7 mg, 0.09 mmol), satd aq Na₂CO₃ (0.5 mL) in PhMe (1.5 mL) and EtOH (1.5 mL) under microwave heating (130° C., 90 min). The title compound was isolated as a white powder (42.5 mg, 60%). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.36 (d, J=1.00 Hz, 1H), 7.83 (d, J=8.78 Hz, 2H), 7.47-7.59 (m, 4H), 7.31-7.45 (m, 3H), 7.07 (d, J=8.78 Hz, 2H), 4.83 (s, 1H), 4.52 (br. s., 1H), 3.46 (s, 3H), 2.85 (br. s., 2H), 2.55 (br. s., 2H), 2.42 (s, 3H), 1.98-2.12 (m, 2H), 1.93-1.82 (br. s., 2H); MS ESI [M+H]⁺ 471.3, calcd for [C₂₈H₃₀N₄O₃+H]⁺ 471.2.

Example A28

N-(3-(4-(piperidin-4-yloxy)phenyl)-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide

[0552]



A. tert-butyl 4-(4-(5-(2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamido)-1H-indazol-3-yl)phenoxy)piperidine-1-carboxylate

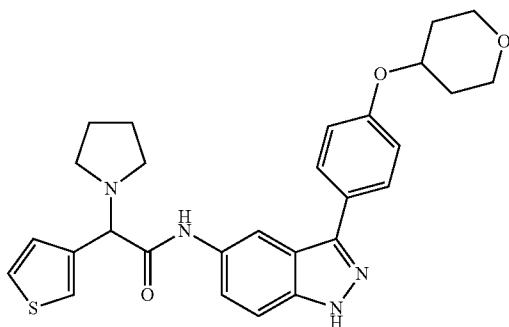
[0553] Using Method C2, N-(3-iodo-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide (132.8 mg, 0.294 mmol) and tert-butyl 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine-1-carboxylate (142.3 mg, 0.352 mmol) gave the title compound after 3 h at 120° C. in the microwave (102.7 mg, 58%) after work-up using a PoraPak Rxn CX followed by purification by flash chromatography (SiO₂, 50-100 EtOAc in DCM). ¹H NMR (400 MHz, CDCl₃) δ ppm 8.42 (s, 1H), 7.89 (d, J=8.8 Hz, 2H), 7.47 (dd, J=8.8, 2.0 Hz, 1H), 7.44 (d, J=8.8 Hz, 1H), 7.34 (s, 1H), 7.29-7.33 (m, 1H), 7.15 (dd, J=5.0, 1.3 Hz, 1H), 7.04 (d, J=8.8 Hz, 2H), 4.54 (dt, J=7.1, 3.6 Hz, 1H), 4.16 (s, 1H), 3.70-3.79 (m, 2H), 3.33-3.41 (m, 2H), 2.67 (d, J=6.8 Hz, 2H), 2.56 (d, J=6.0 Hz, 2H), 1.96 (br. s., 2H), 1.74-1.89 (m, 6H), 1.49 (s, 9H). MS ESI 602.4 [M+H]⁺, calcd for [C₃₃H₃₉N₅O₄S+H]⁺ 602.38.

B. N-(3-(4-(piperidin-4-yloxy)phenyl)-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide

[0554] Tert-butyl 4-(4-(5-(2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamido)-1H-indazol-3-yl)phenoxy)piperidine-1-carboxylate (102 mg, 0.169 mmol) was dissolved in DCM (4 mL) and TFA (1 mL) was added. The resulting mixture was stirred at rt for 3 h. The crude reaction mixture was partitioned between EtOAc (150 mL) and satd aq NaHCO₃ (25 mL). The organic layer was washed with H₂O (25 mL) and brine (25 mL), dried (Na₂SO₄), filtered and concentrated to dryness. Purification by flash chromatography (SiO₂, 0-20% 2 M NH₃-MeOH in DCM) gave the title compound (beige solid, 26.8 mg, 31%). ¹H NMR (400 MHz, CDCl₃) δ ppm 9.25 (s, 1H), 8.41 (d, J=1.0 Hz, 1H), 7.86 (d, J=8.8 Hz, 2H), 7.44 (dd, J=9.0, 1.8 Hz, 1H), 7.40 (d, J=8.6 Hz, 1H), 7.32-7.35 (m, 1H), 7.29-7.32 (m, 1H), 7.15 (dd, J=4.9, 1.1 Hz, 1H), 7.01 (d, J=8.8 Hz, 2H), 4.45 (tt, J=7.7, 3.8 Hz, 1H), 4.16 (s, 1H), 3.15-3.23 (m, 2H), 2.82 (ddd, J=12.4, 8.8, 3.4 Hz, 2H), 2.63-2.71 (m, 2H), 2.51-2.58 (m, 2H), 2.06 (ddt, J=12.7, 6.4, 3.2, 3.2 Hz, 3H), 1.84 (br. s., 4H), 1.75 (dtd, J=12.8, 8.5, 8.5, 3.9 Hz, 2H). MS ESI 502.2 [M+H]⁺, calcd for [C₂₈H₃₁N₅O₂S+H]⁺ 502.23.

Example A29. 2-(pyrrolidin-1-yl)-N-(3-(4-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)-1H-indazol-5-yl)-2-(thiophen-3-yl)acetamide

[0555]

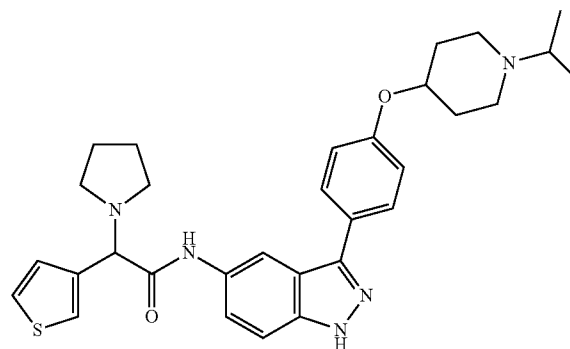


[0556] The title compound was synthesized according to general Method C by using a sealed degassed mixture of N-(3-iodo-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide (800 mg, 1.76 mmol), 4,4,5,5-tetramethyl-2-(4-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)-1,3,2-dioxaborolane (538 mg, 1.76 mmol), Pd(PPh₃)₄ (204 mg, 0.176 mmol), 1 M aq Na₂CO₃ (3.54 mL) in PhMe/EtOH (20 mL, 1:0.5 mixture) under Ar was heated under microwave irradiation at 125° C. for 4 h. The reaction mixture was diluted with EtOAc (120 mL) and washed with H₂O (20 mL) followed by brine (20 mL), dried (Na₂SO₄) and concentrated under vacuum to give brown oily residue. The crude product was purified by Biotage (100 g SiO₂, 0-20% MeOH in DCM; then RP HPLC C18 60 g column, 10-80% MeOH in 0.1% TFA-H₂O) to give the title compound as a TFA salt (light brown solid, 355 mg, 32.5%). ¹H NMR (400 MHz, CD₃OD) δ 8.38 (s, 1H), 7.87-7.80 (m, 3H), 7.64-7.62 (m, 1H), 7.54-7.48 (m, 2H), 7.38 (d, J=5.2 Hz, 1H), 7.09 (d, J=8.4 Hz, 2H), 5.26 (s, 1H), 4.65-4.59 (m, 1H), 3.99-3.86 (br.m, 3H), 3.63-3.57 (br.m, 2H), 3.21-3.08 (br.m, 2H), 2.16-2.03 (br.m, 7H) 1.78-1.72 (br.m, 2H); MS ESI 503.3 [M+H]⁺, calcd for [C₂₈H₃₀N₄O₃S+H]⁺ 503.6.

Example A30

N-(3-(4-((1-isopropylpiperidin-4-yl)oxy)phenyl)-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide

[0557]

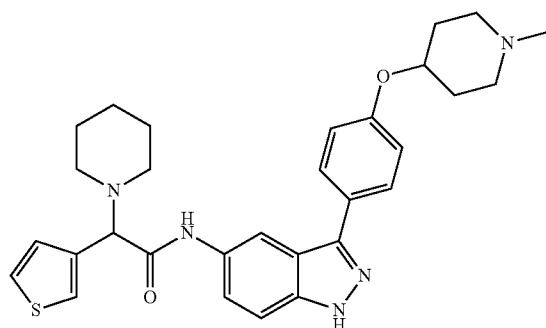


[0558] Using Method C2, N-(3-iodo-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide (53.1 mg, 0.117 mmol) and 1-isopropyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine (47 mg, 0.14 mmol) heated for 3 h at 120° C. in the microwave followed by work-up using a PoraPak RXn CX followed by purification by flash chromatography (RPRPC18, 10-80% MeOH in 0.1% TFA-H₂O; repeated PoraPak work-up; then SiO₂, 0-20% 2 M NH₃-MeOH in DCM) gave the title compound (beige solid, 14.0 mg, 22%). ¹H NMR (400 MHz, CDCl₃) δ ppm 9.23 (s, 1H), 8.39 (d, J=1.3 Hz, 1H), 7.87 (d, J=8.8 Hz, 2H), 7.47 (dd, J=9.0, 1.5 Hz, 1H), 7.39 (d, J=9.0 Hz, 1H), 7.32-7.35 (m, 1H), 7.29-7.32 (m, 1H), 7.15 (dd, J=4.9, 1.1 Hz, 1H), 7.03 (d, J=8.8 Hz, 2H), 4.39 (tt, J=7.3, 3.8 Hz, 1H), 4.15 (s, 1H), 2.77-2.90 (m, 3H), 2.62-2.72 (m, 2H), 2.42-2.59 (m, 4H), 2.03-2.14 (m, 2H), 1.87-1.95 (m, 2H), 1.84 (br. s., 4H), 1.11 (d, J=6.5 Hz, 6H). MS ESI 544.2 [M+H]⁺, calcd for [C₃₁H₃₇N₅O₂S+H]⁺ 544.27.

Example A31

N-(3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazol-5-yl)-2-(piperidin-1-yl)-2-(thiophen-3-yl)acetamide

[0559]

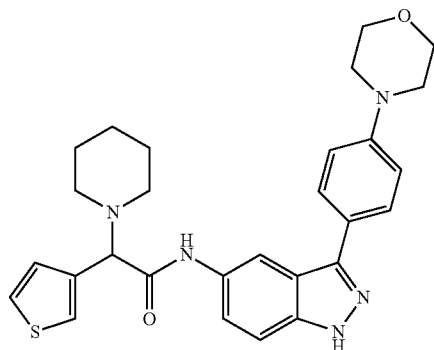


[0560] The title compound was synthesized according to general Method C by using a mixture of N-(3-iodo-1H-indazol-5-yl)-2-(piperidin-1-yl)-2-(thiophen-3-yl)acetamide (125 mg, 0.268 mmol), 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine (103 mg, 0.324 mmol), Pd(PPh₃)₄ (15.5 mg, 0.0134 mmol) and 1 M aq Na₂CO₃ (0.54 mL) in PhMe/EtOH (3.75 mL, 2:1 mixture) in vial under Ar was heated under microwave irradiation at 125° C. for 2 h. The reaction mixture was diluted with EtOAc (10 mL) and washed it with of H₂O (5 mL) followed by brine (5 mL), dried (Na₂SO₄) and concentrated under vacuum. Purification by prep-HPLC gave the title compound as a TFA salt (off white solid, 27 mg, 16%). ¹H NMR (400 MHz, CD₃OD) δ 8.37 (s, 1H), 7.88-7.84 (m, 3H), 7.67-7.65 (m, 1H), 7.55-7.49 (m, 2H), 7.39 (dd, J=5.2 Hz, J=1.2 Hz, 1H), 7.21 (d, J=9.2 Hz, 1H), 7.16 (d, J=8.4 Hz, 1H), 5.21 (s, 1H), 3.78-3.75 (m, 1H), 3.67-3.60 (br.m, 1H), 3.46-3.36 (br.m, 3H), 3.22-3.08 (br.m, 3H), 2.95 (s, 3H), 2.46-2.43 (br.m, 2H), 2.18-1.79 (br.m, 7H), 1.6-1.51 (br.m, 1H), 1H merged with solvent peak; MS ESI 530.2 [M+H]⁺, calcd for [C₃₀H₃₅N₅O₂S+H]⁺ 530.2

Example A32

N-(3-(4-morpholinophenyl)-1H-indazol-5-yl)-2-(piperidin-1-yl)-2-(thiophen-3-yl)acetamide

[0561]

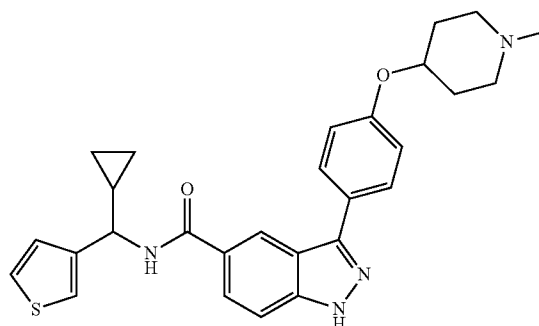


[0562] The title compound was synthesized according to general Method C by using a sealed degassed mixture of N-(3-iodo-1H-indazol-5-yl)-2-(piperidin-1-yl)-2-(thiophen-3-yl)acetamide (125 mg, 0.268 mmol), 4-(Morpholino)phenylboronic acid (67 mg, 0.268 mmol), Pd(PPh₃)₄ (15.5 mg, 0.013 mmol), 1 M aq Na₂CO₃ (0.80 mL) in PhMe/EtOH (3.75 mL, 1:0.5 mixture) under Ar was heated under microwave irradiation at 125° C. for 2 h. The reaction mixture was diluted with EtOAc (25 mL) and washed with H₂O followed by brine (10 mL each), dried (Na₂SO₄) and concentrated under vacuum. Purification by flash chromatography (SiO₂, 0-20% MeOH in DCM, then RP HPLC C18 60 g, 10-80% MeOH in 0.1% TFA-H₂O) gave the title compound as a TFA salt (yellow solid, 51 mg, 26%). ¹H NMR (400 MHz, CD₃OD) δ 8.40 (s, 1H), 7.88-7.83 (m, 3H), 7.66-7.64 (m, 1H), 7.54-7.48 (m, 2H), 7.38 (dd, J=5.2 Hz, J=1.2 Hz, 1H), 7.20 (d, J=8.8 Hz, 2H), 5.20 (s, 1H), 3.89 (t, J=4.8 Hz, 4H), 3.78-3.75 (br.m, 1H), 3.35-3.77 (m, 4H), 3.19-3.07 (br.m, 2H), 2.94-2.88 (br.m, 1H), 2.02-1.82 (br.m, 5H), 1.56-1.54 (br.m, 1H); MS ESI 502.3 [M+H]⁺, calcd for [C₂₈H₃₁N₅O₂S+H]⁺ 502.2.

Example A33

N-(cyclopropyl(thiophen-3-yl)methyl)-3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazole-5-carboxamide

[0563]

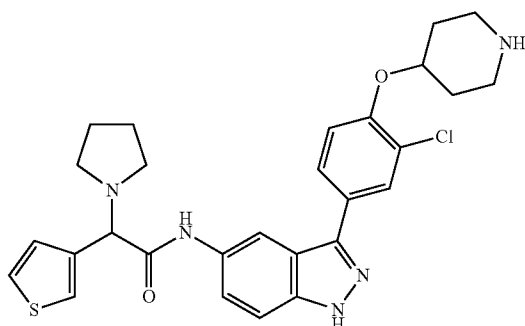


[0564] The title compound was synthesized according to the General Method C, utilizing N-(cyclopropyl(thiophen-3-yl)methyl)-3-iodo-1H-indazole-5-carboxamide (100 mg, 0.24 mmol), (4-((1-methylpiperidin-4-yl)oxy)phenyl)boronic acid pinacol ester (75 mg, 0.24 mmol), PdCl₂dppf (10 mg, 0.012 mmol), satd. aq Na₂CO₃ (1 mL), and 3 mL of PhMe:EtOH (1:1). The vial was charged with Ar and heated in the microwave reactor at 125° C. for 2 h. Purification by RPHPLC, followed by trituration with Et₂O gave the title compound as a TFA salt (beige solid, 70 mg, 49%). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.58 (s, 1H), 7.95 (d, J=8.8 Hz, 3H), 7.61 (d, J=8.8 Hz, 1H), 7.33-7.39 (m, 2H), 7.15-7.23 (m, 3H), 4.74-4.86 (m, 2H), 4.57-4.66 (m, 1H), 3.33-3.50 (m, 3H), 2.93 (s, 3H), 2.04-2.33 (m, 4H), 1.39-1.49 (m, 1H), 0.68-0.76 (m, 1H), 0.59-0.67 (m, 1H), 0.43-0.53 (m, 2H); MS ESI 487.4 [M+H]⁺, calcd for [C₂₈H₃₀N₄O₂S+H]⁺ 487.2.

Example A34

N-(3-(3-chloro-4-(piperidin-4-yloxy)phenyl)-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide

[0565]



A. tert-butyl 4-(2-chloro-4-(5-(2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamido)-1H-indazol-3-yl)phenoxy)piperidine-1-carboxylate

[0566] Using Method C2, N-(3-iodo-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide (71.3 mg, 0.158 mmol) and tert-butyl 4-(2-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine-1-carboxylate (92.3 mg, 90% pure, 0.19 mmol) gave the title compound after 3 h at 120° C. in the microwave (68.4 mg, 68%) after aq. work-up using EtOAc followed by purification by flash chromatography (SiO₂, 50-100% EtOAc in DCM). ¹H NMR (400 MHz, CDCl₃) δ ppm 9.26 (s, 1H), 8.39 (s, 1H), 7.98 (d, J=2.0 Hz, 1H), 7.78 (dd, J=8.5, 2.0 Hz, 1H), 7.48 (dd, J=9.0, 1.8 Hz, 1H), 7.43 (d, J=9.0 Hz, 1H), 7.33-7.35 (m, 1H), 7.31 (dd, J=5.0, 3.0 Hz, 1H), 7.16 (dd, J=4.8, 1.3 Hz, 1H), 7.06 (d, J=8.8 Hz, 1H), 4.60 (tt, J=6.2, 3.1 Hz, 1H), 4.17 (s, 1H), 3.65-3.73 (m, 2H), 3.43-3.53 (m, 2H), 2.68 (d, J=7.0 Hz, 2H), 2.56 (d, J=6.0 Hz, 2H), 1.88-1.99 (m, 4H), 1.85 (br. s., 4H), 1.49 (s, 9H).

B. N-(3-(3-chloro-4-(piperidin-4-yloxy)phenyl)-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide

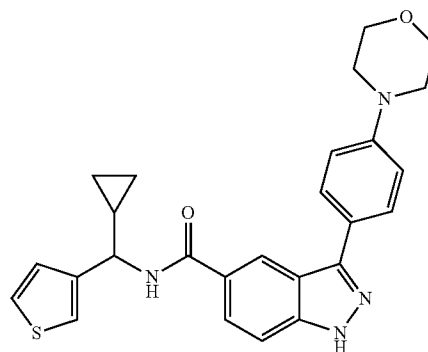
[0567] Tert-butyl 4-(2-chloro-4-(5-(2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamido)-1H-indazol-3-yl)phenoxy)piperidine-1-carboxylate (102 mg, 0.169 mmol) was dissolved in DCM (3 mL) and TFA (0.75 mL) was added. The resulting mixture was stirred at rt for 1 h, then the mixture was concentrated to dryness, and 2 M NH₃-MeOH () was added and the mixture was concentrated to dryness. Purification by flash chromatography (SiO₂, 0-20% 2 M NH₃-MeOH in DCM) followed by PoraPak Rxn Cx work-up gave the title compound (beige solid, 48.3 mg, 85%). ¹H NMR (400 MHz, CDCl₃) δ ppm 8.37 (d, J=1.3 Hz, 1H), 7.98 (d, J=2.0 Hz, 1H), 7.77 (dd, J=8.5, 2.0 Hz, 1H), 7.47 (dd, J=9.0, 1.6 Hz, 1H), 7.41 (d, J=9.0 Hz, 1H), 7.33-7.36 (m, 1H), 7.29-7.33 (m, 1H), 7.16 (dd, J=5.0, 1.3 Hz, 1H), 7.05 (d, J=8.5 Hz, 1H), 4.45-4.53 (m, 1H), 4.16 (s, 1H), 3.16-3.27 (m, 2H), 2.78 (ddd, J=12.4, 8.6, 3.4 Hz, 2H), 2.63-2.72 (m, 2H), 2.51-2.59 (m, 2H), 2.04

(ddt, J=12.8, 6.5, 3.0, 3.0 Hz, 3H), 1.75-1.89 (m, 6H). MS ESI 536.1 [M+H]⁺, calcd for [C₂₈H₃₀ClN₅O₂S+H]⁺ 536.19.

Example A35

N-(cyclopropyl(thiophen-3-yl)methyl)-3-(4-morpholinophenyl)-1H-indazole-5-carboxamide

[0568]

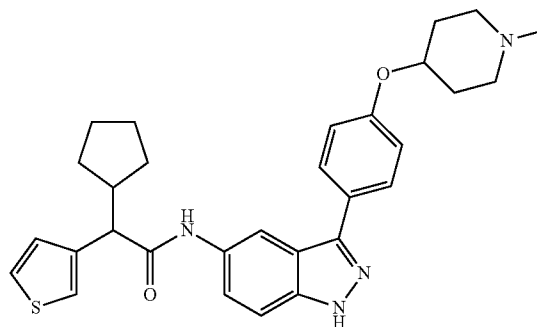


[0569] The title compound was synthesized according to the General Method C, utilizing N-(cyclopropyl(thiophen-3-yl)methyl)-3-iodo-1H-indazole-5-carboxamide (100 mg, 0.24 mmol), 4-morpholinophenylboronic acid pinacol ester (81 mg, 0.28 mmol), PdCl₂dppf (10 mg, 0.012 mmol), satd. Na₂CO₃ (0.5 mL), and 1.5 mL of PhMe:EtOH (1:1). The vial was charged with Ar and heated in the microwave reactor at 125° C. for 2 h. Purification by RPHPLC, followed by trituration with Et₂O gave the title compound as a TFA salt (white solid, 40 mg, 29%). ¹H NMR (400 MHz, DMSO-d₆) δ ppm 13.25 (s, 1H), 9.02 (d, J=8.8 Hz, 1H), 8.57 (s, 1H), 7.87-7.96 (m, 3H), 7.58 (d, J=8.8 Hz, 1H), 7.46-7.51 (m, 1H), 7.40-7.44 (m, 1H), 7.20 (d, J=5.8 Hz, 1H), 7.12 (d, J=9.0 Hz, 2H), 4.58 (t, J=9.3 Hz, 1H), 3.74-3.80 (m, 4H), 3.17-3.23 (m, 4H), 1.33-1.44 (m, 1H), 0.58-0.67 (m, 1H), 0.48-0.57 (m, 1H), 0.35-0.47 (m, 2H); MS ESI 459.3 [M+H]⁺, calcd for [C₂₆H₂₆N₄O₂S+H]⁺ 459.2.

Example A36

2-cyclopentyl-N-(3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazol-5-yl)-2-(thiophen-3-yl)acetamide

[0570]



A. ethyl 2-cyclopentyl-2-(thiophen-3-yl)acetate

[0571] NaH (0.26 g, 6.5 mmol) was added portion wise to a solution of ethyl 3-thiophene acetate (0.88 mL, 5.8 mmol) in DMF (20 mL) at rt under Ar. After stirring for 5 min, cyclopentyl bromide (0.70 mL, 6.9 mmol) was added and stirring was continued for 18 h at 25° C. 20% NH₄Cl (50 mL) was added and the product was extracted using EtOAc (2×50 mL), and the combined EtOAc layer was washed with H₂O and brine and dried (Na₂SO₄) and concentrated under vacuum. Purification by flash chromatography (SiO₂, 0-25% EtOAc in Hexane) gave the title compound (colorless oil, 1.04 g, 74%). ¹H NMR (400 MHz, CDCl₃) δ 7.26-7.25 (m, 1H), 7.16-7.7.15 (m, 1H), 7.12 (dd, J=4.8 Hz, J=1.2 Hz, 1H), 4.18-4.06 (m, 2H), 3.45 (d, J=10.8 Hz, 1H), 2.51-2.49 (m, 1H), 1.86-1.83 (m, 1H), 1.46-1.49 (m, 6H), 1.24 (t, J=7.2 Hz, 3H), 1.12-1.05 (m, 1H).

B. 2-cyclopentyl-2-(thiophen-3-yl)acetic acid

[0572] NaOH (2 M, 5.45 mL, 10.9 mmol) was added to a solution of ethyl 2-cyclopentyl-2-(thiophen-3-yl)acetate (1.04 g, 4.3 mmol) in MeOH (10.4 mL) at rt. The reaction mixture was refluxed for 2.5 h, and then concentrated under reduced pressure. The residue was acidified to pH 2 using conc. HCl and the product was extracted using DCM (25 mL, 10 mL). The combined organic layer was washed with H₂O and brine, dried (Na₂SO₄) and concentrated under vacuum to give the title compound (off white solid, 0.89 g, 97%). ¹H NMR (400 MHz, CDCl₃) δ 7.29-7.27 (m, 1H), 7.18-7.7.17 (m, 1H), 7.12-7.1 (m, 1H), 3.47 (d, J=10.8 Hz, 1H), 2.55-2.45 (m, 1H), 1.95-1.89 (m, 1H), 1.71-1.48 (m, 5H), 1.35-1.26 (m, 1H), 1.12-1.05 (m, 1H).

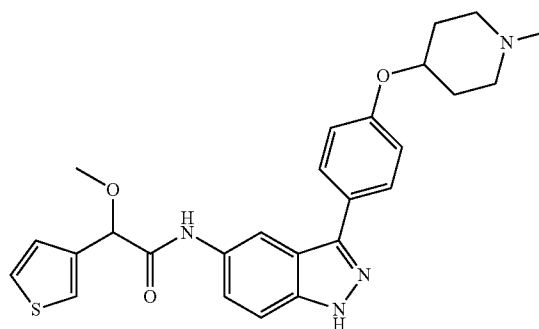
C. 2-cyclopentyl-N-(3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazol-5-yl)-2-(thiophen-3-yl)acetamide

[0573] The title compound was synthesized according to general Method A using 2-cyclopentyl-2-(thiophen-3-yl)acetic acid 19.1 mg, 0.09 mmol), DMF (1.5 mL), 3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazol-5-amine trifluoroacetate (50 mg, 0.09 mmol), DIPEA (80 uL, 0.45 mmol) and TBTU (29.1 mg, 0.09 mmol). After 24 h at rt, direct purification by flash chromatography (SiO₂, 0-25% MeOH in DCM; then RP HPLC C18 60 g, 10-80% MeOH in 0.1% TFA-H₂O) gave the title compound as a TFA salt (off white solid, 31 mg, 54%). ¹H NMR (400 MHz, CD₃OD) δ 10.08 (s, 1H), 8.43-8.42 (m, 1H), 7.88-7.8 (m, 2H), 7.52 (d, J=9.2 Hz, 1H), 7.40-7.35 (m, 2H), 7.31-7.3 (m, 1H), 7.22 (dd, J=5.2 Hz, J=1.2 Hz, 1H), 7.18-7.15 (m, 2H), 4.85 (s, 1H), 3.65-3.54 (m, 2H), 3.44-3.34 (br.m, 3H), 2.94 (d, J=4.4 Hz, 3H), 2.70-2.64 (m, 1H), 2.45-2.28 (m, 2H), 2.15-1.91 (br.m, 3H), 1.75-1.53 (br.m, 5H), 1.40-1.35 (m, 1H), 1.18-1.31 (m, 1H); MS ESI 515.1 [M+H]⁺, calcd for [C₃₀H₃₄N₄O₂S+H]⁺ 515.2

Example A37

2-methoxy-N-(3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazol-5-yl)-2-(thiophen-3-yl)acetamide

[0574]

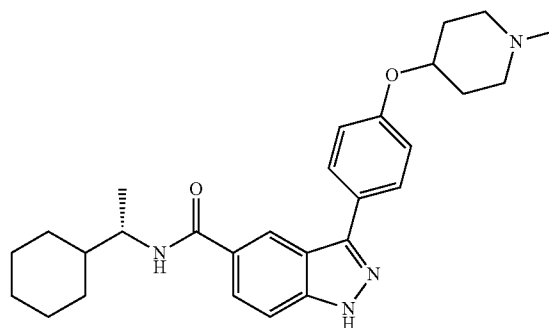


[0575] The title compound was synthesized according to general Method A by using 2-methoxy-2-(thiophen-2-yl)acetic acid (15.6 mg, 0.09 mmol), DMF (1.5 mL), 3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazol-5-amine trifluoroacetate (50 mg, 0.09 mmol), DIPEA (80 uL, 0.45 mmol) and TBTU (29.1 mg, 0.09 mmol). After 24 h at rt, direct purification by flash chromatography (SiO₂, 0-25% MeOH in DCM; then RP HPLC C18 60 g, 10-80% MeOH in 0.1% TFA-H₂O) gave the title compound as a TFA salt (off white solid, 27 mg, 50%). ¹H NMR (400 MHz, CD₃OD) δ 8.41 (s, 1H), 7.89-7.85 (br.t, 2H), 7.55-7.52 (m, 3H), 7.45 (dd, J=4.8 Hz, J=2.8 Hz, 1H), 7.23 (d, J=1.2 Hz, 1H), 7.19-7.112 (m, 2H), 4.95 (s, 1H), 3.65-3.6 (br.m, 1H), 3.38-3.58 (br.m, 1H), 3.48 (s, 3H), 3.62-3.41 (br.m, 3H), 2.94 (s, 3H), 2.45-2.8 (br.m, 2H), 2.14-1.88 (br.m, 2H); MS ESI 477.2 [M+H]⁺, calcd for [C₂₆H₂₈N₄O₃S+H]⁺ 477.2.

Example A38

(S)—N-(1-cyclohexylethyl)-3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazole-5-carboxamide

[0576]



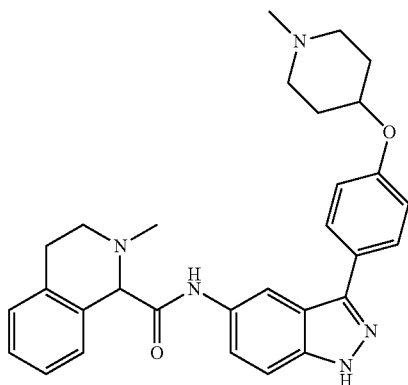
[0577] The title compound was synthesized according to the General Method C, utilizing (S)—N-(1-cyclohexylethyl)-3-iodo-1H-indazole-5-carboxamide (100 mg, 0.25 mmol), (4-((1-methylpiperidin-4-yl)oxy)phenyl)boronic acid pina-

col ester (96 mg, 0.30 mmol), PdCl₂dppf (10 mg, 0.012 mmol), satd. aq Na₂CO₃ (1 mL), and 4 mL of PhMe:EtOH (1:1). The vial was charged with Ar and heated in the microwave reactor at 125° C. for 2 h. Purification by RPHPLC, followed by trituration with Et₂O gave the title compound as a TFA salt (white solid, 35 mg, 24%). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.52 (s, 1H), 7.87-7.99 (m, 3H), 7.60 (d, J=8.5 Hz, 1H), 7.14-7.25 (m, 2H), 4.64-4.74 (m, 0.3H), 3.93-4.05 (m, 1H), 3.60-3.69 (m, 0.7H), 3.34-3.49 (m, 2.7H), 3.13-3.27 (m, 1.3H), 2.95 (s, 3H), 2.42-2.50 (m, 0.7H), 2.27-2.38 (m, 1.3H), 2.05-2.18 (m, 1.3H), 1.73-1.97 (m, 4.7H), 1.62-1.73 (m, 1H), 1.44-1.57 (m, 1H), 1.14-1.35 (m, 6H), 1.01-1.14 (m, 2H); MS ESI 461.4 [M+H]⁺, calcd for [C₂₈H₃₆N₄O₂+H]⁺ 461.3.

Example A39

2-methyl-N-(3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazol-5-yl)-1,2,3,4-tetrahydroisoquinoline-1-carboxamide

[0578]

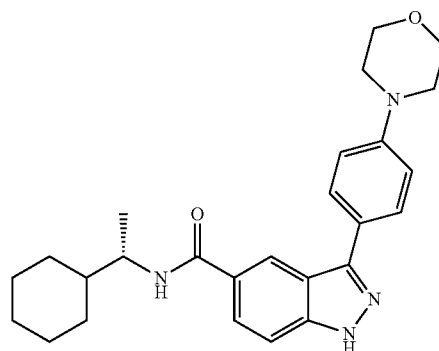


[0579] To a mixture of 2-methyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid hydrochloride (25 mg, 0.1 mmol) and 3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazol-5-amine di-trifluoroacetic acid (55 mg, 0.1 mmol) in DMF (5 mL) at 0° C. was added TBTU (32 mg, 0.1 mmol), followed by ^tPr₂NEt (0.09 mL, 0.5 mmol). The resulting mixture was stirred for 30 min at 0° C. Additional 3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazol-5-amine di-trifluoroacetic acid (5.5 mg, 0.01 mmol) and TBTU (3.2 mg, 0.01 mmol) were added and it was stirred for 30 min at 0° C. After removal of Pr₂NEt, it was purified by prep-HPLC twice to give the title compound as a di-TFA salt (white solid, 51.3 mg, 71%). ¹H NMR (400 MHz, CD₃OD) δ 8.46 (t, J=0.8 Hz, 1H), 7.90-7.84 (m, 2H), 7.64 (dd, J=9.0 Hz, 1.8 Hz, 1H), 7.60 (d, J=9.2 Hz, 1H), 7.49 (d, J=7.2 Hz, 1H), 7.41-7.32 (m, 3H), 7.19-7.10 (m, 2H), 5.34 (s, 1H), 5.34-5.31 (m, 0.7H), 4.68-4.60 (m, 0.3H), 4.03 (brs, 0.8H), 3.65-3.58 (m, 1.7H), 3.45-3.33 (m, 3.4H; partially overlapped with CD₃OD solvent residue), 3.23-3.12 (m, 4.7H; s, 3H at 3.14), 2.92-2.91 (two s at 2.92 and 2.91, total 3H), 2.44-2.37 (m, 0.7H), 2.30-2.23 (m, 1.3H), 2.18-2.08 (m, 1.3H), 1.98-1.86 (m, 0.7H); MS ESI 496.2 [M+H]⁺, calcd for [C₃₀H₃₃N₅O₂+H]⁺ 496.3.

Example A40

(S)—N-(1-cyclohexylethyl)-3-(4-morpholinophenyl)-1H-indazole-5-carboxamide

[0580]

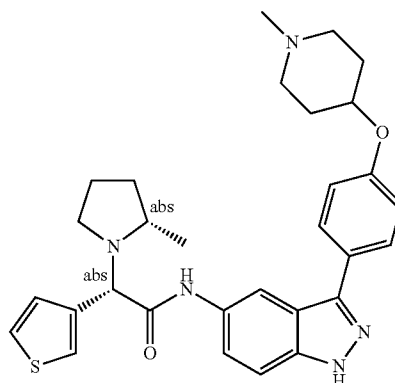


[0581] The title compound was synthesized according to the General Method C, utilizing (S)—N-(1-cyclohexylethyl)-3-iodo-1H-indazole-5-carboxamide (80 mg, 0.20 mmol), 4-morpholinophenylboronic acid pinacol ester (58 mg, 0.20 mmol), PdCl₂dppf (8 mg, 0.01 mmol), satd. aq Na₂CO₃ (0.5 mL), and 1.5 mL of PhMe:EtOH (1:1). The vial was charged with Ar and heated in the microwave reactor at 125° C. for 2 h. Purification by RPHPLC, followed by trituration with Et₂O gave the title compound (white solid, 18 mg, 21%). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.55 (s, 1H), 7.90 (d, J=8.8 Hz, 3H), 7.58 (d, J=8.8 Hz, 1H), 7.13 (d, J=8.5 Hz, 2H), 3.92-4.03 (m, 1H), 3.82-3.89 (m, 4H), 3.24 (br. s, 4H), 1.70-1.90 (m, 4H), 1.61-1.69 (m, 1H), 1.44-1.55 (m, 1H), 1.22 (d, J=6.8 Hz, 6H), 0.97-1.12 (m, 2H); MS ESI 433.4 [M+H]⁺, calcd for [C₂₆H₃₂N₄O₂+H]⁺ 433.3.

Example A41

(S)—N-(3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazol-5-yl)-2-((S)-2-methylpyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide

[0582]

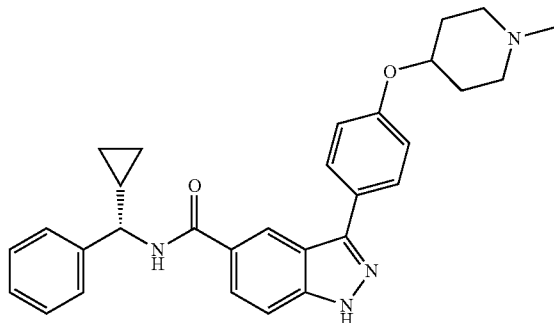


[0583] To a mixture of (S)-2-((S)-2-methylpyrrolidin-1-yl)-2-(thiophen-3-yl)acetic acid (22.5 mg, 0.1 mmol) and 3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazol-5-amine di-trifluoroacetic acid (55 mg, 0.1 mmol) in DMF (5 mL) at 0° C. was added TBUTU (32.1 mg, 0.1 mmol), followed by $i\text{Pr}_2\text{NEt}$ (0.09 mL, 0.5 mmol). The resulting mixture was stirred for 10 min at 0° C. After removal of $i\text{Pr}_2\text{NEt}$, it was purified by prep-HPLC to give the title compound as di-TFA salt (white solid, 31.1 mg, 71%). ^1H NMR (400 MHz, CD_3OD) δ 8.35 (s, 1H), 7.91-7.93 (m, 3H), 7.64 (dd, $J=5.0$ Hz, 3.0 Hz, 1H), 7.54 (s, 2H), 7.41 (d, $J=4.8$ Hz, 1H), 7.21-7.13 (m, 2H), 5.33 (s, 1H), 4.89-4.85 (m, 0.7H), 4.72-4.64 (m, 0.3H), 3.84 (q, $J=7.2$ Hz, 1H), 3.68-3.62 (m, 0.7H), 3.48-3.12 (m, 5.3H; partially overlapped with CD_3OD solvent residue), 2.95-2.94 (two s at 2.95 and 2.94, total 3H), 2.48-2.26 (m, 3H), 2.20-1.82 (m, 5H), 1.53 (d, $J=6.4$ Hz, 3H); MS ESI 530.2 $[\text{M}+\text{H}]^+$, calcd for $[\text{C}_{30}\text{H}_{35}\text{N}_5\text{O}_2\text{S}+\text{H}]^+$ 530.3.

Example A42

(S)-N-(cyclopropyl(phenyl)methyl)-3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazole-5-carboxamide

[0584]

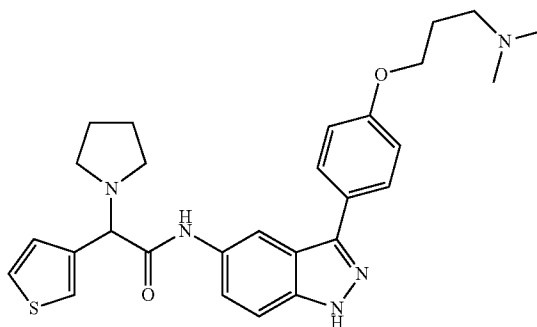


[0585] The title compound was synthesized according to the General Method C, utilizing (S)-N-(cyclopropyl(phenyl)methyl)-3-iodo-1H-indazole-5-carboxamide (110 mg, 0.26 mmol), (4-((1-methylpiperidin-4-yl)oxy)phenyl)boronic acid pinacol ester (84 mg, 0.26 mmol), PdCl_2dppf (11 mg, 0.013 mmol), satd. aq Na_2CO_3 (1 mL), and 4 mL of $\text{PhMe}:\text{EtOH}$ (1:1). The vial was charged with Ar and heated in the microwave reactor at 125° C. for 5 h. Purification by RPHPLC, followed by flash chromatography (SiO_2 , Biotage 25 g, 5-25% MeOH in CH_2Cl_2) and trituration with Et_2O gave the title compound (white solid, 8.5 mg, 7%). ^1H NMR (400 MHz, CD_3OD) δ ppm 8.60 (s, 1H), 7.91 (m, 3H), 7.59 (d, $J=9.5$ Hz, 1H), 7.48 (d, $J=7.3$ Hz, 2H), 7.32 (t, $J=7.5$ Hz, 2H), 7.23 (t, $J=7.3$ Hz, 1H), 7.10 (d, $J=8.8$ Hz, 2H), 4.53 (br. s, 1H), 4.47 (d, $J=9.5$ Hz, 1H), 2.77-2.88 (m, 2H), 2.45-2.59 (m, 2H), 2.39 (s, 3H), 2.01-2.13 (m, 2H), 1.82-1.94 (m, 2H), 1.34-1.45 (m, 1H), 0.60-0.72 (m, 2H), 0.39-0.53 (m, 2H); MS ESI 481.4 $[\text{M}+\text{H}]^+$, calcd for $[\text{C}_{30}\text{H}_{32}\text{N}_4\text{O}_2+\text{H}]^+$ 481.3.

Example A43

N-(3-(4-(3-(dimethylamino)propoxy)phenyl)-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide

[0586]

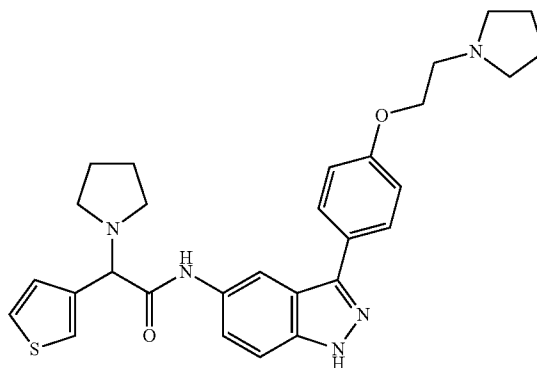


[0587] The title compound was synthesized according to general Method C by using a mixture of N-(3-iodo-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide (75 mg, 0.165 mmol), N,N-dimethyl-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)propan-1-amine (60.7 mg, 0.198 mmol), PdCl_2dppf (11.6 mg, 0.016 mmol) and 1 M aq Na_2CO_3 (0.33 mL) in $\text{PhMe}:\text{EtOH}$ (2.25 mL, 2:1 mixture) under Ar with heating under microwave irradiation at 130° C. for 2 h. The reaction mixture was diluted with EtOAc (22.5 mL) and washed with H_2O (10 mL) and brine (10 mL), dried (Na_2SO_4) and concentrated under vacuum and. Purification by flash chromatography (SiO_2 , 0-10% 2 M $\text{NH}_3\text{-MeOH}$ in DCM; then RP HPLC C18 60 g, 10-80% MeOH in 0.1% TFA- H_2O) to give the title compound as a TFA salt (light pink solid, 20 mg, 17%). ^1H NMR (400 MHz, CD_3OD) δ 8.35 (s, 1H), 7.88-7.83 (m, 3H), 7.66-7.64 (m, 1H), 7.55-7.49 (m, 2H), 7.38 (dd, $J=5.2$ Hz, $J=1.2$ Hz, 1H), 7.13 (d, $J=6.8$ Hz, 2H), 5.24 (s, 1H), 4.21 (t, $J=5.6$ Hz, 2H), 3.88-3.86 (br.m, 1H), 3.41 (t, $J=7.6$ Hz, 2H), 3.26-3.09 (br.m, 2H), 2.98 (s, 6H), 2.31-1.92 (br.m, 6H), 1H merged with solvent peak; MS ESI 504.2 $[\text{M}+\text{H}]^+$, calcd for $[\text{C}_{28}\text{H}_{33}\text{N}_5\text{O}_2\text{S}+\text{H}]^+$ 504.2.

Example A44

2-(pyrrolidin-1-yl)-N-(3-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)-1H-indazol-5-yl)-2-(thiophen-3-yl)acetamide

[0588]

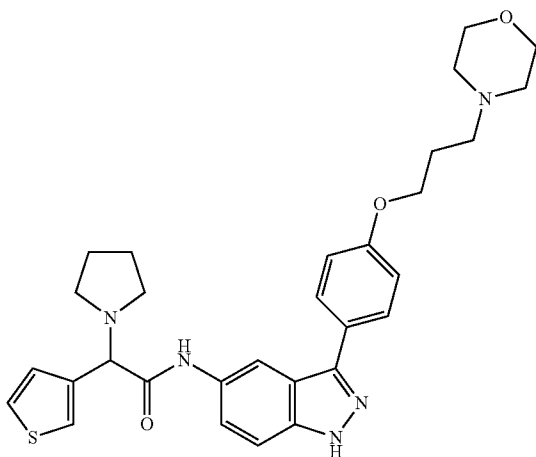


[0589] Using Method C2, N-(3-iodo-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide (59.8 mg, 0.132 mmol) and (4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)boronic acid (42.6 mg, 0.181 mmol) gave the title compound after 3 h at 120° C. in the microwave as the TFA salt (beige solid, 59.1 mg, 60%) after purification by flash chromatography (SiO₂, 0-20% 2 M NH₃-MeOH in DCM; followed by RPRP HPLC, 10-80% MeOH in 0.1% TFA-H₂O). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.36 (t, J=1.5 Hz, 1H), 7.86-7.91 (m, 3H), 7.65 (dd, J=5.0, 3.0 Hz, 1H), 7.50-7.57 (m, 2H), 7.38 (dd, J=5.1, 1.4 Hz, 1H), 7.17-7.22 (m, 2H), 5.28 (s, 1H), 4.41-4.46 (m, 2H), 3.88 (br. s., 1H), 3.78 (dt, J=10.2, 5.1 Hz, 2H), 3.67-3.75 (m, 2H), 3.22-3.30 (m, 3H), 3.19 (br. s., 1H), 3.10 (br. s., 1H), 2.05-2.28 (m, 7H), 1.92-2.04 (m, 1H). MS ESI 516.2 [M+H]⁺, calcd for [C₂₉H₃₃N₅O₂S+H]⁺ 516.24.

Example A45

N-(3-(4-(3-morpholinopropoxy)phenyl)-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide

[0590]

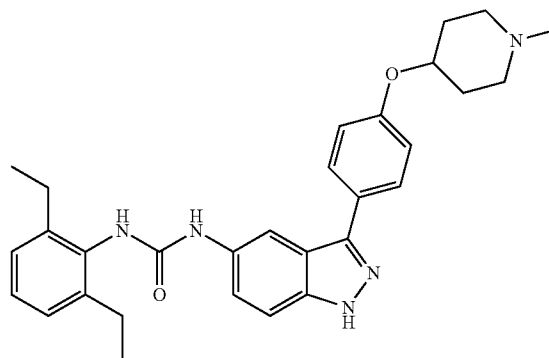


[0591] Using Method C2, N-(3-iodo-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide (59.9 mg, 0.132 mmol) and (4-(3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)propyl)morpholine (60.9 mg, 0.175 mmol) gave the title compound after 3 h at 120° C. in the microwave as the TFA salt (off-white powder, 30.6 mg, 30%) after purification by flash chromatography (SiO₂, 5-15% MeOH in DCM; followed by RPRP HPLC, 10-80% MeOH in 0.1% TFA-H₂O). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.35-8.38 (m, 1H), 7.88 (dd, J=2.9, 1.4 Hz, 1H), 7.85 (d, J=8.8 Hz, 2H), 7.63-7.67 (m, 1H), 7.49-7.56 (m, 2H), 7.38 (dd, J=5.3, 1.3 Hz, 1H), 7.12 (d, J=8.8 Hz, 2H), 5.27 (s, 1H), 4.21 (t, J=5.6 Hz, 2H), 4.11 (d, J=12.3 Hz, 2H), 3.88 (br. s., 1H), 3.81 (t, J=12.3 Hz, 2H), 3.60 (d, J=12.3 Hz, 2H), 3.40-3.48 (m, 2H), 3.16-3.27 (m, 3H), 3.10 (br. s., 1H), 2.27-2.36 (m, 2H), 2.23 (d, J=11.5 Hz, 1H), 2.09-2.19 (m, 2H), 2.01 (br. s., 1H). MS ESI 546.3 [M+H]⁺, calcd for [C₃₀H₃₅N₅O₃S+H]⁺ 546.25.

Example A46

1-(2,6-diethylphenyl)-3-(3-(4-((1-methylpiperidin-4-yloxy)phenyl)-1H-indazol-5-yl)urea

[0592]

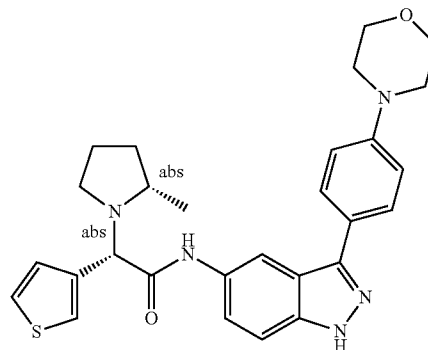


[0593] A solution of 3-(4-((1-methylpiperidin-4-yloxy)phenyl)-1H-indazol-5-amine bis(2,2,2-trifluoroacetate) (40 mg, 0.073 mmol), DIPEA (64 uL, 0.368 mmol), and DMF (1.0 mL) was cooled to 0° C. and then 1,3-diethyl-2-isocyanatobenzene (25 uL, 0.145 mmol) was added dropwise. The reaction was stirred for 2 h while warming to rt. A mixture of mono- and di-urea products were obtained which was treated directly with NaOMe (80 uL of a 25% wt solution in MeOH) and the mixture stirred for 15 min and then transferred to a separatory funnel with EtOAc (15 mL). The mixture was then washed with (satd. aq NaHCO₃ (2×10 mL), H₂O (1×10 mL), brine (1×10 mL)). The organic layer was dried over MgSO₄, filtered, and the solvent removed. The resulting residue was purified by prep-HPLC which gave 19 mg, 43% of the desired product isolated as its TFA salt (a white powder). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.26 (s, 1H), 7.87-7.83 (m, 2H), 7.49 (d, J=8.8 Hz, 1H), 7.30 (d, J=8.8 Hz, 1H), 7.22-7.09 (m, 5H), 4.83 (bs, 1H), 3.62-3.31 (m, 2H), 3.30-3.14 (m, 2H), 2.92-2.91 (m, 3H), 2.72-2.67 (m, 4H), 2.42-2.25 (m, 2H), 2.11-1.86 (m, 2H), 1.22 (t, J=7.6 Hz, 6H); MS ESI 498.5 [M+H]⁺, calcd for [C₃₀H₃₅N₅O₂+H]⁺ 498.29.

Example A47

(S)-2-((S)-2-methylpyrrolidin-1-yl)-N-(3-(4-morpholinophenyl)-1H-indazol-5-yl)-2-(thiophen-3-yl)acetamide

[0594]



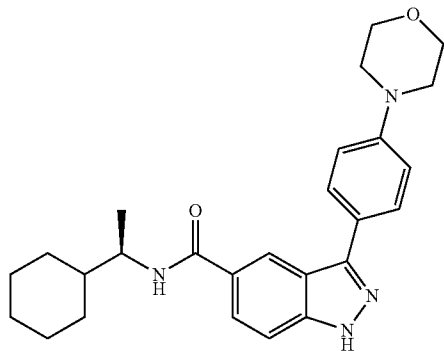
[0595] To a mixture of tert-butyl (3-iodo-1H-indazol-5-yl) carbamate (1.077 g, 3 mmol) and (4-morpholinophenyl)boronic acid (652 mg, 3.15 mmol) in EtOH (12 mL) was added 2 M Na₂CO₃ (3 mL, 6 mmol), followed by Pd(PPh₃)₄ (104 mg, 0.09 mmol). The resulting mixture was purged with Ar and microwaved 3 h at 125° C. Repeated this reaction twice on the same scale. All three reactions were combined, diluted with H₂O, extracted with EtOAc and purified by flash chromatography (MeOH/DCM 0-25%) to give 4.20 g of brown solid. It was redissolved in DCM (20 mL) and treated with TFA (10 mL). After stirring for 3 h at rt, it was concentrated and purified by biotage RP column (5-90% MeOH in 0.1% TFA-H₂O) to give 3-(4-morpholinophenyl)-1H-indazol-5-amine as a di-TFA salt (light purple solid, 866 mg, 55%). ¹H NMR (400 MHz, CD₃OD) δ 8.05 (s, 1H), 7.84 (d, J=7.2 Hz, 2H), 7.72 (d, J=8.0 Hz, 1H), 7.44 (d, J=8.4 Hz, 1H), 7.17 (d, J=7.2 Hz, 2H), 4.00-3.80 (m, 4H), 3.40-3.20 (m, 4H); MS ESI 295.0 [M+H]⁺, calcd for [C₁₇H₁₈N₄O₂+H]⁺ 295.1.

[0596] To a mixture of (S)-2-((S)-2-methylpyrrolidin-1-yl)-2-(thiophen-3-yl)acetic acid (22.5 mg, 0.1 mmol) and 3-(4-morpholinophenyl)-1H-indazol-5-amine di-trifluoroacetic acid (52.2 mg, 0.1 mmol) in DMF (5 mL) at 0° C. was added TBTU (32.1 mg, 0.1 mmol), followed by ^tPr₂NEt (0.07 mL). After stirring for 5 min at 0° C., additional ^tPr₂NEt (0.02 mL) was added and the resulting mixture was stirred for 30 min at 0° C. After removal of ^tPr₂NEt, it was purified by prep-HPLC to give the title compound as a di-TFA salt (white solid, 14.1 mg, 19%). ¹H NMR (400 MHz, CD₃OD) δ 8.37 (t, J=1.6 Hz, 1H), 7.89 (d, J=1.6 Hz, 1H), 7.86 (d, J=8.8 Hz, 2H), 7.65 (dd, J=5.0 Hz, 3.0 Hz, 1H), 7.57-7.49 (m, 2H), 7.41 (d, J=4.8 Hz, 1H), 7.23 (d, J=8.4 Hz, 2H), 5.23 (s, 1H), 3.92 (t, J=4.8 Hz, 4H), 3.84 (q, J=6.7 Hz, 1H), 3.36-3.25 (m, 5H; partially buried under CD₃OD solvent residue), 3.20-3.12 (m, 1H), 2.46-2.36 (m, 1H), 2.06 (quint, J=7.1 Hz, 2H), 1.90-1.83 (m, 1H), 1.54 (d, J=6.4 Hz, 3H); MS ESI 502.3 [M+H]⁺, calcd for [C₂₆H₂₈N₆O₂S+H]⁺ 502.2.

Example A48

(R)—N-(1-cyclohexylethyl)-3-(4-morpholinophenyl)-1H-indazole-5-carboxamide

[0597]



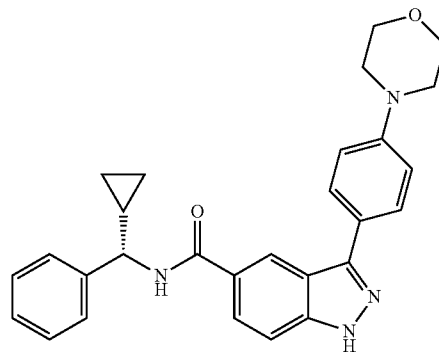
[0598] The title compound was synthesized according to the General Method C, utilizing (R)—N-(1-cyclohexylethyl)-3-iodo-1H-indazole-5-carboxamide (100 mg, 0.25 mmol), 4-morpholinophenylboronic acid pinacol ester (55 mg, 0.25 mmol), PdCl₂dppf (10 mg, 0.013 mmol), satd. aq Na₂CO₃ (1.5 mL), and 3.5 mL of PhMe:EtOH (1:1). The vial was charged with Ar and heated in the microwave reactor at 125° C. for 2 h. Purification by RP HPLC, followed by flash

chromatography (SiO₂, Biotage 25 g, 5-25% MeOH in CH₂Cl₂), and passed through a PoraPak column to give the title compound (beige solid, 32 mg, 30%). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.55 (s, 1H), 7.85-7.92 (m, 3H), 7.57 (d, J=8.8 Hz, 1H), 7.09 (d, J=8.8 Hz, 2H), 3.93-4.02 (m, 1H), 3.81-3.87 (m, 4H), 3.17-3.23 (m, 4H), 1.76 (br. s, 4H), 1.61-1.69 (m, 1H), 1.44-1.55 (m, 1H), 1.22 (d, J=6.8 Hz, 6H), 1.06 (d, J=2.5 Hz, 2H); MS ESI 433.4 [M+H]⁺, calcd for [C₂₆H₃₂N₄O₂+H]⁺ 433.3.

Example A49

(S)—N-(cyclopropyl(phenyl)methyl)-3-(4-morpholinophenyl)-1H-indazole-5-carboxamide

[0599]

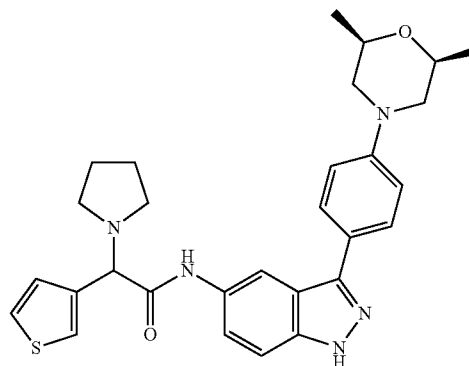


[0600] The title compound was synthesized according to the General Method C, utilizing (S)—N-(cyclopropyl(phenyl)methyl)-3-iodo-1H-indazole-5-carboxamide (50 mg, 0.12 mmol), 4-morpholinophenylboronic acid pinacol ester (35 mg, 0.12 mmol), PdCl₂dppf (10 mg, 0.012 mmol), satd. aq Na₂CO₃ (1.5 mL), and 3.5 mL of PhMe:EtOH (1:1). The vial was charged with Ar and heated in the microwave reactor at 125° C. for 2 h. Purification by RP HPLC, followed by flash chromatography (SiO₂, Biotage 25 g, 5-25% MeOH in CH₂Cl₂) to give the title compound (beige solid, 13 mg, 24%). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.61 (s, 1H), 7.91-7.98 (m, 3H), 7.60 (d, J=8.8 Hz, 1H), 7.48 (d, J=7.3 Hz, 2H), 7.33 (t, J=7.5 Hz, 2H), 7.20-7.28 (m, 3H), 4.48 (d, J=9.5 Hz, 1H), 3.86-3.93 (m, 4H), 3.31-3.35 (m, 4H), 1.35-1.46 (m, 1H), 0.66 (d, J=8.0 Hz, 2H), 0.41-0.53 (m, 2H); MS ESI 453.3 [M+H]⁺, calcd for [C₂₈H₂₈N₄O₂+H]⁺ 453.2.

Example A50

N-(3-(4-((2S,6R)-2,6-dimethylmorpholino)phenyl)-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide

[0601]

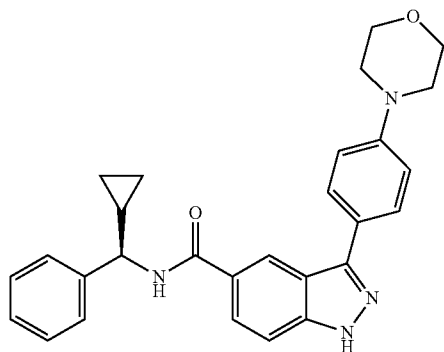


The title compound was synthesized according to the General Method C2 utilizing N-(3-iodo-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide (0.070 g, 0.15 mmol), (2S,6R)-2,6-dimethyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)morpholine (0.064 g, 0.62 mmol) to provide the title compound as a white powder (7.2 mg, 9%). ¹H NMR (400 MHz, acetone-d₆) δ ppm 12.02-12.30 (br, 1H), 9.59 (s, 1H), 8.58 (s, 1H), 7.89 (d, J=8.78 Hz, 2H), 7.67 (d, J=8.78 Hz, 1H), 7.50-7.59 (m, 2H), 7.45 (dd, J=5.02, 3.01 Hz, 1H), 7.34 (dd, J=4.89, 1.13 Hz, 1H), 7.10 (d, J=9.03 Hz, 2H), 4.12 (s, 1H), 3.73-3.83 (m, 2H), 3.69 (d, J=12.30 Hz, 2H), 2.70-2.62 (m, 2H), 2.45-2.56 (m, 2H), 2.32-2.42 (m, 2H), 1.81 (dt, J=6.27, 3.14 Hz, 4H), 1.23 (d, J=6.27 Hz, 6H); MS ESI 516.2 [M+H]⁺, calcd for [C₂₉H₃₃N₅O₂S+H]⁺ 516.2.

Example A51

(R)—N-(cyclopropyl(phenyl)methyl)-3-(4-morpholinophenyl)-1H-indazole-5-carboxamide

[0602]



[0603] The title compound was synthesized according to the General Method C, utilizing (R)—N-(cyclopropyl(phenyl)methyl)-3-iodo-1H-indazole-5-carboxamide (60 mg, 0.14 mmol), 4-morpholinophenylboronic acid pinacol ester (42 mg, 0.14 mmol), PdCl₂dppf (11 mg, 0.014 mmol), satd. aq Na₂CO₃ (1.5 mL), and 3.5 mL of PhMe:EtOH (1:1). The vial was charged with Ar and heated in the microwave reactor at 125° C. for 2 h. Purification by RPHPLC, followed by passing through PoraPak column gave the title compound (beige solid, 18 mg, 28%). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.61 (s, 1H), 7.86-7.97 (m, 3H), 7.59 (d, J=8.8 Hz, 1H), 7.48 (d, J=7.3 Hz, 2H), 7.33 (t, J=7.5 Hz, 2H), 7.23 (t, J=7.3 Hz, 1H), 7.13 (d, J=9.0 Hz, 2H), 4.44-4.51 (m, 1H), 3.86 (s, 4H), 3.25 (s, 4H), 1.36-1.45 (m, 1H), 0.62-0.69 (m, 2H), 0.42-0.52 (m, 2H); MS ESI 453.4 [M+H]⁺, calcd for [C₂₈H₂₈N₄O₂+H]⁺ 453.2.

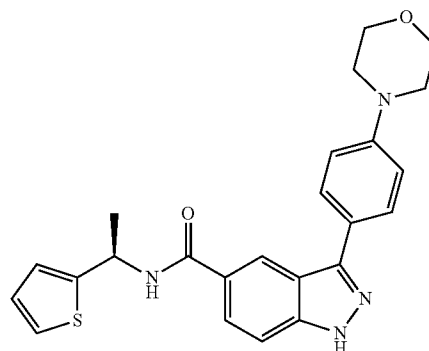
Example A52

Intentionally Omitted

Example A53

(R)-3-(4-morpholinophenyl)-N-(1-(thiophen-2-yl)ethyl)-1H-indazole-5-carboxamide

[0604]



[0605] The title compound was synthesized according to the General Method A, utilizing 3-(4-morpholinophenyl)-1H-indazole-5-carboxylic acid (98 mg, 0.30 mmol), (1R)-1-(2-thienyl)ethylamine ·HCl (50 mg, 0.30 mmol), TBTU (96 mg, 0.30 mmol), DIPEA (0.16 mL, 0.90 mmol), and DMF (5 mL). Purification by RP HPLC, followed by passing through PoraPak column gave the title compound (white solid, 31 mg, 24%). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.59 (s, 1H), 7.86-7.96 (m, 3H), 7.59 (d, J=8.5 Hz, 1H), 7.25-7.30 (m, 1H), 7.13 (d, J=8.8 Hz, 2H), 7.04-7.08 (m, 1H), 6.95-6.99 (m, 1H), 5.56-5.64 (m, 1H), 3.86 (s, 4H), 3.21-3.26 (m, 4H), 1.70 (d, J=7.0 Hz, 3H); MS ESI 433.4 [M+H]⁺, calcd for [C₂₄H₂₄N₄O₂S+H]⁺ 433.2.

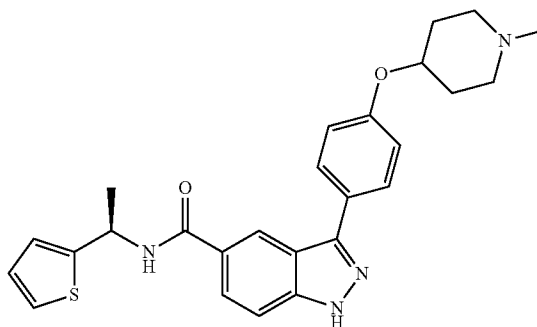
Example A54

Intentionally Omitted

Example A55

(R)-3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-N-(1-(thiophen-2-yl)ethyl)-1H-indazole-5-carboxamide

[0606]

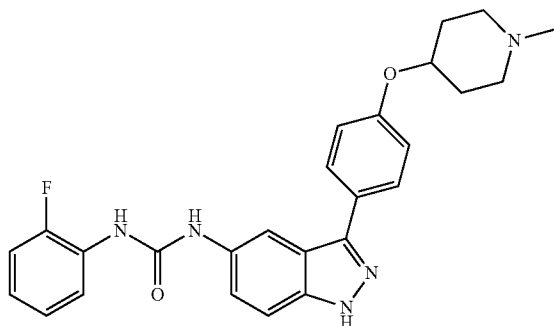


[0607] The title compound was synthesized according to the General Method C, utilizing (R)-3-iodo-N-(1-(thiophen-2-yl)ethyl)-1H-indazole-5-carboxamide (70 mg, 0.18 mmol), (4-((1-methylpiperidin-4-yl)oxy)phenyl)boronic acid pinacol ester (56 mg, 0.18 mmol), PdCl₂dppf (15 mg, 0.018 mmol), satd. aq Na₂CO₃ (1.5 mL), and 3.5 mL of PhMe:EtOH (1:1). The vial was charged with Ar and heated in the microwave reactor at 125° C. for 2 h. Purification by RP HPLC, followed by trituration with Et₂O gave the title compound as a TFA salt (white solid, 44 mg, 43%). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.57 (s, 1H), 7.89-7.99 (m, 3H), 7.60 (d, J=8.8 Hz, 1H), 7.27 (d, J=4.8 Hz, 1H), 7.11-7.22 (m, 2H), 7.05 (br. s, 1H), 6.96 (t, J=4.3 Hz, 1H), 5.59 (s, 1H), 4.58-4.72 (m, 0.3H), 3.60-3.69 (m, 0.7H), 3.33-3.47 (m, 3H), 3.14-3.24 (m, 1H), 2.93 (s, 3H), 2.39-2.48 (m, 0.7H), 2.23-2.35 (m, 1.3H), 2.12 (br. s, 1.3H), 1.83-1.98 (m, 0.7H), 1.70 (d, J=6.8 Hz, 3H); MS ESI 461.3 [M+H]⁺, calcd for [C₂₆H₂₈N₄O₂S+H]⁺ 461.2.

Example A56

1-(2-fluorophenyl)-3-(3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazol-5-yl)urea

[0608]

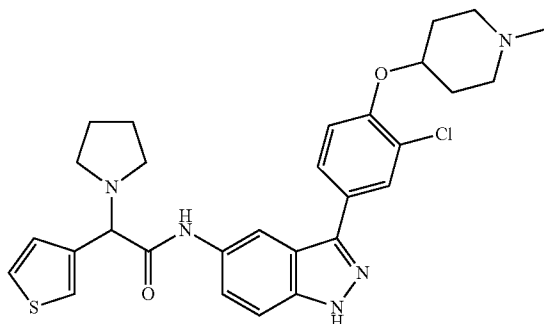


[0609] Using Method J with 3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazol-5-amine bis(2,2,2-trifluoroacetate) (96 mg, 0.174 mmol), 1-fluoro-2-isocyanatobenzene (39 uL, 0.348 mmol), DIPEA (150 uL, 0.87 mmol), and DMF (2.0 mL) gave the title compound as a TFA salt (17 mg, 21%, a tan solid). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.30 (s, 1H), 8.08 (t, J=7.6 Hz, 1H), 7.91-7.88 (m, 2H), 7.51 (d, J=9.0 Hz, 1H), 7.28 (d, J=8.6 Hz, 1H), 7.20-7.02 (m, 5H), 4.83 (bs, 1H), 3.64-3.41 (m, 2H), 3.30-2.93 (m, 2H), 2.93 (bs, 3H), 2.46-2.28 (m, 2H), 2.13-1.89 (m, 2H); MS ESI 460.3 [M+H]⁺, calcd for [C₂₆H₂₆FN₅O₂+H]⁺ 460.21.

Example A57

N-(3-(3-chloro-4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide

[0610]

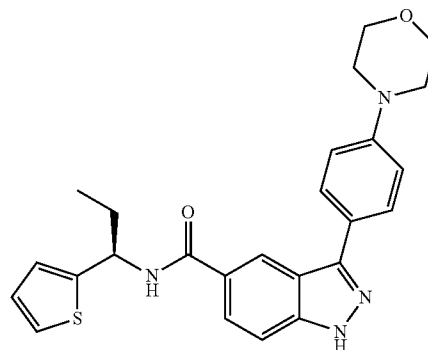


[0611] Using Method C2, N-(3-iodo-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide (52.7 mg, 0.116 mmol) and 4-(2-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)-1-methylpiperidine (61.8 mg, 80% pure, 0.14 mmol) were heated for 3 h at 125° C. in the microwave. Aq. work-up using EtOAc followed by purification by flash chromatography (RP HPLC, 10-80% MeOH in 0.1% TFA-H₂O; then SiO₂, 10-20% MeOH in DCM), gave the title compound (white solid, 15.4 mg, 24%). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.34 (m, J=1.0 Hz, 1H), 7.92 (d, J=2.3 Hz, 1H), 7.79 (dd, J=8.5, 2.3 Hz, 1H), 7.49-7.56 (m, 3H), 7.42 (dd, J=5.0, 3.0 Hz, 1H), 7.34 (dd, J=5.0, 1.3 Hz, 1H), 7.22 (d, J=8.5 Hz, 1H), 4.60 (br. s., 1H), 4.14 (s, 1H), 2.75-2.84 (m, 2H), 2.64-2.73 (m, 2H), 2.47-2.57 (m, 4H), 2.37 (s, 3H), 2.00-2.10 (m, 2H), 1.89-1.99 (m, 2H), 1.85 (t, J=5.8 Hz, 4H). MS ESI 550.1 [M+H]⁺, calcd for [C₂₉H₃₂ClN₅O₂S+H]⁺ 550.20.

Example A58

(R)-3-(4-morpholinophenyl)-N-(1-(thiophen-2-yl)propyl)-1H-indazole-5-carboxamide

[0612]

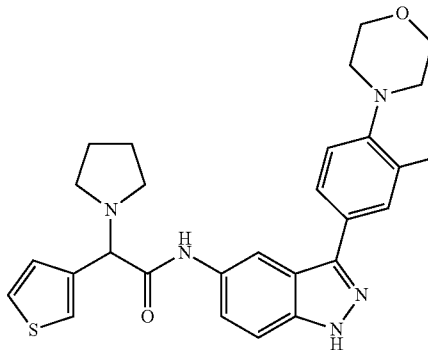


[0613] The title compound was synthesized according to the General Method A, utilizing 3-(4-morpholinophenyl)-1H-indazole-5-carboxylic acid (84 mg, 0.26 mmol), (1R)-1-(2-thienyl)propylamine·HCl (50 mg, 0.26 mmol), TBTU (83 mg, 0.26 mmol), DIPEA (0.14 mL, 0.78 mmol), and DMF (5 mL). Purification by RP HPLC, followed by passing through PoraPak column gave the title compound (white solid, 34 mg, 29%). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.59 (s, 1H), 7.82-7.95 (m, 3H), 7.57 (d, J=8.8 Hz, 1H), 7.26 (dd, J=5.0, 1.0 Hz, 1H), 7.03-7.11 (m, 3H), 6.95 (dd, J=4.9, 3.6 Hz, 1H), 5.31-5.39 (m, 1H), 3.80-3.87 (m, 4H), 3.16-3.23 (m, 4H), 2.06 (d, J=7.3 Hz, 2H), 1.04 (t, J=7.3 Hz, 3H); MS ESI 447.3 [M+H]⁺, calcd for [C₂₅H₂₆N₄O₂S+H]⁺ 447.2.

Example A59

N-(3-(3-methyl-4-morpholinophenyl)-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide

[0614]

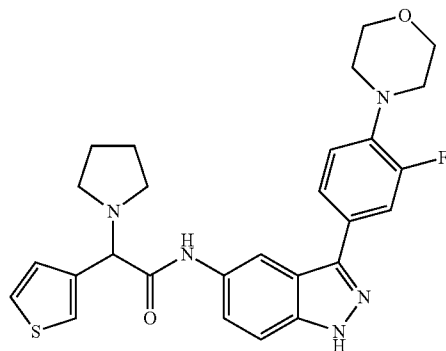


[0615] To a mixture of N-(3-iodo-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide (136 mg, 0.3 mmol) and (3-methyl-4-morpholinophenyl)boronic acid (73 mg, 0.33 mmol) in EtOH (4 mL) was added 1 M aq Na₂CO₃ (0.6 mL, 0.6 mmol), followed by Pd(PPh₃)₄ (17 mg, 0.015 mmol). The resulting mixture was purged with Ar and micro-waved 2 h at 120° C. After removal of solvents, it was redissolved in DMF/TFA (6 mL/0.5 mL), purified by prep-HPLC, followed by PoraPak and acidification with TFA to give the title compound as a di-TFA salt (white solid, 162.4 mg, 74%). ¹H NMR (400 MHz, CD₃OD) δ 8.38 (s, 1H), 7.87 (d, J=1.6 Hz, 1H), 7.81-7.76 (m, 2H), 7.61-7.52 (m, 3H), 7.42 (d, J=8.0 Hz, 1H), 7.38 (dd, J=5.2 Hz, 0.8 Hz, 1H), 5.35 (s, 1H), 4.02-3.96 (m, 4H), 3.90-3.80 (m, 1H), 3.35-3.25 (m, 5H), 3.20-3.04 (m, 2H), 2.48 (s, 3H), 2.25-1.93 (m, 4H); MS ESI 502.2 [M+H]⁺, calcd for [C₂₈H₃₁N₅O₂S+H]⁺ 502.2.

Example A60

N-(3-(3-fluoro-4-morpholinophenyl)-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide

[0616]

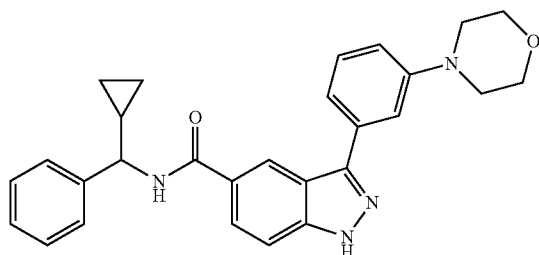


[0617] To a mixture of N-(3-iodo-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide (136 mg, 0.3 mmol) and (3-fluoro-4-morpholinophenyl)boronic acid (74 mg, 0.33 mmol) in EtOH (4 mL) was added 1 M aq Na₂CO₃ (0.6 mL, 0.6 mmol), followed by Pd(PPh₃)₄ (17 mg, 0.015 mmol). The resulting mixture was purged with Ar and micro-waved 2 h at 120° C. After removal of solvents, it was redissolved in DMF/TFA (6 mL/0.5 mL), purified by prep-HPLC to give the title compound as a di-TFA salt (pale yellow solid, 84.3 mg, 38%). ¹H NMR (400 MHz, CD₃OD) δ 8.40 (s, 1H), 7.87 (dd, J=2.8 Hz, 1.2 Hz, 1H), 7.65-7.61 (m, 2H), 7.57 (dd, J=13.8 Hz, 1.8 Hz, 1H), 7.52 (s, 2H), 7.38 (dd, J=5.2 Hz, 1.2 Hz, 1H), 7.07 (t, J=8.6 Hz, 1H), 5.31 (s, 1H), 3.92-3.78 (m, 5H), 3.35-3.25 (m, 1H), 3.22-3.03 (m, 6H), 2.25-1.92 (m, 4H); MS ESI 506.3 [M+H]⁺, calcd for [C₂₇H₂₈FN₅O₂S+H]⁺ 506.2.

Example A61

N-(cyclopropyl(phenyl)methyl)-3-(3-morpholinophenyl)-1H-indazole-5-carboxamide

[0618]

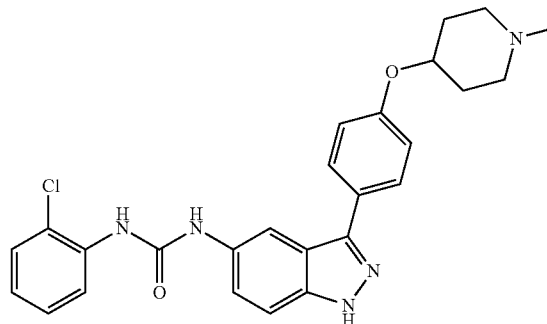


[0619] The title compound was synthesized according to the General Method C, utilizing N-(cyclopropyl(phenyl)methyl)-3-iodo-1H-indazole-5-carboxamide (100 mg, 0.24 mmol), 3-(4-morpholino)phenylboronic acid pinacol ester (69 mg, 0.24 mmol), Pd(PPh₃)₄ (28 mg, 0.024 mmol), satd. aq Na₂CO₃ (1.25 mL), and 3.75 mL of PhMe:EtOH (1:1). The vial was charged with Ar and heated in the microwave reactor at 125° C. for 2 h. Purification by RPHPLC, followed by trituration with Et₂O gave the title compound as beige solid (39 mg, 36%). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.58 (s, 1H), 7.94 (dd, J=8.7, 1.4 Hz, 1H), 7.62 (d, J=8.8 Hz, 1H), 7.40-7.55 (m, 5H), 7.34 (t, J=7.6 Hz, 2H), 7.24 (t, J=7.3 Hz, 1H), 7.05-7.10 (m, 1H), 4.48 (t, J=8.5 Hz, 1H), 3.84-3.89 (m, 4H), 3.22-3.27 (m, 4H), 1.33-1.44 (m, 1H), 0.62-0.69 (m, 2H), 0.41-0.54 (m, 2H); MS ESI 453.4 [M+H]⁺, calcd for [C₂₈H₂₈N₄O₂+H]⁺ 453.2.

Example A62

1-(2-chlorophenyl)-3-(3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazol-5-yl)urea

[0620]

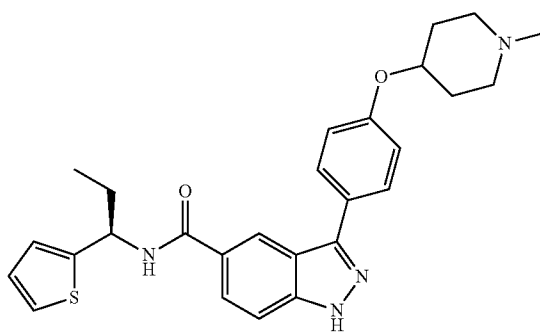


[0621] Using Method J, 3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazol-5-amine bis(2,2,2-trifluoroacetate) (111 mg, 0.202 mmol), 1-chloro-2-isocyanatobenzene (49 uL, 0.404 mmol) and DIPEA (180 uL, 1.01 mmol) in DMF (2.0 mL) gave the title compound as a TFA salt. (34 mg, 35%, an off-white solid). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.33 (s, 1H), 8.11 (d, J=7.3 Hz, 1H), 7.92-7.88 (m, 2H), 7.52 (d, J=8.8 Hz, 1H), 7.41 (d, J=8.4 Hz, 1H), 7.31-7.26 (m, 2H), 7.21-7.13 (m, 2H), 7.04 (t, J=7.9, 1H), 4.83 (bs, 1H), 3.66-3.39 (m, 2H), 3.30-3.18 (m, 2H), 2.95 (bs, 3H), 2.48-2.30 (m, 2H), 2.14-1.89 (m, 2H); MS ESI 476.4 [M+H]⁺, calcd for [C₂₆H₂₆ClN₅O₂+H]⁺ 476.19.

Example A63

(R)-3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-N-(1-(thiophen-2-yl)propyl)-1H-indazole-5-carboxamide

[0622]

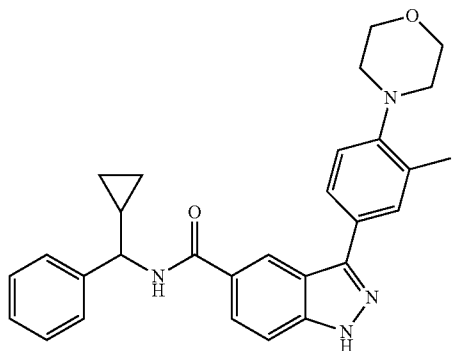


[0623] The title compound was synthesized according to the General Method C, utilizing (R)-3-iodo-N-(1-(thiophen-2-yl)propyl)-1H-indazole-5-carboxamide (90 mg, 0.22 mmol), 4-((1-methylpiperidin-4-yl)oxy)phenylboronic acid pinacol ester (69 mg, 0.22 mmol), PdCl₂dppf (25 mg, 0.022 mmol), satd. Na₂CO₃ (1.25 mL), and 3.75 mL of PhMe: EtOH (1:1). The vial was charged with Ar and heated in the microwave reactor at 125° C. for 2 h. Purification by RPHPLC, followed by flash chromatography (SiO₂, Biotage 25 g, 0-40% MeOH in CH₂Cl₂) gave the title compound (white solid, 18 mg, 17%). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.58 (s, 1H), 7.93 (dd, J=8.8, 1.5 Hz, 1H), 7.88 (d, J=8.8 Hz, 2H), 7.58 (d, J=8.8 Hz, 1H), 7.25 (dd, J=5.0, 1.0 Hz, 1H), 7.05 (s, 3H), 6.94 (dd, J=5.0, 3.5 Hz, 1H), 5.34 (t, J=7.5 Hz, 1H), 4.45 (br. s, 1H), 2.71 (br. s, 2H), 2.36 (br. s, 2H), 2.29 (s, 3H), 1.95-2.12 (m, 4H), 1.82 (br. d, J=7.5 Hz, 2H), 1.03 (t, J=7.3 Hz, 3H); MS ESI 475.3 [M+H]⁺, calcd for [C₂₇H₃₀N₄O₂S+H]⁺ 475.2.

Example A64

N-(cyclopropyl(phenyl)methyl)-3-(3-methyl-4-morpholinophenyl)-1H-indazole-5-carboxamide

[0624]

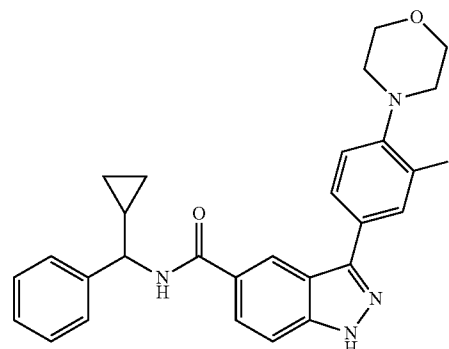


[0625] To a mixture of N-(cyclopropyl(phenyl)methyl)-3-iodo-1H-indazole-5-carboxamide (83.4 mg, 0.2 mmol) and (3-methyl-4-morpholinophenyl)boronic acid (44.2 mg, 0.2 mmol) in EtOH (4 mL) was added 1 M aq Na₂CO₃ (0.4 mL, 0.4 mmol), followed by Pd(PPh₃)₄ (11.6 mg, 0.01 mmol). The resulting mixture was purged with Ar and microwaved 2 h at 125° C. After removal of solvents, it was purified by flash chromatography (MeOH/DCM 0-15%), PoraPak and prep-HPLC to give the title compound as a TFA salt (light yellow solid, 36.3 mg, 31%). ¹H NMR (400 MHz, CD₃OD) δ 8.06 (pseudo s, 1H), 7.96 (dd, J=8.8 Hz, 1.6 Hz, 1H), 7.85-7.80 (m, 2H), 7.60 (dd, J=8.8 Hz, 0.8 Hz, 1H), 7.49 (pseudo d, J=7.2 Hz, 2H), 7.36-7.30 (m, 2H), 7.28-7.21 (m, 2H), 4.48 (d, J=9.6 Hz, 1H), 3.90 (t, J=4.4 Hz, 4H), 3.06 (t, J=4.4 Hz, 4H), 2.44 (s, 3H), 1.46-1.36 (m, 1H), 1.20-1.13 (m, 2H), 1.03-0.93 (m, 2H); MS ESI 467.4 [M+H]⁺, calcd for [C₂₉H₃₀N₄O₂+H]⁺ 467.2.

Example A65

N-(cyclopropyl(phenyl)methyl)-3-(3-fluoro-4-morpholinophenyl)-1H-indazole-5-carboxamide

[0626]

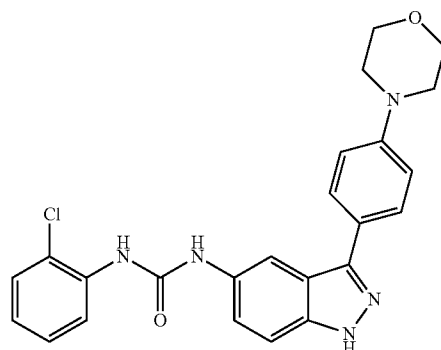


[0627] To a mixture of N-(cyclopropyl(phenyl)methyl)-3-iodo-1H-indazole-5-carboxamide (83.4 mg, 0.2 mmol) and (3-fluoro-4-morpholinophenyl)boronic acid (45 mg, 0.2 mmol) in EtOH (4 mL) was added 1 M aq Na₂CO₃ (0.4 mL, 0.4 mmol), followed by Pd(PPh₃)₄ (11.6 mg, 0.01 mmol). The resulting mixture was purged with Ar and microwaved 2 h at 125° C. After removal of solvents, it was purified by flash chromatography (MeOH/DCM 0-15%), PoraPak and prep-HPLC to give the title compound as a TFA salt (yellowish white solid, 32.4 mg, 28%). ¹H NMR (400 MHz, CD₃OD) δ 8.62 (pseudo s, 1H), 7.96 (dd, J=8.8 Hz, 1.6 Hz, 1H), 7.88 (pseudo d, J=8.4 Hz, 1H), 7.73 (dd, J=14.0 Hz, 2.0 Hz, 1H), 7.61 (d, J=8.8 Hz, 1H), 7.49 (d, J=7.6 Hz, 2H), 7.34 (t, J=7.6 Hz, 2H), 7.24 (t, J=7.4 Hz, 1H), 7.20-7.13 (m, 1H), 4.49 (d, J=9.2 Hz, 1H), 3.87 (t, J=4.6 Hz, 4H), 3.17-3.11 (m, 4H), 1.46-1.38 (m, 1H), 1.21-1.13 (m, 2H), 1.05-0.93 (m, 2H); MS ESI 471.4 [M+H]⁺, calcd for [C₂₈H₂₇N₄O₂+H]⁺ 471.2.

Example A66

1-(2-chlorophenyl)-3-(3-(4-morpholinophenyl)-1H-indazol-5-yl)urea

[0628]

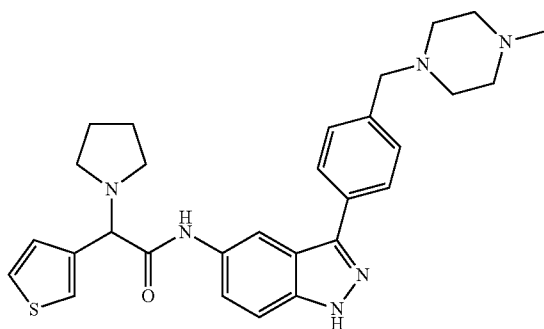


[0629] Using Method J, 3-(4-morpholinophenyl)-1H-indazol-5-amine bis(2,2,2-trifluoroacetate) (69 mg, 0.234 mmol), 1-chloro-2-isocyanatobenzene (58 uL, 0.468 mmol) and DIPEA (160 uL, 0.936 mmol) in DMF (2.0 mL) gave the title compound as a TFA salt (7.6 mg, 7.2%, a white solid). ¹H NMR (400 MHz, DMSO-d₆) δ ppm 12.96 (s, 1H), 9.46-9.48 (m, 1H), 8.28 (s, 2H), 8.20 (dd, J=8.28, 1.51 Hz, 1H), 7.79 (d, J=8.78 Hz, 2H), 7.49 (dd, J=17.44, 8.41 Hz, 1H), 7.28-7.33 (m, 2H), 7.10 (d, J=8.78 Hz, 2H), 7.00-7.05 (m, 1H), 3.75-3.79 (m, 4H), 3.17-3.21 (m, 4H); MS ESI 448.4 [M+H]⁺, calcd for [C₂₄H₂₂ClN₅O₂+H]⁺ 448.15.

Example A67

N-(3-(4-((4-methylpiperazin-1-yl)methyl)phenyl)-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide

[0630]

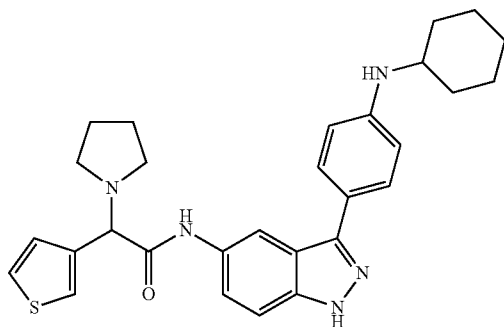


[0631] The title compound was synthesized according to general Method C by using a sealed degassed mixture of N-(3-iodo-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide (75 mg, 0.165 mmol), 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)piperazine (53 mg, 0.165 mmol), PdCl₂dppf (14 mg, 0.0165 mmol), 1 M aq Na₂CO₃ (0.17 mL) in PhMe/EtOH (3 mL, 1:0.5 mixture) under Ar with heating under microwave irradiation at 125° C. for 2.5 h. The reaction mixture was diluted with EtOAc (15 mL) and washed with H₂O (2×5 mL) and brine (5 mL), dried (Na₂SO₄) and concentrated under vacuum. Purification by flash chromatography (SiO₂, 0-80% MeOH in DCM) followed by RPHPLC gave the title compound as a TFA salt (light brown solid, 22 mg, 9%). ¹H NMR (400 MHz, CD₃OD) δ 8.41 (s, 1H), 8.01 (d, J=8.0 Hz, 2H), 7.88-7.87 (m, 1H), 7.66-7.62 (m, 3H), 7.58-7.51 (m, 2H), 7.38-7.37 (m, 1H), 5.26 (s, 1H), 4.20 (s, 2H), 3.88-3.87 (br.s, 1H), 3.51 (br.s, 4H), 3.13-3.10 (br.m, 3H), 2.96 (s, 3H), 2.25-1.96 (br.m, 5H), 3H merged with solvent peak, MS ESI 515.2 [M+H]⁺, calcd for [C₂₉H₃₄N₆OS+H]⁺ 515.2.

Example A68

N-(3-(4-(cyclohexylamino)phenyl)-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide

[0632]



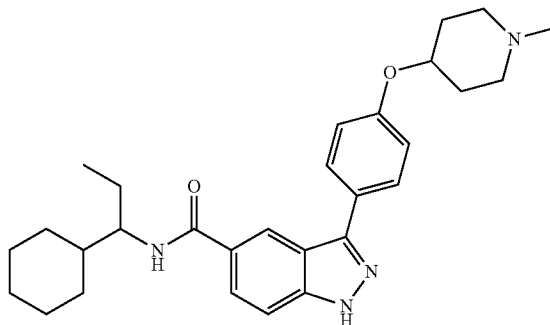
[0633] To a mixture of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (657 mg, 3 mmol) and cyclohexanone (0.31 mL, 3 mmol) in DCE (30 mL) was added NaBH(OAc)₃ (1.272 g, 6 mmol). The resulting mixture was cooled to 0° C. before HOAc (0.5 mL) was added. After stirring O/N at rt, it was quenched with satd aqNaHCO₃ (5 mL) and H₂O (30 mL), extracted with DCM and purified by flash chromatography (EtOAc/hex 0-45%) to give N-cyclohexyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (off white solid, 705 mg, 78%). ¹H NMR (400 MHz, CDCl₃) δ 7.62 (d, J=7.6 Hz, 2H), 6.56 (d, J=7.2 Hz, 2H), 3.35-3.25 (m, 1H), 2.12-2.02 (m, 2H), 1.72-1.62 (m, 2H), 4.45-1.10 (m, 18H); MS ESI 302.1 [M+H]⁺, calcd for [C₁₈H₂₈BNO₂+H]⁺ 302.1.

[0634] To a mixture of N-(3-iodo-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide (136 mg, 0.3 mmol) and N-cyclohexyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline in EtOH (4 mL) was added 1 M aq Na₂CO₃ (0.6 mL, 0.6 mmol), followed by Pd(PPh₃)₄ (17.4 mg, 0.015 mmol). The resulting mixture was purged with Ar and microwaved 2 h at 120° C. Additional Pd(PPh₃)₄ (17.4 mg, 0.015 mmol) was added and the resulting mixture was purged with Ar and microwaved 2 h at 125° C. After removal of solvents, it was redissolved in DMF/TFA (6 mL/0.5 mL), purified by prep-HPLC and PoraPak to give the title compound (white solid, 52.3 mg, 35%). ¹H NMR (400 MHz, CD₃OD) δ 8.33 (s, 1H), 7.65 (pseudo d, J=8.8 Hz, 2H), 7.51-7.43 (m, 3H), 7.38 (dd, J=9.0 Hz, 3.0 Hz, 1H), 7.30 (dd, J=5.2 Hz, 1.2 Hz, 1H), 6.72 (pseudo d, J=8.8 Hz, 2H), 4.08 (s, 1H), 3.29-3.21 (m, 1H), 2.68-2.58 (m, 2H), 2.50-2.42 (m, 2H), 2.07-1.98 (m, 2H), 1.85-1.72 (m, 6H), 1.68-1.62 (m, 1H), 1.45-1.32 (m, 2H), 1.30-1.12 (m, 3H); MS ESI 500.2 [M+H]⁺, calcd for [C₂₉H₃₃N₅OS+H]⁺ 500.2.

Example A69

N-(1-cyclohexylpropyl)-3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazole-5-carboxamide

[0635]

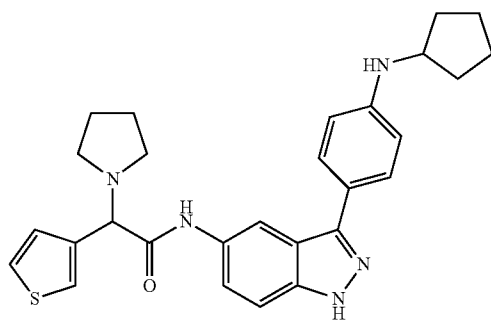


[0636] The title compound was synthesized according to Method C3 utilizing N-(1-cyclohexylpropyl)-3-iodo-1H-indazole-5-carboxamide and 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine and obtained as a yellow solid (20 mg, 18% yield). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.57 (s, 1H), 7.92 (m, 3H), 7.60 (d, J=8.8 Hz, 1H), 7.08 (d, J=8.8 Hz, 2H), 4.47 (m, 1H), 3.87 (m, 1H), 2.72 (br, 2H), 2.37 (br, 2H), 2.30 (s, 3H), 2.05 (br, 2H), 1.83 (m, 3H), 1.74 (m, 3H), 1.65 (m, 1H), 1.51 (m, 2H), 1.22 (m, 4H), 1.08 (m, 2H), 0.95 (t, J=7.2 Hz, 3H); MS ESI [M+H]⁺ 475.4, calcd for [C₂₉H₃₈N₄O₂+H]⁺ 475.31.

Example A70

N-(3-(4-(cyclopentylamino)phenyl)-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide

[0637]



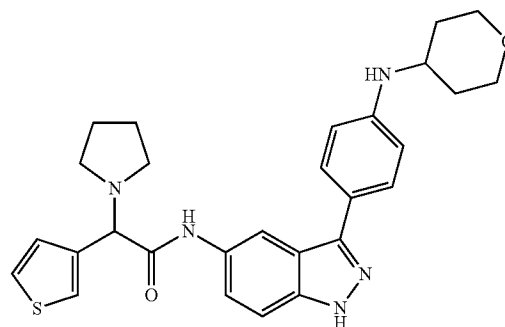
[0638] To a mixture of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (876 mg, 4 mmol) and cyclopentanone (0.36 mL, 4 mmol) in DCE (30 mL) was added NaBH(OAc)₃ (1.484 g, 7 mmol), followed by HOAc (0.5 mL). The resulting mixture was stirred O/N at rt, quenched with satd aq NaHCO₃ (10 mL) and H₂O (30 mL), extracted with DCM and purified by flash chromatography (EtOAc/hex 0-45%) to give N-cyclopentyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (off white solid, 393 mg, 34%). ¹H NMR (400 MHz, CDCl₃) δ 7.63 (d, J=8.0 Hz, 2H), 6.58 (d, J=8.0 Hz, 2H), 3.82 (quint, J=6.2 Hz, 1H), 2.08-1.98 (m, 1H), 1.78-1.56 (m, 4H), 1.52-1.43 (m, 2H), 1.33 (s, 12H); MS ESI 288.1 [M+H]⁺, calcd for [C₁₇H₂₆BNO₂+H]⁺ 288.2.

[0639] To a mixture of N-(3-iodo-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide (136 mg, 0.3 mmol) and N-cyclopentyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (96 mg, 0.33 mmol) in EtOH (4 mL) was added 1 M aq Na₂CO₃ (0.6 mL, 0.6 mmol), followed by Pd(PPh₃)₄ (35 mg, 0.03 mmol). The resulting mixture was purged with Ar and microwaved 3 h at 125° C. After removal of solvents, it was purified by flash chromatography, PoraPak and prep-HPLC to give the title compound as a di-TFA salt (yellow solid, 51.9 mg, 24%). ¹H NMR (400 MHz, CD₃OD) δ 8.43 (pseudo s, 1H), 8.08 (pseudo d, J=8.8 Hz, 2H), 7.87 (dd, J=3.0 Hz, 1.4 Hz, 1H), 7.64 (dd, J=5.0 Hz, 3.0 Hz, 1H), 7.60-7.52 (m, 4H), 7.39 (dd, J=5.2 Hz, 1.2 Hz, 1H), 5.33 (s, 1H), 4.02 (quint, J=6.7 Hz, 1H), 3.86 (brs, 1H), 3.35-3.05 (m, 3H), 2.30-1.95 (m, 6H), 1.93-1.67 (m, 6H); MS ESI 486.2 [M+H]⁺, calcd for [C₂₈H₃₁N₅O₂S+H]⁺ 486.2.

Example A71

2-(pyrrolidin-1-yl)-N-(3-(4-((tetrahydro-2H-pyran-4-yl)amino)phenyl)-1H-indazol-5-yl)-2-(thiophen-3-yl)acetamide

[0640]



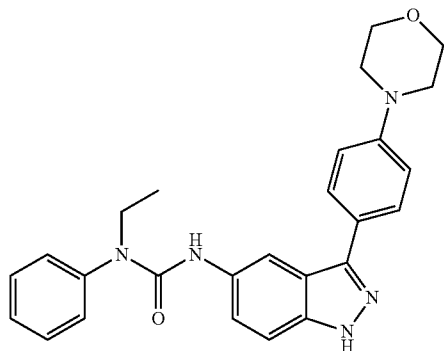
[0641] To a mixture of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.095 mg, 5 mmol), dihydro-2H-pyran-4(3H)-one (550 mg, 5 mmol) and NaBH(OAc)₃ (1.696 g, 8 mmol) in DCE (30 mL) was added HOAc (0.5 mL). The resulting mixture was stirred O/N at rt, quenched with satd aq NaHCO₃ (10 mL) and H₂O (30 mL), extracted with DCM and purified by flash chromatography (EtOAc/hex 0-45%) to give N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl) tetrahydro-2H-pyran-4-amine (beige solid, 0.65 g, 43%). ¹H NMR (400 MHz, CDCl₃) δ 7.64 (d, J=8.0 Hz, 2H), 6.60 (d, J=8.0 Hz, 2H), 4.01 (dt, J=12.0 Hz, 3.2 Hz, 2H), 3.60-3.45 (m, 3H), 2.08-2.00 (m, 2H), 1.60-1.44 (m, 2H), 1.33 (s, 12H); MS ESI 304.1 [M+H]⁺, calcd for [C₁₇H₂₆BNO₃+H]⁺ 304.2.

[0642] To a mixture of N-(3-iodo-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide (136 mg, 0.3 mmol) and N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl) tetrahydro-2H-pyran-4-amine (100 mg, 0.33 mmol) in EtOH (4 mL) was added 1 M aq Na₂CO₃ (0.6 mL, 0.6 mmol), followed by Pd(PPh₃)₄ (34.7 mg, 0.03 mmol). The resulting mixture was purged with Ar and microwaved 3 h at 125° C. After removal of solvents, it was purified by flash chromatography (MeOH/DCM 0-20%), PoraPak and prep-HPLC to give the title compound as a di-TFA salt (yellow solid, 21.9 mg, 10%). ¹H NMR (400 MHz, CD₃OD) δ 8.42 (t, J=0.8 Hz, 1H), 8.03 (d, J=8.8 Hz, 2H), 7.88 (dd, J=3.2 Hz, 1.2 Hz, 1H), 7.65 (dd, J=5.2 Hz, 3.2 Hz, 1H), 7.57 (dd, J=8.8 Hz, 0.4 Hz, 1H), 7.54 (dd, J=8.4 Hz, 1.6 Hz, 1H), 7.43 (d, J=8.8 Hz, 2H), 7.38 (dd, J=8.8 Hz, 1.4 Hz, 1H), 5.23 (s, 1H), 4.08-4.00 (m, 2H), 3.93-3.72 (m, 2H), 3.48 (dt, J=11.8 Hz, 1.8 Hz, 2H), 3.35-3.05 (m, 3H), 2.28-2.09 (m, 3H), 2.06-1.95 (m, 3H), 1.80-1.69 (m, 2H); MS ESI 502.2 [M+H]⁺, calcd for [C₂₈H₃₁N₅O₂S+H]⁺ 502.2.

Example A72

1-ethyl-3-(3-(4-morpholinophenyl)-1H-indazol-5-yl)-1-phenylurea

[0643]



A. 3-(4-morpholinophenyl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-amine

[0644] The same procedure was followed as for 3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazol-5-amine bis (2,2,2-trifluoroacetate) instead using 3-iodo-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-amine (30 mg, 0.087 mmol) and 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine (38 mg, 0.131 mmol). Obtained 36 mg of an impure product which was used for subsequent synthetic steps.

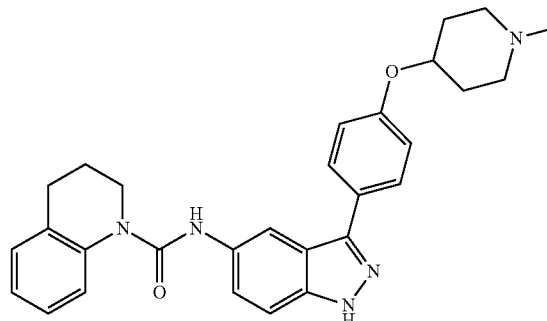
B. 1-ethyl-3-(3-(4-morpholinophenyl)-1H-indazol-5-yl)-1-phenylurea

[0645] To a solution of triphosgene (8 mg, 0.027 mmol) in CH_2Cl_2 (0.4 mL) cooled to 0°C . was added dropwise over 15 min a solution of 3-(4-morpholinophenyl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-amine (30 mg, 0.074 mmol) in DIPEA (28 μL , 0.16 mmol) and CH_2Cl_2 (0.6 mL). After stirring for an additional 15 min a solution of N-ethylaniline (10 μL , 0.074 mmol), DIPEA (13 μL , 0.074 mmol) and CH_2Cl_2 (0.5 mL) was added. After 3 h the reaction was quenched with MeOH (0.5 mL) and the solvent was removed. The residue was taken up in EtOH (0.4 mL) and HCl (0.1 mL of a 1 M solution in Et_2O) was added and the mixture heated to 50°C . for 2 h. The solvent was removed and the residue purified by prep-HPLC which gave 5.0 mg of the product isolated as its TFA salt (29%, a tan solid). ^1H NMR (400 MHz, CDCl_3) δ ppm 8.03 (s, 1H), 7.84 (d, $J=8.0$ Hz, 2H), 7.51-7.17 (m, 6H), 7.02 (d, $J=7.6$ Hz, 2H), 6.14 (s, 1H), 3.92-3.82 (m, 6H), 3.24 (bs, 4H), 1.18 (bs, 3H); MS ESI 442.3 $[\text{M}+\text{H}]^+$, calcd for $[\text{C}_{26}\text{H}_{27}\text{N}_5\text{O}_2+\text{H}]^+$ 442.22.

Example A73

N-(3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazol-5-yl)-3,4-dihydroquinoline-1(2H)-carboxamide

[0646]



A. 3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-amine

[0647] The same procedure was followed as for 3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazol-5-amine bis (2,2,2-trifluoroacetate) instead using 3-iodo-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-amine (300 mg, 0.874 mmol) and 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine (416 mg, 1.31 mmol). Obtained 130 mg of an impure product which was used for subsequent synthetic steps; MS ESI 407.1 $[\text{M}+\text{H}]^+$, calcd for $[\text{C}_{24}\text{H}_{30}\text{N}_4\text{O}_2+\text{H}]^+$ 407.24.

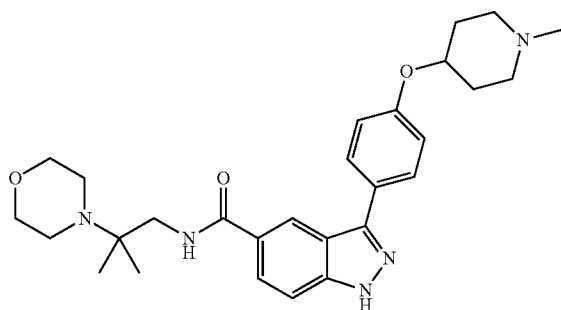
B. N-(3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazol-5-yl)-3,4-dihydroquinoline-1(2H)-carboxamide

[0648] To a solution of triphosgene (14 mg, 0.046 mmol) in CH_2Cl_2 (0.6 mL) cooled to 0°C . was added dropwise over 15 min a solution of 3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-amine (50 mg, 0.123 mmol) in DIPEA (47 μL , 0.271 mmol) and CH_2Cl_2 (0.9 mL). After stirring for an additional 15 min a solution of 1,2,3,4-tetrahydroquinoline (15 μL , 0.123 mmol), DIPEA (21 μL , 0.123 mmol) and CH_2Cl_2 (0.8 mL) was added. After 3 h the reaction was quenched with MeOH (0.5 mL) and the solvent was removed. The residue was taken up in EtOH (0.4 mL) and HCl (0.1 mL of a 1 M solution in Et_2O) was added and the mixture heated to 50°C . for 2 h. The solvent was removed and the residue purified by prep-HPLC which gave the product as its TFA salt (2.0 mg, 3.3%, a white film). ^1H NMR (400 MHz, CD_3OD) δ ppm 8.14 (s, 1H), 7.90-7.86 (m, 2H), 7.49 (d, $J=9.0$ Hz, 1H), 7.43-7.36 (m, 2H), 7.21-7.11 (m, 4H), 7.05 (t, $J=8.5$ Hz, 1H), 4.83 (bs, 1H), 3.82-3.79 (m, 2H), 3.65-3.35 (m, 2H), 3.30-3.18 (m, 2H), 2.93 (bs, 3H), 2.82 (t, $J=6.4$ Hz, 2H), 2.45-2.28 (m, 2H), 2.14-1.88 (m, 4H); MS ESI 482.3 $[\text{M}+\text{H}]^+$, calcd for $[\text{C}_{29}\text{H}_{31}\text{N}_5\text{O}_2+\text{H}]^+$ 482.26.

Example A74

N-(2-methyl-2-morpholinopropyl)-3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazole-5-carboxamide

[0649]

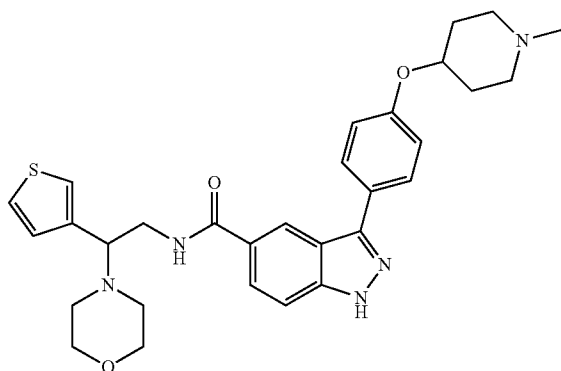


[0650] A TFA salt of the title compound was synthesized according to Method C3 utilizing 3-iodo-N-(2-methyl-2-morpholinopropyl)-1H-indazole-5-carboxamide and 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine obtained as a white solid (38 mg, 35% yield). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.66 (s, 1H), 7.98 (m, 3H), 7.65 (d, J=8.8 Hz, 1H), 7.20 (m, 2H), 4.96, 4.86 (s, m, 1H), 4.13 (m, 2H), 3.86 (m, 2H), 3.70 (m, 4H), 3.60 (m, 1H), 3.33 (m, 4H), 2.93 (s, 3H), 2.42, 2.28 (m, 2H), 2.17, 1.95 (m, 2H), 1.48 (s, 6H); MS ESI [M+H]⁺ 492.2, calcd for [C₂₈H₃₇N₅O₃+H]⁺ 492.30.

Example A75

3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-N-(2-morpholino-2-(thiophen-3-yl)ethyl)-1H-indazole-5-carboxamide

[0651]



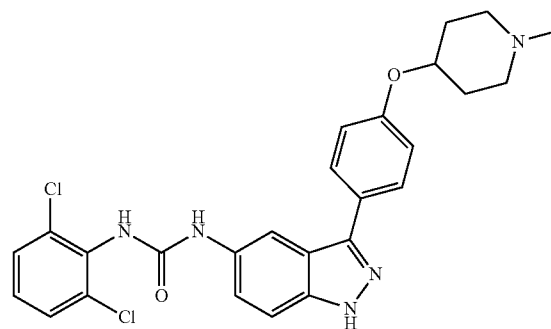
[0652] The title compound was synthesized according to Method C3 utilizing 3-iodo-N-(2-morpholino-2-(thiophen-3-yl)ethyl)-1H-indazole-5-carboxamide and 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine and obtained as a white solid (19 mg, 15% yield). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.35 (s, 1H), 7.87 (d, J=8.78 Hz, 2H), 7.80 (dd, J=8.78, 1.51 Hz, 1H), 7.57 (d, J=8.78 Hz,

1H), 7.43 (dd, J=4.89, 2.89 Hz, 1H), 7.27-7.32 (m, 1H), 7.06-7.15 (m, 3H), 4.52 (br. s., 1H), 3.93-4.04 (m, 2H), 3.63-3.74 (m, 5H), 2.78 (br. s., 2H), 2.39-2.62 (m, 6H), 2.35 (s, 3H), 2.07 (br. s., 2H), 1.89 (br. s., 2H); MS ESI [M+H]⁺ 546.3, calcd for [C₃₀H₃₅N₅O₃S+H]⁺ 546.25.

Example A76

1-(2,6-dichlorophenyl)-3-(3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazol-5-yl)urea

[0653]

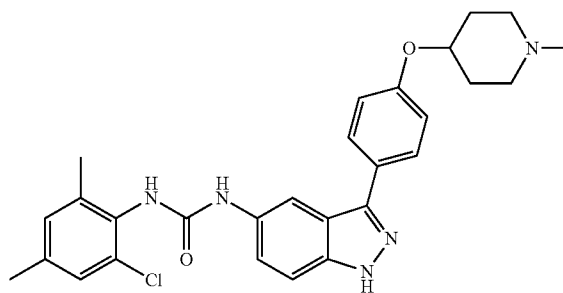


[0654] Using Method J, 3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazol-5-amine bis(2,2,2-trifluoroacetate) (50 mg, 0.11 mmol), 1,3-dichloro-2-isocyanatobenzene (43 mg, 0.23 mmol) and DIPEA (100 uL, 0.58 mmol) in DMF (1.2 mL) gave the title compound as a TFA salt (10 mg, 14%, a brown powder). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.25 (s, 1H), 7.89-7.86 (m, 2H), 7.52-7.41 (m, 3H), 7.34-7.25 (m, 2H), 7.17-7.10 (m, 2H), 4.84 (bs, 1H), 3.63-3.36 (m, 2H), 3.30-3.15 (m, 2H), 2.92 (bs, 3H), 2.43-2.26 (m, 2H), 2.11-1.87 (m, 2H); MS ESI 510.3 [M+H]⁺, calcd for [C₂₆H₂₅Cl₂N₅O₂+H]⁺ 510.15.

Example A77

1-(2-chloro-4,6-dimethylphenyl)-3-(3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazol-5-yl)urea

[0655]



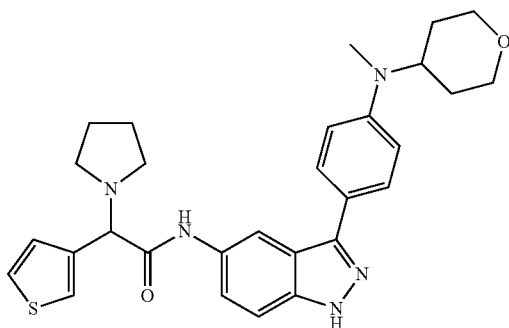
[0656] Using Method J, 3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazol-5-amine bis(2,2,2-trifluoroacetate) (50 mg, 0.11 mmol), 1-chloro-2-isocyanato-3,5-dimethylbenzene (42 mg, 0.23 mmol) and DIPEA (100 uL, 0.58 mmol) in DMF (1.2 mL) gave the title compound as a TFA salt (16 mg, 23%, a brown powder). ¹H NMR (400 MHz,

CD₃OD) δ ppm 8.24 (s, 1H), 7.88-7.84 (m, 2H), 7.49 (d, J=8.9 Hz, 1H), 7.31 (d, J=8.9 Hz, 1H), 7.17-7.09 (m, 3H), 7.05 (s, 1H), 4.83 (bs, 1H), 3.63-3.33 (m, 2H), 3.30-3.15 (m, 2H), 2.92 (bs, 3H), 2.45-2.23 (m, 2H), 2.37 (s, 3H), 2.36 (s, 3H), 2.12-1.87 (m, 2H); MS ESI 504.3 [M+H]⁺, calcd for [C₂₈H₃₀ClN₅O₂+H]⁺ 504.22.

Example A78

N-(3-(4-(methyl(tetrahydro-2H-pyran-4-yl)amino)phenyl)-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide

[0657]



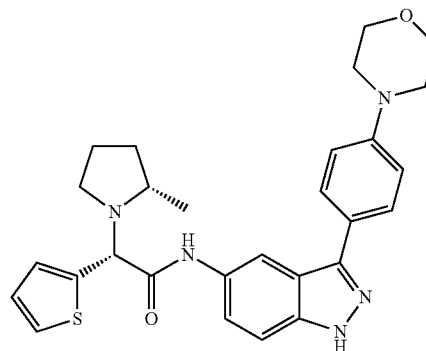
[0658] To a solution of 37% formalin (0.21 mL, 3 mmol) in DCE/MeOH (20 mL/4 mL) was added N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)tetrahydro-2H-pyran-4-amine (303 mg, 1 mmol) and NaBH(OAc)₃ (424 mg, 2 mmol). Additional 37% formalin (37% in H₂O, 0.21 mL, 3 mmol) and NaBH(OAc)₃ (424 mg, 2 mmol) were added and the reaction mixture was stirred for 2 h at rt, and then quenched with satd aq NaHCO₃ (10 mL) and H₂O (30 mL), extracted with DCM and purified by flash chromatography (0-45% MeOH/DCM) to give N-methyl-N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)tetrahydro-2H-pyran-4-amine (pink solid, 224 mg). ¹H NMR (400 MHz, CDCl₃) δ MS ESI 318.1 [M+H]⁺, calcd for [C₁₈H₂₈BNO₃+H]⁺ 318.2.

[0659] To a mixture of N-(3-iodo-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide (136 mg, 0.3 mmol) and N-methyl-N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)tetrahydro-2H-pyran-4-amine (100 mg, 0.315 mmol) in EtOH (4 mL) was added 1 M aq Na₂CO₃ (0.6 mL, 0.6 mmol), followed by Pd(PPh₃)₄ (69 mg, 0.06 mmol). The resulting mixture was purged with Ar and micro-waved 3 h at 125° C. After removal of solvents, it was purified by flash chromatography (0-20% MeOH/DCM), prep-HPLC and PoraPak to give the title compound (white solid, 44.8 mg, 29%). ¹H NMR (400 MHz, CD₃OD) δ 8.38 (s, 1H), 7.72 (d, J=8.8 Hz, 2H), 7.51-7.43 (m, 3H), 7.34 (dd, J=5.0 Hz, 3.0 Hz, 1H), 7.29 (dd, J=5.2 Hz, 0.8 Hz, 1H), 6.87 (d, J=8.8 Hz, 2H), 4.07 (s, 1H), 3.95 (dd, J=11.4 Hz, 4.2 Hz, 2H), 3.84 (tt, J=11.6 Hz, 3.8 Hz, 1H), 3.44 (t, J=11.0 Hz, 2H), 2.72 (s, 3H), 2.64-2.56 (m, 2H), 2.47-2.39 (m, 2H), 1.82-1.70 (m, 6H), 1.60-1.53 (m, 2H); MS ESI 516.3 [M+H]⁺, calcd for [C₂₉H₃₃N₅O₂S+H]⁺ 516.2.

Example A79

(R)-2-((S)-2-methylpyrrolidin-1-yl)-N-(3-(4-morpholinophenyl)-1H-indazol-5-yl)-2-(thiophen-2-yl)acetamide

[0660]



A. (R)-2-((S)-2-methylpyrrolidin-1-yl)-2-(thiophen-2-yl)acetic acid

[0661] Using Method D, (S)-2-methylpyrrolidine (0.135 mL, 1.57 mmol) and thiophen-2-ylboronic acid (201.1 mg, 1.57 mmol) gave the title compound (off-white solid, 330.1 mg, 93%) which was used without purification. NMR (400 MHz, CD₃OD) δ ppm 7.57 (d, J=4.5 Hz, 1H), 7.36 (dd, J=3.5, 1.0 Hz, 1H), 7.10 (dd, J=5.3, 3.5 Hz, 1H), 3.63-3.73 (m, 1H), 3.19-3.28 (m, 1H), 2.24-2.39 (m, 1H), 1.92-2.08 (m, 2H), 1.74-1.85 (m, 1H), 1.50 (d, J=6.53 Hz, 3H).

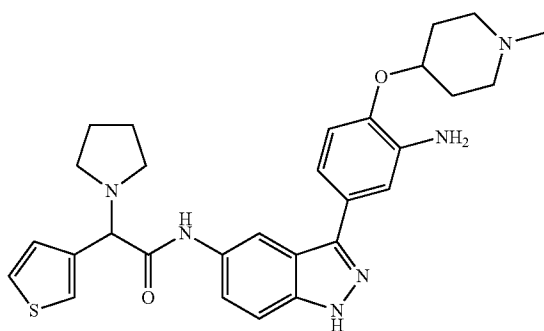
B. (R)-2-((S)-2-methylpyrrolidin-1-yl)-N-(3-(4-morpholinophenyl)-1H-indazol-5-yl)-2-(thiophen-2-yl)acetamide

[0662] (1-Cyano-2-ethoxy-2-oxoethylidenaminoxy)dimethylamino-morpholino-carbenium hexafluorophosphate (35.2 mg, 0.082 mmol) was added to an ice-cooled mixture of (R)-2-((S)-2-methylpyrrolidin-1-yl)-2-(thiophen-2-yl)acetic acid (16.5 mg, 0.073 mmol), 3-(4-morpholinophenyl)-1H-indazol-5-amine bis(2,2,2-trifluoroacetate) (39.9 mg, 0.076 mmol) and DIPEA (0.05 mL, 0.28 mmol) in DMF (1.0 mL) under Ar. The resulting mixture was stirred in ice bath for 1 h, then allowed to warm to rt and stirred for a further 22 h. The product was partitioned between EtOAc (200 mL) and satd aq NaHCO₃ (25 mL), and the aq. layer was extracted with EtOAc (2x25 mL). The combined organic layer was washed with H₂O (25 mL) and brine (25 mL), dried (Na₂SO₄), filtered, and concentrated to dryness. Purification by flash chromatography (SiO₂, 0-10% MeOH in DCM; followed by RPRP HPLC, 10-80% MeOH in 0.1% TFA-H₂O) followed by purification by another prep HPLC gave the title compound as the TFA salt (yellow solid film, 14.0 mg, 26%). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.38 (t, J=1.3 Hz, 1H), 7.85 (d, J=8.3 Hz, 2H), 7.71 (d, J=5.3 Hz, 1H), 7.49-7.59 (m, 3H), 7.20 (m, J=5.0, 3.5 Hz, 3H), 5.50 (s, 1H), 3.90 (t, J=4.8 Hz, 4H), 3.79-3.87 (m, 1H), ~3.30 (4H, obscured by solvent), 2.40 (dd, J=13.3, 7.8 Hz, 1H), 2.06 (t, J=7.0 Hz, 2H), 1.86 (dq, J=13.2, 6.5 Hz, 1H), 1.52 (d, J=6.3 Hz, 3H); MS ESI 502.3 [M+H]⁺, calcd for [C₂₈H₃₁N₅O₂S+H]⁺ 502.23.

Example A80

N-(3-(3-amino-4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide

[0663]



A. 1-methyl-4-(2-nitro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine

[0664] DIAD (0.25 mL, 1.26 mmol) was added drop-wise to a solution of PPh_3 (315 mg, 1.20 mmol), 2-nitro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (199.8 mg, 0.785 mmol) and 1-methylpiperidin-4-ol (138.3 mg, 1.20 mmol) in DCM (8 mL) under Ar and the reaction was stirred at rt for 3.5 d. Purification by flash chromatography without work-up or evaporation (SiO_2 , 5-35% MeOH in DCM) gave the title compound (36.0 mg, 80% pure, 13%). ^1H NMR (400 MHz, CDCl_3) δ ppm 8.25 (d, $J=1.5$ Hz, 1H), 7.93 (dd, $J=8.3$, 1.5 Hz, 1H), 7.63-7.71 (m, 1H), 7.52-7.58 (m, 1H), 7.43-7.50 (m, 1H), 7.06 (d, $J=8.5$ Hz, 1H), 4.82 (br. s., 1H), 2.87-3.05 (m, 4H), 2.61 (s, 3H), 2.28-2.40 (m, 3H), 2.09 (d, $J=13.8$ Hz, 2H), 1.32-1.36 (m, 15H). MS ESI 363.1 $[\text{M}+\text{H}]^+$, calcd for $[\text{C}_{18}\text{H}_{27}\text{BN}_2\text{O}_5+\text{H}]^+$ 363.21.

B. N-(3-(4-((1-methylpiperidin-4-yl)oxy)-3-nitrophenyl)-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide

[0665] Using Method C2, N-(3-iodo-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide (39.9 mg, 0.088 mmol) and 1-methyl-4-(2-nitro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine (35 mg, 80% pure, 0.077 mmol) gave the title compound after 3 h at 125°C . in the microwave (34.8 mg, 57%) after purification by flash chromatography (SiO_2 , 15-30% MeOH in DCM; followed by RPRP HPLC, 10-80% MeOH in 0.1% TFA- H_2O). ^1H NMR (400 MHz, CD_3OD) δ ppm 8.39-8.46 (m, 1.8H), 8.32-8.37 (m, 0.2H), 8.16-8.25 (m, 1H), 7.86-7.91 (m, 1H), 7.62-7.68 (m, 1H), 7.50-7.61 (m, 4H), 7.34-7.43 (m, 1H), 5.28-5.32 (m, 1H), 5.12-5.18 (m, 1H), 3.80-3.95 (m, 1.2H), 3.64-3.73 (m, 0.8H), 3.46-3.55 (m, 2H), 3.33-3.42 (m, 2H), 3.16-3.28 (m, 1H), 3.03-3.15 (m, 1H), 2.96 (s, 3H), 2.43-2.53 (m, 0.8H), 2.31-2.41 (m, 1.6H), 2.10-2.29 (m, 5H), 1.93-2.08 (m, 1H). MS ESI 561.2 $[\text{M}+\text{H}]^+$, calcd for $[\text{C}_{29}\text{H}_{32}\text{N}_6\text{O}_4\text{S}+\text{H}]^+$ 561.23.

C. N-(3-(3-amino-4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide

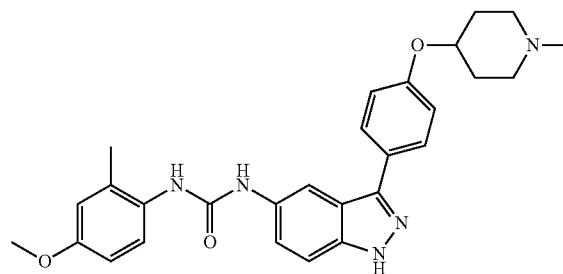
[0666] A mixture of Pd/C (10%, 18.1 mg, 0.017 mmol) and N-(3-(4-((1-methylpiperidin-4-yl)oxy)-3-nitrophenyl)-1H-

indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide (34.8 mg, 0.062 mmol) in MeOH (5 mL) was stirred at rt with H_2 balloon for 2.5 h, and then filtered through Celite, rinsing with MeOH (25 mL). After concentration to dryness, purification by RP HPLC (10-80% MeOH in 0.1% TFA- H_2O) followed by PoraPak Rxn Cx work-up gave the title compound (yellow solid, 6.5 mg, 20%). ^1H NMR (400 MHz, CD_3OD) δ ppm 8.34 (s, 1H), 7.47-7.52 (m, 3H), 7.42 (dd, $J=4.9$, 2.9 Hz, 1H), 7.32-7.35 (m, 2H), 7.22 (dd, $J=8.3$, 2.0 Hz, 1H), 6.98 (d, $J=8.5$ Hz, 1H), 4.47 (br. s., 1H), 4.11 (s, 1H), 2.77 (br. s., 2H), 2.67 (d, $J=6.0$ Hz, 3H), 2.46-2.55 (m, 3H), 2.40 (br. s., 2H), 2.33 (s, 3H), 2.06 (br. s., 2H), 1.89 (d, $J=9.5$ Hz, 2H), 1.84 (br. s., 4H). MS ESI 531.1 $[\text{M}+\text{H}]^+$, calcd for $[\text{C}_{29}\text{H}_{34}\text{N}_6\text{O}_2\text{S}+\text{H}]^+$ 531.25.

Example A81

1-(4-methoxy-2-methylphenyl)-3-(3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazol-5-yl)urea

[0667]

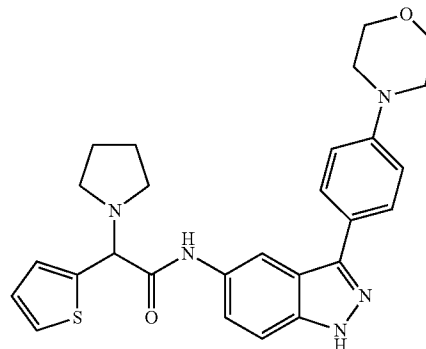


[0668] Using Method J, 3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazol-5-amine bis(2,2,2-trifluoroacetate) (50 mg, 0.11 mmol), 1-isocyanato-4-methoxy-2-methylbenzene (33 μL , 0.23 mmol) and DIPEA (100 μL , 0.58 mmol) in DMF (1.2 mL) gave the title compound as a TFA salt (25 mg, 36%, a beige powder). ^1H NMR (400 MHz, CD_3OD) δ ppm 8.26 (s, 1H), 7.89-7.86 (m, 2H), 7.49 (d, $J=8.8$ Hz, 1H), 7.36 (d, $J=8.8$ Hz, 1H), 7.28 (d, $J=8.9$ Hz, 1H), 7.19-7.12 (m, 2H), 6.81 (d, $J=2.6$ Hz, 1H), 6.75 (dd, $J_1=8.4$ Hz, $J_2=2.5$ Hz, 1H), 4.83 (bs, 1H), 3.77 (s, 3H), 3.64-3.32 (m, 2H), 3.30-3.15 (m, 2H), 2.93 (bs, 3H), 2.47-2.29 (m, 2H), 2.29 (s, 3H), 2.14-1.91 (m, 2H); MS ESI 486.3 $[\text{M}+\text{H}]^+$, calcd for $[\text{C}_{28}\text{H}_{31}\text{N}_5\text{O}_3+\text{H}]^+$ 486.25.

Example A82

N-(3-(4-morpholinophenyl)-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-2-yl)acetamide

[0669]

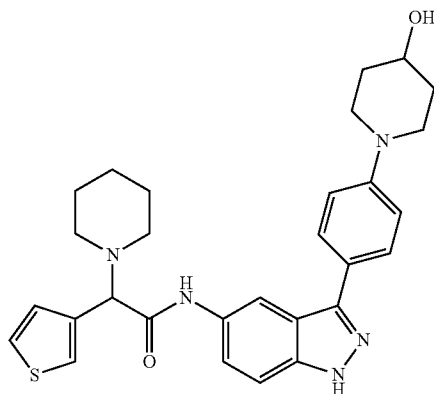


[0670] To a mixture of 2-(pyrrolidin-1-yl)-2-(thiophen-2-yl)acetic acid (85 mg, 0.4 mmol), 3-(4-morpholinophenyl)-1H-indazol-5-amine di-trifluoroacetic acid (229 mg, 0.44 mmol) and TBTU (128 mg, 0.4 mmol) in DMF (6 mL) at 0° C. was added ^tPr₂NEt (0.28 mL, 1.6 mmol). The resulting mixture was stirred for 1 h at 0° C. and purified by prep-HPLC to give the title compound as a di-TFA salt (yellow solid, 263 mg, 92%). ¹H NMR (400 MHz, CD₃OD) δ 8.39 (s, 1H), 7.88 (d, J=8.4 Hz, 2H), 7.52 (d, J=4.8 Hz, 1H), 7.54 (s, 2H), 7.51 (dd, J=3.2 Hz, 0.8 Hz, 1H), 7.33-7.26 (m, 2H), 7.12 (dd, J=5.2 Hz, 3.6 Hz, 1H), 5.78 (s, 1H), 3.89 (t, J=4.6 Hz, 4H), 3.40-3.10 (m, 8H), 2.20-1.90 (m, 4H); MS ESI 488.3 [M+H]⁺, calcd for [C₂₇H₃₂N₅O₂S+H]⁺ 488.2.

Example A83

N-(3-(4-(4-hydroxypiperidin-1-yl)phenyl)-1H-indazol-5-yl)-2-(piperidin-1-yl)-2-(thiophen-3-yl)acetamide

[0671]

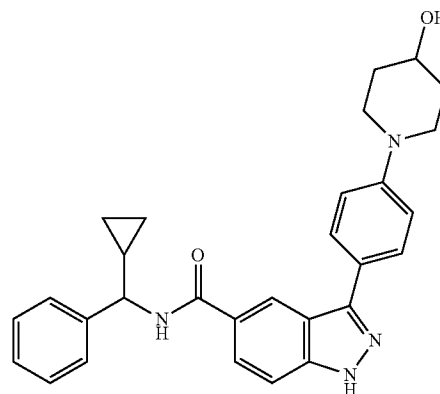


[0672] The title compound was synthesized according to general Method C by using a sealed degassed mixture of N-(3-iodo-1H-indazol-5-yl)-2-(piperidin-1-yl)-2-(thiophen-3-yl)acetamide (75 mg, 0.16 mmol), 1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidin-4-ol (90 mg, 0.17 mmol), Pd(PPh₃)₄ (14 mg, 0.012 mmol), 1 M aq Na₂CO₃ (0.32 mL) in PhMe/EtOH (3 mL, 1:0.5 mixture) under Ar with heating under microwave irradiation at 130° C. for 3 h. The reaction mixture was diluted with EtOAc (20 mL) and washed with H₂O (2×10 mL) and brine (10 mL), dried (Na₂SO₄) and concentrated under vacuum. Purification by flash chromatography (SiO₂, 0-15% MeOH in DCM) followed by RPHPLC and passing through a PoraPak column with 1 M NH₃-MeOH to elute gave the title compound (off white solid, 36 mg, 43%). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.35 (m, 1H), 7.79 (d, J=8.8 Hz, 2H), 7.49 (s, 2H), 7.45-7.41 (m, 1H), 7.42-7.40 (m, 1H), 7.26 (dd, J=4.8 Hz, J=1.2 Hz, 1H), 7.10 (d, J=9.2 Hz, 2H), 4.14 (s, 1H), 3.79-3.74 (m, 1H), 3.68-3.63 (m, 2H), 2.97-2.91 (br.m, 2H), 2.45 (br.s, 4H), 2.04-1.96 (br.m, 2H), 1.70-1.61 (br.m, 6H), 1.49-1.47 (br.m, 2H); MS ESI 516.2 [M+H]⁺, calcd for [C₂₉H₃₃N₅O₂S+H]⁺ 516.2.

Example A84

N-(cyclopropyl(phenyl)methyl)-3-(4-(4-hydroxypiperidin-1-yl)phenyl)-1H-indazole-5-carboxamide

[0673]

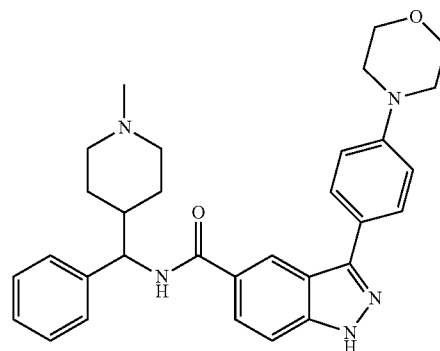


[0674] Using Method C2, N-(cyclopropyl(phenyl)methyl)-3-iodo-1H-indazole-5-carboxamide (51.3 mg, 0.12 mmol) and 1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidin-4-ol (77.8 mg, 65% pure, 0.16 mmol) gave the title compound after 5 h at 125° C. in the microwave as the TFA salt (yellow solid film, 22.2 mg, 31%). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.63 (s, 1H), 8.21 (d, J=8.8 Hz, 2H), 7.99 (dd, J=8.8, 1.5 Hz, 1H), 7.74 (d, J=8.5 Hz, 2H), 7.66 (d, J=8.8 Hz, 1H), 7.50 (d, J=7.3 Hz, 2H), 7.34 (t, J=7.5 Hz, 2H), 7.25 (t, J=7.3 Hz, 1H), 4.50 (d, J=9.5 Hz, 1H), 4.10 (tt, J=7.1, 3.6 Hz, 1H), 3.89 (ddd, J=11.9, 8.3, 3.4 Hz, 2H), 3.55-3.66 (m, 2H), 2.18-2.31 (m, 2H), 2.02 (dtd, J=14.3, 7.2, 7.2, 3.6 Hz, 2H), 1.38-1.48 (m, 1H), 0.62-0.75 (m, 2H), 0.42-0.56 (m, 2H). MS ESI 467.4 [M+H]⁺, calcd for [C₂₉H₃₀N₄O₂+H]⁺ 467.25.

Example A85

N-((1-methylpiperidin-4-yl)(phenyl)methyl)-3-(4-morpholinophenyl)-1H-indazole-5-carboxamide

[0675]



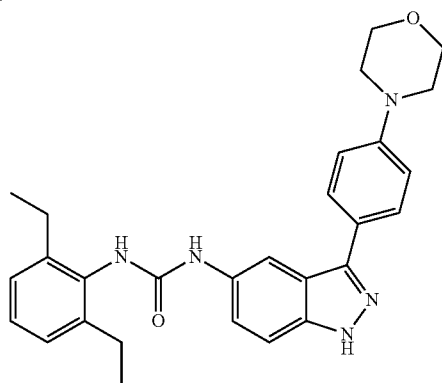
[0676] The title compound was synthesized according to the General Method A, utilizing 3-(4-morpholinophenyl)-1H-indazole-5-carboxylic acid (100 mg, 0.31 mmol), (1-me-

thylpiperidin-4-yl)(phenyl)methanamine (63 mg, 0.31 mmol), TBTU (100 mg, 0.31 mmol), DIPEA (0.16 mL, 0.93 mmol), and DMF (5 mL). Purification by flash chromatography (SiO₂, Biotage 25 g, 5-75% MeOH in CH₂Cl₂) followed by RPHPLC, and trituration with Et₂O gave the title compound as a bis-TFA salt (light yellow solid, 18 mg, 8%). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.55 (s, 1H), 7.87 (s, 3H), 7.59 (d, J=8.53 Hz, 1H), 7.46 (d, J=6.78 Hz, 2H), 7.39 (t, J=7.53 Hz, 2H), 7.30 (t, J=7.50 Hz, 1H), 7.14 (d, J=8.78 Hz, 2H), 4.92-4.96 (m, 1H), 3.83-3.91 (m, 4H), 3.55-3.62 (m, 1H), 3.41-3.49 (m, 1H), 3.21-3.27 (m, 4H), 2.86-3.03 (m, 2H), 2.85 (s, 3H), 2.17-2.35 (m, 2H), 1.40-1.72 (m, 3H); MS ESI 511.2 [M+H]⁺, calcd for [C₃₁H₃₅N₅O₂+H]⁺ 510.3.

Example A86

1-(2,6-diethylphenyl)-3-(3-(4-morpholinophenyl)-1H-indazol-5-yl)urea

[0677]

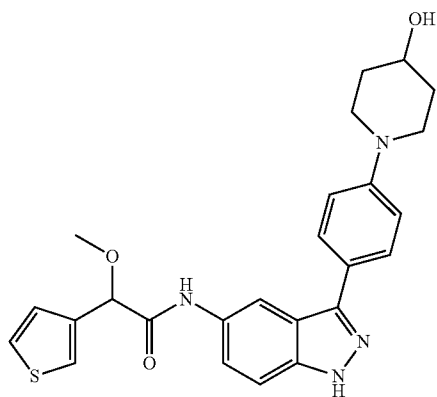


[0678] Using Method J, 3-(4-morpholinophenyl)-1H-indazol-5-amine bis(2,2,2-trifluoroacetate) (78 mg, 0.150 mmol), 1,3-diethyl-2-isocyanatobenzene (52 uL, 0.30 mmol) and DIPEA (130 uL, 0.75 mmol) in DMF (1.5 mL) gave the title compound as a TFA salt (25 mg, 36%, a yellow solid). ¹H NMR (400 MHz, d₆-DMSO) δ ppm 8.77 (s, 1H), 8.26 (s, 1H), 7.77 (d, J=8.8 Hz, 2H), 7.62 (s, 1H), 7.45 (d, J=8.5 Hz, 1H), 7.31 (d, J=8.2 Hz, 1H), 7.18-7.06 (m, 5H), 3.75 (bs, 4H), 3.16 (bs, 4H), 2.60 (q, J=8.0 Hz, 4H), 1.14 (t, J=7.2 Hz, 6H); MS ESI 470.3 [M+H]⁺, calcd for [C₂₈H₃₁N₅O₂+H]⁺ 470.26.

Example A87

N-(3-(4-(4-hydroxypiperidin-1-yl)phenyl)-1H-indazol-5-yl)-2-methoxy-2-(thiophen-3-yl)acetamide

[0679]



A. tert-butyl (3-(4-(4-hydroxypiperidin-1-yl)phenyl)-1H-indazol-5-yl)carbamate

[0680] The title compound was synthesized according to general Method C from tert-butyl (3-iodo-1H-indazol-5-yl)carbamate (445 mg, 1.23 mmol) and 1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidin-4-ol (376 mg, 1.23 mmol) with Pd(PPh₃)₄ (100 mg, 0.086 mmol) and 1 M aq Na₂CO₃ (3.0 mL) in PhMe/EtOH (8.9 mL, 2:1 mixture) under Ar with heating under microwave irradiation at 130° C. for 5 h. The reaction mixture was diluted with EtOAc (25 mL) and washed (H₂O (15 mL), brine (20 mL)), dried (Na₂SO₄) and concentrated under vacuum. Purification by flash chromatography (SiO₂, 0-20% MeOH in DCM) gave the title compound (185 mg). ¹H NMR (400 MHz, CDCl₃) δ 8.17 (s, 1H), 7.79 (d, J=8.4 Hz, 2H), 7.45 (d, J=8.8 Hz, 1H), 7.36 (d, J=9.2 Hz, 1H), 7.08 (d, J=8.8 Hz, 2H), 3.77-3.72 (m, 1H), 3.63-3.62 (br.m, 2H), 2.93-2.86 (m, 2H), 1.98-1.94 (br.m, 2H), 1.68-1.59 (br.m, 2H), 1.53 (s, 9H); MS ESI 409.3 [M+H]⁺, calcd for [C₂₃H₂₈N₄O₃+H]⁺ 409.2.

B. 1-(4-(5-amino-1H-indazol-3-yl)phenyl)piperidin-4-ol

[0681] CF₃COOH (3 mL) was added to a solution of tert-butyl (3-(4-(4-hydroxypiperidin-1-yl)phenyl)-1H-indazol-5-yl)carbamate (185 mg) in DCM (2 mL) at rt and the mixture was stirred for 24 h. Concentration under vacuum gave the title compound as a 2×TFA salt (brown solid, 167 mg, 25%, 2 steps). ¹H NMR (400 MHz, CD₃OD) δ 8.07 (d, J=1.2 Hz, 1H), 7.98 (d, J=8.8 Hz, 2H), 7.76 (d, J=8.8 Hz, 1H), 7.45-7.43 (m, 3H), 5.36-5.30 (m, 1H), 3.74-3.70 (m, 2H), 3.52-3.46 (m, 3H), 2.34-2.29 (m, 2H), 2.15-2.07 (m, 2H); MS ESI 309.1 [M+H]⁺, calcd for [C₁₈H₂₀N₄O+H]⁺ 309.1.

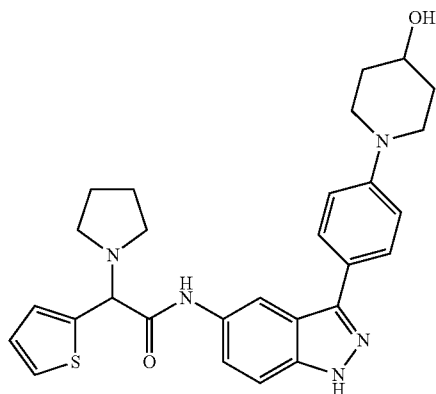
C. N-(3-(4-(4-hydroxypiperidin-1-yl)phenyl)-1H-indazol-5-yl)-2-methoxy-2-(thiophen-3-yl)acetamide

[0682] The title compound was synthesized according to general Method A by using 2-methoxy-2-(thiophen-2-yl)acetic acid (30 mg, 0.172 mmol), DMF (3 mL), 1-(4-(5-amino-1H-indazol-3-yl)phenyl)piperidin-4-ol trifluoroacetate (94 mg, 0.175 mmol), DIPEA (152 uL, 0.80 mmol) and TBTU (56 mg, 0.174 mmol). After stirring for 24 h at rt and concentrated under reduced pressure, direct purification using Biotage (SiO₂, 0-25% MeOH in DCM; then RP HPLC C18 60 g, 10-80% MeOH in 0.1% TFA-H₂O) gave the title compound as a TFA salt (cream color solid, 38 mg, 54%). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.48 (d, J=0.4 Hz, 1H), 8.16 (d, J=8.8 Hz, 2H), 7.77 (d, J=8.8 Hz, 2H), 7.59-7.53 (m, 3H), 7.45 (dd, J=5.2 Hz, J=3.2 Hz, 1H), 7.23 (dd, J=4.8 Hz, J=0.8 Hz, 1H), 4.96 (s, 1H), 4.15-4.09 (m, 1H), 3.91-3.85 (m, 2H), 3.68-3.62 (m, 2H), 3.48 (s, 3H), 2.29-2.23 (br.m, 2H), 2.08-2.201 (br.m, 2H); MS ESI 463.1 [M+H]⁺, calcd for [C₂₅H₂₆N₄O₃S+H]⁺ 463.1

Example A88

N-(3-(4-(4-hydroxypiperidin-1-yl)phenyl)-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-2-yl)acetamide

[0683]

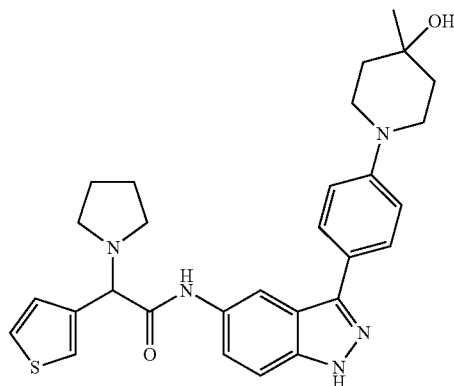


[0684] To a mixture of 2-(pyrrolidin-1-yl)-2-(thiophen-2-yl)acetic acid (25.5 mg, 0.12 mmol), 1-(4-(5-amino-1H-indazol-3-yl)phenyl)piperidin-4-ol di-trifluoroacetic acid (64 mg, 0.12 mmol) and TBTU (39 mg, 0.12 mmol) in DMF (6 mL) at 0° C. was added Pr_2NEt (0.084 mL, 0.48 mmol). The resulting mixture was sonicated to make a clear solution and stirred for 10 min at 0° C. It was quenched with H_2O (30 mL) and satd aq NaHCO_3 (10 mL), extracted with EtOAc and purified by prep-HPLC and Porapak to give the title compound (white solid, 18.5 mg, 31%). ^1H NMR (400 MHz, CD_3OD) δ 8.33 (t, $J=0.8$ Hz, 1H), 7.77 (pseudo d, $J=8.8$ Hz, 2H), 7.53-7.47 (m, 2H), 7.39 (dd, $J=5.0$ Hz, 0.6 Hz, 1H), 7.21 (dd, $J=3.6$ Hz, 1.2 Hz, 1H), 7.09 (pseudo d, $J=8.8$ Hz, 2H), 6.99 (dd, $J=5.2$ Hz, 3.6 Hz, 1H), 4.31 (s, 1H), 3.77 (sept, $J=4.4$ Hz, 1H), 3.66 (tt, $J=12.8$ Hz, 4.0 Hz, 2H), 2.97-2.90 (m, 2H), 2.73-2.65 (m, 2H), 2.60-2.53 (m, 2H), 2.02-1.95 (m, 2H), 1.89-1.80 (m, 4H), 1.70-1.61 (m, 2H); MS ESI 502.2 $[\text{M}+\text{H}]^+$, calcd for $[\text{C}_{28}\text{H}_{31}\text{N}_5\text{O}_2\text{S}+\text{H}]^+$ 502.2.

Example A89

N-(3-(4-(4-hydroxy-4-methylpiperidin-1-yl)phenyl)-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide

[0685]

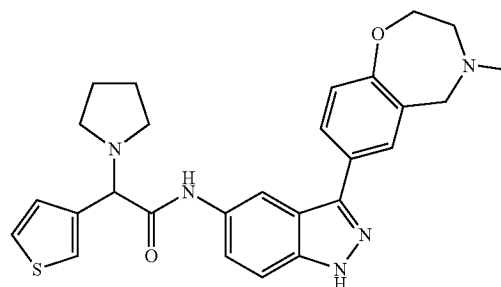


[0686] The title compound was synthesized according to Method C3 utilizing N-(3-iodo-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide and 4-methyl-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidin-4-ol and obtained as a white solid (15 mg, 22% yield). ^1H NMR (400 MHz, CD_3OD) δ ppm 8.33 (s, 1H), 7.77 (d, $J=8.8$ Hz, 2H), 7.49 (m, 3H), 7.40 (m, 1H), 7.33 (dd, $J=4.2$ Hz, 1H, 1H), 7.08 (d, $J=8.8$ Hz, 2H), 4.10 (s, 1H), 3.38 (m, 2H), 3.23 (m, 2H), 2.65 (br, 2H), 2.48 (br, 2H), 1.82 (m, 4H), 1.72 (m, 4H), 1.26 (s, 3H); MS ESI $[\text{M}+\text{H}]^+$ 516.2, calcd for $[\text{C}_{29}\text{H}_{33}\text{N}_5\text{O}_2\text{S}+\text{H}]^+$ 516.25.

Example A90

N-(3-(4-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepin-7-yl)-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide

[0687]



A. 7-bromo-4-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine

[0688] Tert-butyl 7-bromo-2,3-dihydrobenzo[f][1,4]oxazepine-4(5H)-carboxylate (388 mg, 1.18 mmol) was dissolved into CH_2Cl_2 (6.0 mL) and TFA (0.6 mL) and the resulting solution stirred for 3 h and then the solvent was removed. The resulting residue was then dissolved into THF (3.0 mL) and formalin (48 μL , 0.644 mmol), and $\text{NaBH}(\text{OAc})_3$ were added. The reaction was stirred for 2 h at which time the mixture was transferred to a separatory funnel with EtOAc (20 mL) and then washed with satd aq NaHCO_3 (2×20 mL), and brine (1×20 mL). The organic layer was dried over MgSO_4 filtered and the solvent removed to give 82 mg, 58% of the product as a colourless oil. MS ESI 243.9 $[\text{M}+\text{H}]^+$, calcd for $[\text{C}_{10}\text{H}_{12}\text{BrNO}+\text{H}]^+$ 244.02.

B. 4-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine

[0689] To a solution of 7-bromo-4-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine (82 mg, 0.340 mmol), TEA (140 μL , 1.02 mmol), dioxane (1.0 mL), and 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (74 μL , 0.510 mmol) under Ar was added S-Phos (6.0 mg, 0.014 mmol) and $\text{Cl}_2\text{Pd}(\text{CH}_3\text{CN})_2$ (1.0 mg, 0.034 mmol) and the reaction heated to 110° C. for 2 h. The mixture was transferred to a separatory funnel with EtOAc (15 mL) and washed with NaHCO_3 (satd) (10 mL), H_2O (10 mL), and brine (10 mL). The organic layer was dried over MgSO_4 , and the solvent removed to give 82 mg, 84% of the product as brown oil. MS ESI 290.1 $[\text{M}+\text{H}]^+$, calcd for $[\text{C}_{16}\text{H}_{24}\text{BNO}_3+\text{H}]^+$ 290.19.

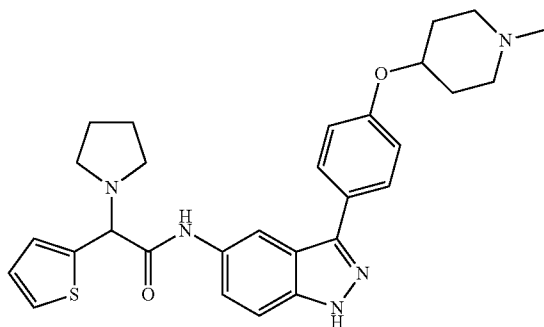
C. N-(3-(4-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepin-7-yl)-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide

[0690] A solution of 4-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine (75 mg, 0.259 mmol), N-(3-iodo-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide (98 mg, 0.216 mmol), LiCl (27 mg, 0.648 mmol), Na₂CO₃ (0.54 mL of a 2 M solution), and dioxane (1.5 mL) was purged with Ar for 15 min at which time Pd(PPh₃)₄ (13 mg, 0.011 mmol) was added and the reaction heated to 125° C. in a microwave reactor for 3 h. The solvent was then removed and the product purified by prep-HPLC which yielded 20 mg of the product as its bis-TFA salt (19%, a white powder). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.31 (s, 1H), 7.77-7.75 (m, 2H), 7.55-7.49 (m, 3H), 7.43-7.41 (m, 1H), 7.33 (d, J=5.1 Hz, 1H), 7.12 (d, J=7.9 Hz, 1H), 4.14-4.10 (m, 3H), 3.87 (s, 2H), 3.03-3.01 (m, 2H), 2.69-2.66 (m, 2H), 2.51-2.49 (m, 2H), 2.47 (s, 3H), 1.86-1.83 (m, 4H); MS ESI 488.1 [M+H]⁺, calcd for [C₂₇H₂₉N₅O₂S+H]⁺ 488.21.

Example A91

N-(3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-2-yl)acetamide

[0691]

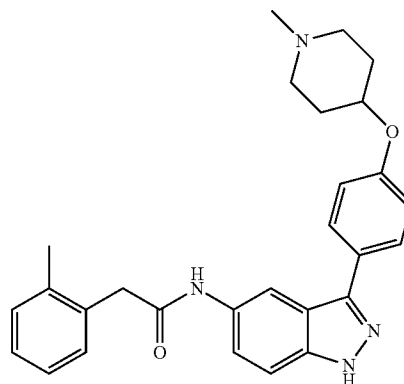


[0692] To a mixture of crude N-(3-iodo-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-2-yl)acetamide (150 mg, assuming 0.3 mmol) and 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine (95 mg, 0.3 mmol) in EtOH (4 mL) was added 1 M aq Na₂CO₃ (0.6 mL, 0.6 mmol), followed by Pd(PPh₃)₄ (17 mg, 0.015 mmol). The resulting mixture was purged with Ar and microwaved 3 h at 125° C. After removal of solvents, it was purified by flash chromatography (EtOAc/hex 0-100%, then MeOH/DCM 0-20%, then 0.02 M NH₃ in MeOH) and prep-HPLC to give the title compound as a di-TFA salt (light brown solid, 25.1 mg, 11%). ¹H NMR (400 MHz, CD₃OD) δ 8.37 (pseudo s, 1H), 7.90-7.83 (m, 2H), 7.69 (d, J=8.8 Hz, 1H), 7.58-7.51 (m, 3H), 7.22-7.14 (m, 3H), 5.50 (s, 1H), 4.90-4.87 (m, 0.7H), 4.73-4.65 (m, 0.3H), 4.00-3.10 (m, 8H), 2.95-2.94 (two s at 2.95 and 2.94, 3H), 2.47-1.88 (m, 8H); MS ESI 516.2 [M+H]⁺, calcd for [C₂₉H₃₃N₅O₂S+H]⁺ 516.2.

Example A92

N-(3-(4-(1-Methylpiperidin-4-yloxy)phenyl)-1H-indazol-5-yl)-2-o-tolylacetamide

[0693]

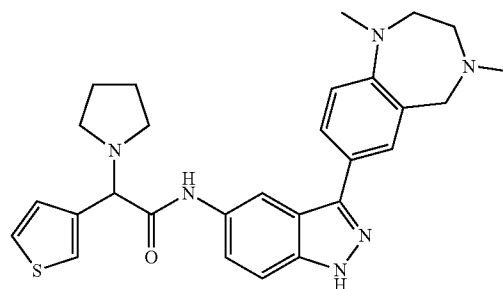


[0694] The title compound was synthesized according to Method C, utilizing N-(3-iodo-1H-indazol-5-yl)-2-o-tolylacetamide (100 mg, 0.26 mmol), 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine (89 mg, 0.28 mmol), Pd(PPh₃)₄ (30 mg, 0.026 mmol), 2 M Na₂CO₃ (0.26 mL), PhMe (4 mL), and EtOH (2 mL). H₂O (30 mL) was added and the product was extracted into EtOAc (4×30 mL). The combined organic layers were dried over MgSO₄, filtered and evaporated in vacuo. Purification by flash chromatography (Biotage, 25 g HP-SIL, 100% EtOAc, then 2-30% MeOH in DCM) followed by RPHPLC gave the title compound as a white solid (163 mg, 11%). The title compound was isolated as a TFA salt. ¹H NMR (400 MHz, CD₃OD) δ ppm 8.44 (d, J=1.2 Hz, 1H), 7.87-7.83 (m, 2H), 7.52 (d, J=8.9 Hz, 1H), 7.43 (dd, J=8.9, 1.8 Hz, 1H), 7.29-7.26 (m, 1H), 7.21-7.09 (m, 5H), 4.81 (m, 0.76H), 4.60 (m, 0.38H), 3.78 (s, 2H), 3.60 (d, J=12 Hz, 0.71H), 3.40-3.32 (m, 2.43H), 3.16 (td, J=12.9, 2.3 Hz, 0.74H), 2.91, 2.90 (2 s, 3H), 2.41-2.38 (m, 3.6H), 2.26 (d, J=16 Hz, 1.4H), 2.13-2.04 (m, 1.4H), 1.93-1.87 (m, 0.72H); MS ESI 455.3 [M+H]⁺, calcd for [C₂₈H₃₀N₄O₂+H]⁺ 455.24.

Example A93

N-(3-(1,4-dimethyl-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepin-7-yl)-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide

[0695]

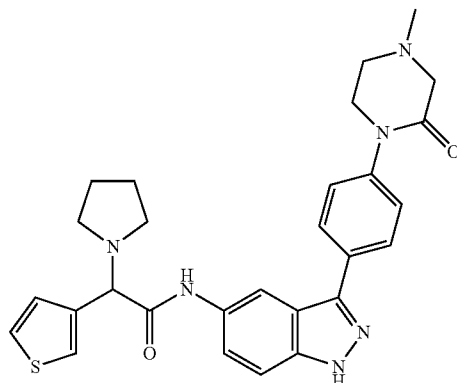


[0696] The title compound was prepared using Method C3 from N-(3-iodo-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide and tert-butyl 7-bromo-2,3-dihydro-1H-benzo[e][1,4]diazepine-4(5H)-carboxylate. The product was isolated as its bis-TFA salt (22%, a pale-yellow solid). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.37 (s, 1H), 7.95 (d, J=8.3 Hz, 1H), 7.90 (s, 1H), 7.87 (s, 1H), 7.66-7.64 (m, 1H), 7.54 (s, 2H), 7.36 (d, J=4.0 Hz, 1H), 7.26 (d, J=8.4 Hz, 1H), 4.58-4.42 (m, 2H), 3.98-3.35 (m, 5H), 3.29-3.09 (m, 4H), 3.06 (s, 3H), 3.03 (s, 3H), 2.25-1.95 (m, 4H); MS ESI 501.2 [M+H]⁺, calcd for [C₂₈H₃₂N₆O₃S+H]⁺ 501.24.

Example A94

N-(3-(4-(4-Methyl-2-oxopiperazin-1-yl)phenyl)-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide

[0697]



A. 1-(4-Iodophenyl)-4-methylpiperazin-2-one

[0698] CuI (0.081 g, 0.42 mmol) was added to an Ar-purged solution of 1,4-diiodobenzene (1.7 g, 5.1 mmol), 4-methylpiperazin-2-one (0.50 g, 4.3 mmol), trans-N¹,N⁴-dimethylcyclohexane-1,4-diamine (0.14 mL, 0.85 mmol), and K₃PO₄ (1.8 g, 8.5 mmol) in dioxane (10 mL). The resulting mixture was heated at 110° C. for 8 h in a Biotage microwave reactor. H₂O (30 mL) was added and the product was extracted into EtOAc (4×30 mL). The combined organic layers were dried over MgSO₄, filtered and evaporated in vacuo. Purification by flash chromatography (Biotage, 25 g HP-SIL, EtOAc then 2-10% MeOH in DCM) gave the title compound as a yellow solid (0.74 g, 55%). ¹H NMR (400 MHz, CD₃OD) δ ppm 7.76 (d, J=8.6 Hz, 2H), 7.11 (d, J=8.7 Hz, 2H), 3.70 (t, J=5.4 Hz, 2H), 3.24 (s, 2H), 3.28 (t, J=5.6 Hz, 2H), 2.40 (s, 3H); MS ESI 316.9 [M+H]⁺, calcd for [C₁₁H₁₃IN₂O+H]⁺ 317.01.

B. 4-Methyl-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazin-2-one

[0699] The title compound was synthesized according to Method F, utilizing 1-(4-iodophenyl)-4-methylpiperazin-2-one (74 mg, 2.3 mmol), 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.44 mL, 3.0 mmol), Cl₂Pd(CH₃CN)₂ (3.0 mg, 0.012 mmol), SPhos (20 mg, 0.047 mmol), NEt₃ (1.0 mL, 7.0 mmol) and dioxane (1.0 mL). H₂O (30 mL) was added and the product was extracted into EtOAc (4×30 mL). The combined

organic layers were dried over MgSO₄, filtered and evaporated in vacuo. Purification by flash chromatography (Biotage, 25 g HP-SIL, EtOAc then 2-20% MeOH in DCM) gave the title compound as a white solid (0.14 g, 20%). ¹H NMR (400 MHz, CD₃OD) δ ppm 7.81 (d, J=8.4 Hz, 2H), 7.33 (d, J=8.4 Hz, 2H), 3.74 (t, J=5.2 Hz, 2H), 3.27 (s, 2H), 2.85 (t, J=5.5 Hz, 2H), 2.42 (s, 3H), 1.35 (s, 12H); MS ESI 317.1 [M+H]⁺, calcd for [C₁₇H₂₃BN₂O₃+H]⁺ 317.20.

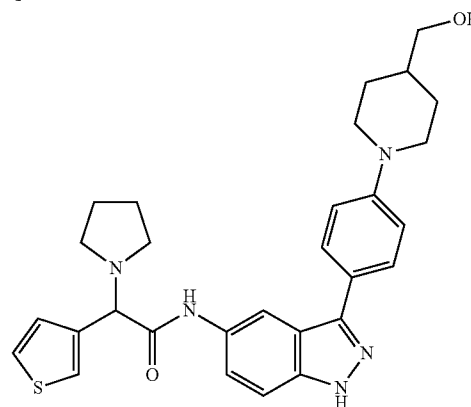
C. N-(3-(4-(4-Methyl-2-oxopiperazin-1-yl)phenyl)-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide

[0700] The title compound was synthesized according to Method C, utilizing N-(3-iodo-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide (182 mg, 0.40 mmol), 4-methyl-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazin-2-one (140 mg, 0.44 mmol), Pd(PPh₃)₄ (51 mg, 0.044 mmol), 2 M Na₂CO₃ (0.44 mL), PhMe (4 mL), and EtOH (2 mL). H₂O (30 mL) was added and the product was extracted into EtOAc (4×30 mL). The combined organic layers were dried over MgSO₄, filtered and evaporated in vacuo. Purification by flash chromatography (Biotage, 50 g HP-SIL, 100% EtOAc, then 2-20% MeOH in DCM) followed by RPHPLC gave the title compound as a white solid (111 mg, 33%). The title compound was isolated as a di-TFA salt. ¹H NMR (400 MHz, CD₃OD) δ ppm 8.24 (d, J=1.0 Hz, 1H), 8.03 (d, J=8.6 Hz, 2H), 7.87 (dd, J=2.9, 1.2 Hz, 1H), 7.66 (dd, J=5.1, 3.0 Hz, 1H), 7.59-7.50 (m, 4H), 7.38 (dd, J=5.0, 1.2 Hz, 1H), 5.24 (s, 1H), 4.18 (s, 2H), 4.10 (t, J=5.4 Hz, 2H), 3.87-3.83 (br m, 1H), 3.82 (t, J=5.9 Hz, 2H), 3.20-3.02 (br m, 2H), 3.13 (s, 3H), 2.26-1.97 (br m, 4H); MS ESI 515.1 [M+H]⁺, calcd for [C₂₈H₃₀N₆O₂S+H]⁺ 515.22.

Example A95

N-(3-(4-(4-(hydroxymethyl)piperidin-1-yl)phenyl)-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide

[0701]

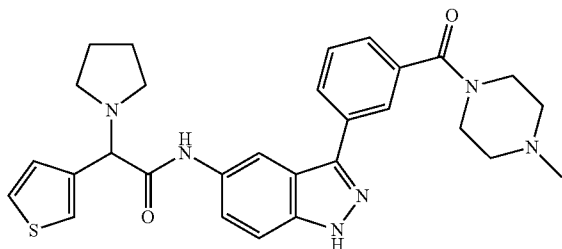


[0702] The title compound was synthesized according to Method C3 utilizing N-(3-iodo-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide and (1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidin-4-yl) methanol and obtained as a white solid (15 mg, 12% yield). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.34 (s, 1H), 7.76 (d, J=8.8 Hz, 2H), 7.49 (m, 3H), 7.39 (m, 1H), 7.33 (m, 1H), 7.06 (d, J=8.8 Hz, 2H), 4.10 (s, 1H), 3.77 (m, 2H), 3.44 (d, J=6.4 Hz, 2H), 2.68 (m, 4H), 2.48 (br, 2H), 1.83 (m, 6H), 1.62 (m, 1H), 1.37 (m, 2H); MS ESI [M+H]⁺ 516.2, calcd for [C₂₉H₃₃N₅O₂S+H]⁺ 516.24.

Example A96

N-(3-(3-(4-Methylpiperazine-1-carbonyl)phenyl)-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide

[0703]

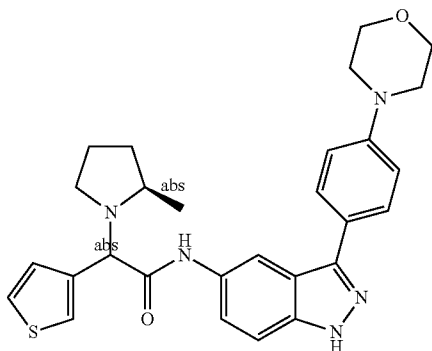


[0704] The title compound was synthesized according to Method C, utilizing N-(3-iodo-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide (200 mg, 0.44 mmol), (4-methylpiperazin-1-yl)(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanone (160 mg, 0.49 mmol), Pd(PPh₃)₄ (51 mg, 0.044 mmol), 2 M Na₂CO₃ (0.50 mL), PhMe (4 mL), and EtOH (2 mL). H₂O (30 mL) was added and the product was extracted into EtOAc (4×30 mL). The combined organic layers were dried over MgSO₄, filtered and evaporated in vacuo. Purification by flash chromatography (Biotage, 50 g HP-SIL, 100% EtOAc, then 2-25% MeOH in DCM) followed by RP HPLC gave the title compound as a light brown solid as isolated as a di-TFA salt (111 mg, 33%). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.41 (s, 1H), 8.08 (d, J=7.9 Hz, 1H), 8.03 (s, 1H), 7.80 (dd, J=2.9, 1.2 Hz, 1H), 7.69-7.64 (m, 2H), 7.57-7.54 (m, 3H), 7.38 (dd, J=5.1, 1.2 Hz, 1H), 5.29 (s, 1H), 3.89-3.36 (br m, 5H), 3.31-3.13 (br m, 4H), 2.96 (s, 3H), 2.25-1.98 (br m, 4H); MS ESI 529.1 [M+H]⁺, calcd for [C₂₉H₃₂N₆O₂S+H]⁺ 529.23.

Example A97

(R)-2-((R)-2-methylpyrrolidin-1-yl)-N-(3-(4-morpholinophenyl)-1H-indazol-5-yl)-2-(thiophen-3-yl)acetamide

[0705]



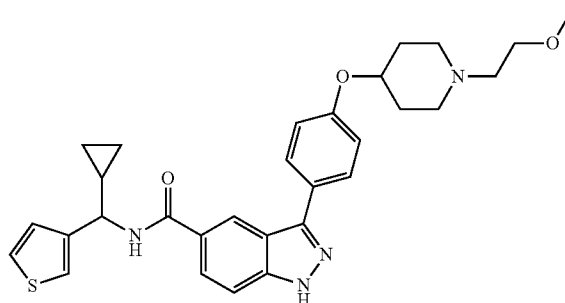
[0706] To a mixture of (R)-2-((R)-2-methylpyrrolidin-1-yl)-2-(thiophen-3-yl)acetic acid (22.5 mg, 0.1 mmol), 3-(4-morpholinophenyl)-1H-indazol-5-amine di-trifluoroacetic acid (57.2 mg, 0.1 mmol) and COMU (47.1 mg, 0.11 mmol) in DMF (6 mL) at -20° C. was added ^tPr₂NEt (0.07 mL, 0.4 mmol). The resulting mixture was stirred for 1 h at -20° C. After removal of ^tPr₂NEt, it was purified by prep-HPLC, PoraPak and flash chromatography/flash chromatography

(EtOAc/hex 0-100%, then MeOH/DCM 10-20%) to give the title compound (pale yellow solid, 18.1 mg, 36%). ¹H NMR (400 MHz, CD₃OD) δ 8.38 (s, 1H), 7.80 (d, J=8.8 Hz, 2H), 7.51 (s, 2H), 7.43 (dd, J=2.8 Hz, 1.2 Hz, 1H), 7.40 (dd, J=4.8 Hz, 2.8 Hz, 1H), 7.23 (dd, J=5.2 Hz, 1.2 Hz, 1H), 7.06 (d, J=8.8 Hz, 2H), 4.56 (s, 1H), 3.83 (t, J=4.8 Hz, 4H), 3.18 (t, J=4.8 Hz, 4H), 2.95-2.86 (m, 1H), 2.83-2.73 (m, 1H), 2.39 (dd, J=13.8 Hz, 8.2 Hz, 1H), 2.30-1.91 (m, 1H), 1.87-1.74 (m, 1H), 1.70-1.59 (m, 1H), 1.55-1.45 (m, 1H), 1.17 (d, J=6.4 Hz, 3H); MS ESI 502.3 [M+H]⁺, calcd for [C₂₆H₂₈N₆O₂S+H]⁺ 502.2.

Example A98

N-(cyclopropyl(phenyl)methyl)-3-(4-((1-(2-methoxyethyl)piperidin-4-yl)oxy)phenyl)-1H-indazole-5-carboxamide

[0707]

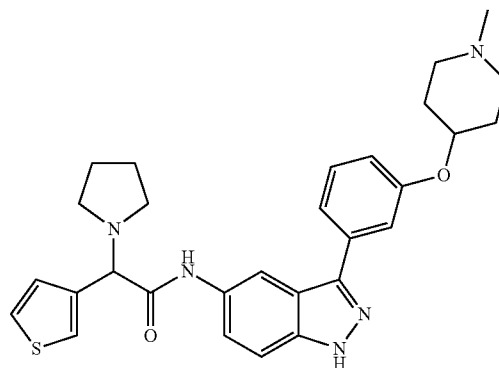


[0708] The title compound was prepared using Method C3 from N-(cyclopropyl(phenyl)methyl)-3-iodo-1H-indazole-5-carboxamide (70 mg, 0.168 mmol) and 1-(2-methoxyethyl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine (79 mg, 0.218 mmol) which gave 42 mg of product isolated as its TFA salt (47%, a pale-yellow powder). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.58 (s, 1H), 7.97-7.93 (m, 3H), 7.61 (d, J=8.8 Hz, 1H), 7.48 (d, J=7.3 Hz, 2H), 7.35-7.31 (m, 2H), 7.26-7.15 (m, 3H), 4.87 (bs, 1H), 4.48 (d, J=9.6 Hz, 1H), 3.76-3.70 (m, 2H), 3.54-3.22 (m, 9H), 2.45-2.28 (m, 2H), 2.19-1.94 (m, 2H), 1.45-1.33 (m, 1H), 0.68-0.63 (m, 2H), 0.50-0.47 (m, 2H); MS ESI 525.4 [M+H]⁺, calcd for [C₃₂H₃₆N₄O₃+H]⁺ 525.29.

Example A99

N-(3-(3-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide

[0709]



A. 4-(3-bromophenoxy)-1-methylpiperidine

[0710] To a solution of 4-(3-bromophenoxy)piperidine (500 mg, 1.7 mmol) in formic acid (13.11 mL) was added formalin (0.51 mL). The solution was heated to 150° C. for 15 min under microwave irradiation. The solvent was removed in vacuo. The residue was made alkaline using 50% KOH (10 mL) and the product was extracted using DCM (2×25 mL). The organic layer was washed with brine, dried (Na₂SO₄) and concentrated to give the title compound as a colorless thick oil (360 mg, 78%). ¹H NMR (400 MHz, CDCl₃) δ 15-7.06 (m, 3H), 6.85-6.82 (m, 1H), 4.29 (br.s, 1H), 2.68 (br.s, 2H), 2.31 (br.s, 5H), 2.02-1.97 (br.m, 2H), 1.88-1.80 (br.m, 2H); MS ESI 272 [M+H]⁺, calcd for [C₁₂H₁₆BrNO+H]⁺ 270

B. 1-methyl-4-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine

[0711] The title compound was synthesized according to general Method E by using a solution of 4-(3-bromophenoxy)-1-methylpiperidine (350 mg, 1.29 mmol) in DMF (5.25 mL) was added Bis(pinacolato)diboron (576 mg, 2.26 mmol), KOAc (381 mg, 3.88 mmol) and PdCl₂dppf (80 mg, 0.097 mmol) under Ar. The degassed suspension was sealed and heated in an oil bath at 125° C. for 3 h. The product was partitioned between EtOAc (50 mL) and H₂O (25 mL). The aq. layer was extracted with EtOAc (50 mL) and the combined EtOAc layer was washed with H₂O and brine, dried (Na₂SO₄) and concentrated under vacuum. Purification by flash chromatography (SiO₂, 0-50% DCM in MeOH) gave title compound (brown thick oil, 148 mg, 36%). ¹H NMR (400 MHz, CDCl₃) δ 7.41 (d, J=7.2 Hz, 1H), 7.35 (d, J=2.0 Hz, 1H), 7.31-7.28 (m, 1H), 7.02 (dd, J=8.0 Hz, J=2.0 Hz, 1H), 4.47 (s, 1H), 2.78-2.76 (br.m, 2H), 2.53-2.48 (br.s, 2H), 2.41 (s, 3H), 2.12 (br.s, 2H), 1.98-1.92 (br.s, 2H), 1.35 (s, 12H); MS ESI 318.2 [M+H]⁺, calcd for [C₁₈H₁₈BNO₃+H]⁺ 318.2.

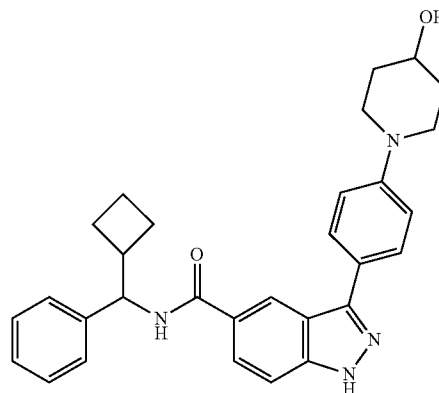
C. N-(3-(3-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide

[0712] The title compound was synthesized according to general Method C from N-(3-iodo-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide (200 mg, 0.44 mmol), 1-methyl-4-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine (141 mg, 0.44 mmol) with PdCl₂dppf (72 mg, 0.088 mmol) and 1 M aq Na₂CO₃ (0.89 mL) in PhMe/EtOH (9 mL, 2:1 mixture) under Ar with heating under microwave irradiation at 125° C. for 5 h. The reaction mixture was diluted with EtOAc (40 mL) and washed with H₂O and brine, dried (Na₂SO₄) and concentrated under vacuum. Purification by flash chromatography (SiO₂, 0-20% 2 M-NH₃-MeOH in DCM), then by RPHPLC gave the title compound as a TFA salt (light brown solid, 31 mg, 9%). ¹H NMR (400 MHz, CD₃OD) δ 8.41 (d, J=8.0 Hz, 1H), 7.88-7.87 (m, 1H), 7.66 (dd, J=5.2 Hz, J=3.2 Hz, 1H), 7.57-7.44 (m, 5H), 7.39 (dd, J=4.8 Hz, J=1.2 Hz, 1H), 7.13-7.05 (m, 1H), 5.27 (s, 1H), 4.7-4.69 (m, 0.39H), 3.88-3.84 (br.s, 1H), 3.67 (br.d, 1H), 3.43-3.37 (br.m, 3H), 3.24-3.11 (br.m, 3H), 2.95 (s, 3H), 2.48-1.89 (br.m, 9H), 0.61H merged with solvent peak, MS ESI 516.1[M+H]⁺, calcd for [C₂₉H₃₃N₅O₂S+H]⁺ 516.2.

Example A100

N-(cyclobutyl(phenyl)methyl)-3-(4-(4-hydroxypiperidin-1-yl)phenyl)-1H-indazole-5-carboxamide

[0713]



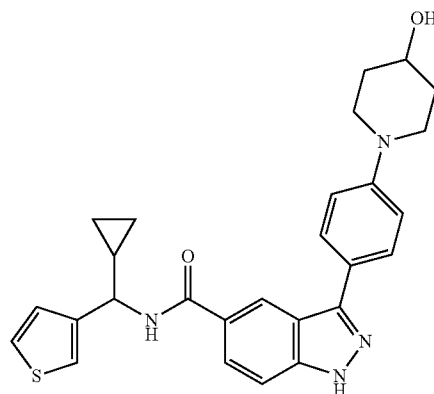
[0714] Using Method C2, N-(cyclobutyl(phenyl)methyl)-3-iodo-1H-indazole-5-carboxamide (69.8 mg, 0.162 mmol) and 1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidin-4-ol (73.1 mg, 80% pure, 0.19 mmol) gave the title compound as the TFA salt (pale pink solid, 42.2 mg, 49%) after heating in a sealed vial at 125° C. for 14 h and purification by flash chromatography (SiO₂, 10-50% acetone in DCM; followed by RPRP HPLC, 10-90% MeOH in 0.1% TFA-H₂O). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.83 (d, J=7.8 Hz, 0.2H partially exchanged), 8.56 (s, 1H), 8.18 (d, J=8.5 Hz, 2H), 7.93 (d, J=8.8 Hz, 1H), 7.73 (d, J=8.5 Hz, 2H), 7.63 (d, J=9.0 Hz, 1H), 7.41 (d, J=7.5 Hz, 2H), 7.32 (t, J=7.5 Hz, 2H), 7.20-7.26 (m, 1H), 5.10 (d, J=10.5 Hz, 1H), 4.05-4.14 (m, 1H), 3.83-3.93 (m, 2H), 3.54-3.67 (m, 2H)

[0715] MS ESI 481.4 [M+H]⁺, calcd for [C₃₀H₃₂N₄O₂+H]⁺ 481.26.

Example A101

N-(cyclopropyl(thiophen-3-yl)methyl)-3-(4-(4-hydroxypiperidin-1-yl)phenyl)-1H-indazole-5-carboxamide

[0716]



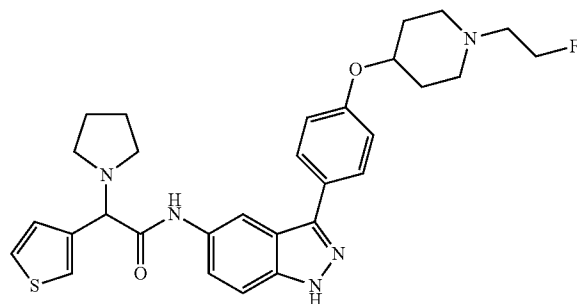
[0717] Using Method C2, N-(cyclopropyl(thiophen-3-yl)methyl)-3-iodo-1H-indazole-5-carboxamide (50.0 mg, 0.118 mmol) and 1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidin-4-ol (53.7 mg, 80% pure, 0.14 mmol) gave the title compound as the TFA salt (pale pink solid, 26.8 mg, 39%) after heating in microwave at 125° C. for 3 h and purification by flash chromatography (SiO₂, 25-50% acetone in DCM; followed by RPRP HPLC, 10-90% MeOH in 0.1%

TFA-H₂O). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.63 (s, 1H), 8.24 (d, J=8.8 Hz, 2H), 7.99 (dd, J=8.9, 1.4 Hz, 1H), 7.78 (d, J=8.8 Hz, 2H), 7.67 (d, J=8.8 Hz, 1H), 7.36-7.40 (m, 2H), 7.21 (t, J=3.3 Hz, 1H), 4.64 (d, J=9.3 Hz, 1H), 4.11 (tt, J=7.0, 3.3 Hz, 1H), 3.91 (ddd, J=12.0, 8.4, 3.4 Hz, 2H), 3.65 (ddd, J=11.9, 7.7, 3.5 Hz, 2H), 2.21-2.31 (m, 2H), 2.04 (dtd, J=14.2, 7.2, 7.2, 3.5 Hz, 2H), 1.41-1.51 (m, 1H), 0.74 (td, J=8.3, 3.8 Hz, 1H), 0.65 (td, J=8.3, 4.8 Hz, 1H), 0.45-0.56 (m, 2H). MS ESI 473.3 [M+H]⁺, calcd for [C₂₇H₂₈N₄O₂S+H]⁺ 473.20.

Example A102

N-(3-(4-((1-(2-fluoroethyl)piperidin-4-yl)oxy)phenyl)-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide

[0718]

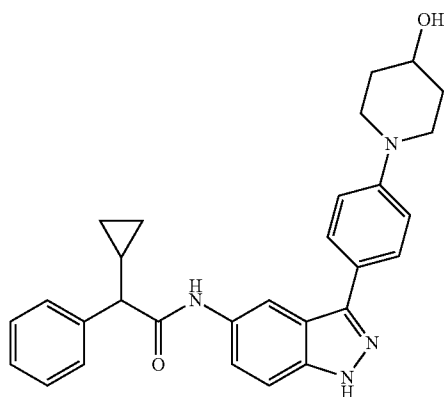


[0719] The title compound was synthesized according to Method C3 utilizing N-(3-iodo-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide and 1-(2-fluoroethyl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine and obtained as a white solid (20 mg, 10% yield). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.33 (s, 1H), 7.82 (d, J=8.8 Hz, 2H), 7.51 (m, 3H), 7.42 (m, 1H), 7.33 (dd, J=4.8 Hz, 0.8 Hz, 1H), 7.08 (d, J=8.8 Hz, 2H), 4.67 (t, J=4.8 Hz, 1H), 4.55 (t, J=4.8 Hz, 1H), 4.51 (m, 1H), 4.13 (s, 1H), 2.86 (m, 2H), 2.80 (t, J=4.8 Hz, 1H), 2.73 (t, J=4.8 Hz, 1H), 2.70 (m, 2H), 2.52 (m, 2H), 1.82 (m, 6H); MS ESI [M+H]⁺ 548.2, calcd for [C₃₀H₃₄FN₅O₂S+H]⁺ 548.25.

Example A103

2-cyclopropyl-N-(3-(4-(4-hydroxypiperidin-1-yl)phenyl)-1H-indazol-5-yl)-2-phenylacetamide

[0720]

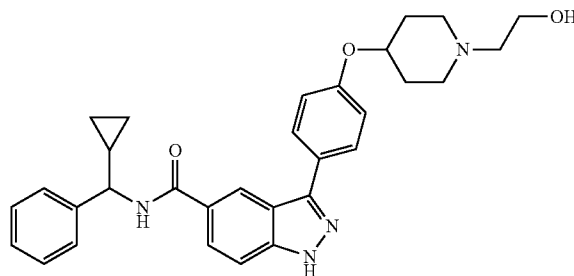


[0721] The title compound was synthesized according to general Method A by using 2-cyclopropyl-2-phenylacetic acid (16 mg, 0.09 mmol), DMF (2 mL), 1-(4-(5-amino-1H-indazol-3-yl)phenyl)piperidin-4-ol trifluoroacetate (48.7 mg, 0.09 mmol), DIPEA (80 uL, 0.55 mmol) and TBTU (29 mg, 0.09 mmol). After stirring for 24 h at rt, concentration under reduced pressure and direct purification using Biotage (SiO₂, 0-25% MeOH in DCM; then RP HPLC C18 60 g, 10-80% MeOH in 0.1% TFA-H₂O) gave the title compound as a TFA salt (beige color solid, 21 mg, 40%). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.50 (m, 1H), 8.16 (d, J=8.0 Hz, 2H), 7.77 (d, J=8.0 Hz, 2H), 7.57 (d, J=9.2 Hz, 1H), 7.51 (d, J=7.6 Hz, 2H), 7.42 (d, J=9.2 Hz, 1H), 7.37-7.33 (m, 2H), 7.28-7.25 (m, 1H), 4.11 (s, 1H), 3.98-3.87 (m, 2H), 3.65 (br.s, 2H), 2.94 (d, J=9.6 Hz, 1H), 2.25-2.23 (br.m, 2H), 2.05 (br.s, 2H), 1.6 (br.s, 1H), 0.70-0.62 (br.m, 2H), 0.48-0.28 (br.m, 2H); MS ESI 467.4 [M+H]⁺, calcd for [C₂₉H₃₀N₄O₂+H]⁺ 467.2.

Example A104

N-(cyclopropyl(phenyl)methyl)-3-(4-((1-(2-hydroxyethyl)piperidin-4-yl)oxy)phenyl)-1H-indazole-5-carboxamide

[0722]

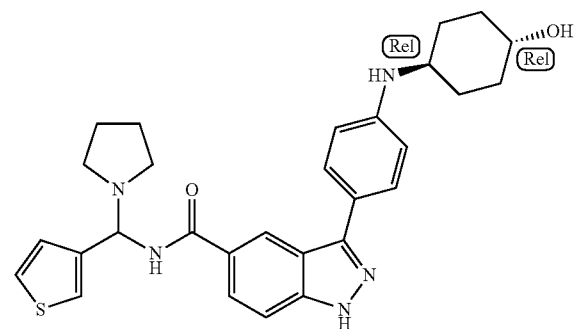


[0723] The title compound was prepared using Method C3 from N-(cyclopropyl(phenyl)methyl)-3-iodo-1H-indazole-5-carboxamide (60 mg, 0.144 mmol) and 2-(4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidin-1-yl)ethanol (70 mg, 0.202 mmol) which gave 23 mg of product isolated as its TFA salt (31%, a white solid). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.58 (s, 1H), 7.97-7.93 (m, 3H), 7.61 (d, J=8.8 Hz, 1H), 7.48 (d, J=7.3 Hz, 2H), 7.36-7.32 (m, 2H), 7.26-7.16 (m, 3H), 4.87 (bs, 1H), 4.48 (d, J=9.5 Hz, 1H), 3.92-3.30 (m, 8H), 2.45-2.29 (m, 2H), 2.22-1.98 (m, 2H), 1.43-1.33 (m, 1H), 0.71-0.64 (m, 2H), 0.50-0.48 (m, 2H); MS ESI 511.5 [M+H]⁺, calcd for [C₃₁H₃₄N₄O₃+H]⁺ 511.27.

Example A105

rel-N-(3-(4-(((1r,4r)-4-hydroxycyclohexyl)amino)phenyl)-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide

[0724]



[0725] To a mixture of 1,4-diiodobenzene (3.299 g, 10 mmol), trans-4-aminocyclohexanol (1.15 g, 10 mmol), CuI (391 mg, 2 mmol), BINOL (572 mg, 2 mmol) and K₃PO₄ (4.24 g, 20 mmol) was added DMF (30 mL). The resulting mixture was purged with Ar and stirred at rt for 2 d. It was diluted with EtOAc (60 mL) and MeOH (30 mL), sonicated, filtered through Celite (rinsed with EtOAc/MeOH), concentrated and purified by flash chromatography (EtOAc/hex 0-100%) to give rel-(1r,4r)-4-((4-iodophenyl)amino)cyclohexanol as blackish white solid (2.367 g, 75%). ¹H NMR (400 MHz, DMSO-d₆) δ 7.28 (d, J=8.8 Hz, 2H), 6.39 (d, J=8.8 Hz, 2H), 5.59 (d, J=8.0 Hz, 1H), 4.54 (br, s, 1H), 3.45-3.35 (m, 1H), 3.14-3.04 (m, 1H), 1.93-1.77 (m, 4H), 1.30-1.18 (m, 2H), 1.17-1.06 (m, 2H); MS ESI 318.0 [M+H]⁺, calcd for [C₁₂H₁₆INO+H]⁺ 318.0.

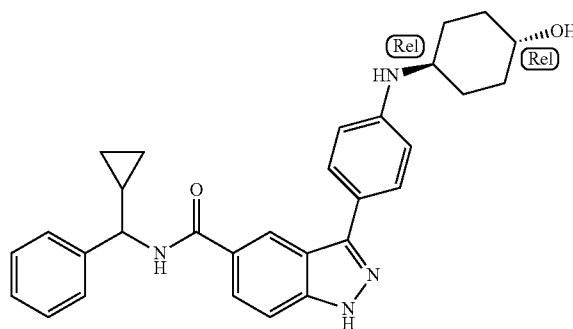
[0726] To a mixture of rel-(1r,4r)-4-((4-iodophenyl)amino)cyclohexanol (951 mg, 3 mmol), Pd(CH₃CN)₂Cl₂ (15.6 mg, 0.06 mmol) and dicyclohexyl(2',6'-dimethoxy-[1,1'-biphenyl]-2-yl)phosphine (98.5 mg, 0.24 mmol) in 1,4-dioxane (4.5 mL) was added Et₃N (1.3 mL, 9 mmol), followed by pinacolborane (1.74 mL, 12 mmol) slowly. After addition, the resulting mixture was purged with Ar and microwaved 2 h at 110° C. It was combined with a 0.4 mmol scale reaction. After removal of solvents, it was purified by flash chromatography (EtOAc/hex 0-100%) to give rel-(1r,4r)-4-((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)amino)cyclohexanol (white solid, 1.028 g, 95%). ¹H NMR (400 MHz, CD₃OD) δ 7.52 (d, J=8.4 Hz, 2H), 6.55 (d, J=8.4 Hz, 2H), 3.61-3.52 (m, 1H), 3.28-3.19 (m, 1H), 2.09-1.92 (m, 4H), 1.46-1.33 (m, 2H), 1.29 (s, 12H), 1.25-1.15 (m, 2H); MS ESI 318.1 [M+H]⁺, calcd for [C₁₈H₂₈BNO₃+H]⁺ 318.2.

[0727] To a mixture of N-(3-iodo-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide (181 mg, 0.4 mmol) and rel-(1r,4r)-4-((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)amino)cyclohexanol (127 mg, 0.4 mmol) in EtOH (10 mL) was added 1 M aq Na₂CO₃ (0.8 mL, 0.8 mmol), followed by Pd(PPh₃)₄ (23 mg, 0.02 mmol). The resulting mixture was purged with Ar and microwaved 3 h at 125° C. Additional Pd(PPh₃)₄ (23 mg, 0.02 mmol) was added and the reaction mixture was purged with Ar and microwaved 3 h at 125° C. After removal of solvents, it was purified by flash chromatography (MeOH/DCM 0-25%), biotage RP column (MeOH/H₂O (1% TFA) 0-50%) and flash chromatography (EtOAc/hex 10-100%, then MeOH/DCM 0-20%) to give the title compound (light brown solid, 21.2 mg, 10%). ¹H NMR (400 MHz, CD₃OD) δ 8.31 (s, 1H), 7.66 (d, J=8.4 Hz, 2H), 7.53-7.45 (m, 3H), 7.42 (dd, J=5.2 Hz, 2.8 Hz, 1H), 7.33 (dd, J=5.2 Hz, 1.2 Hz, 1H), 6.74 (d, J=8.4 Hz, 2H), 4.16 (s, 1H), 3.65-3.56 (m, 1H), 3.32-3.25 (m, 1H), 2.74-2.67 (m, 2H), 2.57-2.48 (m, 2H), 2.15-2.08 (m, 2H), 2.03-1.95 (m, 2H), 1.90-1.80 (m, 4H), 1.49-1.38 (m, 2H), 1.32-1.22 (m, 2H); MS ESI 516.3 [M+H]⁺, calcd for [C₂₉H₃₃N₅O₂S+H]⁺ 516.2.

Example A106

rel-N-(cyclopropyl(phenyl)methyl)-3-(4-(((1r,4r)-4-hydroxycyclohexyl)amino)phenyl)-1H-indazole-5-carboxamide

[0728]

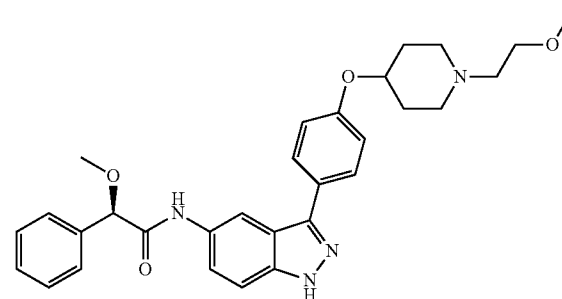


[0729] To a mixture of N-(cyclopropyl(phenyl)methyl)-3-iodo-1H-indazole-5-carboxamide (167 mg, 0.4 mmol) and rel-(r,4r)-4-((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)amino)cyclohexanol (127 mg, 0.4 mmol) in EtOH (10 mL) was added 1 M aq Na₂CO₃ (0.8 mL, 0.8 mmol), followed by Pd(PPh₃)₄ (46 mg, 0.04 mmol). The resulting mixture was purged with Ar and microwaved 5 h at 125° C. After removal of solvents, it was purified by flash chromatography (MeOH/DCM 0-20%), biotage RP column (MeOH/H₂O (1% TFA) 0-100%), PoraPak, flash chromatography (EtOAc/hex 10-100%) and PoraPak to give the title compound (light yellow solid, 55.4 mg, 29%). ¹H NMR (400 MHz, CD₃OD) δ 8.63 (s, 1H), 7.93 (dd, J=8.8 Hz, 1.6 Hz, 1H), 7.73 (d, J=8.4 Hz, 2H), 7.54 (d, J=9.2 Hz, 1H), 7.45 (d, J=7.2 Hz, 2H), 7.29 (t, J=7.6 Hz, 2H), 7.20 (t, J=7.6 Hz, 1H), 6.72 (d, J=8.8 Hz, 2H), 4.46 (d, J=8.8 Hz, 1H), 3.61-3.53 (m, 1H), 3.27-3.19 (m, 1H), 2.11-2.03 (m, 2H), 2.00-1.92 (m, 2H), 1.45-1.32 (m, 3H), 1.28-1.17 (m, 2H), 0.65-0.56 (m, 2H), 0.50-0.37 (m, 2H); MS ESI 481.5 [M+H]⁺, calcd for [C₃₀H₃₂N₄O₂+H]⁺ 481.3.

Example A107

(R)-2-methoxy-N-(3-(4-((1-(2-methoxyethyl)piperidin-4-yl)oxy)phenyl)-1H-indazol-5-yl)-2-phenylacetamide

[0730]

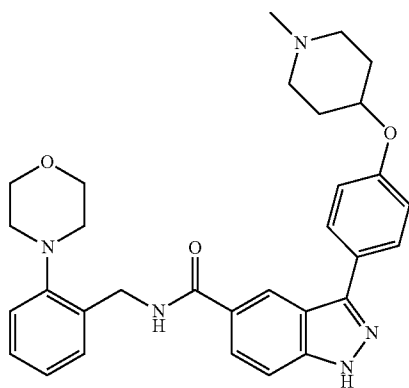


[0731] The title compound was prepared using Method C3 from (R)—N-(3-iodo-1H-indazol-5-yl)-2-methoxy-2-phenylacetamide (60 mg, 0.147 mmol) and 1-(2-methoxyethyl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine (64 mg, 0.176 mmol) which gave 29 mg of product isolated as its TFA salt (38%, an off-white solid). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.40 (s, 1H), 7.87-7.83 (m, 2H), 7.54-7.48 (m, 4H), 7.42-7.33 (m, 3H), 7.18-7.11 (m, 2H), 4.87 (bs, 1H), 4.83 (s, 1H), 3.76-3.21 (m, 8H), 3.50 (s, 3H), 3.46 (s, 3H), 2.43-2.27 (m, 2H), 2.19-1.94 (m, 2H); MS ESI 515.4 [M+H]⁺, calcd for [C₃₀H₃₄N₄O₄+H]⁺ 515.27.

Example A108

3-(4-(1-Methylpiperidin-4-yloxy)phenyl)-N-(2-morpholinobenzyl)-1H-indazole-5-carboxamide

[0732]



A. 3-Iodo-N-(2-morpholinobenzyl)-1H-indazole-5-carboxamide

[0733] The title compound was synthesized according to Method A, utilizing 3-iodo-1H-indazole-5-carboxylic acid (150 mg, 0.52 mmol), (2-morpholinophenyl)methanamine (120 mg, 0.57 mmol), TBTU (184 mg, 0.57 mmol), DIPEA (0.36 mL, 2.1 mmol), and DMF (4 mL). H₂O (20 mL) was added and the product was extracted into EtOAc (4×20 mL). The combined organic layers were dried over MgSO₄, filtered and evaporated in vacuo. The residue was then dissolved in MeOH (20 mL) and poured into a preconditioned 20 mL Porapak Rxn Cx cartridge. The MeOH (30 mL) rinse was discarded and the product was eluted with 2 M NH₃ in MeOH (30 mL). The solvent was removed in vacuo, and the product was used without further purification (99%, 240 mg). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.08 (s, 1H), 7.98-7.96 (m, 1H), 7.57 (d, J=8.9 Hz, 1H), 7.37-7.32 (m, 1H), 7.26 (t, J=7.5 Hz, 1H), 7.18 (d, J=7.8 Hz, 1H), 7.10 (t, J=7.2 Hz, 1H), 4.76 (s, 2H), 3.84 (br m, 4H), 2.92-2.86 (br m, 4H); MS ESI 463.1 [M+H]⁺, calcd for [C₁₉H₁₉N₄O₂+H]⁺ 463.06.

B. 3-(4-(1-Methylpiperidin-4-yloxy)phenyl)-N-(2-morpholinobenzyl)-1H-indazole-5-carboxamide

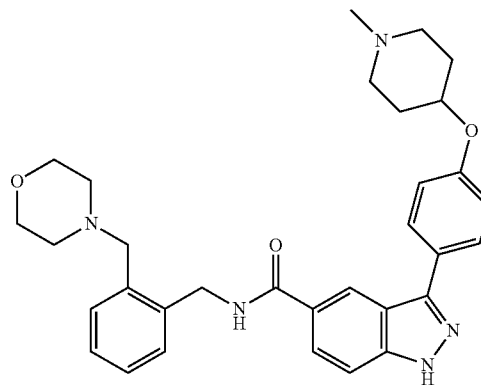
[0734] The title compound was synthesized according to Method C, utilizing 3-iodo-N-(2-morpholinobenzyl)-1H-indazole-5-carboxamide (113 mg, 0.24 mmol), 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)pip-

eridine (85 mg, 0.27 mmol), Pd(PPh₃)₄ (28 mg, 0.024 mmol), 2 M Na₂CO₃ (0.30 mL), PhMe (4 mL), and EtOH (2 mL). H₂O (30 mL) was added and the product was extracted into EtOAc (4×30 mL). The combined organic layers were dried over MgSO₄, filtered and evaporated in vacuo. Purification by flash chromatography (Biotage, 25 g HP-SIL, 2-30% MeOH in DCM) followed by RP HPLC (Biotage, 60 g C18-H, 0.1% TFA-H₂O in MeOH, 10-90%) gave the title compound as a white solid (45 mg, 29%). The title compound was isolated as a TFA salt. ¹H NMR (400 MHz, CD₃OD) δ ppm 8.65 (s, 1H), 8.01 (dd, J=8.8 Hz, 1.4 Hz, 1H), 7.95 (t, J=8.6 Hz, 2H), 7.72 (d, J=7.9 Hz, 1H), 7.55-7.50 (m, 4H), 7.23 (d, J=8.8 Hz, 1.3H), 7.18 (d, J=8.8 Hz, 0.7H), 4.89-4.85 (br m, 1H), 4.77-4.67 (m, 2.4H), 4.24 (br m, 4H), 3.65-3.58 (br m, 4H), 3.47-3.36 (m, 3H), 3.23 (td, J=12.9, 2.8 Hz, 0.85H), 2.94, 2.93 (2 s, 3H), 2.47-2.43 (m, 0.7H), 2.33-2.30 (m, 1.4H), 2.20-2.12 (m, 1.4H), 2.00-1.89 (m, 0.74H); MS ESI 526.3 [M+H]⁺, calcd for [C₃₁H₃₅N₅O₃+H]⁺ 526.27.

Example A109

3-(4-(1-Methylpiperidin-4-yloxy)phenyl)-N-(2-morpholinomethylbenzyl)-1H-indazole-5-carboxamide

[0735]



A. 3-Iodo-N-(2-(morpholinomethyl)benzyl)-1H-indazole-5-carboxamide

[0736] The title compound was synthesized according to Method A, utilizing 3-iodo-1H-indazole-5-carboxylic acid (150 mg, 0.52 mmol), (2-(morpholinomethyl)phenyl)methanamine (118 mg, 0.57 mmol), TBTU (184 mg, 0.57 mmol), DIPEA (0.36 mL, 2.1 mmol), and DMF (4 mL). H₂O (20 mL) was added and the product was extracted into EtOAc (4×20 mL). The combined organic layers were dried over MgSO₄, filtered and evaporated in vacuo. The residue was then dissolved in MeOH (20 mL) and poured into a preconditioned 20 mL Porapak Rxn Cx cartridge. The MeOH/EtOH (30 mL) rinse was discarded and the product was eluted with 2 M NH₃ in MeOH/EtOH (30 mL). The solvent was removed in vacuo, and the product was used without further purification (220 mg, 89%). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.01 (s, 1H), 7.92 (dd, J=8.8, 1.6 Hz, 1H), 7.61 (d, J=8.8 Hz, 1H), 7.45 (d, J=7.5 Hz, 1H), 7.34-7.25 (m, 4H), 4.77 (s, 2H), 3.64 (s, 2H), 3.56 (t, J=4.7 Hz, 4H), 2.47 (br m, 4H); MS ESI 477.2 [M+H]⁺, calcd for [C₂₀H₂₁N₄O₂+H]⁺ 477.07.

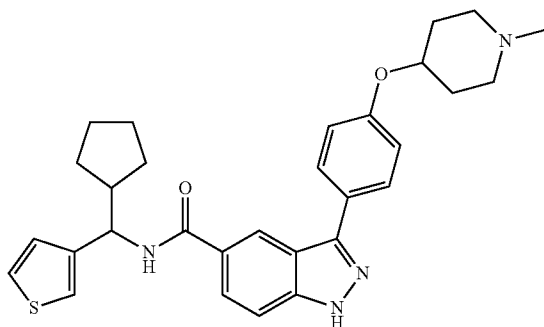
B. 3-(4-(1-Methylpiperidin-4-yloxy)phenyl)-N-(2-(morpholinomethyl)benzyl)-1H-indazole-5-carboxamide

[0737] The title compound was synthesized according to Method C, utilizing 3-iodo-N-(2-(morpholinomethyl)benzyl)-1H-indazole-5-carboxamide (110 mg, 0.23 mmol), 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine (81 mg, 0.25 mmol), Pd(PPh₃)₄ (27 mg, 0.023 mmol), 2 M Na₂CO₃ (0.30 mL), PhMe (4 mL), and EtOH (2 mL). H₂O (30 mL) was added and the product was extracted into EtOAc (4×30 mL). The combined organic layers were dried over MgSO₄, filtered and evaporated in vacuo. Purification by flash chromatography (Biotage, 25 g HP-SIL, EtOAc then 2-30% MeOH in DCM) followed by RP HPLC (Biotage, 60 g Rp-C18-H, 0.1% TFA-H₂O in MeOH, 10-90%) gave the title compound as a white solid (53 mg, 30%). The title compound was isolated as a di-TFA salt. ¹H NMR (400 MHz, CD₃OD) δ ppm 8.65 (s, 1H), 8.00-7.94 (m, 3H), 7.66-7.63 (m, 2H), 7.54 (td, J=7.4, 1.1 Hz, 1H), 7.46 (d, J=6.8 Hz, 1H), 7.40 (t, J=7.4 Hz, 1H), 7.25-7.18 (m, 2H), 4.81-4.69 (m, 0.5H), 4.64, 4.63 (2 s, 2H), 4.13-4.11 (m, 2H), 4.00 (t, J=11.9 Hz, 2H), 3.67-3.65 (m, 0.68H), 3.53-3.40 (m, 5H), 3.24 (td, J=12.7, 2.4 Hz, 1H), 2.96, 2.95 (2 s, 3H), 2.47-2.44 (m, 0.65H), 2.34-2.30 (m, 1.3H), 2.21-2.14 (m, 1.4H), 2.00-1.90 (m, 0.71H); MS ESI 540.3 [M+H]⁺, calcd for [C₃₂H₃₇N₅O₃+H]⁺ 540.29.

Example A 110

N-(cyclopentyl(thiophen-3-yl)methyl)-3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazol-5-carboxamide

[0738]



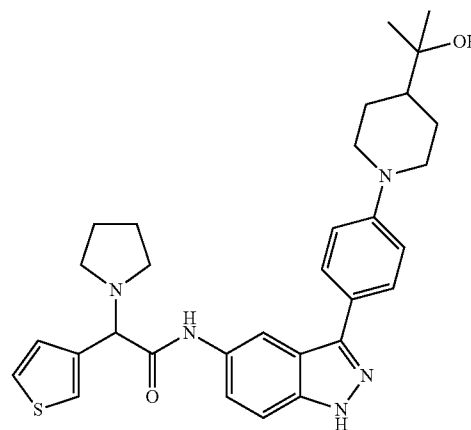
[0739] The title compound was synthesized according to general Method C from N-(cyclopentyl(thiophen-3-yl)methyl)-3-iodo-1H-indazole-5-carboxamide (150 mg, 0.332 mmol) and 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine (106 mg, 0.334 mmol) with PdCl₂dppf (35 mg, 0.042 mmol) and 1 M aq Na₂CO₃ (0.64 mL) in PhMe/EtOH (3.75 mL, 2:1 mixture) under Ar with heating under microwave irradiation at 125° C. for 4 h. The reaction mixture was diluted with EtOAc (25 mL) and washed with H₂O (10 mL) and brine (10 mL), dried (Na₂SO₄) and concentrated under vacuum. Purification by flash chromatography (SiO₂, 0-20% 2 M NH₃-MeOH in DCM; then RP HPLC C18 60 g, 10-80% MeOH in 0.1% TFA-H₂O) gave the title compound as a TFA salt (off white solid, 60 mg, 28%). ¹H NMR (400 MHz, CD₃OD), δ 8.52 (s, 1H), 7.94-7.

88 (m, 3H), 7.6 (d, J=8.8 Hz, 1H), 7.36-7.32 (m, 2H), 7.20-7.13 (m, 3H), 5.08 (d, J=6.0 Hz, 1H), 4.85 (s, 1H), 3.66 (t, J=13.6 Hz, 1H), 3.44-3.32 (m, 5H), 3.23 (br.m, 1H), 2.59-2.53 (br.m, 1H), 2.45-2.27 (m, 2H), 2.16-1.87 (m, 3H), 1.74-1.44 (br.m, 6H), 1.28-1.25 (m, 1H); MS ESI 515.4[M+H]⁺, calcd for [C₃₀H₃₄N₄O₂S+H]⁺ 515.2.

Example A111

N-(3-(4-(4-(2-hydroxypropan-2-yl)piperidin-1-yl)phenyl)-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide

[0740]

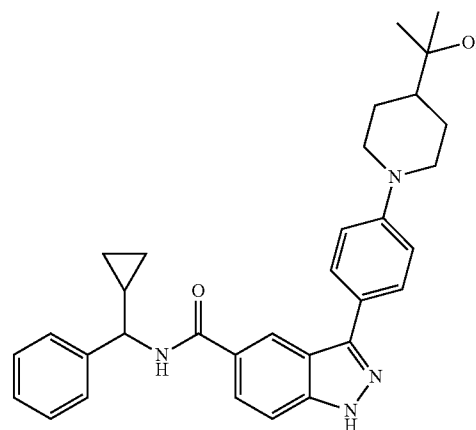


[0741] The title compound was synthesized according to Method C3 utilizing N-(3-iodo-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide and 2-(1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidin-4-yl)propan-2-ol and obtained as a white solid (21 mg, 23% yield). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.43 (s, 1H), 8.15 (d, J=8.8 Hz, 2H), 7.88 (m, 1H), 7.83 (d, J=8.8 Hz, 2H), 7.65 (m, 1H), 7.58 (m, 2H), 7.38 (d, J=5.2 Hz, 1H), 5.31 (s, 1H), 3.83 (m, 3H), 3.70 (m, 2H), 3.33 (m, 2H), 3.15 (m, 2H), 2.16 (m, 5H), 1.92 (m, 3H), 1.27 (s, 6H); MS ESI [M+H]⁺ 544.2, calcd for [C₃₁H₃₇N₅O₂S+H]⁺ 544.27.

Example A112

N-(cyclopropyl(phenyl)methyl)-3-(4-(4-(2-hydroxypropan-2-yl)piperidin-1-yl)phenyl)-1H-indazole-5-carboxamide

[0742]

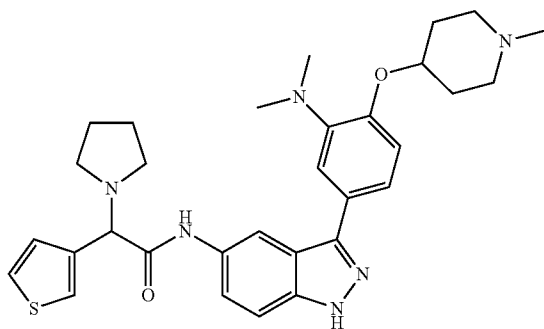


[0743] The title compound was synthesized according to Method C3 utilizing N-(cyclopropyl(phenyl)methyl)-3-iodo-1H-indazole-5-carboxamide and 2-(1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidin-4-yl)propan-2-ol and obtained (white solid, 21 mg, 22% yield). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.63 (s, 1H), 7.95 (dd, J=8.78, 1.51 Hz, 1H), 7.85 (d, J=8.78 Hz, 2H), 7.58 (d, J=8.78 Hz, 1H), 7.48 (d, J=7.28 Hz, 2H), 7.32 (t, J=7.53 Hz, 2H), 7.23 (m, J=7.28 Hz, 1H), 7.09 (d, J=8.78 Hz, 2H), 5.49 (s, 1H), 4.48 (d, J=9.54 Hz, 1H), 3.84 (d, J=12.30 Hz, 2H), 2.66 (t, J=11.04 Hz, 2H), 1.87 (d, J=9.29 Hz, 2H), 1.46 (d, J=3.51 Hz, 3H), 1.18 (s, 6H), 0.65 (d, J=8.28 Hz, 2H), 0.46 (d, J=15.31 Hz, 2H); MS ESI [M+H]⁺ 509.5, calcd for [C₃₂H₃₆N₄O₂+H]⁺ 509.29.

Example A 113

N-(3-(3-(dimethylamino)-4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide

[0744]



A. 4-(4-bromo-2-nitrophenoxy)-1-methylpiperidine

[0745] NaH (0.54 g, 13 mmol) was added portion wise to a solution of N-methyl-4-piperidinol (1.13 g, 11 mmol) in DMF (14 mL) at rt under Ar, followed by a solution of 4-bromo-1-fluoro-2-nitrobenzene (2.0 g, 9 mmol) in DMF (6 mL). The reaction mixture was heated at 75° C. for 16 h. The product was partitioned between 20% NaCl and EtOAc (2×300 mL), and the combined EtOAc layer was washed with H₂O and brine, dried (Na₂SO₄) and concentrated under vacuum to give the title compound (yellowish orange oil, 2.78 g, 97%). ¹H NMR (400 MHz, CD₃Cl₃) 7.94 (d, J=2.4 Hz, 1H), 7.60 (dd, J=8.8 Hz, J=2.4 Hz, 1H), 6.98 (d, J=9.2 Hz, 1H), 4.52 (s, 1H), 2.60 (br.s, 2H), 2.40 (br.s, 2H), 2.31 (s, 3H), 2.03-1.89 (m, 4H); MS ESI 316.9 [M+H]⁺, calcd for [C₁₂H₁₅BrN₂O₃+H]⁺ 315

B. 5-bromo-2-((1-methylpiperidin-4-yl)oxy)aniline

[0746] 1 M HCl (10 mL) was added slowly over 15 min to a suspension 4-(4-bromo-2-nitrophenoxy)-1-methylpiperidine (2.75 g, 8.7 mmol) and iron powder (9.75 g, 174 mmol) in PhMe (30 mL) and EtOH (10 mL) at 60° C. The reaction mixture was gradually heated to 100° C. and stirred for 4 h. The solid sludge was filtered through SiO₂ pad at 90° C. and washed with hot EtOAc. The organic layer was washed with 1 M aq Na₂CO₃ (50 mL) and brine and dried (Na₂SO₄) and

concentrated under vacuum. Purification by flash chromatography (SiO₂, 0-75% MeOH in DCM) gave the title compound (brown solid, 1.0 g, 40%). ¹H NMR (400 MHz, CDCl₃) δ ppm 6.85 (d, J=2.0 Hz, 1H), 6.79 (dd, J=8.8 Hz, J=2.4 Hz, 1H), 6.66 (d, J=8.8 Hz, 1H), 4.28 (s, 1H), 3.86 (s, 2H), 2.69-2.66 (br.s, 2H), 2.31 (s, 5H), 2.06-2.02 (br.m, 2H), 1.91-1.83 (br.m, 2H); MS ESI 287 [M+H]⁺, calcd for [C₁₂H₁₇BrN₂O+H]⁺ 285.

C. 5-bromo-N,N-dimethyl-2-((1-methylpiperidin-4-yl)oxy)aniline

[0747] NaBH(OAc)₃ (3.3 g, 15.5 mmol) was added to an ice cooled solution of 5-bromo-2-((1-methylpiperidin-4-yl)oxy)aniline (0.74 g, 2.6 mmol) and 37% aq. solution of formaldehyde (2.11 g, 26 mmol) in MeCN (22.2 mL). The reaction mixture was stirred overnight at RT and then concentrated under vacuum. The product was partitioned between 2 M Na₂CO₃ and EtOAc. The aq. layer was extracted with EtOAc and the combined EtOAc layer was washed with H₂O and brine, dried (Na₂SO₄) and concentrated under vacuum. Purification by flash chromatography (SiO₂, 0-25% DCM in MeOH) gave the title compound (thick brown oil, 0.65 g, 80%). ¹H NMR (400 MHz, CDCl₃) δ ppm 6.99-6.97 (t, J=2.4 Hz, 2H), 6.73 (d, J=9.2 Hz, 1H), 4.30 (br.t, 1H), 2.80 (s, 6H), 2.76-2.73 (br.s, 2H), 2.31 (s, 3H), 2.29-2.65 (br.m, 2H), 2.05-2.0 (br.m, 2H), 1.92-1.84 (m, 2H); MS ESI 313 [M+H]⁺, calcd for [C₁₄H₂₁BrN₂O+H]⁺ 313.1

D. N,N-dimethyl-2-((1-methylpiperidin-4-yl)oxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline

[0748] Using Method E with 5-bromo-N,N-dimethyl-2-((1-methylpiperidin-4-yl)oxy)aniline (200 mg, 0.638 mmol) in DMF (3 mL) at 125° C. for 4 h, aq. work-up and purification by flash chromatography (SiO₂, 0-30% 2 M NH₃-MeOH in DCM) gave the title compound (brown color solid, 74 mg, 32%). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.41-7.36 (m, 2H), 6.86 (d, J=8 Hz, 1H), 4.44 (br.d, 1H), 2.82 (s, 6H), 2.75-2.73 (br.s, 2H), 2.32 (br.d, 5H), 2.09-2.05 (br.m, 2H), 1.97-1.89 (br.m, 2H), 1.33 (s, 12H); MS ESI 361.2 [M+H]⁺, calcd for [C₂₀H₃₃BN₂O₃+H]⁺ 361.2

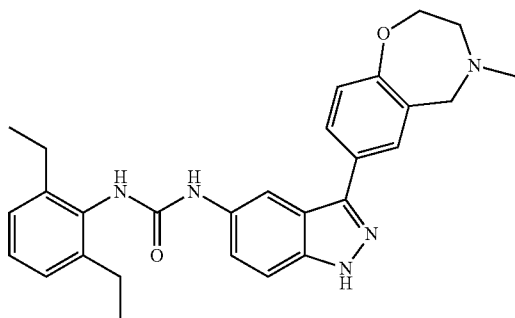
E. N-(3-(3-(dimethylamino)-4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide

[0749] According to general Method C2, N-(3-iodo-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide (90 mg, 0.195 mmol) and N,N-dimethyl-2-((1-methylpiperidin-4-yl)oxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (72 mg, 0.98 mmol) were heated under microwave irradiation at 125° C. for 4 h in PhMe/EtOH (2.7 mL, 2:1 mixture). Purification by flash chromatography (SiO₂, 0-50% 2 M NH₃-MeOH in DCM; then RP HPLC C18RP HPLC C18 60 g, 10-80% MeOH in 0.1% TFA-H₂O) gave the title compound as a TFA salt (off white solid, 30 mg, 19%). ¹H NMR (400 MHz, CD₃OD). ¹H NMR (400 MHz, CD₃OD). δ 8.44 (d, J=12.4 Hz, 1H), 8.26 (s, 1H), 80.8-80.5 (m, 1H), 7.88 (t, J=2.0 Hz, 1H), 7.66 (dd, J=5.2 Hz, J=3.2 Hz, 1H), 7.58-7.54 (m, 3H), 7.39 (d, J=8.0 Hz, 1H), 5.30 (s, 1H), 5.11 (s, 0.6H), 3.87 (br.s, 1H), 3.75-3.71 (br.m, 1H), 3.60-3.57 (br.m, 2H), 3.43 (d, J=16.8 Hz, 6H), 3.28-3.1 (br.m, 3H), 2.97 (s, 3H), 2.56-2.53 (br.m, 1H), 2.46-2.42 (br.m, 1H), 2.31-1.99 (br.m, 6H), 1H merged with solvent peak; MS ESI 559.2 [M+H]⁺, calcd for [C₃₁H₃₈N₆O₂S+H]⁺ 559.3.

Example A114

1-(2,6-diethylphenyl)-3-(3-(4-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepin-7-yl)-1H-indazol-5-yl)urea

[0750]

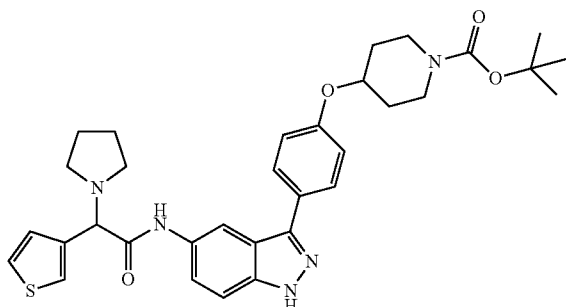


[0751] Using Method J, 3-(4-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepin-7-yl)-1H-indazol-5-amine bis(2,2,2-trifluoroacetate) (74 mg, 0.152 mmol), 1,3-diethyl-2-isocyanatobenzene (52 μ L, 0.300 mmol) and DIPEA (130 μ L, 0.750 mmol) in DMF (1.5 mL) gave the title compound as a TFA salt (29 mg, 41%, a brown solid). ^1H NMR (400 MHz, CD_3OD) δ ppm 8.39 (s, 1H), 7.99-7.96 (m, 2H), 7.52 (d, $J=8.8$ Hz, 1H), 7.28-7.10 (m, 5H), 4.62 (s, 2H), 4.54-4.51 (bs, 1H), 4.18-4.10 (bs, 1H), 3.73 (bs, 2H), 3.08-3.03 (m, 3H), 2.71 (q, $J=7.2$ Hz, 4H), 1.24 (t, $J=7.6$ Hz, 6H); MS ESI 470.4 $[\text{M}+\text{H}]^+$, calcd for $[\text{C}_{28}\text{H}_{31}\text{N}_5\text{O}_2+\text{H}]^+$ 470.26.

Example A115

tert-butyl 4-(4-(5-(2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamido)-1H-indazol-3-yl)phenoxy)piperidine-1-carboxylate

[0752]



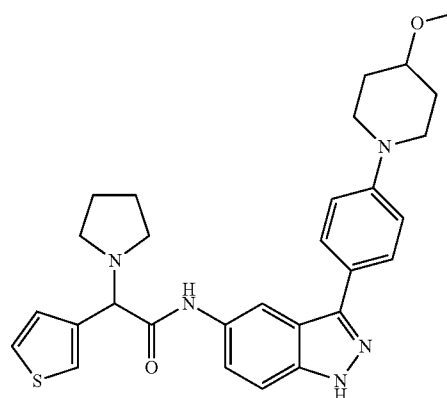
[0753] The title compound was synthesized according to Method C3 utilizing N-(3-iodo-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide and tert-butyl 4-(4-(4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine-1-carboxylate and obtained as a pale white solid (14 mg, 21% yield). ^1H NMR (400 MHz, CD_3OD) δ ppm 8.33 (s, 1H), 7.81 (d, $J=8.8$ Hz, 2H), 7.50 (m, 3H), 7.42 (dd, $J=4.8$ Hz, 2.8 Hz, 1H), 7.33 (m, 1H), 7.07 (d, $J=8.8$ Hz, 2H), 4.63 (m, 1H), 4.14 (s, 1H), 3.73 (m, 2H), 3.33 (m, 2H), 2.69 (m, 2H), 2.51

(m, 2H), 1.90 (m, 2H), 1.70 (m, 4H), 1.48 (s, 9H); MS ESI $[\text{M}+\text{H}]^{+602.4}$, calcd for $[\text{C}_{33}\text{H}_{39}\text{N}_5\text{O}_4\text{S}+\text{H}]^+$ 602.28.

Example A116

N-(3-(4-(4-methoxypiperidin-1-yl)phenyl)-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide

[0754]



[0755] To a solution of 1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidin-4-ol (152 mg, 0.5 mmol) in DMF (5 mL) at rt was added 60% NaH (40 mg, 1 mmol). The resulting mixture was stirred at rt for 10 min before MeI (0.031 mL, 0.5 mmol) was added. After addition, the resulting mixture was stirred O/N at rt. This reaction was repeated on 1 mmol scale (rt, 2 h). Both reactions were combined, quenched with satd aq NH_4Cl (5 mL) and H_2O (100 mL), extracted with EtOAc and purified by flash chromatography (EtOAc/hex 0-30%) to give 4-methoxy-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidine (white solid, 95 mg, 20%). MS ESI 318.1 $[\text{M}+\text{H}]^+$, calcd for $[\text{C}_{18}\text{H}_{28}\text{BNO}_3+\text{H}]^+$ 318.2.

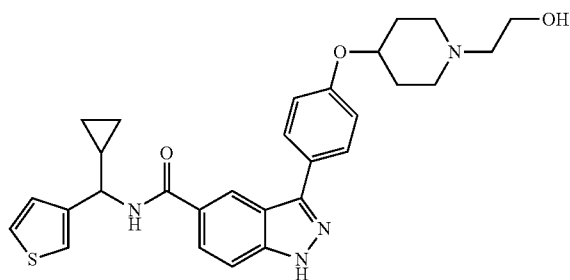
[0756] To a mixture of N-(3-iodo-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide (136 mg, 0.3 mmol) and 4-methoxy-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidine (95 mg, 0.3 mmol) in EtOH (4 mL) was added 1 M aq Na_2CO_3 (0.6 mL, 0.6 mmol), followed by $\text{Pd}(\text{PPh}_3)_4$ (17.4 mg, 0.015 mmol). The resulting mixture was purged with Ar and microwaved 4 h at 125°C . After removal of solvents, it was purified by flash chromatography (EtOAc/hex 0-100%, then MeOH/DCM 15%), biotage RP column (MeOH/ H_2O (1% TFA) 0-100%) to give the title compound as a di-TFA salt

[0757] (light yellow solid, 57.6 mg, 26%). ^1H NMR (400 MHz, CD_3OD) δ 8.42 (s, 1H), 8.11 (d, $J=8.4$ Hz, 2H), 7.88 (dd, $J=2.8$ Hz, 1.2 Hz, 1H), 7.74 (br d, $J=8.0$ Hz, 2H), 7.64 (dd, $J=5.0$ Hz, 3.0 Hz, 1H), 7.60-7.53 (m, 2H), 7.39 (dd, $J=4.8$ Hz, 1.2 Hz, 1H), 5.33 (s, 1H), 3.90-3.77 (m, 3H), 3.71-3.64 (m, 1H), 3.62-3.53 (m, 2H), 3.44 (s, 3H), 3.35-3.05 (m, 3H), 2.31-1.93 (m, 8H); MS ESI 516.2 $[\text{M}+\text{H}]^+$, calcd for $[\text{C}_{27}\text{H}_{32}\text{N}_5\text{O}_2\text{S}+\text{H}]^+$ 516.2.

Example A117

N-(cyclopropyl(thiophen-3-yl)methyl)-3-(4-((1-(2-hydroxyethyl)piperidin-4-yl)oxy)phenyl)-1H-indazole-5-carboxamide

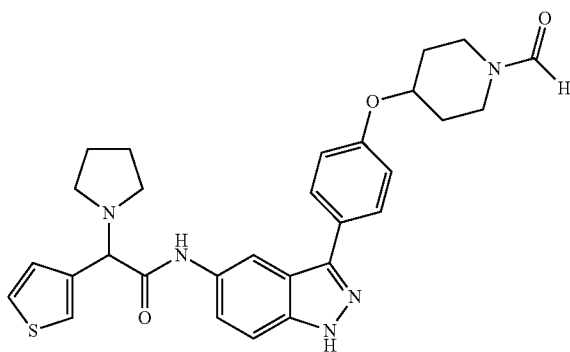
[0758]



[0759] The title compound was prepared using Method C3 from N-(cyclopropyl(thiophen-3-yl)methyl)-3-iodo-1H-indazole-5-carboxamide (40 mg, 0.095 mmol) and 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidin-1-yl)ethanol (43 mg, 0.124 mmol) which gave 14 mg of product isolated as its TFA salt (23%, a white solid). ¹H NMR (400 MHz, CD₃OD) δ ppm 9.04 (bs, 1H), 8.58 (s, 1H), 7.96-7.94 (m, 3H), 7.61 (d, J=8.8 Hz, 1H), 7.37 (bs, 2H), 7.22-7.15 (m, 3H), 4.87 (bs, 1H), 4.65-4.61 (m, 1H), 3.91-3.28 (m, 12H), 2.45-2.29 (m, 2H), 2.21-1.95 (m, 2H), 1.44-1.40 (m, 1H), 0.73-0.63 (m, 2H), 0.50-0.48 (m, 2H); MS ESI 517.3 [M+H]⁺, calcd for [C₂₉H₃₂N₄O₃S+H]⁺ 517.23.

Example A 118. N-(3-(4-((1-formylpiperidin-4-yl)oxy)phenyl)-1H-indazol-5-yl)-2-(thiophen-3-yl)acetamide

[0760]



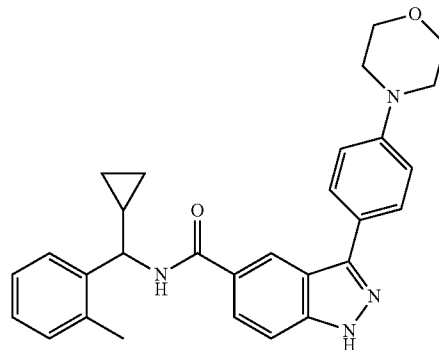
[0761] The title compound was synthesized according to Method C3 utilizing N-(3-iodo-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide and 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine-1-carbaldehyde and obtained as a yellow solid (39 mg, 35% yield). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.35 (s, 1H), 8.04 (s, 1H), 7.82 (d, J=8.8 Hz, 2H), 7.50 (m, 3H), 7.40 (m, 1H), 7.33 (m, 1H), 7.08 (d, J=8.8 Hz, 2H), 4.72 (m, 1H), 4.16 (s, 1H), 3.75 (m, 2H), 3.67 (m, 2H), 3.52 (m, 2H), 3.41 (m, 2H),

2.67 (m, 2H), 2.51 (m, 2H), 1.98 (m, 2H), 1.80 (m, 6H); MS ESI [M+H]⁺ 530.4, calcd for [C₂₉H₃₁N₅O₃S+H]⁺ 530.22.

Example A119

N-(cyclopropyl(o-tolyl)methyl)-3-(4-morpholinophenyl)-1H-indazole-5-carboxamide

[0762]



[0763] To a 20 mL microwave vial charged with Mg powder (240 mg, 10 mmol), THF (10 mL) was added bromocyclopropane (1.21 g, 10 mmol). The resulting mixture was stirred for 30 min at rt before 2-methylbenzonitrile (468 mg, 4 mmol) was added. It was microwaved 10 min at 100° C., cooled to rt and added dropwise to a cold solution of NaBH₄ (380 mg, 10 mmol) in MeOH (25 mL) at 0° C. The resulting mixture was stirred for 15 min at rt, concentrated and purified by flash chromatography (MeOH/DCM 0-20%) to give cyclopropyl(o-tolyl)methanamine (yellow oil which solidified upon standing, 0.70 g, 87%). ¹H NMR (400 MHz, CD₃OD) δ 8.49 (d, J=7.6 Hz, 1H), 7.27-7.22 (m, 1H), 7.20-7.17 (m, 2H), 3.75 (d, J=8.4 Hz, 1H), 2.35 (s, 3H), 1.37-1.27 (m, 1H), 0.71-0.63 (m, 1H), 0.53-0.46 (m, 1H), 0.38-0.31 (m, 1H), 0.29-0.33 (m, 1H); MS ESI 145.0 [M+H], calcd for [C₁₁H₁₅N—NH₃+H]⁺ 145.1.

[0764] To a solution of 3-iodo-1H-indazole-5-carboxylic acid (1.44 g, 5 mmol) and (4-morpholinophenyl)boronic acid (1.09 g, 5.25 mmol) in DMF (10 mL) was added a solution of K₃PO₄ (3.18 g, 15 mmol) in H₂O (4 mL), followed by Pd(PPh₃)₄ (116 mg, 0.1 mmol). The resulting mixture was purged with Ar and microwaved 5 h at 120° C. Repeated this reaction on the same scale and the two reactions were combined. After separation of DMF layer, the aq. layer was extracted with EtOAc. The combined organic layers were concentrated to dryness, suspended in MeOH (60 mL), treated with 4 mL of TFA, sonicated and filtered to give 3-(4-morpholinophenyl)-1H-indazole-5-carboxylic acid (yellow solid, 1.162 g, 36%). ¹H NMR (400 MHz, DMSO-d₆) δ 13.4 (s, 1H), 12.8 (br, s, 1H), 8.61 (s, 1H), 7.94 (dd, J=8.8 Hz, 1H), 7.83 (d, J=8.8 Hz, 2H), 7.61 (d, J=8.8 Hz, 1H), 7.13 (d, J=8.8 Hz, 2H), 3.77 (t, J=4.8 Hz, 4H), 3.20 (t, J=4.8 Hz, 4H); MS ESI 324.1 [M+H]⁺, calcd for [C₁₈H₁₇N₃O₃+H]⁺ 324.1.

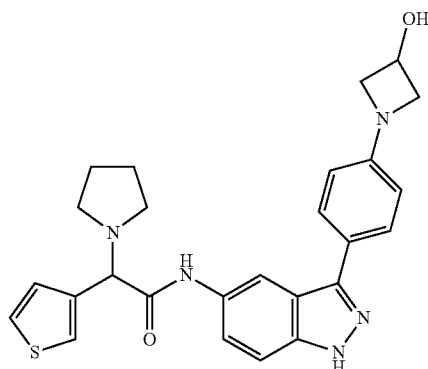
[0765] To a solution of cyclopropyl(o-tolyl)methanamine (80.5 mg, 0.5 mmol), 3-(4-morpholinophenyl)-1H-indazole-5-carboxylic acid (194 mg, 0.6 mmol) and TBTU (160.5 mg, 0.5 mmol) in DMF (6 mL) was added ^tPr₂NEt (0.174 mL, 1 mmol). The resulting mixture was stirred for 30 min at rt. After removal of ^tPr₂NEt, it was purified by prep-HPLC,

PoraPak and flash chromatography (MeOH/DCM 10-20%) to give the title compound (white solid, 88.7 mg, 38%). ¹H NMR (400 MHz, CD₃OD) δ 8.99 (d, J=8.0 Hz, 0.5H, NH), 8.58 (s, 1H), 7.91 (d, J=8.8 Hz, 1H), 7.78 (d, J=8.4 Hz, 2H), 7.56 (d, J=7.6 Hz, 1H; partially overlapped with the peak at 7.53), 7.53 (d, J=8.8 Hz, 1H; partially overlapped with the peak at 7.56), 7.14-7.04 (m, 3H), 6.92 (d, J=8.8 Hz, 2H), 4.90-4.86 (m, 1H; partially buried under H₂O peak), 3.74 (t, J=4.6 Hz, 4H), 3.05 (t, J=4.8 Hz, 4H), 2.37 (s, 3H), 1.45-1.35 (m, 1H), 0.63-0.42 (m, 3H), 0.33-0.27 (m, 1H); MS ESI 467.5 [M+H]⁺, calcd for [C₂₉H₃₀N₄O₂+H]⁺ 467.2.

Example A120

N-(3-(4-(3-Hydroxyazetidin-1-yl)phenyl)-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide

[0766]



A. Azetidin-3-ol

[0767] A solution of tert-butyl 3-hydroxyazetidine-1-carboxylate (1.0 g, 5.84 mmol) and TFA (5 mL) in DCM (10 mL) was stirred at rt for 1 h. The solvent was removed in vacuo. The residue was then dissolved in MeOH (20 mL) and poured into a preconditioned 20 mL PoraPak Rxn Cx cartridge. The MeOHEtOH (30 mL) rinse was discarded and the product was eluted with 2 M NH₃ in MeOHEtOH (30 mL). The solvent was removed in vacuo, and the product was used without further purification. ¹H NMR (400 MHz, CD₃OD) δ ppm 4.56 (quint, J=6.8 Hz, 1H), 3.64 (t, J=7.0 Hz, 2H), 3.50 (t, J=7.0 Hz, 2H); MS ESI 74.2 [M+H]⁺, calcd for [C₆H₇NO+H]⁺ 74.05.

B. 1-(4-Iodophenyl)azetidin-3-ol

[0768] The title compound was synthesized according to Method I, utilizing 1,4-diiodobenzene (470 mg, 1.4 mmol), azetidin-3-ol (125 mg, 1.7 mmol), CuI (54 mg, 0.29 mmol), BINOL (82 mg, 0.29 mmol), and K₃PO₄ (610 mg, 2.9 mmol) in DMF (5 mL). The mixture was diluted with EtOAc, filtered through a cake of Celite and the filtrate was concentrated to give the crude product. Purification by flash chromatography (Biotage, 25 g HP-SIL, 20-100% EtOAc in Hexanes) gave the title compound as a white solid (262 mg, 67%). ¹H NMR (400 MHz, CD₃OD) δ ppm 7.43 (d, J=8.8 Hz, 2H), 6.27 (d, J=8.8

Hz, 2H), 4.65 (quint, J=4.9 Hz, 1H), 4.10 (t, J=7.4 Hz, 2H), 3.57 (dd, J=8.4, 4.9 Hz, 2H); MS ESI 275.9 [M+H]⁺, calcd for [C₉H₁₀INO+H]⁺ 275.98.

C. 1-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)azetidin-3-ol

[0769] The title compound was synthesized according to Method E, utilizing 1-(4-Iodophenyl)azetidin-3-ol (290 mg, 0.96 mmol), bis(pinacolato)diboron (366 mg, 1.4 mmol), PdCl₂(dppf) (39 mg, 0.048 mmol), KOAc (280 mg, 2.9 mmol) and DMSO (4.0 mL). The reaction was quenched with satd aqNaHCO₃ solution, extracted with EtOAc, dried over MgSO₄, filtered, and concentrated to dryness. Purification by flash chromatography (Biotage, 50 g HP-SIL, 10-50% EtOAc in Hexanes) gave the title compound as a yellow oil (260 mg, 100%). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.65 (d, J=8.4 Hz, 2H), 6.40 (d, J=8.4 Hz, 2H), 4.98 (quint, J=4.8 Hz, 1H), 4.18 (dd, J=15, 8.0 Hz, 2H), 3.76 (dd, J=8.4, 4.6 Hz, 2H), 1.31 (s, 12H); MS ESI 276.0 [M+H]⁺, calcd for [C₁₅H₂₂BNO₃+H]⁺ 276.17.

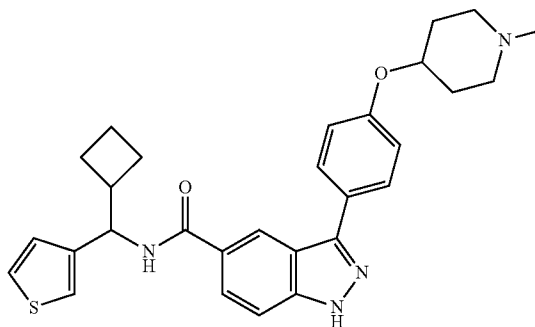
D. N-(3-(4-(3-Hydroxyazetidin-1-yl)phenyl)-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide

[0770] The title compound was synthesized according to Method C, utilizing N-(3-iodo-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide (360 mg, 0.79 mmol), 1-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)azetidin-3-ol (240 mg, 0.87 mmol), Pd(PPh₃)₄ (92 mg, 0.079 mmol), 2 M Na₂CO₃ (0.80 mL), PhMe (4 mL), and EtOH (2 mL). H₂O (30 mL) was added and the product was extracted into EtOAc (4x30 mL). The combined organic layers were dried over MgSO₄, filtered and evaporated in vacuo. Purification by flash chromatography (Biotage, 50 g HP-SIL, 20-100% EtOAc in hexanes, then 2-15% MeOH in DCM) followed by RPHPLC gave the title compound as a bright yellow solid (90 mg, 16%). The title compound was isolated as a di-TFA salt. ¹H NMR (400 MHz, CD₃OD) δ ppm 8.37 (s, 1H), 7.87 (dd, J=2.9, 1.3 Hz, 2H), 7.80 (d, J=8.6 Hz, 2H), 7.63 (dd, J=5.1, 3.0 Hz, 1H), 7.52 (d, J=1.1 Hz, 2H), 7.38 (dd, J=5.1, 1.2 Hz, 1H), 6.84 (br d, J=7.4 Hz, 2H), 5.27 (s, 1H), 4.74 (quint, J=5.1 Hz, 1H), 4.39-4.34 (br m, 2H), 3.90-3.78 (br m, 3H), 3.30-3.02 (br m, 3H), 3.13 (s, 3H), 2.16-1.90 (br m, 4H); MS ESI 474.1 [M+H]⁺, calcd for [C₂₆H₂₇N₅O₂S+H]⁺ 474.19.

Example A121

N-(cyclobutyl(thiophen methyl-3-yl)(4-((methylpiperidin-4-yl)oxy)phenyl)-1H-indazole-5-carboxamide

[0771]



[0772] A mixture of cyclobutyl(thiophen-3-yl)methanone (1.04 g, 6.27 mmol), NH_4OAc (5.85 g, 75.24 mmol) and NaCNBH_3 (1.58 g, 25.08 mmol) in MeOH (30 mL) was heated at 65° C. for 3 h, then left O/N at 65° C. After removal of solvent, it was purified by flash chromatography (MeOH/DCM 0-30%) to give cyclobutyl(thiophen-3-yl)methanamine (colorless oil, 1.194 g). ^1H NMR (400 MHz, CD_3OD) δ 7.55-7.50 (m, 2H), 7.17 (dd, $J=4.8$ Hz, 1.2 Hz, 1H), 4.37 (d, $J=10.0$ Hz, 1H), 2.93-2.82 (m, 1H), 2.29-2.19 (m, 1H), 2.05-1.75 (m, 5H); MS ESI 151.0 $[\text{M}+\text{H}]^+$, calcd for $[\text{C}_9\text{H}_{13}\text{NS}+\text{H}]^+$ 151.1.

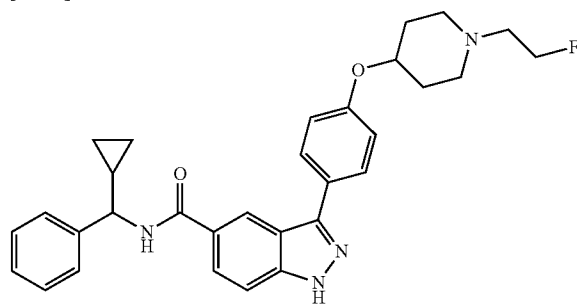
[0773] To a solution of cyclobutyl(thiophen-3-yl)methanamine (1.194 g, 6.27 mmol), 3-iodo-1H-indazole-5-carboxamide (1.81 g, 6.27 mmol) in DMF (20 mL) at 0° C. was added TBTU (2.01 g, 6.27 mmol), followed by $i\text{Pr}_2\text{NEt}$ (2.18 mL, 12.54 mmol). The resulting mixture was stirred at 0° C. for 1 h, quenched with H_2O (70 mL) and stirred for 1.5 h at rt. Suction filtration gave crude N-(cyclobutyl(thiophen-3-yl)methyl)-3-iodo-1H-indazole-5-carboxamide (light beige solid, 2.512 g). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 13.69 (s, 1H), 8.75 (d, $J=8.8$ Hz, 1H), 8.04 (s, 1H), 7.94 (dd, $J=4.6$ Hz, 1.4 Hz, 1H), 7.58 (d, $J=8.8$ Hz, 1H), 7.45 (dd, $J=4.8$ Hz, 2.8 Hz, 1H), 7.35 (d, $J=3.2$ Hz, 1H), 7.14 (dd, $J=4.8$ Hz, 0.8 Hz, 1H), 5.19 (t, $J=9.4$ Hz, 1H), 2.10-2.00 (m, 1H), 2.00-1.88 (m, 1H), 1.86-1.70 (m, 5H); MS ESI 438.0 $[\text{M}+\text{H}]^+$, calcd for $[\text{C}_{17}\text{H}_{16}\text{IN}_3\text{OS}+\text{H}]^+$ 438.0.

[0774] To a mixture of crude N-(cyclobutyl(thiophen-3-yl)methyl)-3-iodo-1H-indazole-5-carboxamide (262 mg, 0.6 mmol) and 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine (159 mg, 0.5 mmol) in EtOH (15 mL) was added 1 M aq Na_2CO_3 (1 mL, 1 mmol), followed by $\text{Pd}(\text{PPh}_3)_4$ (29 mg, 0.025 mmol). The resulting mixture was purged with Ar and microwaved 4 h at 125° C. After removal of solvents, it was purified by flash chromatography (MeOH/DCM 0-100%, then 0.05 NH_3 in MeOH/DCM 20%), PoraPak and prep-HPLC to give the title compound as a TFA salt (light yellow solid, 65.8 mg, 21%). ^1H NMR (400 MHz, CD_3OD) δ 8.55 (s, 1H), 7.94-7.88 (m, 3H), 7.59 (d, $J=8.8$ Hz, 1H), 7.33 (dd, $J=5.0$ Hz, 3.0 Hz, 1H), 7.26 (pseudo d, $J=3.2$ Hz, 1H), 7.17-7.10 (m, 3H), 5.26 (d, $J=6.4$ Hz, 1H), 4.83-4.78 (m, 0.7H), 4.68-4.58 (m, 0.3H), 3.66-3.58 (m, 0.7H), 3.45-3.33 (m, 2.6H), 3.23-3.15 (m, 0.7H), 2.98-2.87 (m, 4H; s, 3H at 2.93), 2.45-1.80 (m, 10H); MS ESI 501.5 $[\text{M}+\text{H}]^+$, calcd for $[\text{C}_{29}\text{H}_{32}\text{N}_4\text{O}_2\text{S}+\text{H}]^+$ 501.2.

Example A122

N-(cyclopropyl(phenyl)methyl)-3-(4-((1-(2-fluoroethyl)piperidin-4-yl)oxy)phenyl)-1H-indazole-5-carboxamide

[0775]

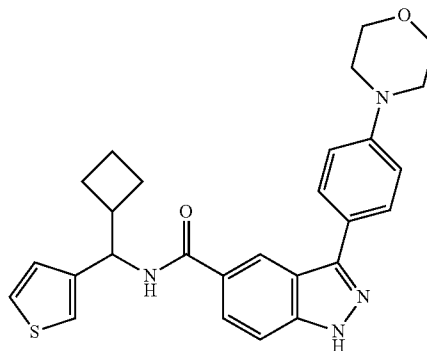


[0776] The title compound was synthesized according to Method C3 utilizing N-(cyclopropyl(phenyl)methyl)-3-iodo-1H-indazole-5-carboxamide and 1-(2-fluoroethyl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine and obtained (white solid, 8 mg, 11% yield). ^1H NMR (400 MHz, CD_3OD) δ ppm 8.61 (s, 1H), 7.96 (dd, $J=8.8$ Hz, 1.6 Hz, 1H), 7.91 (d, $J=8.8$ Hz, 2H), 7.60 (d, $J=8.8$ Hz, 1H), 7.49 (d, $J=7.2$ Hz, 2H), 7.34 (m, 2H), 7.24 (m, 1H), 7.12 (d, $J=8.8$ Hz, 2H), 4.66 (t, $J=4.8$ Hz, 1H), 4.54 (t, $J=4.8$ Hz, 1H), 4.48 (d, $J=9.6$ Hz, 1H), 2.87 (m, 2H), 2.80 (t, $J=4.8$ Hz, 1H), 2.73 (t, $J=4.8$ Hz, 1H), 2.51 (t, $J=8.8$ Hz, 1H), 2.08 (m, 2H), 1.87 (m, 2H), 1.41 (m, 2H), 0.66 (m, 2H), 0.47 (m, 2H); MS ESI $[\text{M}+\text{H}]^+$ 513.4, calcd for $[\text{C}_{31}\text{H}_{33}\text{FN}_4\text{O}_2+\text{H}]^+$ 513.27.

Example A123

N-(cyclobutyl(thiophen-3-yl)methyl)-3-(4-morpholinophenyl)-1H-indazole-5-carboxamide

[0777]

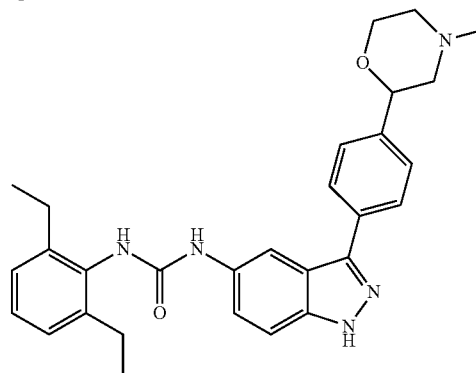


[0778] To a mixture of crude N-(cyclobutyl(thiophen-3-yl)methyl)-3-iodo-1H-indazole-5-carboxamide (262 mg, 0.6 mmol) and (4-morpholinophenyl)boronic acid (104 mg, 0.5 mmol) in EtOH (15 mL) was added 1 M aq Na_2CO_3 (1 mL, 1 mmol), followed by $\text{Pd}(\text{PPh}_3)_4$ (29 mg, 0.025 mmol). The resulting mixture was purged with Ar and microwaved 4 h at 125° C. It was diluted with H_2O , extracted with DCM and purified by flash chromatography (MeOH/DCM 0-20%), PoraPak, prep-HPLC, flash chromatography (EtOAc/hex 0-95%) and trituration with MeOH to give the title compound (white solid, 57.1 mg, 24%). ^1H NMR (400 MHz, CDCl_3) δ 11.14 (s, 1H, NH), 8.49 (s, 1H), 7.87 (d, $J=8.0$ Hz, 2H), 7.74 (d, $J=8.4$ Hz, 1H), 7.36 (d, $J=8.8$ Hz, 1H), 7.17 (s, 1H), 7.09 (d, $J=4.4$ Hz, 1H), 7.01 (d, $J=8.4$ Hz, 2H), 6.40 (d, $J=8.8$ Hz, 1H), 5.40 (t, $J=8.6$ Hz, 1H), 3.89 (pseudo s, 4H), 3.22 (pseudo s, 4H), 2.91-2.80 (m, 1H), 2.20-1.75 (m, 8H); MS ESI 473.4 $[\text{M}+\text{H}]^+$, calcd for $[\text{C}_{27}\text{H}_{28}\text{N}_4\text{O}_2\text{S}+\text{H}]^+$ 473.2.

Example A124

1-(2,6-diethylphenyl)-3-(3-(4-(4-methylmorpholin-2-yl)phenyl)-1H-indazol-5-yl)urea

[0779]



A. 2-(4-bromophenyl)-4-tosylmorpholine

[0780] To an ice-cooled solution of 2-amino-1-(4-bromophenyl)ethanol (500 mg, 2.31 mmol) in NEt_3 (0.48 mL, 3.47 mmol) and CH_2Cl_2 (10 mL) was added tosyl chloride (440 mg, 2.31 mmol) and the reaction stirred for 18 h. The mixture was diluted with CH_2Cl_2 (100 mL), washed with brine (2x50 mL) and the organic layer dried over MgSO_4 . The organic layer was filtered and the solvent removed to give the intermediate N-(2-(4-bromophenyl)-2-hydroxyethyl)-4-methylbenzenesulfonamide which was dissolved into CH_2Cl_2 (15 mL). The solution was cooled to 0° C., NaH (245 mg of 60% wt suspension) was added, the mixture stirred for 5 min and then (2-bromoethyl)diphenylsulfonium trifluoromethanesulfonate (931 mg, 2.10 mmol) was added and the reaction was allowed to warm to rt overnight. The reaction was then quenched with H_2O (2 mL) and extracted with CH_2Cl_2 (50 mL) and the organic layer washed with brine (1x25 mL). The solvent was removed and the residue titrated with 9:1 hexanes/ Et_2O which gave after drying 613 mg, 88% of the product as a white solid. MS ESI 396.7 $[\text{M}+\text{H}]^+$, calcd for $[\text{C}_{17}\text{H}_{18}\text{BrNO}_3\text{S}+\text{H}]^+$ 396.03.

B. 2-(4-bromophenyl)-4-methylmorpholine

[0781] 2-(4-Bromophenyl)-4-tosylmorpholine (509 mg, 1.28 mmol), phenol (242 mg, 2.57 mmol) were dissolved into HBr (33% wt solution in AcOH) and the mixture heated to 55° C. for 3 h. The reaction was cooled and the product precipitated with Et_2O and filtered washing with Et_2O to give the de-protected material which was then dissolved into THF (7.5 mL) and then formalin (0.24 mL, 3.26 mmol) followed by $\text{NaBH}(\text{OAc})_3$ (752 mg, 3.55 mmol) were added and the mixture stirred for 18 h. The reaction was poured into a separatory funnel containing NaHCO_3 (50 mL) and then extracted with EtOAc (2x50 mL). The organic layers were separated and washed with brine (1x50 mL), dried over MgSO_4 and the solvent removed to give the 243 mg, 64% of the product as a brown oil. MS ESI 257.9 $[\text{M}+\text{H}]^+$, calcd for $[\text{C}_{11}\text{H}_{14}\text{BrNO}+\text{H}]^+$ 258.03.

C. 3-(4-(4-methylmorpholin-2-yl)phenyl)-1H-indazole-5-amine bis(2,2,2-trifluoroacetate)

[0782] The boronic ester was prepared from 2-(4-bromophenyl)-4-methylmorpholine using general Method F which was used directly for the Suzuki coupling. The same procedure was then followed as for 3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazole-5-amine bis(2,2,2-trifluoroacetate) using tert-butyl (3-iodo-1H-indazole-5-yl)carbamate (112 mg, 0.312 mmol) and 4-methyl-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)morpholine (123 mg, 0.406 mmol). Obtained 45 mg of an impure brown solid which was used for subsequent synthetic steps; MS ESI 309.1 $[\text{M}+\text{H}]^+$, calcd for $[\text{C}_{18}\text{H}_{20}\text{N}_4\text{O}+\text{H}]^+$ 309.17.

D. 1-(2,6-diethylphenyl)-3-(3-(4-(4-methylmorpholin-2-yl)phenyl)-1H-indazole-5-yl)urea

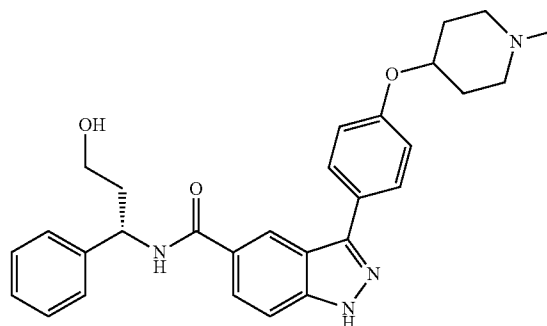
[0783] Using Method J, 3-(4-(4-methylmorpholin-2-yl)phenyl)-1H-indazole-5-amine bis(2,2,2-trifluoroacetate) (45 mg, 0.085 mmol), 1,3-diethyl-2-isocyanatobenzene (29 μL , 0.168 mmol) and DIPEA (73 μL , 0.42 mmol) in DMF (0.5 mL) gave the title compound as a TFA salt (23 mg, 56%, a white solid). ^1H NMR (400 MHz, CD_3OD) δ ppm 8.29 (s, 1H), 7.97 (d, J=8.3 Hz, 2H), 7.56-7.51 (m, 3H), 7.31 (d, J=8.8

Hz, 1H), 7.21-7.16 (m, 3H), 4.78-4.75 (m, 1H), 4.34-4.30 (m, 1H), 4.00-3.94 (m, 1H), 3.70-3.67 (m, 1H), 3.56-3.52 (m, 1H), 3.31-3.28 (m, 1H), 3.17-3.13 (m, 1H), 2.97 (s, 3H), 2.70 (q, J=7.6 Hz, 4H), 1.23 (t, J=7.6 Hz, 6H); MS ESI 484.5 $[\text{M}+\text{H}]^+$, calcd for $[\text{C}_{29}\text{H}_{33}\text{N}_5\text{O}_2+\text{H}]^+$ 484.27.

Example A125

(S)—N-(3-hydroxy-1-phenylpropyl)-3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazole-5-carboxamide

[0784]

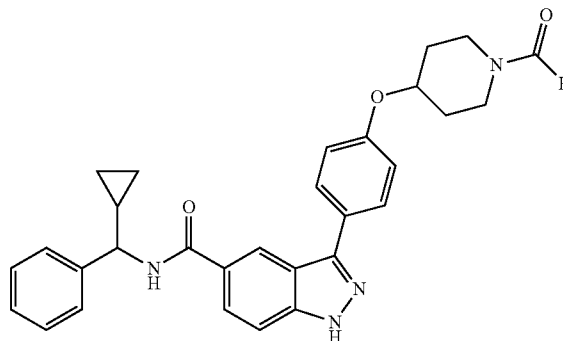


[0785] The title compound was synthesized according to the General Method C, utilizing (S)—N-(3-hydroxy-1-phenylpropyl)-3-iodo-1H-indazole-5-carboxamide (50 mg, 0.11 mmol), (4-((1-methylpiperidin-4-yl)oxy)phenyl)boronic acid pinacol ester (41 mg, 0.13 mmol), $\text{Pd}(\text{PPh}_3)_4$ (6.4 mg, 0.0055 mmol), satd. Na_2CO_3 (1.5 mL), and 3.5 mL of PhMe:EtOH (1:1). The vial was charged with Ar and heated in the microwave reactor at 125° C. for 2 h. Purification by RPHPLC, followed by trituration with Et_2O gave the title compound as a TFA salt (white solid, 20 mg, 30%). ^1H NMR (400 MHz, CD_3OD) δ ppm 8.56 (s, 1H), 7.87-7.97 (m, 3H), 7.61 (d, J=8.5 Hz, 1H), 7.44 (d, J=7.8 Hz, 2H), 7.34 (t, J=7.5 Hz, 1H), 7.12-7.27 (m, 3H), 5.29-5.38 (m, 1H), 4.62-4.73 (m, 0.3H), 3.58-3.73 (m, 2.7H), 3.34-3.49 (m, 3H), 3.15-3.27 (m, 1H), 2.94 (s, 3H), 2.39-2.50 (m, 0.7H), 2.25-2.35 (m, 1.3H), 2.05-2.22 (m, 3.3H), 1.83-1.98 (m, 0.7H); MS ESI 485.4 $[\text{M}+\text{H}]^+$, calcd for $[\text{C}_{29}\text{H}_{32}\text{N}_4\text{O}_3+\text{H}]^+$ 485.3.

Example A126

N-(cyclopropyl(phenyl)methyl)-3-(4-((1-formylpiperidin-4-yl)oxy)phenyl)-1H-indazole-5-carboxamide

[0786]



[0787] The title compound was synthesized according to Method C3 utilizing N-(cyclopropyl(phenyl)methyl)-3-iodo-1H-indazole-5-carboxamide and 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine-1-carbaldehyde and obtained as a yellow solid (14 mg, 27% yield). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.61 (s, 1H), 8.03 (s, 1H), 7.89-7.98 (m, 3H), 7.59 (d, J=8.78 Hz, 1H), 7.48 (d, J=7.28 Hz, 2H), 7.32 (t, J=7.53 Hz, 2H), 7.23 (m, J=7.53 Hz, 1H), 7.12 (d, J=8.78 Hz, 2H), 4.69-4.77 (m, 1H), 4.45-4.51 (m, 1H), 3.62-3.79 (m, 2H), 3.49-3.58 (m, 1H), 3.37-3.46 (m, 1H), 1.91-2.08 (m, 2H), 1.72-1.91 (m, 2H), 1.34-1.46 (m, 1H), 0.65 (d, J=8.28 Hz, 2H), 0.41-0.53 (m, 2H); MS ESI [M+H]⁺ 495.3, calcd for [C₃₀H₃₀N₄O₃+H]⁺ 495.24.

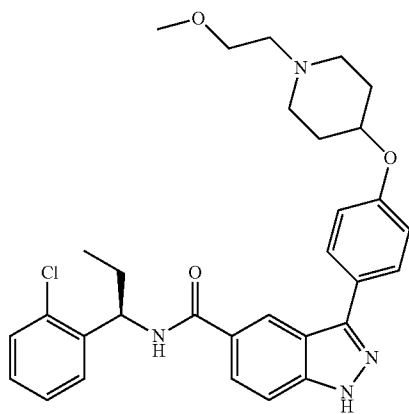
Example A127

Intentionally Omitted

Example A128

(R)—N-(1-(2-chlorophenyl)propyl)-3-(4-((1-(2-methoxyethyl)piperidin-4-yl)oxy)phenyl)-1H-indazole-5-carboxamide

[0788]

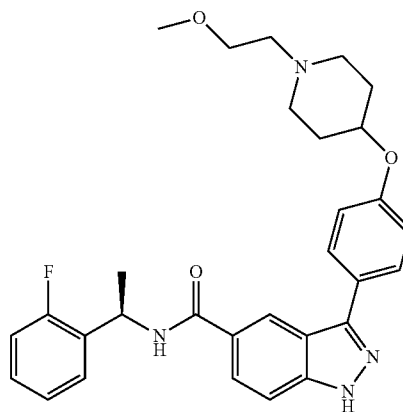


[0789] Using Method C3, (R)—N-(1-(2-chlorophenyl)propyl)-3-iodo-1H-indazole-5-carboxamide (66 mg, 0.150 mmol) and 1-(2-methoxyethyl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine (69 mg, 0.190 mmol) gave the title compound as a TFA salt (10 mg, 12%, a pale-yellow solid). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.88 (bs, 1H), 8.57 (s, 1H), 7.96-7.93 (m, 3H), 7.62 (d, J=8.0 Hz, 1H), 7.49 (d, J=6.0 Hz, 1H), 7.42-7.16 (m, 4H), 5.47-5.45 (m, 1H), 4.87 (bs, 1H), 3.76-3.70 (m, 3H), 3.54-3.30 (m, 9H), 2.44-2.29 (m, 2H), 2.18-1.90 (m, 4H), 1.05 (t, J=7.5 Hz, 3H); MS ESI 547.7 [M+H]⁺, calcd for [C₃₁H₃₅ClN₄O₃+H]⁺ 547.25.

Example A129

(R)—N-(1-(2-fluorophenyl)ethyl)-3-(4-((1-(2-methoxyethyl)piperidin-4-yl)oxy)phenyl)-1H-indazole-5-carboxamide

[0790]

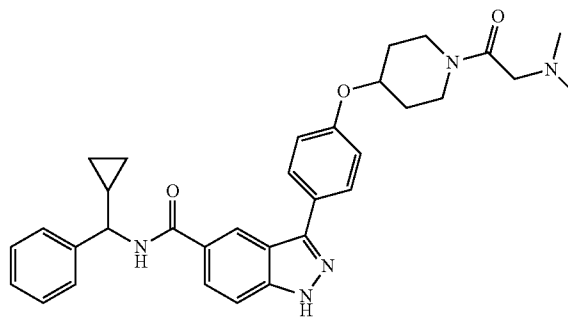


[0791] Using Method C3, (R)—N-(1-(2-fluorophenyl)ethyl)-3-iodo-1H-indazole-5-carboxamide (61 mg, 0.150 mmol) and 1-(2-methoxyethyl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine (69 mg, 0.190 mmol) gave the title compound as a TFA salt (24 mg, 31% a white solid). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.57 (s, 1H), 7.97-7.93 (m, 3H), 7.61 (d, J=8.8 Hz, 1H), 7.47-7.43 (m, 1H), 7.29-7.06 (m, 5H), 5.55-5.50 (m, 1H), 4.87 (bs, 1H), 3.77-3.70 (m, 3H), 3.54-3.22 (m, 8H), 2.45-2.28 (m, 2H), 2.17-1.97 (m, 2H), 1.60 (d, J=7.2 Hz, 3H); MS ESI 517.4 [M+H]⁺, calcd for [C₃₀H₃₃FN₄O₃+H]⁺ 517.26.

Example A130

N-(cyclopropyl(phenyl)methyl)-3-(4-((1-(2-(dimethylamino)acetyl)piperidin-4-yl)oxy)phenyl)-1H-indazole-5-carboxamide

[0792]



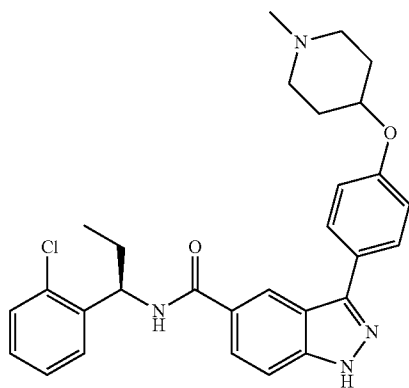
[0793] The title compound was synthesized according to Method C3 utilizing N-(cyclopropyl(phenyl)methyl)-3-iodo-1H-indazole-5-carboxamide and 2-(dimethylamino)-1-(4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidin-1-yl)ethanone and obtained as a pale yellow solid (66 mg, 56% yield). ¹H NMR (400 MHz, CD₃OD) δ ppm

8.60 (s, 1H), 7.95 (m, J=8.53 Hz, 3H), 7.61 (d, J=8.78 Hz, 1H), 7.50 (d, J=7.03 Hz, 2H), 7.35 (t, J=7.65 Hz, 2H), 7.25 (m, J=7.28 Hz, 1H), 7.16 (d, J=8.78 Hz, 2H), 4.73-4.80 (m, 1H), 4.49 (d, J=9.54 Hz, 1H), 3.74-3.92 (m, 2H), 3.67 (s, 3H), 3.47-3.55 (m, 1H), 2.58 (s, 6H), 1.96-2.14 (m, 2H), 1.76-1.93 (m, 2H), 1.37-1.47 (m, 1H), 0.64-0.70 (m, 2H), 0.44-0.53 (m, 2H); MS ESI $[M+H]^+$ 552.5, calcd for $[C_{33}H_{37}N_5O_3+H]^+$ 552.30.

Example A131

(R)—N-(1-(2-chlorophenyl)propyl)-3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazole-5-carboxamide

[0794]

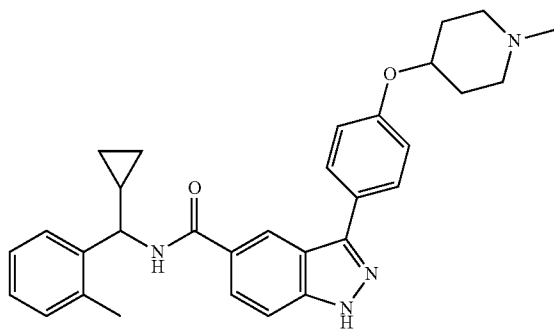


[0795] The title compound was prepared using Method C3 from (R)—N-(1-(2-chlorophenyl)propyl)-3-iodo-1H-indazole-5-carboxamide (58 mg, 0.132 mmol) and 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine (55 mg, 0.172 mmol) which gave 39 mg of product isolated as its TFA salt (59%, an orange solid). ^1H NMR (400 MHz, CD_3OD) δ ppm 8.57 (s, 1H), 7.95-7.91 (m, 3H), 7.61 (d, J=8.8 Hz, 1H), 7.55 (d, J=7.0 Hz, 1H), 7.39 (d, J=8.0 Hz, 1H), 7.30-7.14 (m, 4H), 5.47-5.43 (m, 1H), 4.87 (bs, 1H), 3.65-3.17 (m, 4H), 2.93-2.92 (m, 3H), 2.44-2.27 (m, 2H), 2.15-1.86 (m, 4H), 1.07 (t, J=7.2 Hz, 3H); MS ESI 503.5 $[M+H]^+$, calcd for $[C_{29}H_{31}ClN_4O_2+H]^+$ 503.22.

Example A132

N-(cyclopropyl(o-tolyl)methyl)-3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazole-5-carboxamide

[0796]



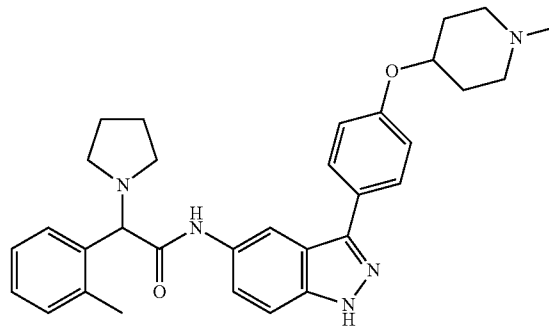
[0797] To a solution of cyclopropyl(o-tolyl)methanamine (2.82 g, 17.5 mmol), 3-iodo-1H-indazole-5-carboxamide (5.04 g, 17.5 mmol) in DMF (20 mL) at 0° C. was added TBTU (5.62 g, 17.5 mmol), followed by $^iPr_2NEt$ (6.08 mL, 35 mmol). The resulting mixture was stirred at 0° C. for 30 min, quenched with H_2O till total volume about 250 mL and stirred for 30 min at rt. Suction filtration gave crude N-(cyclopropyl(o-tolyl)methyl)-3-iodo-1H-indazole-5-carboxamide (beige solid, 7.53 g). MS ESI 432.1 $[M+H]^+$, calcd for $[C_{19}H_{18}IN_3O+H]^+$ 432.0.

[0798] To a mixture of crude N-(cyclopropyl(o-tolyl)methyl)-3-iodo-1H-indazole-5-carboxamide (190 mg, 0.44 mmol) and 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine (127 mg, 0.4 mmol) in EtOH (12 mL) was added 1 M aq Na_2CO_3 (0.8 mL, 0.8 mmol), followed by $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (33 mg, 0.04 mmol). The resulting mixture was purged with Ar and micro-waved 4 h at 125° C. It was diluted with H_2O , extracted with DCM and purified by flash chromatography (MeOH/DCM 0-100%, then 0.05 NH_3 in MeOH), biotage RP column (MeOH/ H_2O (1% TFA) 5-80%) and prep-HPLC to give the title compound as a TFA salt (white solid, 24.0 mg, 10%). ^1H NMR (400 MHz, CD_3OD) δ 8.54 (s, 1H), 7.98-7.90 (m, 3H), 7.61 (d, J=7.6 Hz, 1H; partially overlapped with the peak at 7.59), 7.59 (d, J=8.8 Hz, 1H; partially overlapped with the peak at 7.61), 7.22-7.12 (m, 5H), 4.90 (1H, buried under H_2O peak?), 4.88-4.85 (m, 0.7H; partially buried under H_2O peak), 4.71-4.62 (m, 0.3H), 3.67-3.62 (m, 0.7H), 3.47-3.34 (m, 2.6H), 3.25-3.17 (m, 0.7H), 2.95-2.94 (two s at 2.95 and 2.94, 3H), 2.47-2.38 (m, 3.7H; s, 3H at 2.42), 2.33-2.26 (m, 1.3H), 2.17-2.07 (m, 1.3H), 1.98-1.86 (0.7H), 1.52-1.42 (m, 1H), 0.71-0.64 (m, 1H), 0.63-0.56 (m, 1H), 0.55-0.46 (m, 1H), 0.40-0.33 (m, 1H); MS ESI 495.4 $[M+H]^+$, calcd for $[C_{31}H_{34}N_4O_2+H]^+$ 495.4.

Example A133

N-(3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(o-tolyl)acetamide

[0799]



[0800] To a solution of 2-(pyrrolidin-1-yl)-2-(o-tolyl)acetic acid (3.00 g, assuming 10 mmol), 3-iodo-1H-indazole-5-amine hydrochloride salt (2.94 g, 10 mmol) in DMF (40 mL) at 0° C. was added TBTU (3.21 g, 10 mmol), followed by $^iPr_2NEt$ (5.22 mL, 30 mmol). The resulting mixture was stirred at 0° C. for 2 h, quenched with H_2O (300 mL) and stirred for 30 min at rt. Suction filtration gave crude N-(3-

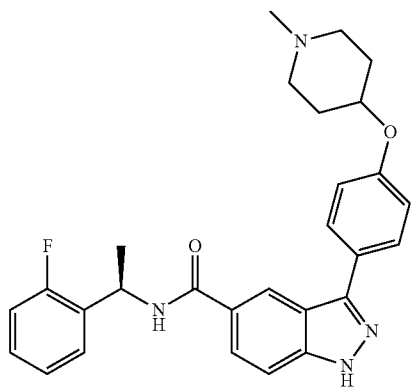
iodo-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(o-tolyl)acetamide (brown solid, 3.19 g). LC-MS indicated a mixture of desired product N-(3-iodo-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(o-tolyl)acetamide and di-acylated byproduct. MS ESI 461.1 [M+H]⁺, calcd for [C₂₀H₂₁N₄O+H]⁺ 461.1.

[0801] To a mixture of crude N-(3-iodo-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(o-tolyl)acetamide (213 mg, assuming 0.4 mmol) and 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine (127 mg, 0.4 mmol) in EtOH (12 mL) was added 1 M aq Na₂CO₃ (1.0 mL, 1.0 mmol), followed by Pd(dppf)Cl₂·CH₂Cl₂ (33 mg, 0.04 mmol). The resulting mixture was purged with Ar and micro-waved 4 h at 125° C. It was diluted with H₂O, extracted with DCM and purified by flash chromatography (MeOH/DCM 0-100%, then 0.05 NH₃ in MeOH), biotage RP column (MeOH/H₂O (1% TFA) 5-60%) and prep-HPLC to give the title compound as a TFA salt (light brown solid, 56.1 mg, 19%). ¹H NMR (400 MHz, CD₃OD) δ 8.23 (s, 1H), 7.88-7.83 (m, 2H), 7.76 (d, J=7.6 Hz, 1H), 7.54 (pseudo t, J=9.0 Hz, 2H), 7.43-7.34 (m, 3H), 7.20-7.13 (m, 2H), 5.45 (s, 1H), 4.90-4.85 (m, 0.7H), 4.72-4.64 (m, 0.3H), 3.92 (br s, 0.7H), 3.58-3.52 (m, 0.7H), 3.50-2.98 (m, 6.4H), 2.95-2.94 (two s at 2.95 and 2.94, 3H), 2.67 (s, 3H), 2.47-1.88 (m, 8H); MS ESI 524.2 [M+H]⁺, calcd for [C₃₂H₃₇N₅O₂+H]⁺ 524.3.

Example A134

(R)—N-(1-(2-fluorophenyl)ethyl)-3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazole-5-carboxamide

[0802]

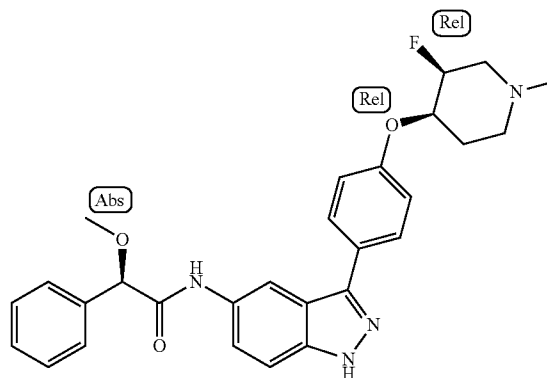


[0803] The title compound was prepared using Method C3 from (R)—N-(1-(2-fluorophenyl)ethyl)-3-iodo-1H-indazole-5-carboxamide (47 mg, 0.115 mmol) and 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine (48 mg, 0.150 mmol) which gave 23 mg of product isolated as its TFA salt (43%, a white solid). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.57 (s, 1H), 7.97-7.93 (m, 3H), 7.61 (d, J=8.8 Hz, 1H), 7.47-7.43 (m, 1H), 7.28-7.07 (m, 5H), 5.55-5.50 (m, 1H), 4.87 (bs, 1H), 3.66-3.20 (m, 4H), 2.95-2.94 (m, 3H), 2.48-2.30 (m, 2H), 2.15-1.89 (m, 2H), 1.60 (d, J=6.8 Hz, 3H); MS ESI 473.4 [M+H]⁺, calcd for [C₂₈H₂₉FN₄O₂+H]⁺ 473.24.

Example A135

(R)—N-(3-(4-(((3S,4R)-3-fluoro-1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazol-5-yl)-2-methoxy-2-phenylacetamide

[0804]

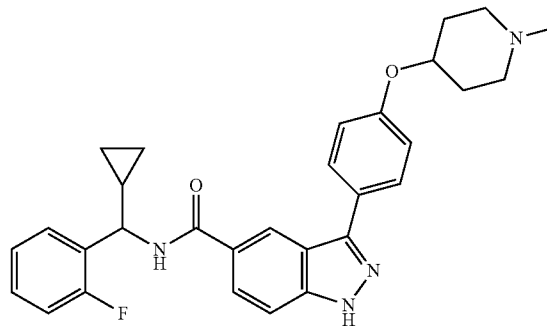


The title compound was synthesized according to the General Method C2 utilizing ((R)—N-(3-iodo-1H-indazol-5-yl)-2-methoxy-2-phenylacetamide (0.14 g, 0.34 mmol), a crude mixture of 4-((3-fluoro-1-methylpiperidin-4-yl)oxy)phenylboronic acid and diisopropyl 4-((cis-3-fluoro-1-methylpiperidin-4-yl)oxy)phenylboronate diisopropyl (0.16 g, ~0.48 mmol) to provide the title compound as a white powder (22 mg, 13%). ¹H NMR (400 MHz, acetone-d₆) δ ppm 11.82-12.49 (br.s., 1H), 9.43 (br. s., 1H), 8.63 (d, J=1.51 Hz, 1H), 7.94 (d, J=9.03 Hz, 2H), 7.74 (dd, J=8.91, 1.88 Hz, 1H), 7.51-7.59 (m, 3H), 7.30-7.44 (m, 3H), 7.16 (d, J=9.03 Hz, 2H), 4.91-4.98 (m, 0.5H), 4.85 (s, 1H), 4.80-4.83 (m, 0.5H), 4.69 (br. s., 1H), 3.47 (s, 3H), 2.94 (br. s., 1H), 2.46-2.74 (m, 2H), 2.40-2.31 (m., 1H), 2.29 (s, 3H), 1.99-2.18 (m, 1H), 1.84-1.99 (m, 1H); MS ESI 489.3 [M+H]⁺, calcd for [C₂₈H₂₉FN₄O₃+H]⁺ 489.2.

Example A136

N-(cyclopropyl(2-fluorophenyl)methyl)-3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazole-5-carboxamide

[0805]



[0806] To a 20 mL microwave vial charged with Mg powder (480 mg, 20 mmol), THF (15 mL) was added bromocyclopropane (2.42 g, 20 mmol). The resulting mixture was stirred for 30 min at rt before 2-fluorobenzonitrile (1.21 g, 10 mmol) was added. It was microwaved 20 min at 100° C., cooled to rt and added dropwise to a cold solution of NaBH₄ (760 mg, 20 mmol) in MeOH (60 mL) at 0° C. The resulting mixture was stirred for 30 min at rt, quenched with H₂O, extracted with DCM and purified by flash chromatography (MeOH/DCM 0-20%) to give cyclopropyl(2-fluorophenyl)methanamine (yellow oil, 843 mg, 51%). ¹H NMR (400 MHz, CDCl₃) δ 7.52 (dt, J=7.4 Hz, 1H), 7.31-7.24 (m, 1H), 7.18 (t, J=7.6 Hz, 1H), 7.10-7.04 (m, 1H), 3.45 (d, J=9.2 Hz, 1H), 1.25-1.16 (m, 1H), 0.67-0.60 (m, 1H), 0.49-0.37 (m, 2H), 0.29-0.22 (m, 1H); MS ESI 149.0 [M+H]⁺, calcd for [C₁₀H₁₂FN—NH₃+H]⁺ 149.1.

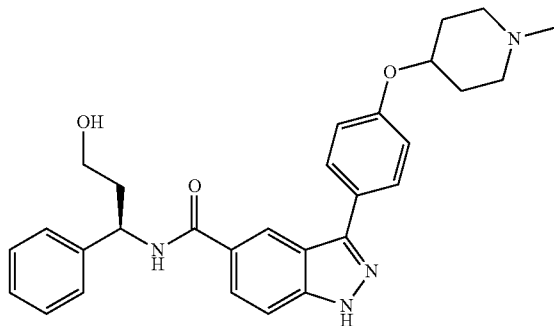
[0807] To a solution of cyclopropyl(2-fluorophenyl)methanamine (828 mg, 5.02 mmol), 3-iodo-1H-indazole-5-carboxamide (1.45 g, 5.02 mmol) in DMF (20 mL) at 0° C. was added TBTU (1.62 g, 5.02 mmol), followed by ^tPr₂NEt (1.75 mL, 10.05 mmol). The resulting mixture was stirred at 0° C. for 30 min, quenched with H₂O till total volume about 130 mL and stirred for 15 min at rt. Suction filtration gave crude N-(cyclopropyl(2-fluorophenyl)methyl)-3-iodo-1H-indazole-5-carboxamide (pale yellow solid, 2.068 g). ESI 436.1 [M+H]⁺, calcd for [C₁₈H₁₅FIN₃O+H]⁺ 436.0.

[0808] To a mixture of crude N-(cyclopropyl(2-fluorophenyl)methyl)-3-iodo-1H-indazole-5-carboxamide (218 mg, 0.5 mmol) and 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine (127 mg, 0.4 mmol) in EtOH (12 mL) was added 1 M aq Na₂CO₃ (0.8 mL, 0.8 mmol), followed by Pd(PPh₃)₄ (46 mg, 0.04 mmol). The resulting mixture was purged with Ar and microwaved 4 h at 125° C. After removal of solvents, it was purified by prep-HPLC to give the title compound as a TFA salt (off white solid, 69.4 mg, 28%). ¹H NMR (400 MHz, CD₃OD) δ 8.56 (s, 1H), 7.96-7.88 (m, 3H), 7.61-7.53 (m, 2H), 7.28-7.22 (m, 1H), 7.16-7.04 (m, 4H), 4.81-4.78 (m, 0.7H; partially overlapped with the peak at 4.76), 4.76 (d, J=9.6 Hz, 1H; partially overlapped with the peak at 4.81-4.78), 4.66-4.58 (m, 0.3H), 3.65-3.58 (m, 0.7H), 3.43-3.28 (m, 2.6H), 3.22-3.13 (m, 0.7H), 2.91 (s, 3H), 2.41-2.35 (m, 0.7H), 2.27-2.20 (m, 1.3H), 2.15-2.05 (m, 1.3H), 1.96-1.85 (m, 0.7H), 1.48-1.38 (m, 1H), 1.22-1.13 (m, 1H), 1.10-1.03 (m, 1H), 1.02-0.90 (m, 2H); MS ESI 499.4 [M+H]⁺, calcd for [C₃₀H₃₁FN₄O₂+H]⁺ 499.2.

Example A137

(R)—N-(3-hydroxy-1-phenylpropyl)-3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazole-5-carboxamide

[0809]

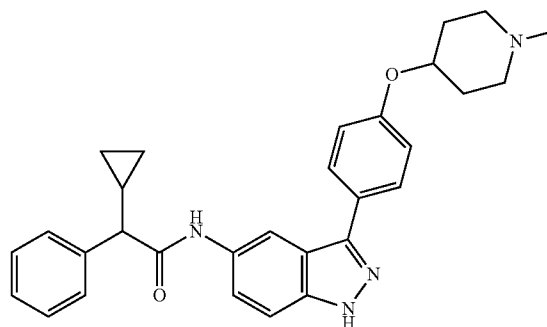


[0810] The title compound was synthesized according to the General Method C, utilizing (R)—N-(3-hydroxy-1-phenylpropyl)-3-iodo-1H-indazole-5-carboxamide (50 mg, 0.11 mmol), 4-((1-methylpiperidin-4-yl)oxy)phenyl)boronic acid pinacol ester (41 mg, 0.13 mmol), Pd(PPh₃)₄ (6.4 mg, 0.0055 mmol), satd. Na₂CO₃ (1.5 mL), and 3.5 mL of PhMe:EtOH (1:1). The vial was charged with Ar and heated in the microwave reactor at 125° C. for 2 h. Purification by RPHPLC, followed by trituration with Et₂O gave the title compound as a TFA salt (white solid, 23 mg, 35%). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.56 (s, 1H), 7.89-7.97 (m, 3H), 7.61 (d, J=9.0 Hz, 1H), 7.44 (d, J=7.0 Hz, 2H), 7.34 (t, J=7.6 Hz, 2H), 7.13-7.27 (m, 3H), 5.29-5.38 (m, 1H), 4.63-4.73 (m, 0.3H), 3.59-3.75 (m, 2.7H), 3.33-3.52 (m, 3H), 3.15-3.27 (m, 1H), 2.91-2.97 (m, 3H), 2.40-2.49 (m, 0.7H), 2.26-2.36 (m, 1.3H), 2.05-2.21 (m, 3.3H), 1.85-1.98 (m, 0.7H); MS ESI 485.4 [M+H]⁺, calcd for [C₂₉H₃₂N₄O₃+H]⁺ 485.3.

Example A138

2-cyclopropyl-N-(3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazol-5-yl)-2-phenylacetamide

[0811]

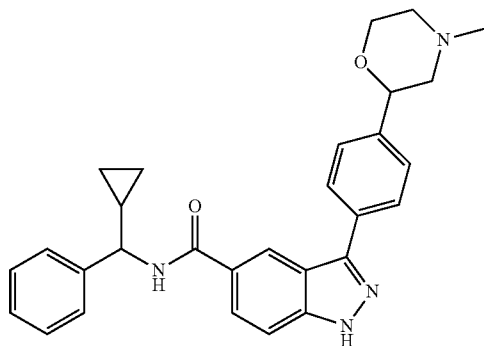


[0812] To a solution of 2-cyclopropyl-2-phenylacetic acid (20 mg, 0.113 mmol) in DMF (2 mL) was added 3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazol-5-amine trifluoroacetate (62.5 mg, 0.113 mmol), DIPEA (102 uL, 0.565 mmol) and TBTU (36 mg, 0.113 mmol). The reaction mass was stirred for 24 h at rt and concentrated under reduced pressure. Purification by flash chromatography (SiO₂, 0-40% 2 M NH₃-MeOH in DCM; then RP HPLC C18RP 60 g, 10-80% MeOH in 0.1% TFA-H₂O) followed by passing through a PoraPak column with 2 M NH₃-MeOH to elute gave the title compound (white solid, 29 mg, 51%). ¹H NMR (400 MHz, CD₃OD) δ 8.45 (d, J=1.2 Hz, 1H), 7.88-7.84 (m, 2H), 7.52-7.48 (m, 3H), 7.43-7.42 (m, 1H), 7.41-7.40 (m, 2H), 7.36-7.32 (m, 1H), 7.17-7.10 (m, 2H), 4.83 (s, 1H), 3.64 (m, 1H), 3.42-3.37 (m, 3H), 3.21-3.19 (br.m, 1H), 2.93-2.90 (m, 3H), 2.43-2.26 (m, 2H), 2.14-2.10 (m, 2H), 1.60-1.57 (br.m, 1H), 0.71-0.61 (m, 2H), 0.48-0.44 (m, 1H), 0.27-0.23 (m, 1H); MS ESI 481.4. [M+H]⁺, calcd for [C₃₀H₃₂N₄O₂+H]⁺ 481.6.

Example A139

N-(cyclopropyl(phenyl)methyl)-3-(4-(4-methylmorpholin-2-yl)phenyl)-1H-indazole-5-carboxamide

[0813]

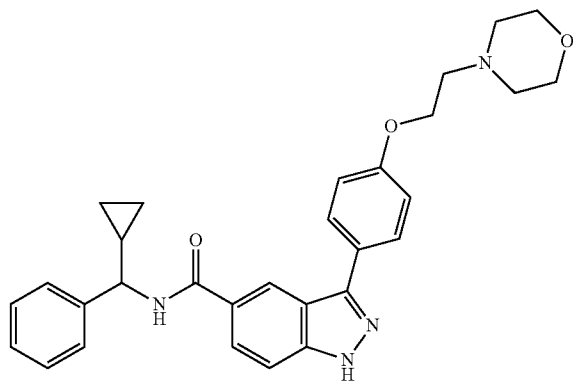


[0814] The title compound was prepared using Method C3 from N-(cyclopropyl(phenyl)methyl)-3-iodo-1H-indazole-5-carboxamide (65 mg, 0.155 mmol) and 4-methyl-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)morpholine (61 mg, 0.201 mmol) which gave 36 mg of product isolated as its TFA salt (50%, a white solid). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.61 (s, 1H), 8.06 (d, J=8.3 Hz, 2H), 7.97 (d, J=8.8 Hz, 1H), 7.64-7.59 (m, 3H), 7.48 (d, J=7.5 Hz, 2H), 7.36-7.22 (m, 3H), 4.89 (bs, 1H), 4.49 (d, J=9.6 Hz, 1H), 4.34-4.31 (m, 1H), 4.03-3.98 (m, 1H), 3.72-3.69 (m, 1H), 3.57-3.54 (m, 1H), 3.31-3.13 (m, 2H), 2.98 (s, 3H), 1.44-1.34 (m, 1H), 0.71-0.64 (m, 2H), 0.52-0.48 (m, 2H); MS ESI 467.4 [M+H]⁺, calcd for [C₂₉H₃₀N₄O₂+H]⁺ 467.24.

Example A140

N-(cyclopropyl(phenyl)methyl)-3-(4-(2-morpholinoethoxy)phenyl)-1H-indazole-5-carboxamide

[0815]



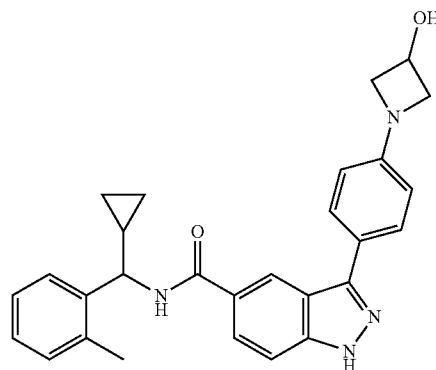
A TFA salt of the title compound was synthesized according to Method C3 utilizing N-(cyclopropyl(phenyl)methyl)-3-iodo-1H-indazole-5-carboxamide and 4-(2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)ethyl)morpholine without running through PoraPak and obtained as a white solid (56 mg, 77% yield). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.59 (s, 1H), 7.96 (d, J=8.78 Hz, 3H), 7.61 (d, J=8.78 Hz, 1H), 7.49 (d, J=7.28 Hz, 2H), 7.33 (t, J=7.53 Hz, 2H), 7.21-7.28 (m, 1H), 7.17 (d, J=8.78 Hz, 2H), 4.40-4.53 (m, 3H), 3.96-4.15 (m, 2H), 3.86 (br. s., 2H), 3.51-3.71 (m, 4H), 3.32

(br. s., 2H), 1.34-1.47 (m, 1H), 0.66 (d, J=8.03 Hz, 2H), 0.42-0.53 (m, 2H); MS ESI [M+H]⁺ 497.4, calcd for [C₃₀H₃₂N₄O₃+H]⁺ 497.26.

Example A141

N-(Cyclopropyl(o-tolyl)methyl)-3-(4-(3-hydroxyazetidin-1-yl)phenyl)-1H-indazole-5-carboxamide

[0816]

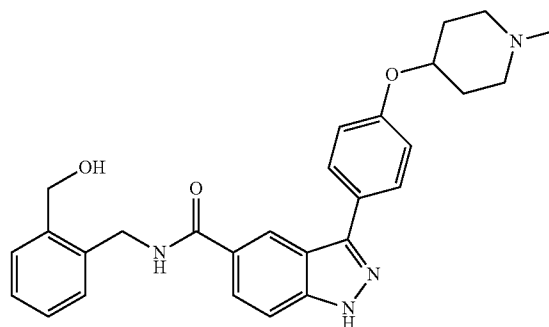


[0817] The title compound was synthesized according to Method C, utilizing N-(cyclopropyl(o-tolyl)methyl)-3-iodo-1H-indazole-5-carboxamide (142 mg, 0.33 mmol), 1-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)azetidin-3-ol (100 mg, 0.36 mmol), Pd(PPh₃)₄ (38 mg, 0.033 mmol), 2 M Na₂CO₃ (0.40 mL), PhMe (4 mL), and EtOH (2 mL). H₂O (30 mL) was added and the product was extracted into EtOAc (4×30 mL). The combined organic layers were dried over MgSO₄, filtered and evaporated in vacuo. Purification by flash chromatography (Biotage, 50 g HP-SIL, 20-100% EtOAc in hexanes) followed by RP flash chromatography (Biotage, 60 g RP HPLC C18-, 0.1% TFA-H₂O in MeOH, 10-90%) gave the title compound as a yellow solid (44 mg, 23%). The title compound was isolated as a TFA salt. ¹H NMR (400 MHz, CD₃OD) δ ppm 8.54 (s, 1H), 7.90 (dd, J=8.8, 1.5 Hz, 1H), 7.86 (d, J=8.5 Hz, 2H), 7.61 (d, J=7.6 Hz, 1H), 7.56 (d, J=8.8 Hz, 1H), 7.21-7.13 (m, 3H), 6.78 (d, J=8.5 Hz, 2H), 4.89-4.84 (m, 1H), 4.72 (quint, J=5.4 Hz, 1H), 4.30 (t, J=7.9 Hz, 2H), 7.79 (dd, J=8.7, 5.0 Hz, 2H), 2.41 (s, 3H), 1.48-1.41 (br m, 1H), 0.69-0.63 (br m, 1H), 0.61-0.54 (br m, 1H), 0.52-0.46 (br m, 1H), 0.38-0.32 (br m, 1H); MS ESI 453.2 [M+H]⁺, calcd for [C₂₈H₂₈N₄O₂+H]⁺ 453.22.

Example A142

N-(2-(hydroxymethyl)benzyl)-3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazole-5-carboxamide

[0818]

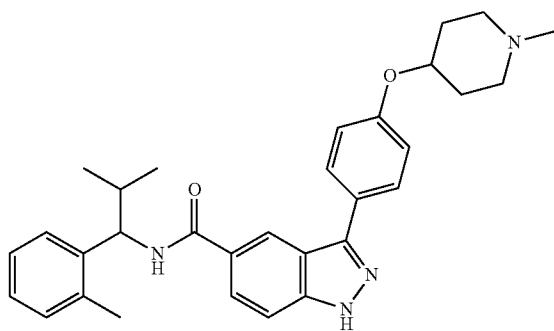


[0819] The title compound was synthesized according to the General Method A utilizing 3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazole-5-carboxylic acid (34 mg, 0.1 mmol), (2-aminomethyl-phenyl)-MeOHEtOH (14 mg, 0.1 mmol), TBTU (32 mg, 0.1 mmol), DIPEA (52 μ L, 0.3 mmol), and DMF (4 mL). Purification by RPHPLC, followed by trituration with Et₂O gave the title compound as a TFA salt (white solid, 50 mg, 86%). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.58 (s, 1H), 7.89-7.97 (m, 3H), 7.60 (d, J=8.8 Hz, 1H), 7.37-7.44 (m, 2H), 7.24-7.31 (m, 2H), 7.17 (d, J=8.8 Hz, 2H), 4.78 (s, 2H), 4.72 (s, 2H), 3.44 (br. s, 2H), 3.32 (br. s, 2H), 2.92 (s, 3H), 2.06-2.32 (m, 4H); MS ESI 471.3 [M+H]⁺, calcd for [C₂₈H₃₀N₄O₃+H]⁺ 471.2.

Example A143

N-(2-methyl-1-(o-tolyl)propyl)-3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazole-5-carboxamide

[0820]



[0821] To a 20 mL microwave vial charged with Mg powder (240 mg, 20 mmol), THF (15 mL) was added 2-bromopropane (2.46 g, 20 mmol). The resulting mixture was stirred for 30 min at rt before 2-methylbenzonitrile (1.21 g, 10 mmol) was added. It was microwaved 15 min at 100° C., cooled to rt and added dropwise to a cold solution of NaBH₄ (760 mg, 20 mmol) in MeOH (45 mL) at 0° C. The resulting mixture was stirred for 30 min at rt, quench with H₂O, extracted with DCM and purified by flash chromatography (MeOH/DCM 0-20%) to give crude 2-methyl-1-(o-tolyl)propan-1-amine (yellow oil, 167 mg). ¹H NMR (400 MHz, CDCl₃) δ 7.37 (d, J=7.6 Hz, 1H), 7.23-7.18 (m, 1H), 7.12 (d, J=4.0 Hz, 2H), 3.88 (d, J=7.6 Hz, 1H), 2.34 (s, 3H), 1.95-1.85 (m, 1H), 1.02 (d, J=6.4 Hz, 3H), 0.81 (d, J=6.8 Hz, 3H); MS ESI 147.0 [M+H]⁺, calcd for [C₁₁H₁₇N+H]⁺ 147.1.

[0822] To a solution of 3-iodo-1H-indazole-5-carboxylic acid (576 g, 2 mmol) and 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine (634 mg, 2) in DMF (9 mL) was added a solution of K₃PO₄ (1.272 g, 6 mmol) in H₂O (3 mL), followed by Pd(dppf)Cl₂-CH₂Cl₂ (82 mg, 0.1 mmol). The resulting mixture was purged with Ar and microwaved 5 h at 120° C. The DMF layer was separated, concentrated and purified by flash chromatography (MeOH/DCM 0-100% then 0.05 M NH₃ in MeOH) to give 3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazole-5-carboxylic acid (brown solid, 140 mg, 20%). ¹H NMR (400 MHz, DMSO-d₆) δ 13.4 (s, 1H), 8.60 (s, 1H), 7.96 (dd, J=8.8 Hz, 1.2 Hz, 1H), 7.87 (d, J=8.8 Hz, 2H), 7.60 (d, J=8.8 Hz, 1H), 7.13 (d, J=8.8 Hz, 2H), 4.48-4.40 (m, 1H), 2.70-2.55 (m, 2H),

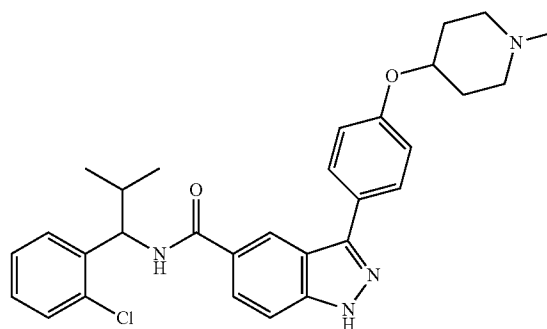
2.25-2.10 (m, 5H; s, 3H at 2.20), 2.05-1.90 (m, 2H), 1.74-1.60 (m, 2H); MS ESI 352.2 [M+H]⁺, calcd for [C₂₀H₂₁N₃O₃+H]⁺ 352.2.

[0823] To a flask charged with crude 2-methyl-1-(o-tolyl)propan-1-amine (32 mg, 0.2 mmol) and TBTU (32 mg, 0.1 mmol) was added a solution of 3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazole-5-carboxylic acid (33 mg, 0.1 mmol) in DMF (2.5 mL) followed by ^tPr₂NEt (0.05 mL, 0.3 mmol). The resulting mixture was stirred for 30 min at rt and purified by prep-HPLC and PoraPak to give the title compound (pale yellow solid, 24.2 mg, 49%). ¹H NMR (400 MHz, CD₃OD) δ 8.52 (s, 1H), 7.90-7.93 (m, 3H), 7.56 (d, J=8.8 Hz, 1H), 7.44 (d, J=7.6 Hz, 1H), 7.18-7.07 (m, 3H), 7.05 (d, J=8.8 Hz, 2H), 5.10 (d, J=10.4 Hz, 1H), 4.50-4.42 (m, 1H), 2.77-2.68 (m, 2H), 2.53 (s, 3H), 2.44-2.33 (m, 2H), 2.32 (s, 3H), 2.28-2.18 (m, 1H), 2.07-1.99 (m, 2H), 1.87-1.78 (m, 2H), 1.18 (d, J=6.4 Hz, 3H), 0.80 (d, J=6.8 Hz, 3H); MS ESI 497.4 [M+H]⁺, calcd for [C₃₁H₃₆N₄O₂+H]⁺ 497.3.

Example A144

N-(1-(2-chlorophenyl)-2-methylpropyl)-3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazole-5-carboxamide

[0824]



Method 1

A. 1-(2-chlorophenyl)-2-methylpropan-1-amine

[0825] To a 20 mL microwave vial charged with Mg powder (240 mg, 20 mmol), THF (15 mL) was added 2-bromopropane (2.46 g, 20 mmol). The resulting mixture was stirred for 30 min at rt before 2-chlorobenzonitrile (1.10 g, 8 mmol) was added. It was microwaved 15 min at 100° C., cooled to rt and added dropwise to a cold solution of NaBH₄ (760 mg, 20 mmol) in MeOH (45 mL) at 0° C. The resulting mixture was stirred for 20 min at rt, quench with H₂O, extracted with DCM and purified by flash chromatography (MeOH/DCM 0-20%) to give crude 1-(2-chlorophenyl)-2-methylpropan-1-amine (brown oil, 543 mg). ¹H NMR (400 MHz, CDCl₃) δ 7.48 (dd, J=7.6 Hz, 1.6 Hz, 1H), 7.38 (dd, J=8.0 Hz, 1.2 Hz, 1H), 7.33 (dt, J=7.6 Hz, 1.2 Hz, 1H), 7.23 (dt, J=7.6 Hz, 1.4 Hz, 1H), 4.13 (d, J=7.2 Hz, 1H), 2.03-1.95 (m, 1H), 1.02 (d, J=6.4 Hz, 3H), 0.83 (d, J=6.8 Hz, 3H); MS ESI 166.9 [M+H]⁺, calcd for [C₁₀H₁₄ClN+H]⁺ 167.1.

B. N-(1-(2-chlorophenyl)-2-methylpropyl)-3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazole-5-carboxamide

[0826] To a flask charged with crude 1-(2-chlorophenyl)-2-methylpropan-1-amine (36 mg, 0.2 mmol) and TBTU (32 mg, 0.1 mmol) was added a solution of 3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazole-5-carboxylic acid (33 mg, 0.1 mmol) in DMF (2.5 mL) followed by i Pr₂NEt (0.05 mL, 0.3 mmol). The resulting mixture was stirred for 30 min at rt and purified by prep-HPLC to give the title compound as a TFA salt (light brown solid, 36.8 mg, 58%). ¹H NMR (400 MHz, CD₃OD) δ 8.85 (d, J=8.0 Hz, 0.2H, NH), 8.52 (s, 1H), 7.93-7.87 (m, 3H), 7.59 (d, J=8.8 Hz, 1H), 7.55 (dd, J=7.8 Hz, 1.4 Hz, 1H), 7.39 (dd, J=8.0 Hz, 1.2 Hz, 1H), 7.30 (dd, J=7.6 Hz, 1.2 Hz, 1H), 7.22 (dt, J=7.6 Hz, 1.6 Hz, 1H), 7.19-7.12 (m, 2H), 5.38 (d, J=9.6 Hz, 1H), 4.87-4.82 (m, 0.7H), 4.70-4.62 (m, 0.3H), 3.67-3.62 (m, 0.7H), 3.46-3.33 (m, 2.6H), 3.25-3.17 (m, 0.7H), 2.94-2.93 (two s at 2.94 and 2.93, 3H), 2.47-2.38 (m, 0.7H), 2.33-2.24 (m, 2.3H), 2.18-2.07 (m, 1.3H), 1.98-1.87 (m, 0.7H), 1.17 (d, J=6.8 Hz, 3H), 0.87 (d, J=6.8 Hz, 3H); MS ESI 517.5 [M+H]⁺, calcd for [C₃₀H₃₃ClN₄O₂+H]⁺ 517.2.

Method 2

[0827] The title compound was synthesized according to general Method C2 using N-(1-(2-chlorophenyl)-2-methylpropyl)-3-iodo-1H-indazol-5-carboxamide (400 mg, 0.88 mmol) and 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine (280 mg, 0.88 mmol) with PdCl₂dppf (68 mg, 0.083 mmol) and 1 M aq Na₂CO₃ (1.76 mL, 1.76 mmol) in PhMe/EtOH (13 mL, 1:1 mixture) with heating under microwave irradiation at 125° C. for 3.5 h. The product was extracted with EtOAc (50 mL), washed with H₂O (15 mL) and brine (15 mL), dried (Na₂SO₄) and concentrated under vacuum. Purification by flash chromatography (SiO₂, 0-50% 1 M NH₃-MeOH in DCM; then RP HPLC C18 120 g, 10-80% MeOH 0.1% TFA-H₂O) gave the title compound as a TFA salt (light brown solid, 231 mg, 41.6%). ¹H NMR and MS ESI were identical to that obtained in Method 1.

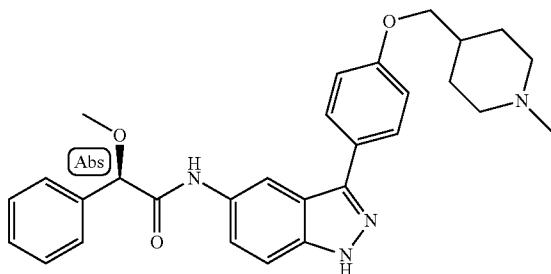
Example A144

Intentionally Omitted

Example A145

(R)-2-methoxy-N-(3-(4-((1-methylpiperidin-4-yl)methoxy)phenyl)-1H-indazol-5-yl)-2-phenylacetamide

[0828]



[0829] A. 4-((4-iodophenoxy)methyl)-1-methylpiperidine was synthesized according to General Method H utilizing 1-fluoro-4-iodobenzene (0.70 g, 3.1 mmol), ((1-methylpiperidin-4-yl)methanol (0.41 g, 3.1 mmol) and NaH (60% in oil, 0.15 g, 3.7 mmol (3.7) in DMF (10 mL) as a light orange solid (0.82 g, 79%). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.53 (d, J=7.50 Hz, 2H), 6.65 (d, J=7.50 Hz, 2H), 3.75 (d, J=6.27 Hz, 2H), 2.88 (d, J=11.54 Hz, 2H), 2.28 (s, 3H), 1.95 (td, J=11.80, 2.26 Hz, 2H), 1.69-1.86 (m, 3H), 1.33-1.47 (m, 2H); MS ESI [M+H]⁺ 332.0, calcd for [C₁₃H₁₈INO+H]⁺ 332.0.

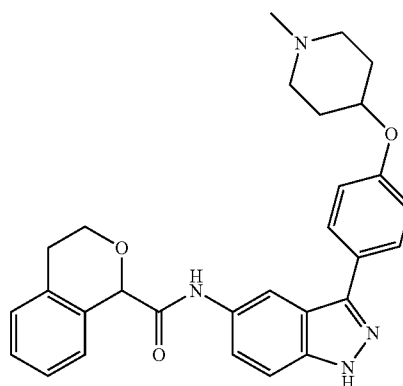
[0830] B. A stirred solution of 4-((4-iodophenoxy)methyl)-1-methylpiperidine (0.40 g, 1.2 mmol) in anhyd THF (10 mL) under Ar was treated with n-BuLi (1.6 M in hexanes, 1.5 mL, 2.4 mmol) dropwise at 78° C. After 20 min of stirring at the temperature, B(Oi-Pr)₃ (2.8 mL, 12.0 mmol) was added rapidly. After additional 1 h at the temperature, the reaction was removed from the cooling bath and stirred for 1 h at rt before it was concentrated under reduced pressure to afford a crude mixture of the title compound and 4-((1-methylpiperidin-4-yl)methoxy)phenylboronic acid as a light orange solid (1.0 g) that was used without further purification. MS ESI 250.0 [M+H]⁺, calcd for [C₁₃H₂₀BNO₃+H]⁺ 250.1.

[0831] C. (R)-2-methoxy-N-(3-(4-((1-methylpiperidin-4-yl)methoxy)phenyl)-1H-indazol-5-yl)-2-phenylacetamide was synthesized according to the General Method C2 utilizing ((R)-N-(3-iodo-1H-indazol-5-yl)-2-methoxy-2-phenylacetamide (0.14 g, 0.34 mmol), a crude mixture of diisopropyl 4-((1-methylpiperidin-4-yl)methoxy)phenyl boronate (0.33 g, ~0.4 mmol) to provide the title compound as a TFA salt: a white powder (30 mg, 25%). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.39 (s, 1H), 7.84 (d, J=8.78 Hz, 2H), 7.49-7.58 (m, 4H), 7.30-7.45 (m, 3H), 7.07 (d, J=8.78 Hz, 2H), 4.84 (s, 1H), 3.98 (d, J=5.27 Hz, 2H), 3.63-3.53 (m, 2H), 3.47 (s, 3H), 3.11-3.01 (br. m., 2H), 2.89 (s, 3H), 2.20-2.09 (m, 3H), 1.76-1.61 (br. m., 2H); MS ESI 485.3 [M+H]⁺, calcd for [C₂₉H₃₂N₄O₃+H]⁺ 485.2.

Example A146

N-(3-(4-(1-Methylpiperidin-4-yloxy)phenyl)-1H-indazol-5-yl)isochroman-1-carboxamide

[0832]



A. Isochroman-1-carboxylic acid

[0833] A mixture of 2-phenylEtOH (4 mL, 33 mmol) and glyoxylic acid hydrate (3.4 g, 37 mmol) in TFA (15 mL) was heated in a microwave reactor at 120° C. for 16 h. The solvent was removed in vacuo. The residue was then dissolved in H₂O and aq NH₄OH was added until the pH of the solution was over 7. The aq layer was washed with EtOAc (3×40 mL). 2 M HCl was added to the aq layer until the pH of the solution was less than 3. The product was extracted into EtOAc (4×40 mL). The combined organic layers were dried over MgSO₄, filtered and evaporated in vacuo. Trituration with hexanes provided the title compound as a yellow solid (4.4 g, 74%). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.56-7.54 (m, 2H), 7.27-7.22 (m, 2H), 7.17-7.15 (m, 1H), 5.39 (s, 1H), 4.34-4.28 (m, 1H), 4.05-3.99 (m, 1H), 2.98-2.84 (m, 2H); MS ESI 178.9 [M+H]⁺, calcd for [C₁₀H₁₀O₃+H]⁺ 179.06.

B. N-(3-Iodo-1-(isochroman-1-carbonyl)-1H-indazol-5-yl)isochroman-1-carboxamide

[0834] The title compound was synthesized according to Method A, utilizing 3-iodo-1H-indazol-5-amine (400 mg, 1.5 mmol), isochroman-1-carboxylic acid (300 mg, 1.7 mmol), TBTU (545 mg, 1.7 mmol), DIPEA (1.1 mL, 6.2 mmol), and DMF (8 mL). H₂O (20 mL) was added and the precipitate was collected, rinsing with H₂O (10 mL×3). Purification by flash chromatography (Biotage, 25 g HP-SIL, 10-50% EtOAc in hexanes) gave the title compound as a light yellow solid (270 mg, 30%). ¹H NMR (400 MHz, CDCl₃) δ ppm 8.71 (s, 1H), 8.33 (d, J=8.9 Hz, 1H), 8.09 (dd, J=4.4, 1.9 Hz, 1H), 7.85-7.82 (m, 1H), 7.62-7.58 (m, 1H), 7.29-7.08 (m, 5H), 6.78 (s, 1H), 5.38 (s, 1H), 4.54-4.49 (m, 1H), 4.37-4.33 (m, 1H), 4.11-4.05 (m, 1H), 4.01-3.95 (m, 1H), 3.19-3.13 (m, 1H), 3.01-2.95 (m, 2H), 2.83-2.78 (m, 1H); MS ESI 580.1 [M+H]⁺, calcd for [C₂₇H₂₂IN₃O₄+H]⁺ 580.07.

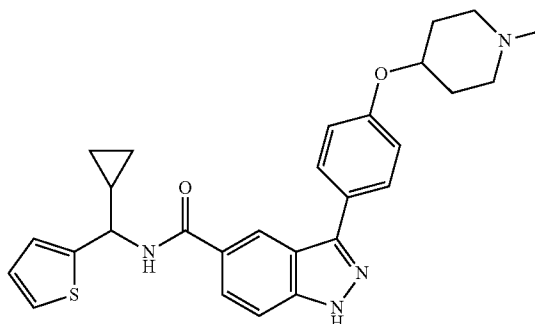
C. N-(3-(4-(1-methylpiperidin-4-yloxy)phenyl)-1H-indazol-5-yl)isochroman-1-carboxamide

[0835] The title compound was synthesized according to Method C, utilizing N-(3-iodo-1-(isochroman-1-carbonyl)-1H-indazol-5-yl)isochroman-1-carboxamide (120 mg, 0.21 mmol), 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine (72 mg, 0.23 mmol), Pd(PPh₃)₄ (24 mg, 0.021 mmol), 2 M Na₂CO₃ (0.4 mL), PhMe (4 mL), and EtOH (2 mL). H₂O (30 mL) was added and the product was extracted into EtOAc (4×30 mL). The combined organic layers were dried over MgSO₄, filtered and evaporated in vacuo. Purification by flash chromatography (Biotage, 25 g HP-SIL, 100% EtOAc, then 2-10% MeOH in DCM) followed by RPHPLC gave the title compound as a TFA salt. The salt was then dissolved in MeOH (20 mL) and poured into a preconditioned 20 mL PoraPak Rxn Cx cartridge. The MeOHEtOH (30 mL) rinse was discarded and the product was eluted with 2 M NH₃ in MeOHEtOH (30 mL). The solvent was removed in vacuo to afford the title compound as a white solid (32 mg, 32%). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.34 (s, 1H), 7.81 (d, J=8.6 Hz, 2H), 7.55-7.48 (m, 3H), 7.23-7.15 (m, 3H), 7.03 (d, J=8.6 Hz, 2H), 5.33 (s, 1H), 4.50-4.40 (m, 1H), 4.33-4.28 (m, 1H), 3.94-3.88 (m, 1H), 3.17-3.09 (m, 1H), 2.78-2.70 (m, 3H), 2.40-2.29 (m, 1H), 2.10-1.90 (m, 2H), 1.85-1.75 (m, 2H); MS ESI 483.4 [M+H]⁺, calcd for [C₂₉H₃₀N₄O₃+H]⁺ 483.23.

Example A147

N-(cyclopropyl(thiophen-2-yl)methyl-3-(4-((methyl)-3-(4-((1-methylpiperidin-4-yl)oxy)phen)-1H-indazole-5-carboxamide

[0836]



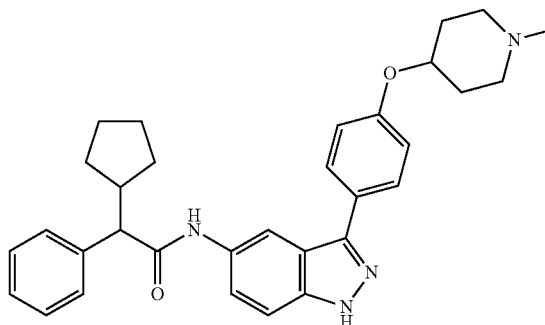
[0837] A mixture of cyclopropyl(thiophen-2-yl)methanone (3.04 g, 10 mmol), NH₄OAc (18.48 g, 240 mmol) and NaCNBH₃ (5.04 g, 80 mmol) in MeOH (60 mL) was heated at 65° C. O/N. After removal of solvent, it was purified by flash chromatography (MeOH/DCM 0-20%) to give cyclopropyl(thiophen-2-yl)methanamine (colorless oil, 876 mg, 42%). ¹H NMR (400 MHz, CD₃Cl₃) δ 7.33 (dd, J=5.2 Hz, 1H), 7.20 (d, J=7.6 Hz, 1H), 7.04 (dd, J=5.2 Hz, 3.8 Hz, 1H), 3.78 (d, J=10.0 Hz, 1H), 1.50-1.38 (m, 1H), 0.90-0.75 (m, 2H), 0.67-0.60 (m, 1H), 0.52-0.43 (m, 1H); MS ESI 137.0 [M+H]⁺, calcd for [C₈H₁₁NS—NH₃+H]⁺ 137.0.

[0838] To a flask charged with crude cyclopropyl(thiophen-2-yl)methanamine (30 mg, 0.2 mmol) and TBTU (32 mg, 0.1 mmol) was added a solution of 3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazole-5-carboxylic acid (33 mg, 0.1 mmol) in DMF (2.5 mL) followed by ^tPr₃NEt (0.05 mL, 0.3 mmol). The resulting mixture was stirred for 30 min at rt and purified by prep-HPLC, PoraPak, flash chromatography (MeOH/CM 0-100%, then 0.05 M NH₃ in MeOH) and prep-HPLC to give the title compound as a TFA salt (white solid, 7.9 mg, 13%). ¹H NMR (400 MHz, CD₃OD) δ 8.61 (s, 1H), 8.00-7.94 (m, 3H), 7.63 (d, J=8.8 Hz, 1H), 7.29 (d, J=5.2 Hz, 1H), 7.23-7.13 (m, 3H), 6.98 (t, J=4.2 Hz, 1H), 4.85-4.65 (m, 2H; 1H, J=5.6 Hz at 4.77), 3.68-3.18 (m, 4H), 2.95-2.94 (two s at 2.95 and 2.94, 3H), 2.49-2.28 (m, 2H), 2.18-1.87 (m, 2H), 1.57-1.47 (m, 1H), 0.82-0.75 (m, 1H), 0.71-0.62 (m, 1H), 0.60-0.50 (m, 2H); MS ESI 487.4 [M+H]⁺, calcd for [C₂₈H₃₀N₄O₂S+H]⁺ 487.2.

Example A148

2-cyclopentyl-N-(3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazol-5-yl)-2-phenylacetamide

[0839]



[0840] To a mixture of 2-cyclopentyl-2-phenylacetic acid (1.02 g, 5 mmol), 3-iodo-1H-indazol-5-amine (1.30 g, 5 mmol) in DMF (10 mL) at 0° C. was added TBTU (1.61 g, 5 mmol), followed by ^tPr₂NEt (1.74 mL, 10 mmol). The resulting mixture was stirred at rt for 2 h, quenched with H₂O, extracted with EtOAc and purified by flash chromatography (EtOAc:hex 0-100%) to give N-(cyclopentyl(phenyl)methyl)-3-iodo-1H-indazole-5-carboxamide (light brown solid, 422 mg, 19%). ¹H NMR (400 MHz, DMSO-d₆) δ 13.40 (s, 1H), 7.92 (s, 1H), 7.47-7.41 (m, 4H), 7.32 (t, J=7.4 Hz, 2H), 7.24 (d, J=8.0 Hz, 1H), 2.70-2.50 (m, 1H), 1.90-0.95 (m, 8H).

[0841] To a mixture of N-(cyclopentyl(phenyl)methyl)-3-iodo-1H-indazole-5-carboxamide (214 mg, 0.5 mmol) and 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine (127 mg, 0.4 mmol) in EtOH (12 mL) was added 1 M aq Na₂CO₃ (0.8 mL, 0.8 mmol), followed by Pd(PPh₃)₄ (46 mg, 0.04 mmol). The resulting mixture was purged with Ar and microwaved 4 h at 125° C. After removal of solvents, it was purified by prep-HPLC and PoraPak to give the title compound (light brown solid, 60.2 mg, 30%). ¹H NMR (400 MHz, CD₃OD) δ 8.38 (s, 1H), 7.76 (d, J=8.8 Hz, 2H), 7.48-7.45 (m, 4H), 7.27 (t, J=7.4 Hz, 2H), 7.20 (d, J=7.2 Hz, 1H), 6.95 (d, J=8.8 Hz, 2H), 4.38-4.31 (m, 1H), 3.39 (d, J=7.2 Hz, 1H), 2.78-2.60 (m, 3H), 2.36-2.23 (m, 5H; s, 3H at 2.26), 2.00-1.90 (m, 3H), 1.81-1.32 (m, 8H), 1.10-1.00 (m, 1H); MS ESI 509.5 [M+H]⁺, calcd for [C₃₂H₃₆N₄O₂+H]⁺ 509.3.

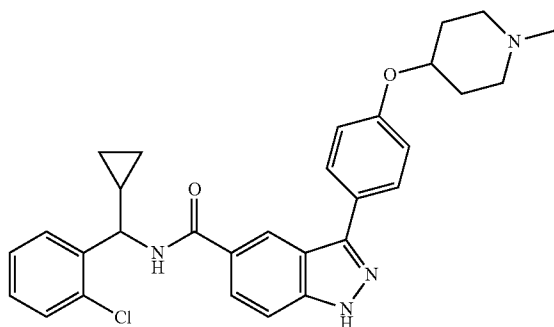
Example A149

Intentionally Omitted

Example A150

N-((2-chlorophenyl)(cyclopropyl)methyl)-3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazole-5-carboxamide

[0842]



[0843] To a 20 mL microwave vial charged with Mg powder (480 mg, 20 mmol), THF (15 mL) was added bromocyclopropane (2.42 g, 20 mmol). The resulting mixture was stirred for 30 min at rt before 2-chlorobenzonitrile (1.10 g, 8 mmol) was added. It was microwaved 15 min at 100° C., cooled to rt and added dropwise to a cold solution of NaBH₄ (760 mg, 20 mmol) in MeOH (45 mL) at 0° C. The resulting mixture was stirred for 20 min at rt, quenched with H₂O, extracted with DCM and purified by flash chromatography (MeOH/DCM 0-20%) to give cyclopropyl(2-chlorophenyl)methanamine (light orange oil, 1.12 g, 77%). ¹H NMR (400 MHz, CD₃OD) δ 7.62 (dd, J=8.0 Hz, 1.6 Hz, 1H), 7.37 (dd, J=8.0 Hz, 1.2 Hz, 1H), 7.33 (dt, J=7.6 Hz, 1.2 Hz, 1H), 7.23

(dd, J=7.6 Hz, 1.6 Hz, 1H), 3.74 (d, J=8.8 Hz, 1H), 1.28-1.19 (m, 1H), 0.67-0.60 (m, 1H), 0.48-0.35 (m, 2H), 0.32-0.26 (m, 1H); MS ESI 164.9 [M+H]⁺, calcd for [C₁₀H₁₂ClN—NH₃+H]⁺ 165.0.

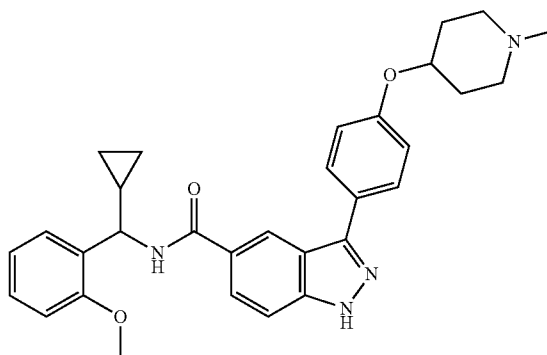
[0844] To a solution of cyclopropyl(2-chlorophenyl)methanamine (1.12 g, 6.17 mmol), 3-iodo-1H-indazole-5-carboxamide (1.68 g, 5.85 mmol) in DMF (30 mL) was added TBTU (1.88 g, 5.85 mmol), followed by ^tPr₂NEt (2.03 mL, 11.7 mmol). The resulting mixture was stirred at rt for 30 min, quenched with H₂O and stirred for 30 min at rt. Suction filtration gave crude N-((2-chlorophenyl)(cyclopropyl)methyl)-3-iodo-1H-indazole-5-carboxamide (pale yellow solid, 2.582 g). MS ESI 452.2 [M+H]⁺, calcd for [C₁₈H₁₅ClN₃O+H]⁺ 452.0.

[0845] To a mixture of crude N-((2-chlorophenyl)(cyclopropyl)methyl)-3-iodo-1H-indazole-5-carboxamide (226 mg, 0.5 mmol) and 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine (127 mg, 0.4 mmol) in EtOH (10 mL) was added 1 M aq Na₂CO₃ (1 mL, 1 mmol), followed by Pd(PPh₃)₄ (46 mg, 0.04 mmol). The resulting mixture was purged with Ar and microwaved 4 h at 125° C. After removal of solvents, it was purified by prep-HPLC and PoraPak to give the title compound (white solid, 59.0 mg, 29%). ¹H NMR (400 MHz, CD₃OD) δ 8.58 (s, 1H), 7.92 (dd, J=9.0 Hz, 1.4 Hz, 1H), 7.84 (d, J=8.4 Hz, 2H), 7.63 (dd, J=7.8 Hz, 1.4 Hz, 1H), 7.55 (d, J=8.8 Hz, 1H), 7.32 (dd, J=8.0 Hz, 0.8 Hz, 1H), 7.23 (t, J=7.6 Hz, 1H), 7.16 (dt, J=7.6 Hz, 1.6 Hz, 1H), 6.99 (d, J=8.8 Hz, 2H), 4.99 (d, J=8.8 Hz, 1H), 4.40-4.30 (m, 1H), 2.71-2.62 (m, 2H), 2.37-2.25 (m, 5H; s, 3H at 2.27), 2.02-1.93 (m, 2H), 1.83-1.73 (m, 2H), 1.45-1.35 (m, 1H), 0.67-0.60 (m, 1H), 0.55-0.45 (m, 3H); MS ESI 515.4 [M+H]⁺, calcd for [C₃₀H₃₁ClN₄O₂+H]⁺ 515.2.

Example A151

N-(cyclopropyl(2-methoxyphenyl)methyl)-3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazole-5-carboxamide

[0846]



[0847] To a 20 mL microwave vial charged with Mg powder (480 mg, 20 mmol), THF (15 mL) was added bromocyclopropane (2.42 g, 20 mmol). The resulting mixture was stirred for 30 min at rt before 2-methoxybenzonitrile (1.064 g, 8 mmol) was added. It was microwaved 15 min at 100° C., cooled to rt and added dropwise to a cold solution of NaBH₄ (760 mg, 20 mmol) in MeOH (45 mL) at 0° C. The resulting mixture was stirred for 20 min at rt, quenched with H₂O, extracted with DCM and purified by flash chromatography (MeOH/DCM 0-20%) to give cyclopropyl(2-methoxyphenyl)methanamine (light orange oil which partially solidified

upon standing, 933 mg, 77%). ¹H NMR (400 MHz, CD₃OD) δ 7.36 (dd, J=7.4 Hz, 1.4 Hz, 1H), 7.25 (dt, J=7.4 Hz, 1.6 Hz, 1H), 6.98 (d, J=8.4 Hz, 1H), 6.94 (dt, J=7.4 Hz, 1.0 Hz, 1H), 3.86 (s, 3H), 3.76 (d, J=9.2 Hz, 1H), 1.34-1.24 (m, 1H), 0.66-0.59 (m, 1H), 0.49-0.41 (m, 1H), 0.40-0.33 (m, 1H), 0.23-0.16 (m, 1H); MS ESI 161.0 [M+H]⁺, calcd for [C₁₁H₁₅NO—NH₃+H]⁺ 161.1.

[0848] To a solution of cyclopropyl(2-methoxyphenyl)methanamine (933 mg, 5.27 mmol), 3-iodo-1H-indazole-5-carboxamide (1.44 g, 5 mmol) in DMF (25 mL) was added TBTU (1.61 g, 5 mmol), followed by ^tPr₂NEt (2.03 mL, 11.7 mmol). The resulting mixture was stirred at rt for 30 min, quenched with H₂O and stirred for 30 min at rt. Suction filtration gave crude N-(cyclopropyl(2-methoxyphenyl)methyl)-3-iodo-1H-indazole-5-carboxamide (off white solid, 2.068 g). MS ESI 448.1 [M+H]⁺, calcd for [C₁₉H₂₁N₃O₃+H]⁺ 448.0.

[0849] To a mixture of crude N-(cyclopropyl(2-methoxyphenyl)methyl)-3-iodo-1H-indazole-5-carboxamide (224 mg, 0.5 mmol) and 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine (127 mg, 0.4 mmol) in EtOH (10 mL) was added 1 M aq Na₂CO₃ (1 mL, 1 mmol), followed by Pd(PPh₃)₄ (46 mg, 0.04 mmol). The resulting mixture was purged with Ar and microwaved 4 h at 125° C. After removal of solvents, it was purified by prep-HPLC and PoraPak to give the title compound (white solid, 53.7 mg, 26%). ¹H NMR (400 MHz, CD₃OD) δ 8.55 (s, 1H), 7.90 (dd, J=8.8 Hz, 1.6 Hz, 1H), 7.86 (d, J=8.8 Hz, 2H), 7.56 (d, J=8.8 Hz, 1H), 7.40 (dd, J=7.6 Hz, 1.6 Hz, 1H), 7.19 (dt, J=7.8 Hz, 1.6 Hz, 1H), 7.02 (d, J=8.8 Hz, 2H), 6.94 (d, J=8.8 Hz, 1H), 6.89 (t, J=7.4 Hz, 1H), 4.83 (d, J=9.2 Hz, 1H), 4.43-4.35 (m, 1H), 3.84 (s, 3H), 2.73-2.64 (m, 2H), 2.37-2.25 (m, 5H; s, 3H at 2.27), 2.03-1.94 (m, 2H), 1.85-1.74 (m, 2H), 1.49-1.39 (m, 1H), 0.62-0.52 (m, 1H), 0.50-0.38 (m, 3H); MS ESI 511.4 [M+H]⁺, calcd for [C₃₁H₃₄N₄O₃+H]⁺ 511.3.

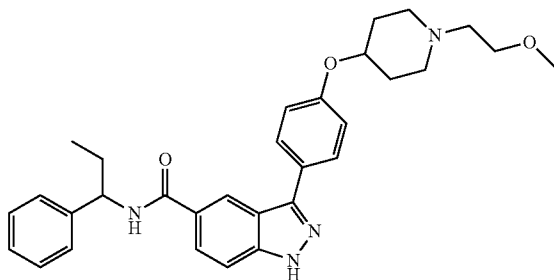
Example A152

Intentionally Omitted

Example A153

3-(4-((1-(2-methoxyethyl)piperidin-4-yl)oxy)phenyl)-N-(1-phenylpropyl)-1H-indazole-5-carboxamide

[0850]



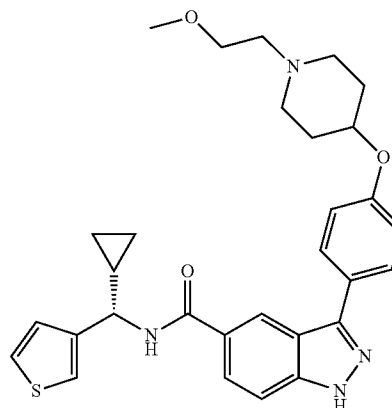
[0851] The title compound was synthesized according to Method C3 utilizing 3-iodo-N-(1-phenylpropyl)-1H-indazole-5-carboxamide and 1-(2-methoxyethyl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine and obtained as a yellow solid (30 mg, 32% yield). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.58 (s, 1H), 7.94 (dd, J=8.78, 1.51 Hz, 1H), 7.90 (d, J=8.53 Hz, 2H), 7.59 (d, J=8.78 Hz,

1H), 7.41 (d, J=7.53 Hz, 2H), 7.32 (t, J=7.53 Hz, 2H), 7.19-7.25 (m, 1H), 7.10 (d, J=8.78 Hz, 2H), 5.03 (t, J=7.53 Hz, 1H), 4.58 (br. s., 1H), 3.62 (t, J=5.40 Hz, 2H), 3.38 (s, 3H), 3.08 (t, J=8.16 Hz, 2H), 2.92 (t, J=5.02 Hz, 2H), 2.82 (br. s., 2H), 2.05-2.16 (m, 2H), 1.85-2.04 (m, 4H), 1.00 (t, J=7.28 Hz, 3H); MS ESI [M+H]⁺ 513.5, calcd for [C₃₁H₃₆N₄O₃+H]⁺ 513.29.

Example A154

(S)—N-(cyclopropyl(thiophen-3-yl)methyl)-3-(4-((1-(2-methoxyethyl)piperidin-4-yl)oxy)phenyl)-1H-indazole-5-carboxamide

[0852]

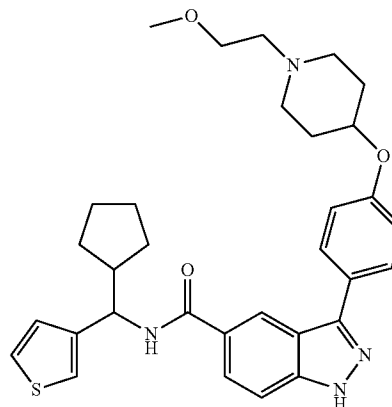


[0853] The title compound was prepared using Method C3 from (S)—N-(cyclopropyl(thiophen-3-yl)methyl)-3-iodo-1H-indazole-5-carboxamide (60 mg, 0.142 mmol) and 1-(2-methoxyethyl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine (67 mg, 0.185 mmol) which gave 48 mg of product isolated as its TFA salt (64%, a pale-yellow solid). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.58 (s, 1H), 7.98-7.94 (m, 3H), 7.61 (d, J=8.7 Hz, 1H), 7.38-7.36 (m, 2H), 7.22-7.16 (m, 3H), 4.87 (bs, 1H), 4.61 (d, J=9.6 Hz, 1H), 3.76-3.22 (m, 11H), 2.46-2.29 (m, 2H), 2.20-1.97 (m, 2H), 1.48-1.43 (m, 1H), 0.76-0.64 (m, 2H), 0.55-0.47 (m, 2H); MS ESI 531.4 [M+H]⁺, calcd for [C₃₀H₃₄N₄O₃S+H]⁺ 531.24.

Example A155

N-(cyclopentyl(thiophen-3-yl)methyl)-3-(4-((1-(2-methoxyethyl)piperidin-4-yl)oxy)phenyl)-1H-indazole-5-carboxamide

[0854]

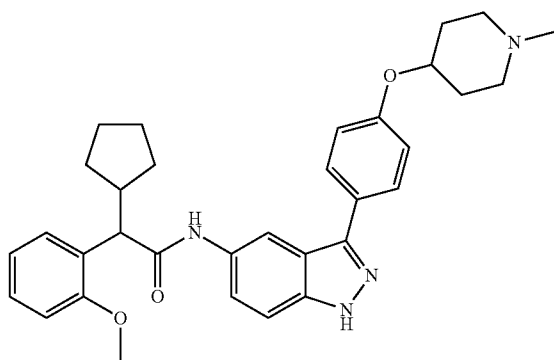


[0855] The title compound was prepared using Method C3 from N-(cyclopentyl(thiophen-3-yl)methyl)-3-iodo-1H-indazole-5-carboxamide (75 mg, 0.166 mmol) and 1-(2-methoxyethyl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine (78 mg, 0.216 mmol) which gave 34 mg of product isolated as its TFA salt (37%, a pale-yellow solid). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.51 (s, 1H), 7.95-7.88 (m, 3H), 7.60 (d, J=8.8 Hz, 1H), 7.37-7.32 (m, 2H), 7.22-7.15 (m, 3H), 5.05 (d, J=10.4 Hz, 1H), 4.87 (bs, 1H), 3.77-3.19 (m, 11H), 2.59-1.92 (m, 6H), 1.69-1.23 (m, 7H); MS ESI 559.4 [M+H]⁺, calcd for [C₃₂H₃₈N₄O₃S+H]⁺ 559.27.

Example A156

2-cyclopentyl-2-(2-methoxyphenyl)-N-(3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazol-5-yl)acetamide

[0856]

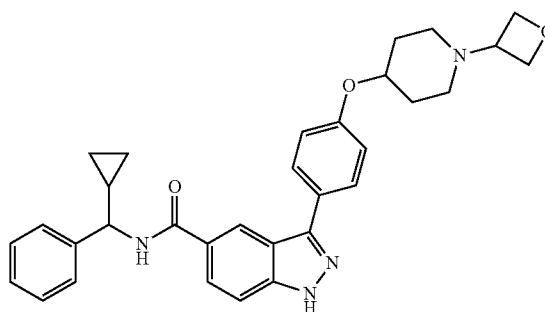


[0857] The title compound was synthesized according to the General Method C, utilizing 2-cyclopentyl-N-(3-iodo-1H-indazol-5-yl)-2-(2-methoxyphenyl)acetamide (50 mg, 0.10 mmol), (4-((1-methylpiperidin-4-yl)oxy)phenyl)boronic acid pinacol ester (33 mg, 0.1 mmol), Pd(PPh₃)₄ (6 mg, 0.005 mmol), satd. Na₂CO₃ (1.25 mL), and 3.75 mL of PhMe:EtOH (1:1). The vial was charged with Ar and heated in the microwave reactor at 125° C. for 2 h. Purification by RPHPLC, followed by trituration with Et₂O gave the title compound as a TFA salt (a beige solid, 16 mg, 25%). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.40 (s, 1H), 7.81-7.89 (m, 2H), 7.55 (dd, J=7.8, 1.5 Hz, 1H), 7.49 (d, J=9.3, 1H), 7.38 (dd, J=8.9, 1.9 Hz, 1H), 7.08-7.25 (m, 3H), 6.91-7.00 (m, 2H), 4.57-4.69 (m, 0.3H), 4.01 (d, J=11.0 Hz, 1H), 3.89 (s, 3H), 3.57-3.65 (m, 0.7H), 3.32-3.47 (m, 3H), 3.13-3.25 (m, 0.7H), 2.89-2.96 (m, 3H), 2.66-2.79 (m, 1H), 2.37-2.48 (m, 0.7H), 2.23-2.34 (m, 1.3H), 2.03-2.16 (m, 1.3H), 1.82-2.00 (m, 1.3H), 1.70-1.81 (m, 1H), 1.40-1.70 (m, 5.7H), 1.03-1.16 (m, 1H); MS ESI 539.4 [M+H]⁺, calcd for [C₃₃H₃₈N₄O₃+H]⁺ 539.3.

Example A157

N-(cyclopropyl(phenyl)methyl)-3-(4-((1-oxetan-3-yl)piperidin-4-yl)oxy)phenyl)-1H-indazole-5-carboxamide

[0858]

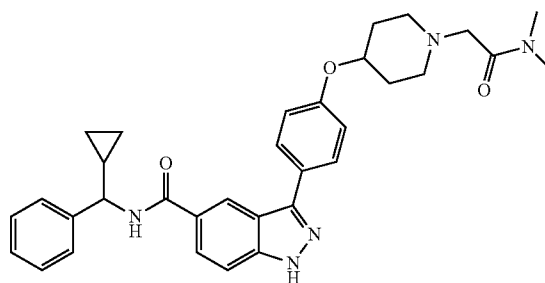


[0859] The title compound was synthesized according to Method C3 utilizing N-(cyclopropyl(phenyl)methyl)-3-iodo-1H-indazole-5-carboxamide and 1-(oxetan-3-yl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine and obtained as a yellow solid (38 mg, 38% yield). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.62 (s, 1H), 7.96 (dd, J=8.78, 1.51 Hz, 1H), 7.89 (d, J=8.78 Hz, 2H), 7.59 (d, J=8.78 Hz, 1H), 7.47 (d, J=7.28 Hz, 2H), 7.27-7.33 (t, J=7.6 Hz, 2H), 7.18-7.24 (m, 1H), 7.03 (d, J=8.78 Hz, 2H), 4.69 (t, J=6.27 Hz, 2H), 4.58 (t, J=6.27 Hz, 2H), 4.47 (d, J=9.54 Hz, 1H), 4.39-4.45 (m, 1H), 3.47 (quin, J=6.46 Hz, 1H), 2.55 (br. s., 2H), 2.20 (d, J=7.78 Hz, 2H), 1.96-2.06 (m, 2H), 1.74-1.86 (m, 2H), 1.33-1.44 (m, 1H), 0.58-0.68 (m, 2H), 0.39-0.51 (m, 2H); MS ESI [M+H]⁺ 523.3, calcd for [C₃₂H₃₄N₄O₃+H]⁺ 523.27.

Example A158

N-(cyclopropyl(phenyl)methyl)-3-(4-((1-(2-(dimethylamino)-2-oxoethyl)piperidin-4-yl)oxy)phenyl)-1H-indazole-5-carboxamide

[0860]



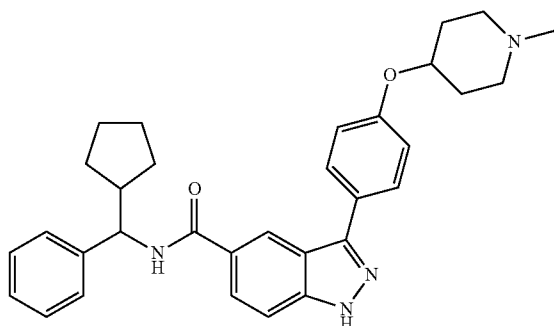
[0861] The title compound was synthesized according to Method C3 utilizing N-(cyclopropyl(phenyl)methyl)-3-iodo-1H-indazole-5-carboxamide and N,N-dimethyl-2-(4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidin-1-yl)acetamide and obtained as a white solid (28 mg, 27% yield). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.61 (s, 1H), 7.96 (dd, J=8.78, 1.51 Hz, 1H), 7.91 (d, J=8.78 Hz, 2H), 7.60 (d,

J=8.78 Hz, 1H), 7.48 (d, J=7.28 Hz, 2H), 7.32 (t, J=7.53 Hz, 2H), 7.19-7.26 (m, 1H), 7.09 (d, J=8.78 Hz, 2H), 4.43-4.59 (m, 2H), 3.55 (br. s., 2H), 3.07 (s, 3H), 3.01 (m, J=7.03 Hz, 2H), 2.96 (s, 3H), 2.73 (br. s., 2H), 2.06-2.16 (m, 2H), 1.95 (br. s., 2H), 1.40 (m, J=8.66, 4.14 Hz, 1H), 0.65 (d, J=8.28 Hz, 2H), 0.47 (dd, J=9.41, 4.64 Hz, 2H); MS ESI [M+H]⁺ 552.4, calcd for [C₃₃H₃₇N₅O₃+H]⁺ 552.30.

Example A159

N-(cyclopentyl(phenyl)methyl)-3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazole-5-carboxamide

[0862]

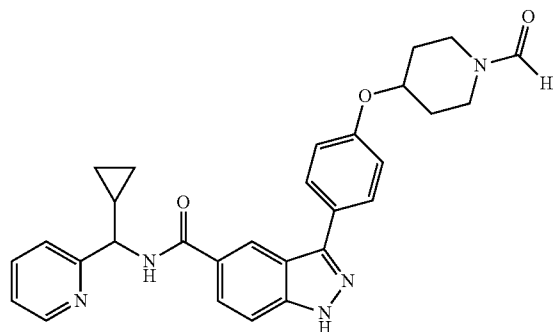


[0863] The title compound was synthesized according to the General Method C, utilizing N-(cyclopentyl(phenyl)methyl)-3-iodo-1H-indazole-5-carboxamide (100 mg, 0.21 mmol), (4-((1-methylpiperidin-4-yl)oxy)phenyl)boronic acid pinacol ester (67 mg, 0.21 mmol), Pd(PPh₃)₄ (12 mg, 0.010 mmol), satd. Na₂CO₃ (1.25 mL), and 3.75 mL of PhMe:EtOH (1:1). The vial was charged with Ar and heated in the microwave reactor at 125° C. for 2 h. Purification by RPHPLC, followed by trituration with Et₂O gave the title compound as a TFA salt (light yellow solid, 44 mg, 34%). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.51 (s, 1H), 7.86-7.95 (m, 3H), 7.58 (d, J=8.8 Hz, 1H), 7.44 (d, J=7.3 Hz, 2H), 7.32 (t, J=7.5 Hz, 2H), 7.11-7.25 (m, 3H), 4.83 (d, J=10.8 Hz, 1H), 4.60-4.72 (m, 0.3H), 3.59-3.67 (m, 0.7H), 3.33-3.47 (m, 2.7H), 3.14-3.25 (m, 0.7H), 2.91-2.96 (m, 3H), 2.47-2.59 (m, 1H), 2.38-2.47 (m, 0.7H), 2.24-2.33 (m, 1.3H), 2.04-2.18 (m, 1.3H), 1.84-2.04 (m, 1.7H), 1.58-1.78 (m, 3.3H), 1.36-1.58 (m, 3.3H), 1.13-1.26 (m, 1H); MS ESI 509.4 [M+H]⁺, calcd for [C₃₂H₃₆N₄O₂+H]⁺ 509.3.

Example A160

N-(cyclopropyl(pyridin-2-yl)methyl)-3-(4-((1-formylpiperidin-4-yl)oxy)phenyl)-1H-indazole-5-carboxamide

[0864]

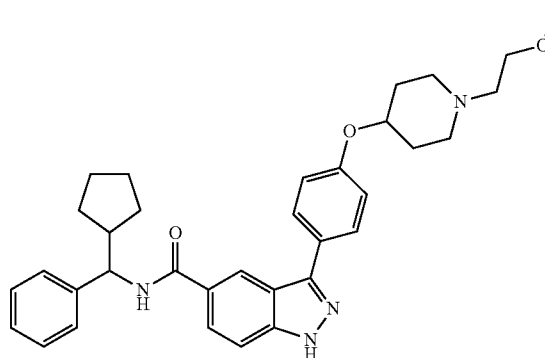


[0865] The title compound was synthesized according to Method C3 utilizing N-(cyclopropyl(pyridin-2-yl)methyl)-3-iodo-1H-indazole-5-carboxamide and 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine-1-carbaldehyde and obtained as a white solid (36 mg, 29% yield). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.77 (dd, J=5.77, 0.75 Hz, 1H), 8.70 (s, 1H), 8.56 (t, J=7.15 Hz, 1H), 8.20 (d, J=8.03 Hz, 1H), 7.90-8.01 (m, 4H), 7.63 (d, J=8.78 Hz, 1H), 7.15 (d, J=8.78 Hz, 2H), 4.72-4.80 (m, 1H), 4.49 (d, J=10.04 Hz, 1H), 3.64-3.82 (m, 2H), 3.39-3.58 (m, 2H), 1.92-2.10 (m, 2H), 1.71-1.90 (m, 2H), 1.45-1.58 (m, 1H), 0.84-0.95 (m, 1H), 0.58-0.81 (m, 3H); MS ESI [M+H]⁺ 496.3, calcd for [C₂₉H₂₉N₅O₃+H]⁺ 496.23.

Example A161

N-(cyclopentyl(phenyl)methyl)-3-(4-((1-(2-methoxyethyl)piperidin-4-yl)oxy)phenyl)-1H-indazole-5-carboxamide

[0866]

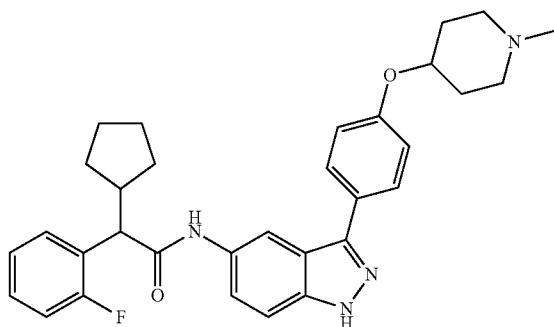


[0867] The title compound was synthesized according to the General Method C, utilizing N-(cyclopentyl(phenyl)methyl)-3-iodo-1H-indazole-5-carboxamide (100 mg, 0.21 mmol), (4-((1-(2-methoxyethyl)piperidin-4-yl)oxy)phenyl)boronic acid pinacol ester (76 mg, 0.21 mmol), Pd(PPh₃)₄ (12 mg, 0.010 mmol), satd. Na₂CO₃ (1.25 mL), and 3.75 mL of PhMe:EtOH (1:1). The vial was charged with Ar and heated in the microwave reactor at 125° C. for 2 h. Purification by RPHPLC, followed by trituration with Et₂O gave the title compound as a TFA salt (white solid, 42 mg, 30%). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.51 (s, 1H), 7.86-7.94 (m, 3H), 7.58 (d, J=8.5 Hz, 1H), 7.43 (d, J=7.3 Hz, 2H), 7.31 (t, J=7.5 Hz, 2H), 7.10-7.25 (m, 3H), 4.83 (d, J=8.3 Hz, 1H), 4.60-4.71 (m, 0.3H), 3.66-3.77 (m, 2.7H), 3.45-3.56 (m, 1.3H), 3.43 (s, 3H), 3.31-3.43 (m, 3.3H), 3.14-3.27 (m, 1H), 2.46-2.59 (m, 1H), 2.34-2.45 (m, 0.7H), 2.10-2.32 (m, 3H), 1.90-2.05 (m, 1.7H), 1.35-1.77 (m, 6H), 1.12-1.25 (m, 1H); MS ESI 554.2 [M+H]⁺, calcd for [C₃₄H₄₀N₄O₃+H]⁺ 553.3.

Example A162

2-cyclopentyl-2-(2-fluorophenyl)-N-(3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazol-5-yl)acetamide

[0868]

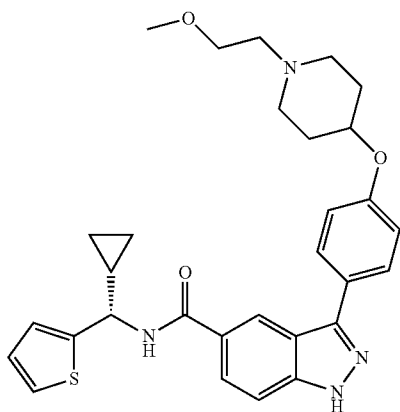


[0869] The title compound was synthesized according to the General Method C, utilizing 2-cyclopentyl-N-(1-(2-cyclopentyl-2-(2-fluorophenyl)acetyl)-3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazol-5-yl)-2-(2-fluorophenyl)acetamide (100 mg, 0.15 mmol), (4-((1-methylpiperidin-4-yl)oxy)phenyl)boronic acid pinacol ester (48 mg, 0.15 mmol), Pd(PPh₃)₄ (9 mg, 0.0075 mmol), satd. Na₂CO₃ (1.25 mL), and 3.75 mL of PhMe:EtOH (1:1). The vial was charged with Ar and heated in the microwave reactor at 125° C. for 2 h. Purification by RPHPLC, followed by trituration with Et₂O gave the title compound as a TFA salt (white solid, 38 mg, 40%). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.40 (dd, J=4.8, 1.2 Hz, 1H), 7.82-7.89 (m, 2H), 7.66-7.73 (m, 1H), 7.50 (d, J=9.0 Hz, 1H), 7.37-7.43 (m, 1H), 7.23-7.30 (m, 1H), 7.05-7.20 (m, 4H), 4.59-4.71 (m, 0.3H), 3.88 (m, J=11.3, 1 H), 3.58-3.67 (m, 0.7H), 3.33-3.47 (m, 3H), 3.13-3.26 (m, 0.7H), 2.89-2.96 (m, 3H), 2.64-2.77 (m, 1H), 2.37-2.48 (m, 0.7H), 2.23-2.35 (m, 1.3H), 2.03-2.16 (m, 1.3H), 1.84-2.00 (m, 1.7H), 1.40-1.81 (m, 6.3H), 1.05-1.18 (m, 1H); MS ESI 527.4 [M+H]⁺, calcd for [C₃₂H₃₅FN₄O₂+H]⁺ 527.3.

Example A163

(S)-N-(cyclopropyl(thiophen-2-yl)methyl)-3-(4-((1-(2-methoxyethyl)piperidin-4-yl)oxy)phenyl)-1H-indazole-5-carboxamide

[0870]

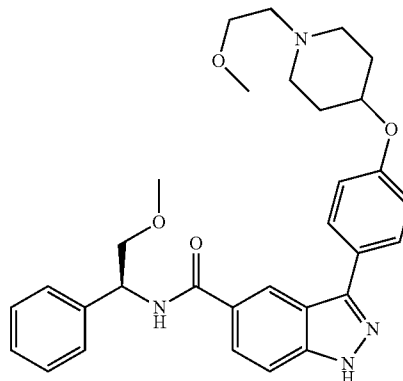


[0871] The title compound was prepared using Method C3 from (S)-N-(cyclopropyl(thiophen-2-yl)methyl)-3-iodo-1H-indazole-5-carboxamide (110 mg, 0.260 mmol) and 1-(2-methoxyethyl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine (122 mg, 0.338 mmol) which gave 77 mg of product isolated as its TFA salt (56%, an off-white solid). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.60 (s, 1H), 7.97-7.94 (m, 3H), 7.61 (d, J=8.9 Hz, 1H), 7.27 (d, J=5.3 Hz, 1H), 7.20-7.12 (m, 3H), 6.98-6.96 (m, 1H), 4.87 (bs, 1H), 4.75 (d, J=9.6 Hz, 1H), 3.76-3.19 (m, 11H), 2.42-1.95 (m, 4H), 1.54-1.48 (m, 1H), 0.80-0.67 (m, 2H), 0.55-0.49 (m, 2H); MS ESI 531.5 [M+H]⁺, calcd for [C₃₀H₃₄N₄O₃S+H]⁺ 531.24.

Example A164

(S)-N-(2-methoxy-1-phenylethyl)-3-(4-((1-(2-methoxyethyl)piperidin-4-yl)oxy)phenyl)-1H-indazole-5-carboxamide

[0872]



[0873] The title compound was prepared using Method C3 from (S)-3-iodo-N-(2-methoxy-1-phenylethyl)-1H-indazole-5-carboxamide (110 mg, 0.260 mmol) and 1-(2-methoxyethyl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine (122 mg, 0.338 mmol) which gave 97 mg of product isolated as its TFA salt (71%, off white solid). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.58 (s, 1H), 7.96-7.93 (m, 3H), 7.61 (d, J=8.8 Hz, 1H), 7.43 (d, J=7.6 Hz, 2H), 7.28-7.15 (m, 5H), 5.42-5.38 (m, 1H), 4.87 (bs, 1H), 3.84-3.68 (m, 5H), 3.53-3.19 (m, 11H), 2.43-2.27 (m, 2H), 2.19-1.96 (m, 2H); MS ESI 529.5 [M+H]⁺, calcd for [C₃₁H₃₆N₄O₄+H]⁺ 529.28.

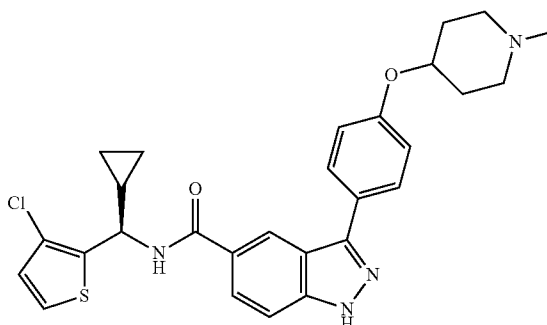
Example A165

Intentionally Omitted

Example A166

(R)-N-((3-chlorothiophen-2-yl)(cyclopropyl)methyl)-3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazole-5-carboxamide

[0874]

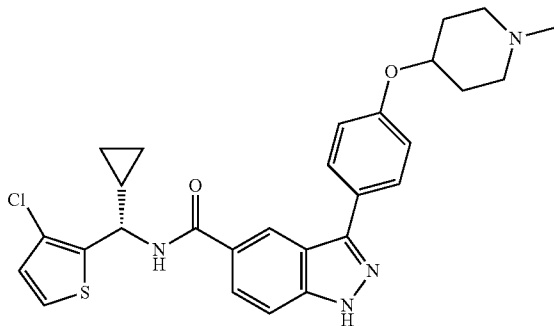


[0875] Using Method C2, (R)—N-((3-chlorothiophen-2-yl)(cyclopropyl)methyl)-3-iodo-1H-indazole-5-carboxamide (76.6 mg, 85% pure, 0.142 mmol) and 1-methyl-4-(4-(4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine (46.1 mg, 0.145 mmol) for 2 h at 125° C. in the microwave, the mixture was passed through a PoraPak Rxn Cx with acetone/MeOH and the product was eluted with 2 M NH₃-MeOH. Purification by flash chromatography (SiO₂, 5-25% MeOH in DCM, then 25% 2 M NH₃-MeOH in DCM; followed by RPRP HPLC, 10-90% MeOH in 0.1% TFA-H₂O) gave the title compound as the TFA salt (beige solid, 28.9 mg, 32%). ¹H NMR (400 MHz, CD₃OD) δ ppm 9.15 (d, J=7.5 Hz, 0.2H partially exchanged), 8.57 (s, 1H), 7.88-7.98 (m, 3H), 7.61 (d, J=9.0 Hz, 1H), 7.38 (d, J=5.3 Hz, 1H), 7.11-7.23 (m, 2H), 6.94 (s, 1H), 4.97 (d, J=8.8 Hz, 1H), 4.61-4.72 (m, 0.35H), 3.65 (d, J=12.5 Hz, 0.65H), 3.34-3.48 (m, 3H), 3.16-3.26 (m, 65H), 2.95, 2.94 (2-s, 3H), 2.44 (d, J=14.6 Hz, 0.7H), 2.26-2.35 (m, 1.3H), 2.06-2.19 (m, 1.3H), 1.86-1.99 (m, 0.7H), 1.45-1.56 (m, 1H), 0.61-0.73 (m, 2H), 0.50-0.61 (m, 2H). MS ESI 521.4 [M+H]⁺, calcd for [C₂₈H₂₉ClN₄O₂S+H]⁺ 521.18.

Example A167

(S)—N-((3-chlorothiophen-2-yl)(cyclopropyl)methyl)-3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazole-5-carboxamide

[0876]



[0877] Using Method C2, (S)—N-((3-chlorothiophen-2-yl)(cyclopropyl)methyl)-3-iodo-1H-indazole-5-carboxamide (102.1 mg, 85% pure, 0.19 mmol) and 1-methyl-4-(4-(4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine (60.4 mg, 0.19 mmol) for 2 h at 130° C. in the microwave, the mixture was passed through a PoraPak Rxn Cx with acetone/MeOH and the product was eluted with 2 M NH₃-MeOH. Purification by flash chromatography (SiO₂, 15% MeOH in DCM, then 15-35% 2 M NH₃-MeOH in DCM; followed by RPRP HPLC, 10-90% MeOH in 0.1% TFA-H₂O) gave the title compound as the TFA salt (beige solid, 31.8 mg, 26%). ¹H NMR (400 MHz, CD₃OD) δ ppm 9.15 (d, J=7.5 Hz, 0.2H partially exchanged), 8.57 (s, 1H), 7.88-7.98 (m, 3H), 7.61 (d, J=9.0 Hz, 1H), 7.38 (d, J=5.3 Hz, 1H), 7.11-7.23 (m, 2H), 6.94 (s, 1H), 4.97 (d, J=8.8 Hz, 1H), 4.61-4.72 (m, 0.35H), 3.65 (d, J=12.5 Hz, 0.65H), 3.34-3.48 (m, 3H), 3.16-3.26 (m, 65H), 2.95, 2.94 (2-s, 3H), 2.44 (d, J=14.6 Hz, 0.7H), 2.26-2.35 (m, 1.3H), 2.06-2.19 (m, 1.3H), 1.86-1.99 (m, 0.7H), 1.45-1.56 (m, 1H), 0.61-0.73 (m, 2H), 0.50-0.61 (m, 2H). MS ESI 521.4 [M+H]⁺, calcd for [C₂₈H₂₉ClN₄O₂S+H]⁺ 521.18.

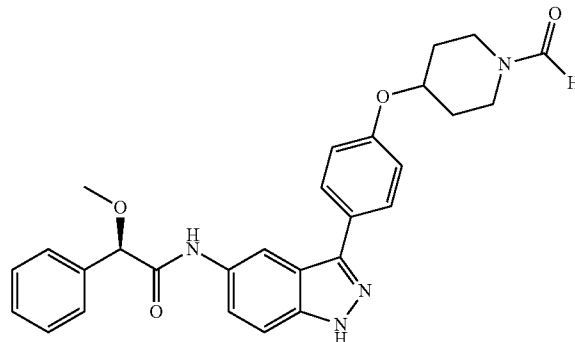
Example A168

Intentionally Omitted

Example A169

(R)—N-(3-(4-((1-formylpiperidin-4-yl)oxy)phenyl)-1H-indazol-5-yl)-2-methoxy-2-phenylacetamide

[0878]

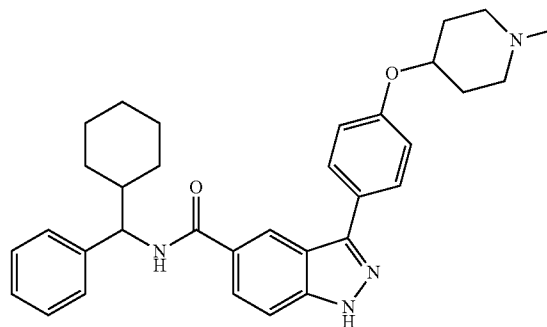


The title compound was synthesized according to Method C3 utilizing (R)—N-(3-iodo-1H-indazol-5-yl)-2-methoxy-2-phenylacetamide and 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine-1-carbaldehyde and obtained as an off-white solid (59 mg, 50% yield). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.39 (d, J=1.00 Hz, 1H), 7.95 (s, 1H), 7.78 (d, J=8.78 Hz, 2H), 7.44-7.56 (m, 4H), 7.25-7.38 (m, 3H), 6.96 (d, J=8.78 Hz, 2H), 4.80 (s, 1H), 4.54 (dt, J=6.53, 3.51 Hz, 1H), 3.59-3.69 (m, 1H), 3.47-3.57 (m, 1H), 3.37-3.45 (m, 4H), 3.20-3.30 (m, 1H), 1.75-1.92 (m, 2H), 1.57-1.74 (m, 2H); MS ESI [M+H]⁺ 485.4, calcd for [C₂₈H₂₈N₄O₄+H]⁺ 485.22.

Example A170

N-(cyclohexyl(phenyl)methyl)-3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazole-5-carboxamide

[0879]



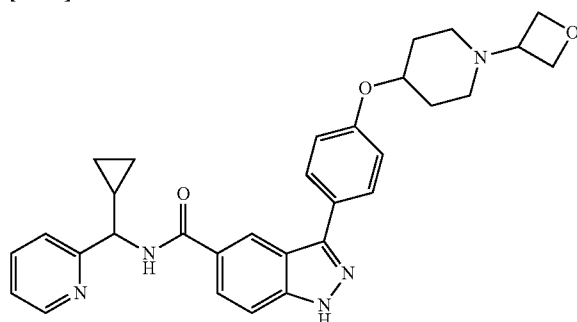
[0880] The title compound was synthesized according to the General Method C, utilizing N-(cyclohexyl(phenyl)methyl)-3-iodo-1H-indazole-5-carboxamide (100 mg, 0.22 mmol), (4-((1-methylpiperidin-4-yl)oxy)phenyl)boronic acid pinacol ester (70 mg, 0.22 mmol), Pd(PPh₃)₄ (13 mg, 0.01 mmol), satd. aq Na₂CO₃ (1.25 mL), and 3.75 mL of PhMe:EtOH (1:1). The vial was charged with Ar and heated in the microwave reactor at 125° C. for 2 h. Purification by RPRPHPLC gave the title compound as a TFA salt (white solid, 46 mg, 33%). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.51

(s, 1H), 7.85-7.96 (m, 3H), 7.58 (d, J=8.8 Hz, 1H), 7.40 (d, J=7.3 Hz, 2H), 7.32 (t, J=7.6 Hz, 2H), 7.10-7.26 (m, 3H), 4.81 (d, J=10.0 Hz, 1H), 4.60-4.70 (m, 0.3H), 3.59-3.68 (m, 0.7H), 3.33-3.47 (m, 3H), 3.13-3.25 (m, 0.7H), 2.89-2.96 (m, 3H), 2.37-2.45 (m, 0.7H), 2.23-2.33 (m, 1.3H), 2.03-2.17 (m, 2.4H), 1.84-1.97 (m, 1.7H), 1.74-1.84 (m, 1H), 1.60-1.71 (m, 2H), 1.08-1.39 (m, 6.3H), 0.86-0.99 (m, 1H); MS ESI 523.5 [M+H]⁺, calcd for [C₃₃H₃₈N₄O₂+H]⁺ 523.3.

Example A171

N-(cyclopropyl(pyridin-2-yl)methyl)-3-(4-((1-(oxetan-3-yl)piperidin-4-yl)oxy)phenyl)-1H-indazole-5-carboxamide

[0881]

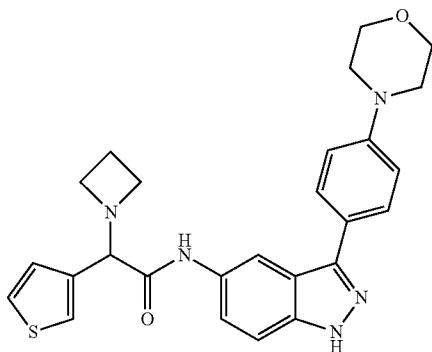


The title compound was synthesized according to Method C3 utilizing N-(cyclopropyl(pyridin-2-yl)methyl)-3-iodo-1H-indazole-5-carboxamide and 1-(oxetan-3-yl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine and obtained as a white solid (23 mg, 23% yield). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.65 (s, 1H), 8.52 (d, J=4.02 Hz, 1H), 7.96 (dd, J=8.91, 1.38 Hz, 1H), 7.92 (d, J=8.53 Hz, 2H), 7.81 (td, J=7.65, 1.76 Hz, 1H), 7.60 (d, J=9.29 Hz, 1H), 7.53 (d, J=8.03 Hz, 1H), 7.27-7.34 (m, 1H), 7.09 (d, J=8.78 Hz, 2H), 4.65-4.74 (m, 2H), 4.61 (t, J=6.27 Hz, 2H), 4.51 (d, J=9.54 Hz, 2H), 3.52 (quin, J=6.40 Hz, 1H), 2.61 (br. s., 2H), 2.25 (br. s., 2H), 2.01-2.11 (m, 2H), 1.78-1.90 (m, 2H), 1.35-1.46 (m, 1H), 0.69 (br. s., 1H), 0.48-0.63 (m, 3H); MS ESI [M+H]⁺ 524.2, calcd for [C₃₁H₃₃N₅O₃+H]⁺ 524.27.

Example A172

2-(azetidin-1-yl)-N-(3-(4-morpholinophenyl)-1H-indazol-5-yl)-2-(thiophen-3-yl)acetamide

[0882]



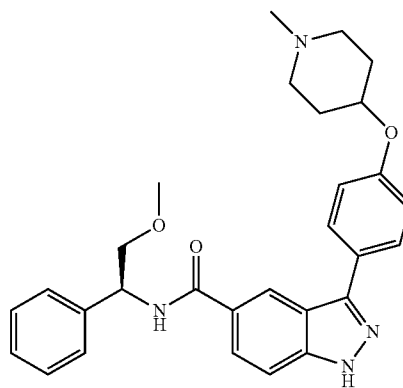
[0883] A mixture of thiophen-3-ylboronic acid (5.61 g, 43.9 mmol) and glyoxylic acid monohydrate (4.04 g, 43.9 mmol) in DCM (200 mL) was stirred for 5 min at rt before azetidine (2.50 g, 43.9 mmol) was added. The resulting mixture was stirred O/N at rt. White precipitates formed were collected by suction filtration, rinsed with DCM and dried to give 2-(azetidin-1-yl)-2-(thiophen-3-yl)acetic acid as a H₃BO₃ salt (light beige solid, 10.968 g). ¹H NMR (400 MHz, CD₃OD) δ 7.64 (s, 1H), 7.52 (t, 1H), 7.19 (d, J=4.8 Hz, 1H), 4.45-3.50 (m, 4H), 2.60-2.30 (m, 2H); MS ESI 197.9 [M+H]⁺, calcd for [C₉H₁₁NO₂S+H]⁺ 198.0.

[0884] To a mixture of 2-(azetidin-1-yl)-2-(thiophen-3-yl)acetic acid H₃BO₃ salt (52 mg, 0.2 mmol), 3-(4-morpholinophenyl)-1H-indazol-5-amine di-trifluoroacetic acid (259 mg, 90% pure, 0.2 mmol) in DMF (5 mL) at 0° C. was added TBTU (65 mg, 0.2 mmol), followed by ^tPr₂NEt (0.14 mL, 0.8 mmol). The resulting mixture was stirred for 30 min at 0° C. It was purified by prep-HPLC and PoraPak to give the title compound (pale yellow solid, 8.0 mg, 8%). ¹H NMR (400 MHz, CD₃OD) δ 8.32 (s, 1H), 7.80 (d, J=8.8 Hz, 2H), 7.52-7.49 (m, 3H), 7.41 (dd, J=8.6 Hz, 3.0 Hz, 1H), 7.25 (d, J=4.8 Hz, 1H), 7.09 (d, J=8.8 Hz, 2H), 4.21 (s, 1H), 3.86 (t, J=4.8 Hz, 4H), 3.40 (q, J=6.8 Hz, 2H), 3.27-3.18 (m, 6H), 2.15 (quint, 7.0 Hz, 2H); MS ESI 474.2 [M+H]⁺, calcd for [C₂₆H₂₇N₅O₂S+H]⁺ 474.2.

Example A173

(S)-N-(2-methoxy-1-phenylethyl)-3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazole-5-carboxamide

[0885]

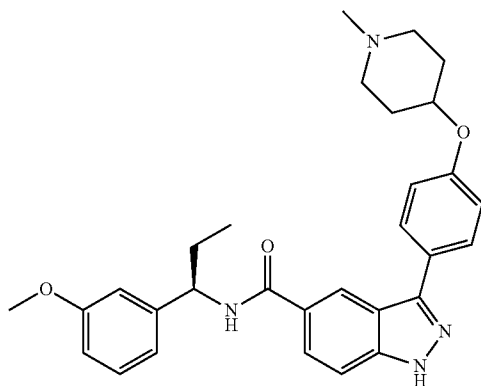


[0886] The title compound was prepared using Method C3 from (S)-3-iodo-N-(2-methoxy-1-phenylethyl)-1H-indazole-5-carboxamide (68 mg, 0.166 mmol) and 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine (70 mg, 0.216 mmol) which gave product as a white solid (34 mg, 43% yield) isolated as its TFA salt. ¹H NMR (400 MHz, CD₃OD) δ ppm 8.58 (s, 1H), 7.97-7.93 (m, 3H), 7.62 (d, J=8.8 Hz, 1H), 7.44 (d, J=7.6 Hz, 2H), 7.28-7.15 (m, 5H), 5.42-5.39 (m, 1H), 4.87 (bs, 1H), 3.84-3.68 (m, 3H), 3.42-3.30 (m, 6H), 2.95-2.93 (m, 3H), 2.47-2.30 (m, 2H), 2.15-2.10 (m, 2H); MS ESI 485.4 [M+H]⁺, calcd for [C₂₉H₃₂N₄O₃+H]⁺ 485.26.

Example A174

(R)—N-(1-(3-methoxyphenyl)propyl)-3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazole-5-carboxamide

[0887]

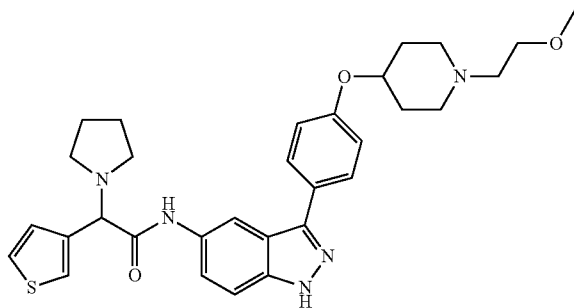


[0888] The title compound was prepared using Method C3 from (R)-3-iodo-N-(1-(3-methoxyphenyl)propyl)-1H-indazole-5-carboxamide (70 mg, 0.161 mmol) and 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine (66 mg, 0.209 mmol) which gave of product (26 mg) isolated as its TFA salt (gave 26 mg, 33%, a white solid). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.55 (s, 1H), 7.95-7.91 (m, 3H), 7.60 (d, J=8.8 Hz, 1H), 7.26-7.13 (m, 3H), 6.99-6.87 (m, 2H), 6.79 (m, 1H), 5.01-4.97 (m, 1H), 4.87 (bs, 1H), 3.97 (s, 3H), 3.65-3.17 (m, 4H), 2.94-2.93 (m, 3H), 2.45-2.27 (m, 2H), 2.15-1.89 (m, 2H), 1.00 (t, J=7.2 Hz, 3H); MS ESI 500.2 [M+H]⁺, calcd for [C₃₀H₃₄N₄O₃+H]⁺ 499.27.

Example A175

N-(3-(4-((1-(2-methoxyethyl)piperidin-4-yl)oxy)phenyl)-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide

[0889]



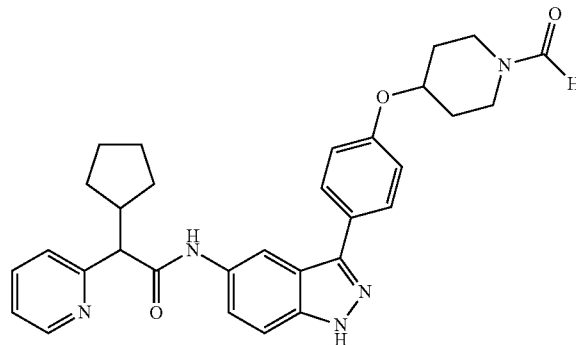
[0890] The title compound was prepared using Method C3 from N-(3-iodo-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide (42 mg, 0.093 mmol) and 1-(2-methoxyethyl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine (44 mg, 0.121 mmol) which gave 10 mg of product isolated as its di-TFA salt (10 mg, 19%,

a white solid). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.35 (s, 1H), 7.87-7.83 (m, 3H), 7.66-7.64 (m, 1H), 7.55-7.48 (m, 2H), 7.37 (d, J=5.1 Hz, 1H), 7.21-7.14 (m, 2H), 5.21 (bs, 1H), 4.87 (bs, 1H), 3.89-3.71 (m, 4H), 3.55-3.05 (m, 11H), 2.44-2.28 (m, 2H), 2.18-1.95 (m, 2H); MS ESI 560.2 [M+H]⁺, calcd for [C₃₁H₃₇N₅O₃S+H]⁺ 560.27.

Example A176

2-cyclopentyl-N-(3-(4-((1-formylpiperidin-4-yl)oxy)phenyl)-1H-indazol-5-yl)-2-(pyridin-2-yl)acetamide

[0891]

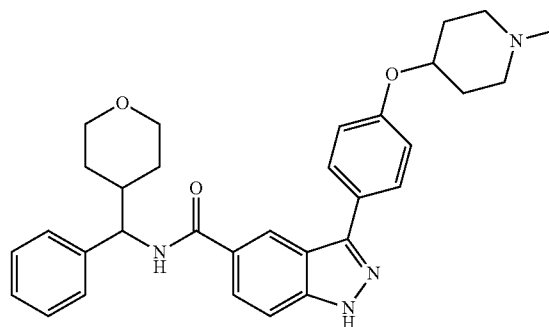


[0892] The mixture of 2-cyclopentyl-N-(3-iodo-1H-indazol-5-yl)-2-(pyridin-2-yl)acetamide (50 mg, 0.112 mmol), 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine-1-carbaldehyde (41 mg, 0.123 mmol), Pd(PPh₃)₄ (13 mg, 0.011 mmol), LiCl (14 mg, 0.336 mmol), 2 M aq Na₂CO₃ solution (0.28 mL, 0.56 mmol) in dioxane (1 mL) was stirred at 125° C. for 3 h with microwave irradiation under Ar. The resulting reaction mixture was filtered through Celite and the filtrate was concentrated under reduced pressure. The residue was purified by prep HPLC followed by running through PoraPak to give the title compound as a peach solid (39 mg, 67% yield). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.48 (d, J=5.02 Hz, 1H), 8.41 (s, 1H), 8.00 (s, 1H), 7.79 (d, J=8.53 Hz, 2H), 7.75 (td, J=7.78, 1.76 Hz, 1H), 7.62 (d, J=8.03 Hz, 1H), 7.43-7.51 (m, 2H), 7.23-7.29 (m, 1H), 7.01 (d, J=8.78 Hz, 2H), 4.62 (tt, J=6.87, 3.42 Hz, 1H), 3.69 (td, J=8.53, 4.02 Hz, 1H), 3.56-3.65 (m, 2H), 3.40-3.49 (m, 1H), 3.28-3.38 (m, 1H), 2.79 (m, J=10.79 Hz, 1H), 1.82-2.01 (m, 3H), 1.36-1.79 (m, 8H), 1.08 (dd, J=12.30, 8.03 Hz, 1H); MS ESI [M+H]⁺ 524.4, calcd for [C₃₁H₃₃N₅O₃+H]⁺ 524.27.

Example A177

3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-N-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1H-indazole-5-carboxamide

[0893]

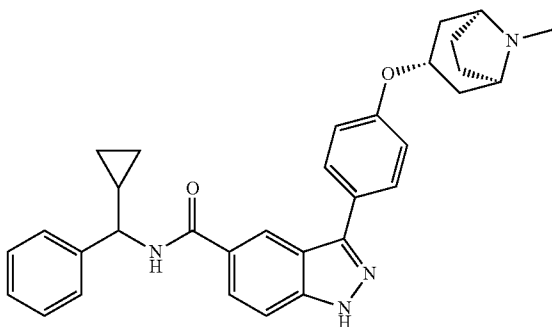


[0894] The title compound was synthesized according to the General Method C, utilizing 3-iodo-N-(phenyl(tetrahydro-2H-pyran-4-yl)methyl)-1H-indazole-5-carboxamide (100 mg, 0.22 mmol), (4-((1-methylpiperidin-4-yl)oxy)phenyl)boronic acid pinacol ester (70 mg, 0.22 mmol), Pd(PPh₃)₄ (13 mg, 0.01 mmol), satd. aq Na₂CO₃ (1.25 mL), and 3.75 mL of PhMe:EtOH (1:1). The vial was charged with Ar and heated in the microwave reactor at 125° C. for 2 h. Purification by RPRPHPLC, followed by trituration with Et₂O gave the title compound as a TFA salt (white solid, 25 mg, 18%). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.52 (s, 1H), 7.90 (dd, J=8.9, 2.9 Hz, 3H), 7.58 (d, J=8.8 Hz, 1H), 7.42 (d, J=6.8 Hz, 2H), 7.33 (t, J=7.5 Hz, 2H), 7.25 (d, J=7.3 Hz, 1H), 7.09-7.18 (m, 2H), 4.85 (d, J=10.5 Hz, 1H), 4.59-4.69 (m, 0.3H), 3.94-4.02 (m, 1H), 3.81-3.89 (m, 1H), 3.57-3.67 (m, 0.7H), 3.34-3.46 (m, 3.7H), 3.28 (d, J=2.0 Hz, 0.7H), 2.89-2.95 (m, 3H), 2.34-2.45 (m, 0.7H), 2.24 (br. s., 1.5H), 2.04-2.21 (m, 2.7H), 1.84-2.00 (m, 1.7H), 1.38-1.53 (m, 1H), 1.12-1.31 (m, 3H); MS ESI 525.4 [M+H]⁺, calcd for [C₃₂H₃₆N₄O₃+H]⁺ 525.3.

Example A178

N-(cyclopropyl(phenyl)methyl)-3-(4-(((1R,3r,5S)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)phenyl)-1H-indazole-5-carboxamide

[0895]

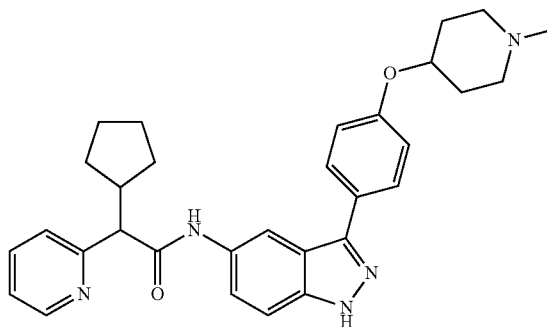


[0896] The title compounds was synthesized according to the General Method C2 utilizing 2-cyclopropyl-N-(3-iodo-1H-indazol-5-yl)-2-phenylacetamide (90 mg, 0.22 mmol) and (1R,3r,5S)-8-methyl-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)-8-azabicyclo[3.2.1]octane (0.14 g, ~0.31 mmol) to afford the title compound as a white powder (7.5 mg, 7%). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.61 (s, 1H), 7.89-8.00 (m, 3H), 7.61 (d, J=8.78 Hz, 1H), 7.49 (d, J=7.28 Hz, 2H), 7.33 (t, J=7.53 Hz, 2H), 7.24 (t, J=7.30 Hz, 1H), 7.04 (d, J=8.78 Hz, 2H), 4.69 (t, J=4.77 Hz, 1H), 4.48 (d, J=9.29 Hz, 1H), 3.44 (br. s., 2H), 2.50 (s, 3H), 2.02-2.37 (m, 8H), 1.48-1.37 (m, 1H), 0.70-0.62 (m, 2H), 0.52-0.42 (m, 2H); MS ESI 507.3 [M+H]⁺, calcd for [C₃₂H₃₄N₄O₂+H]⁺ 507.3.

Example A179

2-cyclopentyl-N-(3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazol-5-yl)-2-(pyridin-2-yl)acetamide

[0897]

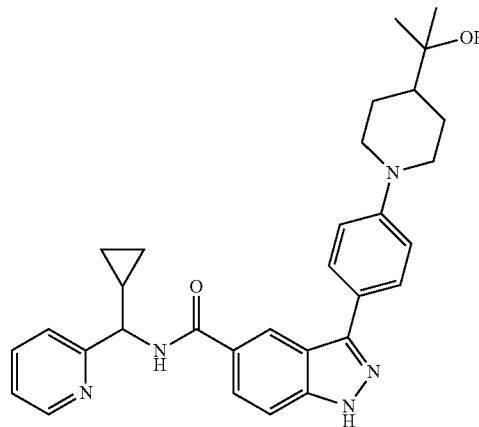


[0898] The title compound was synthesized according to Method C3 utilizing 2-cyclopentyl-N-(3-iodo-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-yl)-2-(pyridin-2-yl)acetamide and 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine and obtained as a white solid (18 mg, 32% yield). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.47-8.53 (m, 1H), 8.37 (d, J=1.00 Hz, 1H), 7.75-7.85 (m, 3H), 7.64 (d, J=8.03 Hz, 1H), 7.43-7.52 (m, 2H), 7.31 (ddd, J=7.28, 5.02, 1.00 Hz, 1H), 7.05 (d, J=8.78 Hz, 2H), 4.46 (br. s., 1H), 3.61 (d, J=11.04 Hz, 1H), 2.64-2.87 (m, 3H), 2.39 (br. s., 2H), 2.27-2.33 (m, 3H), 1.90-2.09 (m, 3H), 1.40-1.89 (m, 8H), 1.11 (m, J=12.55, 8.03 Hz, 1H); MS ESI [M+H]⁺ 510.2, calcd for [C₃₁H₃₅N₅O₂+H]⁺ 510.29.

Example A180

N-(cyclopropyl(pyridin-2-yl)methyl)-3-(4-(4-(2-hydroxypropan-2-yl)piperidin-1-yl)phenyl)-1H-indazole-5-carboxamide

[0899]



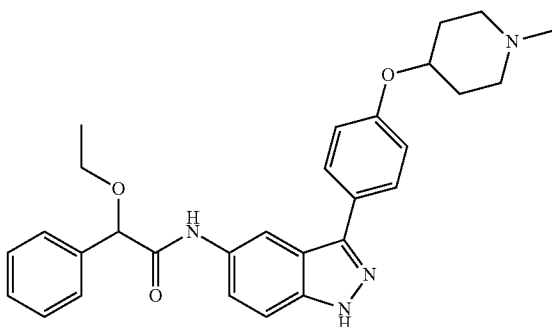
[0900] The title compound was synthesized according to Method C3 utilizing N-(cyclopropyl(pyridin-2-yl)methyl)-3-iodo-1H-indazole-5-carboxamide and 2-(1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidin-1-yl)ethanol and obtained as a white solid (18 mg, 32% yield).

ramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidin-4-yl)propan-2-ol and obtained as a white solid (16 mg, 16% yield). ^1H NMR (400 MHz, CD_3OD) δ ppm 8.67 (s, 1H), 8.51 (d, $J=4.77$ Hz, 1H), 7.95 (dd, $J=8.78, 1.51$ Hz, 1H), 7.86 (d, $J=8.78$ Hz, 2H), 7.79 (td, $J=7.78, 1.76$ Hz, 1H), 7.58 (d, $J=8.78$ Hz, 1H), 7.52 (d, $J=7.78$ Hz, 1H), 7.29 (ddd, $J=6.90, 5.65, 1.00$ Hz, 1H), 7.09 (d, $J=9.03$ Hz, 2H), 4.50 (d, $J=9.29$ Hz, 1H), 3.84 (d, $J=12.05$ Hz, 2H), 2.65 (t, $J=11.29$ Hz, 2H), 1.86 (d, $J=9.79$ Hz, 2H), 1.34-1.54 (m, 4H), 1.17 (s, 6H), 0.67 (m, $J=8.00$ Hz, 1H), 0.47-0.61 (m, 3H); MS ESI $[\text{M}+\text{H}]^+$ 510.2, calcd for $[\text{C}_{31}\text{H}_{35}\text{N}_5\text{O}_2+\text{H}]^+$ 510.29.

Example A181

2-ethoxy-N-(3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazol-5-yl)-2-phenylacetamide

[0901]



[0902] A. 2-Ethoxy-N-(3-iodo-1H-indazol-5-yl)-2-phenylacetamide was synthesized according to Method A utilizing 3-iodo-1H-indazol-5-amine (200 mg, 0.77 mmol) and 2-ethoxy-2-phenylacetic acid (155 mg, 0.86 mmol), TBTU (250 mg, 0.78 mmol) and DIPEA (0.36 mL, 2.3 mmol) in DMF (5 mL). The crude material was precipitated by adding H_2O , collected by filtration, dried and taken into MeOH (5 mL). Heating with MeONa (1.3 mL, 25%_{w/v} in MeOH, 6.0 mmol) at 50°C for 45 min, cooling to rt, concentration to dryness followed by flash chromatography (SiO_2 , 2-25% MeOH in DCM) provided 2-ethoxy-N-(3-iodo-1H-indazol-5-yl)-2-phenylacetamide as an off-white solid (121 mg, 37%). MS ESI $[\text{M}+\text{H}]^+$, calcd for $[\text{C}_{17}\text{H}_{16}\text{IN}_3\text{O}+\text{H}]^+$ 422.0.

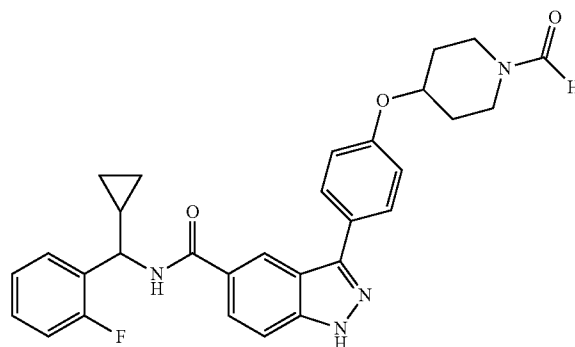
[0903] B. 2-Ethoxy-N-(3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazol-5-yl)-2-phenylacetamide synthesized according to the General Method C2 utilizing 2-ethoxy-N-(3-iodo-1H-indazol-5-yl)-2-phenylacetamide (63 mg, 0.15 mmol), 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine (62 mg, 0.19 mmol), $\text{PdCl}_2\text{dppfCH}_2\text{Cl}_2$ (7 mg, 0.009 mmol), satd aq Na_2CO_3 (0.5 mL) in PhMe (1.5 mL) and EtOH (1.5 mL) under microwave heating (130°C , 2 h). The title compound was isolated after flash chromatography (SiO_2 , 0-60% MeOH-DCM) followed by four separate purifications using: (a) RP HPLC (Biotage C18 column, MeOH— $\text{H}_2\text{O}+0.1\%$ TFA), (b) PoraPak, (c) prepTLC (SiO_2 , 10% 7M NH_3/MeOH in DCM) and (d) trituration with hexanes; as a white powder (9.6 mg, 13%). ^1H NMR (400 MHz, CD_3OD) δ ppm 8.35 (d, $J=1.00$ Hz, 1H), 7.84 (d, $J=8.78$ Hz, 2H), 7.48-7.59 (m, 4H), 7.30-7.44 (m, 3H), 7.09 (d,

$J=8.78$ Hz, 2H), 4.94 (s, 1H), 4.55 (br. s., 1H), 3.56-3.75 (m, 2H), 2.88 (br. s., 2H), 2.57 (br. s., 2H), 2.43 (s, 3H), 2.07 (br. s., 2H), 1.92 (br. s., 2H), 1.33 (t, $J=7.03$ Hz, 3H); MS ESI $[\text{M}+\text{H}]^+$ 485.3, calcd for $[\text{C}_{29}\text{H}_{32}\text{N}_4\text{O}_3+\text{H}]^+$ 485.2.

Example A182

N-(cyclopropyl(2-fluorophenyl)methyl)-3-(4-((1-formylpiperidin-4-yl)oxy)phenyl)-1H-indazole-5-carboxamide

[0904]

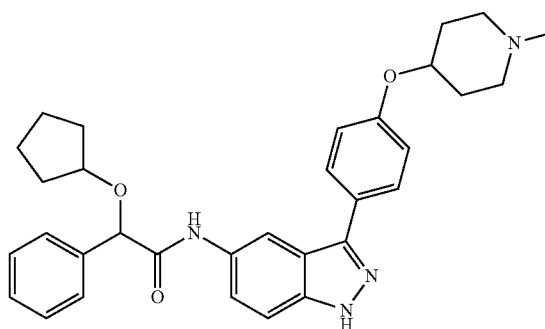


[0905] The title compound was synthesized according to Method C3 utilizing N-(cyclopropyl(2-fluorophenyl)methyl)-3-iodo-1H-indazole-5-carboxamide and 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine-1-carbaldehyde and obtained as a white solid (10 mg, 14% yield). ^1H NMR (400 MHz, CD_3OD) δ ppm 8.59 (s, 1H), 8.04 (s, 1H), 7.88-7.96 (m, 3H), 7.52-7.62 (m, 2H), 7.26 (m, $J=7.78$ Hz, 1H), 7.02-7.19 (m, 4H), 4.69-4.79 (m, 2H), 3.76 (s, 2H), 3.47-3.56 (m, 1H), 3.38-3.46 (m, 1H), 1.91-2.08 (m, 2H), 1.78 (br. s., 2H), 1.38-1.49 (m, 1H), 0.67 (d, $J=4.02$ Hz, 1H), 0.38-0.62 (m, 3H); MS ESI $[\text{M}+\text{H}]^+$ 513.4, calcd for $[\text{C}_{30}\text{H}_{29}\text{FN}_4\text{O}_3+\text{H}]^+$ 513.23.

Example A183

2-(cyclopentyloxy)-N-(3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazol-5-yl)-2-phenylacetamide

[0906]



[0907] A. To a DCM (20 mL) solution of tert-butyl (3-iodo-1H-indazol-5-yl)carbamate (200 mg, 0.56 mmol) was

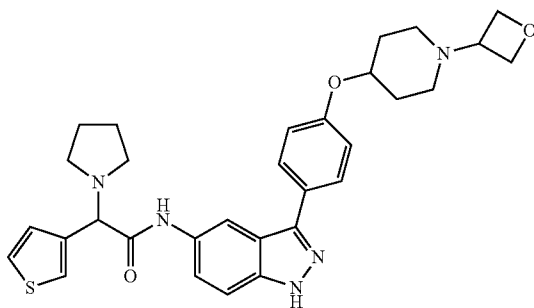
added TFA (2 mL) dropwise at rt. The reaction was stirred to 70 min before more TFA (1 mL). The stirring was continued overnight. The reaction mixture was concentrated to dryness under reduced pressure to provide 3-iodo-1H-indazol-5-amine 2,2,2-trifluoroacetate. The light brown residue was taken into anh. DMF (8 mL) and subjected to the conditions described by method A utilizing tert-butyl (3-iodo-1H-indazol-5-yl)carbamate (200 mg, 0.56 mmol) and sodium 2-(cyclopentyloxy)-2-phenylacetate (0.28 mg, 1.2 mmol), TBTU (0.51 g, 2.8 mmol) and DIPEA (0.5 mL, 3.2 mmol) in DMF (5 mL). The crude material was precipitated by adding H₂O, collected by filtration, dried (0.29 g, brown solid) and taken into MeOH (20 mL). The reaction was heated with MeONa (1.0 mL, 25%_{w/w} in MeOH, 4.6 mmol) at 50° C. for 1 h and left standing at rt overnight. Concentration to dryness under reduced pressure, followed by flash chromatography (SiO₂, 0-20% MeOH in DCM) followed by RP HPLC (Biotage C18, 10-90% MeOH—H₂O+0.1% TFA) provided 2-(cyclopentyloxy)-N-(3-iodo-1H-indazol-5-yl)-2-phenylacetamide (71 mg, 28%) as a light tan solid. MS ESI 462.2 [M+H]⁺, calcd for [C₂₀H₂₀IN₃O₂+H]⁺ 462.1.

[0908] B. 2-(Cyclopentyloxy)-N-(3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazol-5-yl)-2-phenylacetamide was synthesized according to the General Method C2 utilizing 2-(cyclopentyloxy)-N-(3-iodo-1H-indazol-5-yl)-2-phenylacetamide (71 mg, 0.15 mmol), 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine (68 mg, 0.21 mmol), PdCl₂dppfCH₂Cl₂ (6.3 mg, 0.0077 mmol), satd aq Na₂CO₃ (0.5 mL) in PhMe (1.5 mL) and EtOH (1.5 mL) under microwave heating (130° C., 2 h). A TFA salt of the title compound was isolated after flash chromatography (SiO₂, 0-60% MeOH-DCM) followed by RP HPLC (Biotage C18 column, MeOH—H₂O+0.1% TFA) as a white powder (36.8 mg, 38%). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.35 (s, 1H), 7.82 (d, J=8.78 Hz, 2H), 7.48-7.58 (m, 4H), 7.37 (d, J=7.28 Hz, 3H), 7.05 (d, J=8.78 Hz, 2H), 4.98 (s, 1H), 4.38-4.54 (m, 1H), 4.11 (br. s., 1H), 2.73 (br. s., 2H), 2.39 (br. s., 2H), 2.31 (s, 3H), 2.03 (br. s., 2H), 1.70-1.96 (m, 8H), 1.58 (dd, J=7.53, 4.77 Hz, 2H); MS ESI [M+H]⁺ 524.4, calcd for [C₃₂H₃₆N₄O₃+H]⁺ 524.3.

Example A184

N-(3-(4-((1-(oxetan-3-yl)piperidin-4-yl)oxy)phenyl)-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide

[0909]

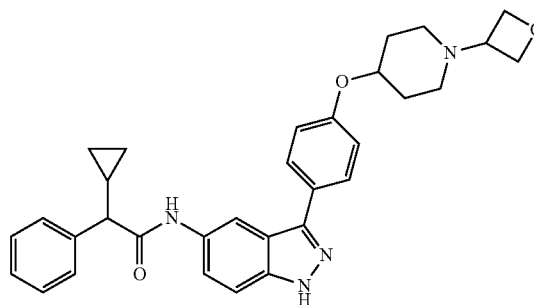


[0910] The title compound was synthesized according to Method C3 utilizing N-(3-iodo-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide and 1-(oxetan-3-yl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine and obtained as a pale solid (20 mg, 20% yield). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.36 (s, 1H), 7.81 (d, J=8.78 Hz, 2H), 7.46-7.52 (m, 3H), 7.35-7.42 (m, 1H), 7.29-7.35 (m, 1H), 7.02 (d, J=8.78 Hz, 2H), 4.66 (m, J=13.30 Hz, 2H), 4.57 (t, J=6.27 Hz, 2H), 4.37-4.47 (m, 1H), 4.10 (s, 1H), 3.41-3.50 (m, 1H), 2.59-2.69 (m, 2H), 2.44-2.59 (m, 4H), 2.12-2.23 (m, 2H), 1.95-2.05 (m, 2H), 1.82 (br. s., 6H); MS ESI [M+H]⁺ 558.2, calcd for [C₃₁H₃₅N₅O₃S+H]⁺ 558.25.

Example A185

2-cyclopropyl-N-(3-(4-((1-(oxetan-3-yl)piperidin-4-yl)oxy)phenyl)-1H-indazol-5-yl)-2-phenylacetamide

[0911]

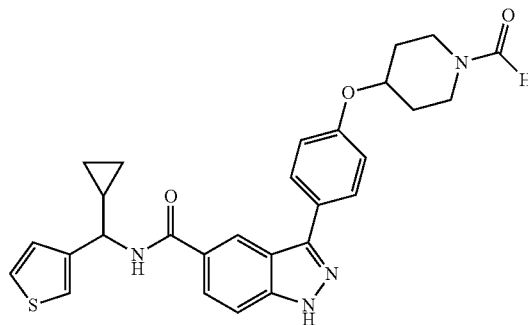


[0912] The title compound was synthesized according to Method C3 utilizing 2-cyclopropyl-N-(3-iodo-1H-indazol-5-yl)-2-phenylacetamide and 1-(oxetan-3-yl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine and obtained as a pale solid (21 mg, 42% yield). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.42 (s, 1H), 7.80 (d, J=8.78 Hz, 2H), 7.48 (dd, J=7.28, 3.01 Hz, 4H), 7.28-7.35 (m, 2H), 7.24 (m, J=7.28 Hz, 1H), 7.01 (d, J=8.78 Hz, 2H), 4.62-4.69 (m, 2H), 4.57 (t, J=6.27 Hz, 2H), 4.37-4.46 (m, 1H), 3.46 (quin, J=6.46 Hz, 1H), 2.91 (d, J=10.04 Hz, 1H), 2.50-2.59 (m, 2H), 2.12-2.23 (m, 2H), 1.94-2.05 (m, 2H), 1.73-1.85 (m, 2H), 1.53-1.63 (m, 1H), 0.55-0.73 (m, 2H), 0.39-0.50 (m, 1H), 0.18-0.28 (m, 1H); MS ESI [M+H]⁺ 523.4, calcd for [C₃₂H₃₄N₄O₃+H]⁺ 523.27.

Example A186

N-(cyclopropyl(thiophen-3-methyl-3-yl)methyl)-3-(4-((1-formylpiperidin-4-yl)oxy)phenyl)-1H-indazole-5-carboxamide

[0913]

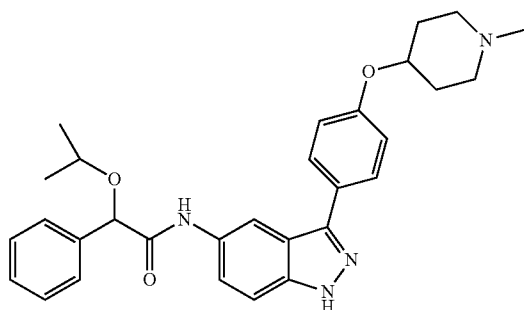


[0914] The title compound was synthesized according to Method C3 utilizing N-(cyclopropyl(thiophen-3-yl)methyl)-3-iodo-1H-indazole-5-carboxamide and 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine-1-carbaldehyde and obtained as a pale solid (18 mg, 31% yield). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.61 (s, 1H), 8.02 (s, 1H), 7.96 (dd, J=8.78, 1.51 Hz, 1H), 7.90 (d, J=8.53 Hz, 2H), 7.59 (d, J=8.78 Hz, 1H), 7.31-7.36 (m, 2H), 7.15-7.21 (m, 1H), 7.08 (d, J=8.78 Hz, 2H), 4.69 (dt, J=6.84, 3.48 Hz, 1H), 4.62 (d, J=9.54 Hz, 1H), 3.60-3.77 (m, 2H), 3.44-3.53 (m, 1H), 3.36-3.43 (m, 1H), 1.89-1.99 (m, 2H), 1.67-1.84 (m, 2H), 1.42 (dd, J=9.16, 4.64 Hz, 1H), 0.70 (dd, J=8.78, 4.52 Hz, 1H), 0.61 (dd, J=8.03, 4.27 Hz, 1H), 0.47 (td, J=8.41, 4.77 Hz, 2H); MS ESI [M+H]⁺ 501.3, calcd for [C₂₈H₂₈N₄O₃S+H]⁺ 501.20.

Example A187

2-isopropoxy-N-(3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazol-5-yl)-2-phenylacetamide

[0915]



[0916] N-(3-iodo-1H-indazol-5-yl)-2-isopropoxy-2-phenylacetamide was synthesized according to Method A utilizing 3-iodo-1H-indazole-5-amine 2,2,2-trifluoroacetate (300 mg, 0.80 mmol), and 2-isopropoxy-2-phenylacetic acid (312 mg, 1.6 mmol), TBTU (516 mg, 1.6 mmol) and DIPEA (0.50 mL, 3.2 mmol) in DMF (5 mL). The crude material was partitioned between H₂O and EtOAc. The organic layer was washed (satd aq NaHCO₃, H₂O), dried (Na₂SO₄) and concentrated under reduced pressure. The resultant pale orange oil (0.55 g) was taken into MeOH (20 mL) and heated with MeONa (2.0 mL, 25%_{w/w} in MeOH, 9.2 mmol) at 50° C. for 2 h. Later the reaction mixture was cooled to rt, concentrated under reduced pressure and purified by flash chromatography (SiO₂, 0-10% MeOH in DCM) provided N-(3-iodo-1H-indazol-5-yl)-2-isopropoxy-2-phenylacetamide as a light tan foam (141 mg, 40%). ¹H NMR (400 MHz, METHANOL-d₄) δ ppm 7.83 (s, 1H), 7.54-7.61 (m, 3H), 7.50 (d, J=7.50 Hz, 1H), 7.26-7.44 (m, 3H), 5.06 (s, 1H), 3.71-3.86 (m, 1H), 1.33 (d, J=6.02 Hz, 3H), 1.26 (d, J=6.02 Hz, 3H); MS ESI 436.1 [M+H]⁺, calcd for [C₁₈H₁₈N₃O₂+H]⁺ 436.0.

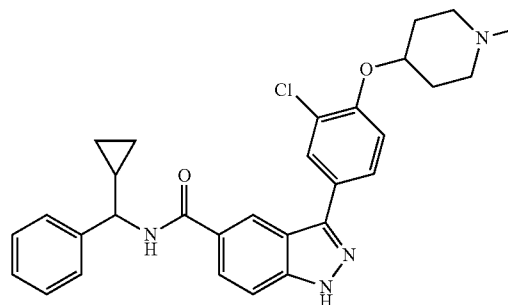
[0917] 2-isopropoxy-N-(3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazol-5-yl)-2-phenylacetamide was synthesized according to the General Method C2 utilizing N-(3-

iodo-1H-indazol-5-yl)-2-isopropoxy-2-phenylacetamide (100 mg, 0.23 mmol), 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine (94.7 mg, 0.30 mmol), PdCl₂dppfCH₂Cl₂ (9.4 mg, 0.011 mmol), satd aq Na₂CO₃ (0.5 mL) in PhMe (1.5 mL) and EtOH (1.5 mL) under microwave heating (130° C., 2 h). A TFA salt of 2-isopropoxy-N-(3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazol-5-yl)-2-phenylacetamide was isolated after flash chromatography (SiO₂, 5-90% MeOH-DCM) followed by RP HPLC (Biotage C18 column, MeOH—H₂O+0.1% TFA) as a white powder (39.3 mg, 28%). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.34 (s, 1H), 7.82 (d, J=8.78 Hz, 2H), 7.46-7.60 (m, 4H), 7.27-7.42 (m, 3H), 7.07 (d, J=8.78 Hz, 2H), 5.05 (s, 1H), 4.48 (br. s., 1H), 3.79 (spt, J=6.30 Hz, 1H), 2.74 (br. s., 2H), 2.40 (br. s., 2H), 2.32 (s, 3H), 2.04 (br. s., 2H), 1.85 (br. s., 2H), 1.32 (d, J=6.02 Hz, 3H), 1.25 (d, J=6.27 Hz, 3H); MS ESI [M+H]⁺ 499.4, calcd for [C₃₀H₃₄N₄O₃+H]⁺ 499.3.

Example A188

3-(3-chloro-4-((1-methylpiperidin-4-yl)oxy)phenyl)-N-(cyclopropyl(phenyl)methyl)-1H-indazole-5-carboxamide

[0918]

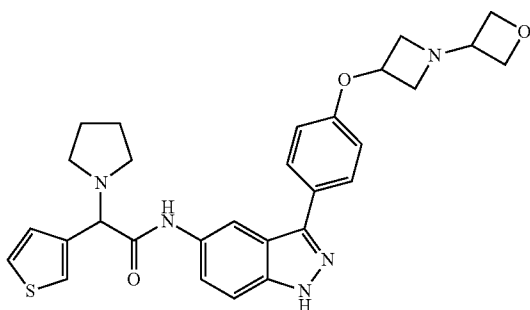


[0919] The title compound was synthesized according to the General Method C, utilizing N-(cyclopropyl(phenyl)methyl)-3-iodo-1H-indazole-5-carboxamide (100 mg, 0.24 mmol), 4-(2-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)-1-methylpiperidine (84 mg, 0.24 mmol), Pd(PPh₃)₄ (14 mg, 0.012 mmol), satd. aq Na₂CO₃ (1.25 mL), and 3.75 mL of PhMe:EtOH (1:1). The vial was charged with Ar and heated in the microwave reactor at 125° C. for 2 h. Purification by RPRPHPLC, followed by trituration with Et₂O gave the title compound as a TFA salt (white solid, 58 mg, 38%). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.57 (s, 1H), 8.04-8.09 (m, 1H), 7.91-7.99 (m, 2H), 7.63 (d, J=8.5 Hz, 1H), 7.49 (d, J=7.5 Hz, 2H), 7.30-7.39 (m, 3H), 7.25 (t, J=7.5 Hz, 1H), 4.68-4.78 (m, 0.3H), 4.46-4.53 (m, 1H), 3.62-3.70 (m, 0.7H), 3.35-3.53 (m, 3H), 3.14-3.26 (m, 1H), 2.91-2.98 (m, 3H), 2.42-2.51 (m, 0.7H), 2.29-2.38 (m, 1.3H), 2.08-2.20 (m, 1.3H), 1.92-2.06 (m, 0.7H), 1.36-1.46 (m, 1H), 0.63-0.71 (m, 2H), 0.43-0.54 (m, 2H); MS ESI 515.5 [M+H]⁺, calcd for [C₃₀H₃₁ClN₄O₂+H]⁺ 515.2.

Example A189

N-(3-(4-((1-(oxetan-3-yl)azetidin-3-yl)oxy)phenyl)-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide

[0920]



[0921] To a solution of tert-butyl 3-hydroxyazetidine-1-carboxylate (8.65 g, 50 mmol) in DMF (100 mL) at rt was added NaH (60% in mineral oil, 2.20 g, 55 mmol). After stirring for 5 min at rt, 1-fluoro-4-iodobenzene (11.10 g, 50 mmol) was added and the resulting mixture was heated at 85° C. (oil temp.) for 5 h, then O/N at 80° C. (oil temp.). After cooling to rt, it was quenched with H₂O (350 mL) and stirred for 15 min at rt. The resulting precipitates were collected by suction filtration, washed with H₂O and dried to give tert-butyl 3-(4-iodophenoxy)azetidine-1-carboxylate (yellow solid, 12.792 g, 68%). ¹H NMR (400 MHz, CDCl₃) δ 7.56 (d, J=9.2 Hz, 2H), 6.53 (d, J=8.8 Hz, 2H), 4.87-4.80 (m, 1H), 4.29 (dd, J=7.4 Hz, 2.6 Hz, 2H), 4.99 (dd, J=9.8 Hz, 4.2 Hz, 2H), 4.46 (s, (H); MS ESI 319.9 [M+H]⁺, calcd for [C₁₄H₁₈INO₃—C₄H₉+H]⁺ 320.0.

[0922] To a solution of tert-butyl 3-(4-iodophenoxy)azetidine-1-carboxylate (2.66 g, 7.10 mmol) in DCM (30 mL) was added TFA (10 mL). The resulting mixture was stirred O/N at rt. After removal of solvents, it was basified with satd aq NaHCO₃ (50 mL), extracted with DCM and evaporated to give 3-(4-iodophenoxy)azetidine (off white solid, 1.87 g, 96%). ¹H NMR (400 MHz, DMSO-d₆) δ 7.61 (d, J=8.8 Hz, 2H), 6.90 (d, J=8.8 Hz, 2H), 5.00 (quint, J=5.6 Hz, 1H), 4.18-4.40 (m, 2H), 3.80-3.74 (m, 2H); MS ESI 275.8 [M+H]⁺, calcd for [C₉H₁₀INO+H]⁺ 276.0.

[0923] To a suspension of 3-(4-iodophenoxy)azetidine (2.20 g, 8 mmol) in DCE (100 mL) was added oxetan-3-one (860 mg, 12 mmol), followed by NaBH(OAc)₃ (3.40 g, 16 mmol) and HOAc (0.2 mL). The resulting mixture was stirred O/N at rt. Additional oxetan-3-one (126 mg, 3 mmol) and NaBH(OAc)₃ (850 mg, 4 mmol) and the resulting mixture was stirred for 3 h at rt. It was quenched with satd aq NaHCO₃ (30 mL) and H₂O (30 mL), extracted with DCM and evaporated to give crude 3-(4-iodophenoxy)-1-(oxetan-3-yl)azetidine (light yellow solid, 2.34 g). ¹H NMR (400 MHz, DMSO-d₆) δ 7.58 (d, J=8.8 Hz, 2H), 6.68 (d, J=8.8 Hz, 2H), 4.81 (quint, J=5.6 Hz, 1H), 4.55 (t, J=6.6 Hz, 2H), 4.33 (t, J=5.8 Hz, 2H), 3.78-3.68 (m, 3H), 3.13-3.07 (m, 2H); MS ESI 331.9 [M+H]⁺, calcd for [C₁₂H₁₄IN₂O+H]⁺ 332.0.

[0924] To a mixture of crude 3-(4-iodophenoxy)-1-(oxetan-3-yl)azetidine (1.17 g, 3.53 mmol), Bis(pinacolato)diboron (988 mg, 3.89 mmol), KOAc (1.04 g, 10.6 mmol) was added DMF (10 mL), followed by Pd(dppf)Cl₂-CH₂Cl₂ (86

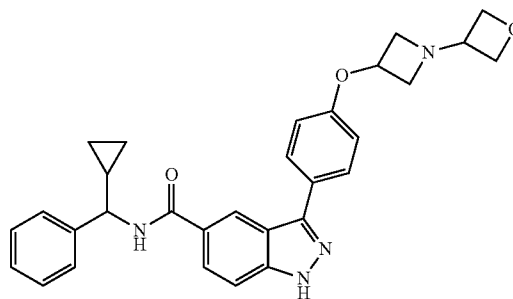
mg, 3 mol %). The resulting mixture was purged with Ar and microwaved 2 h at 85° C. This reaction was repeated on the same scale, combined, diluted with H₂O, extracted with EtOAc and purified by flash chromatography (MeOH/DCM 0-15%) twice to give crude 1-(oxetan-3-yl)-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)azetidine (brown oil, 1.996 g). ¹H NMR (400 MHz, CDCl₃) δ 8.02 (s, 1H), 7.74 (d, J=8.4 Hz, 2H), 6.77 (d, J=8.4 Hz, 2H), 4.93-4.86 (quint, 1H), 4.73 (t, J=6.8 Hz, 2H), 4.57 (pseudo t, J=6.0 Hz, 2H), 3.92-3.85 (m, 3H), 3.33-3.28 (m, 2H), 1.33 (s, 12H); MS ESI 332.1 [M+H]⁺, calcd for [C₁₈H₂₆BNO₄+H]⁺ 332.2.

[0925] To a mixture of N-(3-iodo-1H-indazol-5-yl)-2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetamide (181 mg, 0.4 mmol) and 1-(oxetan-3-yl)-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)azetidine (125 mg, 0.38 mmol) in EtOH (10 mL) was added 1 M aq Na₂CO₃ (0.8 mL, 0.8 mmol), followed by Pd(PPh₃)₄ (23 mg, 0.02 mmol). The resulting mixture was purged with Ar and microwaved 3 h at 125° C. After removal of solvents, it was purified by prep-HPLC, PoraPak and flash chromatography (MeOH/DCM 0-20%) to give the title compound (white solid, 54.5 mg, 26%). ¹H NMR (400 MHz, CD₃OD) δ 8.34 (s, 1H), 7.80 (d, J=8.8 Hz, 2H), 7.51-7.47 (m, 3H), 7.38 (dd, J=8.8 Hz, 2.8 Hz, 1H), 7.31 (dd, J=9.0 Hz, 1.0 Hz, 1H), 6.88 (d, J=8.8 Hz, 2H), 4.85 (quint, J=5.6 Hz, 1H), 4.72 (t, J=6.8 Hz, 2H), 4.48 (dd, J=6.8 Hz, 5.2 Hz, 2H), 4.13 (s, 1H), 3.85-3.77 (m, 3H), 3.29 (dd, J=9.2 Hz, 5.2 Hz, 2H), 2.70-2.62 (m, 2H), 2.53-2.45 (m, 2H), 1.85-1.76 (m, 4H); MS ESI 530.2 [M+H]⁺, calcd for [C₂₉H₃₁N₅O₃S+H]⁺ 530.2.

Example A190

N-(cyclopropyl(phenyl)methyl)-3-(4-((1-(oxetan-3-yl)azetidin-3-yl)oxy)phenyl)-1H-indazole-5-carboxamide

[0926]



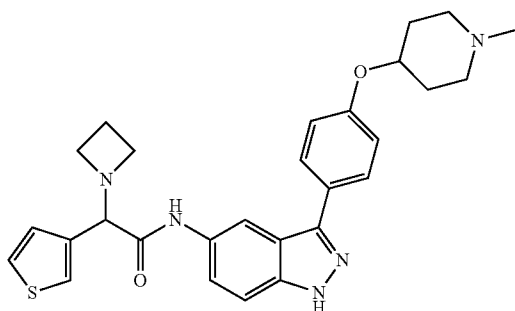
[0927] To a mixture of N-(cyclopropyl(phenyl)methyl)-3-iodo-1H-indazole-5-carboxamide (168 mg, 0.4 mmol) and 1-(oxetan-3-yl)-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)azetidine (125 mg, 0.38 mmol) in EtOH (10 mL) was added 1 M aq Na₂CO₃ (0.8 mL, 0.8 mmol), followed by Pd(PPh₃)₄ (23 mg, 0.02 mmol). The resulting mixture was purged with Ar and microwaved 3 h at 125° C. After removal of solvents, it was purified by prep-HPLC, PoraPak and flash chromatography (MeOH/DCM 0-20%) to give the title compound (white solid, 43.6 mg, 22%). ¹H NMR (400 MHz, CD₃OD) δ 8.61 (s, 1H), 7.96 (d, J=8.8 Hz, 1H), 7.90 (d, J=8.8 Hz, 2H), 7.59 (d, J=8.8 Hz, 1H), 7.47 (d, J=7.6 Hz, 2H), 7.31 (t, J=7.4 Hz, 2H), 7.22 (t, J=7.2 Hz, 1H),

6.93 (d, $J=8.8$ Hz, 2H), 4.90-4.86 (m, 1H, partially buried by H_2O peak), 4.74 (t, $J=6.8$ Hz, 2H), 4.45-4.45 (m, 3H), 3.89-3.80 (m, 3H), 3.35-3.28 (m, 2H; overlapped with CD_3OD solvent residue), 1.44-1.34 (m, 1H), 0.68-0.59 (m, 2H), 0.51-0.39 (m, 2H); MS ESI 495.4 $[M+H]^+$, calcd for $[C_{30}H_{30}N_4O_3+H]^+$ 495.2.

Example A191

2-(azetidin-1-yl)-N-(3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazol-5-yl)-2-(thiophen-3-yl)acetamide

[0928]



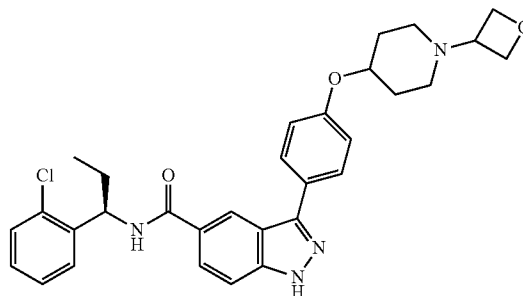
[0929] A suspension of 2-(azetidin-1-yl)-2-(thiophen-3-yl)acetic acid H_3BO_3 salt (2.59 g, 10 mmol) and 3-iodo-1H-indazol-5-amine (2.59 g, 10 mmol) in DMF (50 mL) was sonicated and stirred for 15 min at rt until a homogeneous suspension was obtained. TBUTU (3.21 g, 10 mmol) was added at $0^\circ C$, followed by iPr_2NEt (5.22 mL, 30 mmol). The resulting mixture was stirred for 1 h at $0^\circ C$, quenched with H_2O (200 mL), stirred for 10 min at rt, suction filtered and dried to give crude 2-(azetidin-1-yl)-N-(3-iodo-1H-indazol-5-yl)-2-(thiophen-3-yl)acetamide (brown solid, 2.973 g). LC-MS indicated a mixture of desired product 2-(azetidin-1-yl)-N-(3-iodo-1H-indazol-5-yl)-2-(thiophen-3-yl)acetamide and di-acylated byproduct. ^1H NMR (400 MHz, $CDCl_3$) δ 6 MS ESI 439.0 $[M+H]^+$, calcd for $[C_{16}H_{15}IN_4OS+H]^+$ 439.0.

[0930] To a mixture of crude 2-(azetidin-1-yl)-N-(3-iodo-1H-indazol-5-yl)-2-(thiophen-3-yl)acetamide (290 mg, assuming 0.5 mmol) and 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine (158 mg, 0.5 mmol) in EtOH (12 mL) was added 1 M aq Na_2CO_3 (1.5 mL, 1.5 mmol), followed by $Pd(PPh_3)_4$ (58 mg, 0.05 mmol). The resulting mixture was purged with Ar and microwaved 4 h at $125^\circ C$. After removal of solvents, it was purified by prep-HPLC, PoraPak, flash chromatography (MeOH/DCM 0-100%), biotage RP column (MeOH/ H_2O (1% TFA) 5-80%) and PoraPak to give the title compound (white solid, 35 mg, 14%). ^1H NMR (400 MHz, CD_3OD) δ 8.33 (s, 1H), 7.81 (d, $J=8.8$ Hz, 2H), 7.52-7.47 (m, 3H), 7.39 (dd, $J=9.0$ Hz, 3.0 Hz, 1H), 7.24 (dd, $J=5.0$ Hz, 1.0 Hz, 1H), 7.03 (d, $J=8.8$ Hz, 2H), 4.47-4.40 (m, 1H), 4.18 (s, 1H), 3.37 (q, $J=7.1$ Hz, 2H), 3.20 (q, $J=7.1$ Hz, 2H), 2.76-2.66 (m, 2H), 2.42-2.32 (m, 2H), 2.29 (s, 3H), 2.12 (quint, $J=7.2$ Hz, 2H), 2.06-1.97 (m, 2H), 1.86-1.76 (m, 2H); MS ESI 502.2 $[M+H]^+$, calcd for $[C_{28}H_{31}N_5O_2S+H]^+$ 502.2.

Example A192

(R)-N-(1-(2-chlorophenyl)propyl)-3-(4-((1-(oxetan-3-yl)piperidin-4-yl)oxy)phenyl)-1H-indazole-5-carboxamide

[0931]

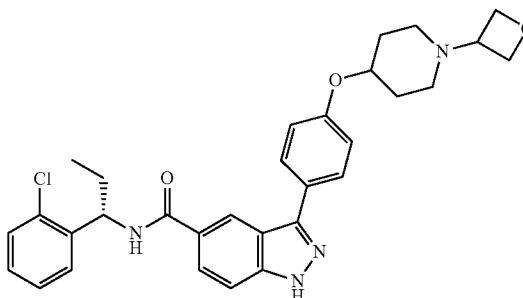


[0932] Using Method C2, (R)-N-(1-(2-chlorophenyl)propyl)-3-iodo-1H-indazole-5-carboxamide (45.1 mg, 95% pure, 0.097 mmol) and 1-(oxetan-3-yl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine (39.4 mg, 80% pure, 0.088 mmol) gave the title compound (off-white solid, 18.8 mg, 39%) after 14 h at $125^\circ C$ in reaction block with purification by flash chromatography (SiO_2 , 50-100% EtOAc in DCM, then 0-15% MeOH in EtOAc; followed by RPRP HPLC, 10-75% MeOH in 0.1% TFA- H_2O) and PoraPak RXn Cx work-up. ^1H NMR (400 MHz, CD_3OD) δ ppm 8.60 (s, 1H), 7.87-7.96 (m, 3H), 7.47-7.52 (m, 1H), 7.39 (d, $J=7.8$ Hz, 1H), 7.25-7.31 (m, 1H), 7.18-7.24 (m, 1H), 7.09 (d, $J=8.8$ Hz, 2H), 5.46 (dd, $J=9.0$, 5.8 Hz, 1H), 4.67-4.73 (m, 2H), 4.62 (t, $J=6.3$ Hz, 2H), 4.51 (br s., 1H), 3.53 (quin, $J=6.5$ Hz, 1H), 2.55-2.67 (m, 2H), 2.19-2.31 (m, 2H), 2.01-2.11 (m, 2H), 1.79-2.00 (m, 4H), 1.07 (t, $J=7.4$ Hz, 3H). MS ESI 545.4 $[M+H]^+$, calcd for $[C_{31}H_{33}ClN_4O_3+H]^+$ 545.23.

Example A193

(S)-N-(1-(2-chlorophenyl)propyl)-3-(4-((1-(oxetan-3-yl)piperidin-4-yl)oxy)phenyl)-1H-indazole-5-carboxamide

[0933]

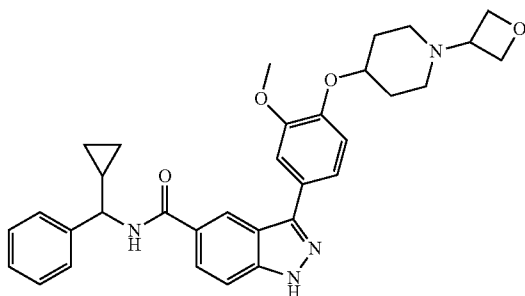


[0934] Using Method C2, (S)—N-(1-(2-chlorophenyl)propyl)-3-iodo-1H-indazole-5-carboxamide (45.3 mg, 0.103 mmol) and 1-(oxetan-3-yl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine (39.4 mg, 80% pure, 0.088 mmol) gave the title compound (off-white solid, 19.8 mg, 42%) after 14 h at 125° C. in reaction block with purification by flash chromatography (SiO₂, 100% EtOAc, then 0-100% DCM, then 0-10% MeOH in DCM; followed by RPRP HPLC, 10-90% MeOH in 0.1% TFA-H₂O) and Porapak RXn Cx work-up. ¹H NMR (400 MHz, CD₃OD) δ ppm 8.60 (s, 1H), 7.87-7.96 (m, 3H), 7.47-7.52 (m, 1H), 7.39 (d, J=7.8 Hz, 1H), 7.25-7.31 (m, 1H), 7.18-7.24 (m, 1H), 7.09 (d, J=8.8 Hz, 2H), 5.46 (dd, J=9.0, 5.8 Hz, 1H), 4.67-4.73 (m, 2H), 4.62 (t, J=6.3 Hz, 2H), 4.51 (br. s., 1H), 3.53 (quin, J=6.5 Hz, 1H), 2.55-2.67 (m, 2H), 2.19-2.31 (m, 2H), 2.01-2.11 (m, 2H), 1.79-2.00 (m, 4H), 1.07 (t, J=7.4 Hz, 3H). MS ESI 545.4 [M+H]⁺, calcd for [C₃₁H₃₃ClN₄O₃+H]⁺ 545.23.

Example A194

N-(cyclopropyl(phenyl)methyl)-3-(3-methoxy-4-((1-(oxetan-3-yl)piperidin-4-yl)oxy)phenyl)-1H-indazole-5-carboxamide

[0935]

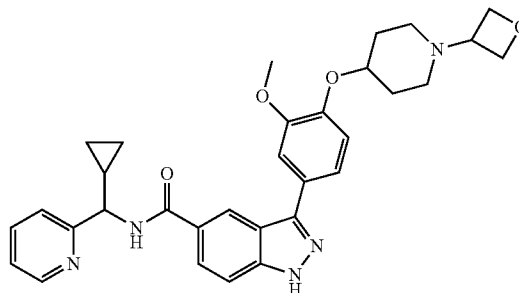


[0936] The title compound was synthesized according to the General Method C, utilizing N-(cyclopropyl(phenyl)methyl)-3-iodo-1H-indazole-5-carboxamide (50 mg, 0.12 mmol), 4-(2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)-1-(oxetan-3-yl)piperidine (46 mg, 0.12 mmol), Pd(PPh₃)₄ (7 mg, 0.006 mmol), satd. aq Na₂CO₃ (1.25 mL), and 3.75 mL of PhMe:EtOH (1:1). The vial was charged with Ar and heated in the microwave reactor at 125° C. for 2 h. Purification by RPRPHPLC, followed by trituration with Et₂O gave the title compound as a TFA salt (white solid, 30 mg, 38%). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.58 (s, 1H), 7.96 (d, J=8.8 Hz, 1H), 7.54-7.66 (m, 3H), 7.49 (d, J=7.8 Hz, 2H), 7.34 (t, J=7.4 Hz, 2H), 7.25 (t, J=7.8 Hz, 2H), 4.89-4.95 (m, 2H), 4.79-4.86 (m, 2H), 4.44-4.53 (m, 2H), 3.97 (s, 3H), 3.44-3.52 (m, 1H), 3.35-3.44 (m, 2H), 2.21-2.45 (m, 2H), 1.96-2.20 (m, 2H), 1.34-1.46 (m, 1H), 0.62-0.70 (m, 2H), 0.41-0.54 (m, 2H); MS ESI 553.5 [M+H]⁺, calcd for [C₃₃H₃₆N₄O₄+H]⁺ 553.3.

Example A195

N-(cyclopropyl(pyridin-2-yl)methyl)-3-(3-methoxy-4-((1-(oxetan-3-yl)piperidin-4-yl)oxy)phenyl)-1H-indazole-5-carboxamide

[0937]

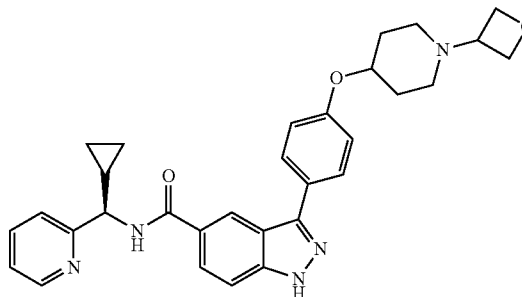


[0938] The title compound was synthesized according to the General Method C, utilizing N-(cyclopropyl(pyridin-2-yl)methyl)-3-iodo-1H-indazole-5-carboxamide (50 mg, 0.12 mmol), 4-(2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)-1-(oxetan-3-yl)piperidine (46 mg, 0.12 mmol), Pd(PPh₃)₄ (7 mg, 0.006 mmol), satd. aq Na₂CO₃ (1.25 mL), and 3.75 mL of PhMe:EtOH (1:1). The vial was charged with Ar and heated in the microwave reactor at 125° C. for 2 h. Purification by RPRPHPLC, followed by flash chromatography (SiO₂, Biotage 25 g, 0-30% MeOH in CH₂Cl₂) and trituration with Et₂O gave the title compound (white solid, 23 mg, 35%). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.65 (s, 1H), 8.49 (d, J=4.0 Hz, 1H), 7.95 (d, J=9.0 Hz, 1H), 7.78 (t, J=7.6 Hz, 1H), 7.46-7.63 (m, 4H), 7.28 (t, J=6.0 Hz, 1H), 7.06 (d, J=8.0 Hz, 1H), 4.66 (t, J=6.3 Hz, 2H), 4.58 (t, J=6.0 Hz, 2H), 4.50 (d, J=9.3 Hz, 1H), 4.33-4.42 (m, 1H), 3.91 (s, 3H), 3.48 (m, 1H), 2.60 (br. s., 2H), 2.16 (br. s., 2H), 1.97 (br. s., 2H), 1.84 (br. s., 2H), 1.32-1.44 (m, 1H), 0.60-0.70 (m, 1H), 0.45-0.59 (m, 3H); MS ESI 554.2 [M+H]⁺, calcd for [C₃₂H₃₅N₅O₄+H]⁺ 554.3.

Example A196

(R)—N-(cyclopropyl(pyridin-2-yl)methyl)-3-(4-((1-(oxetan-3-yl)piperidin-4-yl)oxy)phenyl)-1H-indazole-5-carboxamide

[0939]



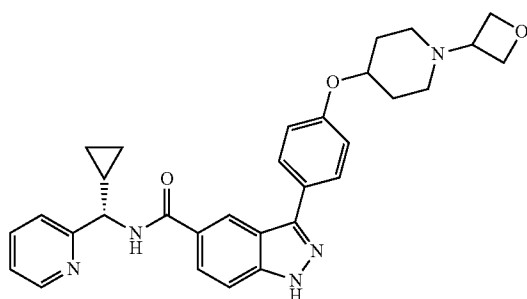
[0940] The title compound was synthesized according to Method C3 utilizing (R)-2-cyclopropyl-N-(3-iodo-1H-indazol-5-yl)-2-(pyridin-2-yl)acetamide and 1-(oxetan-3-yl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine and obtained as a white solid (42 mg, 42% yield). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.67 (s, 1H), 8.49 (d,

J=4.77 Hz, 1H), 7.96 (dd, J=8.78, 1.25 Hz, 1H), 7.89 (d, J=8.78 Hz, 2H), 7.75 (td, J=7.72, 1.63 Hz, 1H), 7.58 (d, J=8.78 Hz, 1H), 7.49 (d, J=8.03 Hz, 1H), 7.22-7.29 (m, 1H), 7.00 (d, J=8.78 Hz, 2H), 4.59-4.67 (m, 2H), 4.55 (t, J=6.15 Hz, 2H), 4.50 (d, J=9.54 Hz, 1H), 4.34-4.43 (m, 1H), 3.42 (quin, J=6.46 Hz, 1H), 2.51 (br. s., 2H), 2.12 (d, J=7.53 Hz, 2H), 1.96 (br. s., 2H), 1.76 (d, J=8.28 Hz, 2H), 1.30-1.43 (m, 1H), 0.58-0.69 (m, 1H), 0.44-0.58 (m, 3H); MS ESI $[M+H]^+$ 524.2, calcd for $[C_{31}H_{33}N_5O_3+H]^+$ 524.27.

Example A197

(S)—N-(cyclopropyl(pyridin-2-yl)methyl)-3-(4-((1-(oxetan-3-yl)piperidin-4-yl)oxy)phenyl)-1H-indazole-5-carboxamide

[0941]

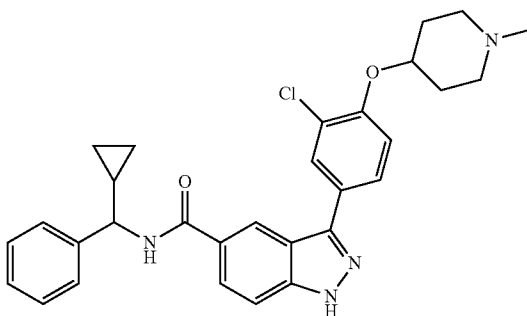


The title compound was synthesized according to Method C3 utilizing (S)-2-cyclopropyl-N-(3-iodo-1H-indazol-5-yl)-2-(pyridin-2-yl)acetamide and 1-(oxetan-3-yl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine and obtained as a white solid (44 mg, 44% yield). ^1H NMR (400 MHz, CD_3OD) δ ppm 8.67 (s, 1H) 8.49 (d, J=4.77 Hz, 1H), 7.96 (dd, J=8.78, 1.25 Hz, 1H), 7.89 (d, J=8.78 Hz, 2H), 7.75 (td, J=7.72, 1.63 Hz, 1H), 7.58 (d, J=8.78 Hz, 1H), 7.49 (d, J=8.03 Hz, 1H), 7.22-7.29 (m, 1H), 7.00 (d, J=8.78 Hz, 2H), 4.59-4.67 (m, 2H), 4.55 (t, J=6.15 Hz, 2H), 4.50 (d, J=9.54 Hz, 1H), 4.34-4.43 (m, 1H), 3.42 (quin, J=6.46 Hz, 1H), 2.51 (br. s., 2H), 2.12 (d, J=7.53 Hz, 2H), 1.96 (br. s., 2H), 1.76 (d, J=8.28 Hz, 2H), 1.30-1.43 (m, 1H), 0.58-0.69 (m, 1H), 0.44-0.58 (m, 3H); MS ESI $[M+H]^+$ 524.2, calcd for $[C_{31}H_{33}N_5O_3+H]^+$ 524.27.

Example A198

3-(3-chloro-4-((1-methylpiperidin-4-yl)oxy)phenyl)-N-(cyclopropyl(pyridin-2-yl)methyl)-1H-indazole-5-carboxamide

[0942]

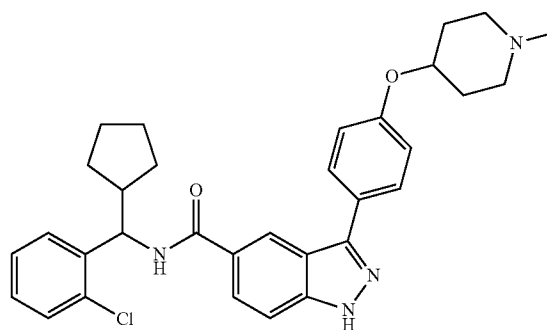


[0943] The title compound was synthesized according to the General Method C, utilizing N-(cyclopropyl(pyridin-2-yl)methyl)-3-iodo-1H-indazole-5-carboxamide (100 mg, 0.24 mmol), 4-(2-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)-1-methylpiperidine (84 mg, 0.24 mmol), $Pd(PPh_3)_4$ (14 mg, 0.012 mmol), satd. aq Na_2CO_3 (1.25 mL), and 3.75 mL of PhMe:EtOH (1:1). The vial was charged with Ar and heated in the microwave reactor at 125° C. for 2 h. Purification by RPRPHPLC, followed by flash chromatography (SiO_2 , Biotage 25 g, 0-30% MeOH in CH_2Cl_2) gave the title compound (white solid, 35 mg, 28%). ^1H NMR (400 MHz, CD_3OD) δ ppm 8.61 (s, 1H), 8.51 (d, J=4.8 Hz, 1H), 8.00 (d, J=2.3 Hz, 1H), 7.95 (dd, J=8.8, 1.2 Hz, 1H), 7.88 (dd, J=8.5, 2.3 Hz, 1H), 7.80 (td, J=7.7, 1.6 Hz, 1H), 7.59 (d, J=8.8 Hz, 1H), 7.53 (d, J=8.0 Hz, 1H), 7.30 (dd, J=6.9, 5.4 Hz, 1H), 7.23 (d, J=8.8 Hz, 1H), 4.61 (br. s., 1H), 4.50 (d, J=9.5 Hz, 1H), 2.80-2.92 (m, 2H), 2.54 (br. s., 2H), 2.37 (s, 3H), 2.00-2.09 (m, 2H), 1.88-1.99 (m, 2H), 1.35-1.45 (m, 1H), 0.65-0.72 (m, 1H), 0.49-0.62 (m, 3H); MS ESI 516.2 $[M+H]^+$, calcd for $[C_{29}H_{30}ClN_5O_2+H]^+$ 516.2.

Example A199

N-((2-chlorophenyl)(cyclopentyl)methyl)-3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazole-5-carboxamide

[0944]



[0945] A mixture of (2-chlorophenyl)(cyclopentyl)methanone (2.085 g, 10 mmol), NH_4OAc (9.24 g, 120 mmol) and $NaCNBH_3$ (2.52 g, 40 mmol) in MeOH (60 mL) was heated at 65° C. for 1 h, then left O/N at 60° C. After removal of solvent, it was purified by flash chromatography (MeOH/DCM 0-20%) to give (2-chlorophenyl)(cyclopentyl)methanamine (colorless oil, 876 mg, 42%). ^1H NMR (400 MHz, CD_3OD) δ 7.58 (dd, J=7.6 Hz, 1.6 Hz, 1H), 7.54 (dd, J=7.8 Hz, 1.4 Hz, 1H), 7.48 (dt, J=7.6 Hz, 1.6 Hz, 1H), 7.43 (dt, J=7.8 Hz, 1.8 Hz, 1H), 2.58-2.46 (m, 1H), 2.10-2.01 (m, 1H), 1.90-1.78 (m, 1H), 1.77-1.64 (m, 2H), 1.63-1.40 (m, 3H), 1.25-1.14 (m, 1H); MS ESI 193.0 $[M+H]^+$, calcd for $[C_{12}H_{16}ClN-NH_3+H]^+$ 193.1.

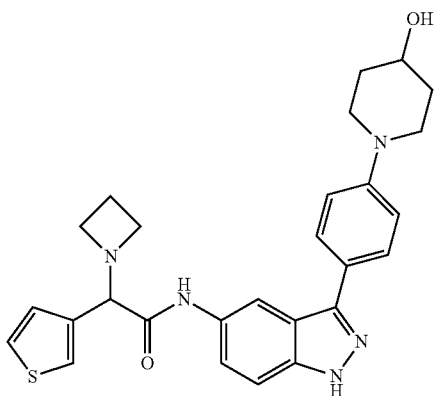
[0946] To a solution of (2-chlorophenyl)(cyclopentyl)methanamine (876 mg, 4.18 mmol), 3-iodo-1H-indazole-5-carboxamide (1.20 g, 4.18 mmol) in DMF (10 mL) at 0° C. was added TBTU (1.34 g, 4.18 mmol), followed by $^iPr_2NEt$ (1.45 mL, 8.36 mmol). The resulting mixture was stirred at 0° C. for 30 min, quenched with H_2O and stirred for 10 min at rt. Suction filtration gave crude N-((2-chlorophenyl)(cyclopentyl)methyl)-3-iodo-1H-indazole-5-carboxamide (light beige solid, 1.796 g). ^1H NMR (400 MHz, $CDCl_3$) δ 6 MS ESI 480.2 $[M+H]^+$, calcd for $[C_{20}H_{19}ClN_3O+H]^+$ 480.0.

[0947] To a mixture of crude N-((2-chlorophenyl)(cyclopentyl)methyl)-3-iodo-1H-indazole-5-carboxamide (241 mg, 0.5 mmol) and 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine (158 mg, 0.5 mmol) in EtOH (12 mL) was added 1 M aq Na₂CO₃ (1 mL, 1 mmol), followed by Pd(PPh₃)₄ (29 mg, 0.025 mmol). The resulting mixture was purged with Ar and microwaved 3 h at 125° C. After removal of solvents, it was purified by flash chromatography (MeOH/DCM 0-20%), prep-HPLC and PoraPak to give the title compound (white solid, 14.4 mg, 5%). ¹H NMR (400 MHz, CD₃OD) δ 8.53 (s, 1H), 7.88 (d, J=8.4 Hz, 3H), 7.60-7.55 (m, 2H), 7.38 (dd, J=7.8 Hz, 2.8 Hz, 1H), 7.29 (dt, J=7.6 Hz, 0.8 Hz, 1H), 7.20 (dt, J=7.8 Hz, 1.5 Hz, 1H), 7.08 (d, J=8.8 Hz, 2H), 5.44 (d, J=10.8 Hz, 1H), 4.53-4.46 (m, 1H), 2.80-2.70 (m, 2H), 2.65-2.52 (m, 1H), 2.47-2.36 (m, 2H), 2.33 (s, 3H), 2.10-1.94 (m, 3H), 1.90-1.50 (m, 7H), 1.45-1.38 (m, 2H); MS ESI 543.5 [M+H]⁺, calcd for [C₃₂H₃₅ClN₄O₂+H]⁺ 543.2.

Example A200

2-(azetidin-1-yl)-N-(3-(4-(4-hydroxypiperidin-1-yl)phenyl)-1H-indazol-5-yl)-2-(thiophen-3-yl)acetamide

[0948]

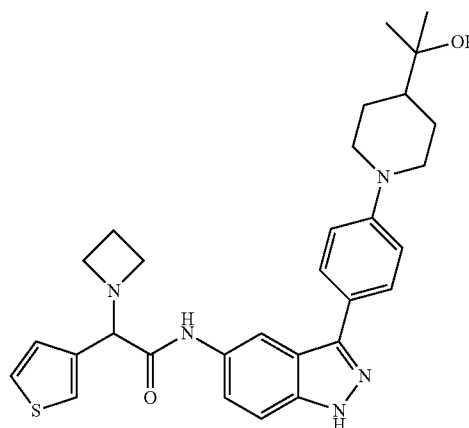


[0949] To a mixture of 2-(azetidin-1-yl)-2-(thiophen-3-yl)acetic acid H₃BO₃ salt (34 mg, 0.13 mmol), 1-(4-(5-amino-1H-indazol-3-yl)phenyl)piperidin-4-ol di-trifluoroacetic acid (70 mg, 0.13 mmol) in DMF (5 mL) at 0° C. was added TBTU (42 mg, 0.13 mmol), followed by ^tPr₂NEt (0.16 mL, 0.91 mmol). The resulting mixture was stirred for 1 h at 0° C. It was purified by prep-HPLC and PoraPakPoraPak to give the title compound (white solid, 30.2 mg, 31%). ¹H NMR (400 MHz, CD₃OD) δ 8.32 (s, 1H), 7.76 (d, J=8.8 Hz, 2H), 7.52-7.46 (m, 3H), 7.39 (dd, J=5.0 Hz, 3.0 Hz, 1H), 7.24 (d, J=4.8 Hz, 1H), 7.07 (d, J=8.4 Hz, 2H), 4.18 (s, 1H), 3.80-3.72 (m, 1H), 3.68-3.60 (m, 2H), 3.37 (q, J=6.9 Hz, 2H), 3.20 (q, J=6.9 Hz, 2H), 2.96-2.87 (m, 2H), 2.12 (quint, J=7.1 Hz, 2H), 2.00-1.92 (m, 2H), 1.70-1.59 (m, 2H); MS ESI 488.2 [M+H]⁺, calcd for [C₂₇H₂₉N₅O₂S+H]⁺ 488.2.

Example A201

2-(azetidin-1-yl)-N-(3-(4-(4-(2-hydroxypropan-2-yl)piperidin-1-yl)phenyl)-1H-indazol-5-yl)-2-(thiophen-3-yl)acetamide

[0950]

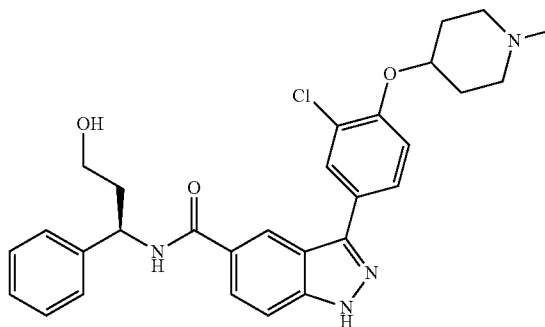


[0951] A di-TFA salt of the title compound was synthesized according to Method C3 utilizing 2-(azetidin-1-yl)-N-(3-iodo-1H-indazol-5-yl)-2-(thiophen-3-yl)acetamide and 2-(1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidin-4-yl)propan-2-ol obtained as an off-white solid (22 mg, 24% yield). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.41 (d, J=1.25 Hz, 1H), 8.15 (d, J=8.78 Hz, 2H), 7.86-7.90 (m, 1H), 7.84 (d, J=8.78 Hz, 2H), 7.64 (dd, J=5.14, 2.89 Hz, 1H), 7.56-7.61 (m, 1H), 7.49-7.55 (m, 1H), 7.30 (dd, J=5.02, 1.25 Hz, 1H), 5.51 (s, 1H), 4.27 (br. s., 3H), 3.63-3.87 (m, 5H), 2.53-2.71 (m, 1H), 2.36-2.53 (m, 1H), 2.21 (d, J=13.80 Hz, 2H), 1.87-2.03 (m, 2H), 1.84 (d, J=12.05 Hz, 1H), 1.23-1.31 (m, 6H); MS ESI [M+H]⁺ 530.2, calcd for [C₃₁H₃₃N₅O₃+H]⁺ 530.26.

Example A202

(R)-3-(3-chloro-4-((1-methylpiperidin-4-yl)oxy)phenyl)-N-(3-hydroxy-1-phenylpropyl)-1H-indazole-5-carboxamide

[0952]

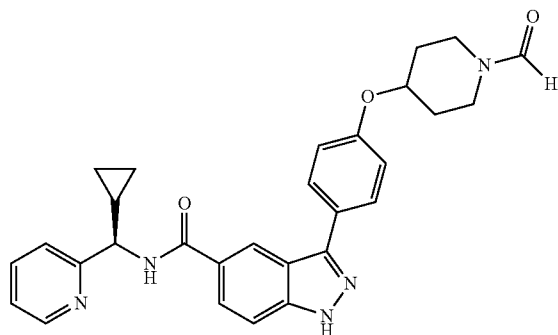


[0953] The title compound was synthesized according to the General Method C, utilizing (R)—N-(3-hydroxy-1-phenylpropyl)-3-iodo-1H-indazole-5-carboxamide (60 mg, 0.14 mmol), 4-(2-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)-1-methylpiperidine (50 mg, 0.14 mmol), Pd(PPh₃)₄ (8 mg, 0.007 mmol), satd. aq Na₂CO₃ (1.25 mL), and 3.75 mL of PhMe:EtOH (1:1). The vial was charged with Ar and heated in the microwave reactor at 125° C. for 2 h. Purification by RPHPLC, followed by flash chromatography (SiO₂, Biotage 25 g, 0-30% MeOH in CH₂Cl₂) gave the title compound (white solid, 22 mg, 30%). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.54 (s, 1H), 7.99 (d, J=2.0 Hz, 1H), 7.82-7.94 (m, 2H), 7.59 (d, J=8.8 Hz, 1H), 7.44 (d, J=7.8 Hz, 2H), 7.34 (t, J=7. Hz, 2H), 7.20-7.27 (m, 2H), 5.34 (dd, J=8.0, 6.8 Hz, 1H), 4.59 (br. s, 1H), 3.59-3.72 (m, 2H), 2.73 (br. s, 2H), 2.45 (br. s, 2H), 2.32 (s, 3H), 2.09-2.21 (m, 2H), 2.03 (d, J=3.5 Hz, 2H), 1.86-1.97 (m, 2H); MS ESI 519.5 [M+H]⁺, calcd for [C₂₉H₃₁ClN₄O₃+H]⁺ 519.2.

Example A203

(R)—N-(cyclopropyl(pyridin-2-yl)methyl)-3-(4-((1-formylpiperidin-4-yl)oxy)phenyl)-1H-indazole-5-carboxamide

[0954]

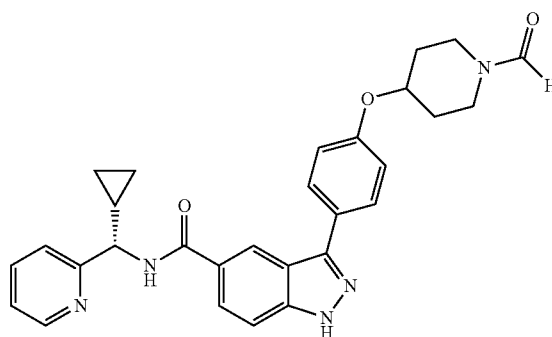


[0955] A TFA salt of the title compound was synthesized according to Method C3 utilizing (R)-2-cyclopropyl-N-(3-iodo-1H-indazol-5-yl)-2-(pyridin-2-yl)acetamide and 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine-1-carbaldehyde obtained as a white solid (33 mg, 38% yield). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.77 (dd, J=5.77, 0.75 Hz, 1H), 8.70 (s, 1H), 8.56 (t, J=7.15 Hz, 1H), 8.20 (d, J=8.03 Hz, 1H), 7.90-8.01 (m, 4H), 7.63 (d, J=8.78 Hz, 1H), 7.15 (d, J=8.78 Hz, 2H), 4.72-4.80 (m, 1H), 4.49 (d, J=10.04 Hz, 1H), 3.64-3.82 (m, 2H), 3.39-3.58 (m, 2H), 1.92-2.10 (m, 2H), 1.71-1.90 (m, 2H), 1.45-1.58 (m, 1H), 0.84-0.95 (m, 1H), 0.58-0.81 (m, 3H); MS ESI [M+H]⁺ 496.3, calcd for [C₂₉H₂₉N₅O₃+H]⁺ 496.23.

Example A204

(S)—N-(cyclopropyl(pyridin-2-yl)methyl)-3-(4-((1-formylpiperidin-4-yl)oxy)phenyl)-1H-indazole-5-carboxamide

[0956]

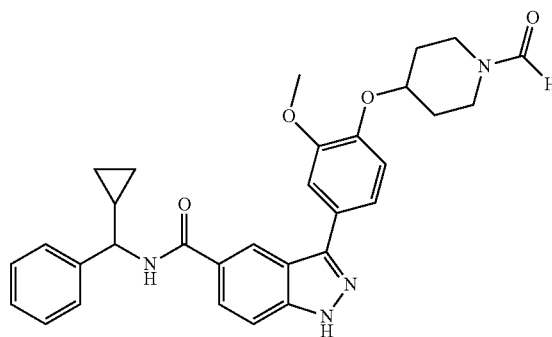


[0957] A TFA salt of the title compound was synthesized according to Method C3 utilizing (S)-2-cyclopropyl-N-(3-iodo-1H-indazol-5-yl)-2-(pyridin-2-yl)acetamide and 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine-1-carbaldehyde and obtained as a white solid (32 mg, 38% yield). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.77 (dd, J=5.77, 0.75 Hz, 1H), 8.70 (s, 1H), 8.56 (t, J=7.15 Hz, 1H), 8.20 (d, J=8.03 Hz, 1H), 7.90-8.01 (m, 4H), 7.63 (d, J=8.78 Hz, 1H), 7.15 (d, J=8.78 Hz, 2H), 4.72-4.80 (m, 1H), 4.49 (d, J=10.04 Hz, 1H), 3.64-3.82 (m, 2H), 3.39-3.58 (m, 2H), 1.92-2.10 (m, 2H), 1.71-1.90 (m, 2H), 1.45-1.58 (m, 1H), 0.84-0.95 (m, 1H), 0.58-0.81 (m, 3H); MS ESI [M+H]⁺ 496.3, calcd for [C₂₉H₂₉N₅O₃+H]⁺ 496.23.

Example A205

N-(cyclopropyl(phenyl)methyl)-3-(4-((1-formylpiperidin-4-yl)oxy)-3-methoxyphenyl)-1H-indazole-5-carboxamide

[0958]



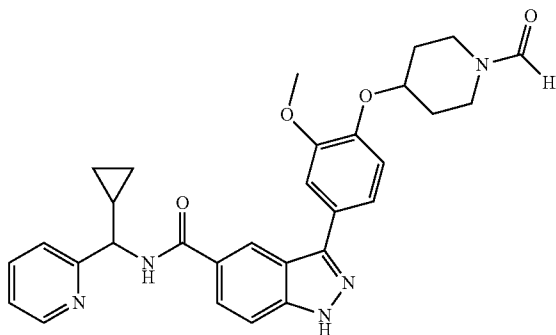
[0959] The title compound was synthesized according to the General Method C, utilizing N-(cyclopropyl(phenyl)methyl)-3-iodo-1H-indazole-5-carboxamide (100 mg, 0.24 mmol), 4-(2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine-1-carbaldehyde (86 mg, 0.24 mmol), Pd(PPh₃)₄ (14 mg, 0.012 mmol), satd. aq

Na_2CO_3 (1.25 mL), and 3.75 mL of PhMe:EtOH (1:1). The vial was charged with Ar and heated in the microwave reactor at 125° C. for 2 h. Purification by RPHPLC, followed by flash chromatography (SiO_2 , Biotage 25 g, 0-30% MeOH in CH_2Cl_2 , twice) gave the title compound (white solid, 25 mg, 20%). ^1H NMR (400 MHz, CD_3OD) δ ppm 8.61 (s, 1H), 8.01 (s, 1H), 7.94 (d, $J=8.8$ Hz, 1H), 7.50-7.61 (m, 3H), 7.46 (d, $J=7.3$ Hz, 2H), 7.31 (t, $J=7.5$ Hz, 2H), 7.22 (t, $J=7.3$ Hz, 1H), 7.10 (d, $J=8.0$ Hz, 1H), 4.61 (br. s, 1H), 4.47 (d, $J=9.3$ Hz, 1H), 3.91 (s, 3H), 3.63-3.78 (m, 2H), 3.44-3.53 (m, 1H), 3.33-3.41 (m, 1H), 1.69-1.99 (m, 4H), 1.32-1.43 (m, 1H), 0.56-0.72 (m, 2H), 0.39-0.53 (m, 2H); MS ESI 525.3 $[\text{M}+\text{H}]^+$, calcd for $[\text{C}_{31}\text{H}_{32}\text{N}_4\text{O}_4+\text{H}]^+$ 525.2.

Example A206

N-(cyclopropyl(pyridin-2-yl)methyl)-3-(4-((1-formylpiperidin-4-yl)oxy)-3-methoxyphenyl)-1H-indazole-5-carboxamide

[0960]

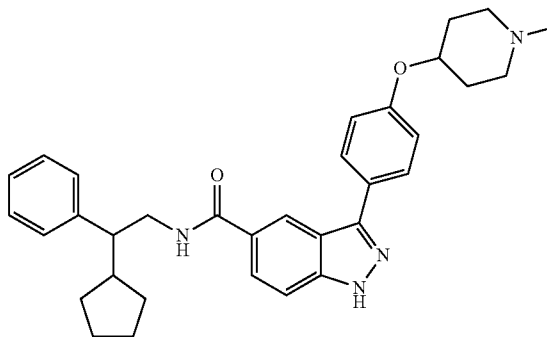


[0961] The title compound was synthesized according to the General Method C, utilizing N-(cyclopropyl(pyridin-2-yl)methyl)-3-iodo-1H-indazole-5-carboxamide (100 mg, 0.24 mmol), 4-(2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine-1-carbaldehyde (86 mg, 0.24 mmol), $\text{Pd}(\text{PPh}_3)_4$ (14 mg, 0.012 mmol), satd. aq Na_2CO_3 (1.25 mL), and 3.75 mL of PhMe:EtOH (1:1). The vial was charged with Ar and heated in the microwave reactor at 125° C. for 2 h. Purification by RPHPLC and trituration with Et_2O gave the title compound (white solid, 43 mg, 34%). ^1H NMR (400 MHz, CD_3OD) δ ppm 8.73 (d, $J=5.5$ Hz, 1H), 8.68 (s, 1H), 8.41-8.49 (m, 1H), 8.10 (d, $J=8.0$ Hz, 1H), 8.04 (s, 1H), 7.98 (dd, $J=8.9, 1.4$ Hz, 1H), 7.85 (t, $J=6.8$ Hz, 1H), 7.63 (d, $J=9.0$ Hz, 1H), 7.54-7.60 (m, 2H), 7.17 (d, $J=8.3$ Hz, 1H), 4.63-4.70 (m, 1H), 4.49 (d, $J=10.0$ Hz, 1H), 3.68-3.80 (m, 2H), 3.48-3.57 (m, 1H), 3.41 (d, $J=4.8$ Hz, 1H), 1.73-2.03 (m, 4H), 1.43-1.54 (m, 1H), 0.81-0.90 (m, 1H), 0.58-0.77 (m, 3H); MS ESI 526.4 $[\text{M}+\text{H}]^+$, calcd for $[\text{C}_{30}\text{H}_{31}\text{N}_5\text{O}_4+\text{H}]^+$ 526.2.

Example A207

N-(2-cyclopentyl-2-phenylethyl)-3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazole-5-carboxamide

[0962]

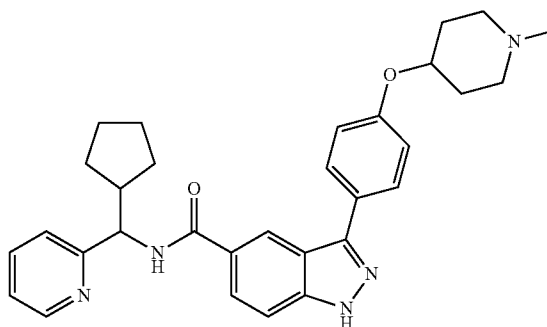


[0963] The title compound was synthesized according to the General Method C, utilizing N-(2-cyclopentyl-2-phenylethyl)-3-iodo-1H-indazole-5-carboxamide (50 mg, 0.11 mmol), 4-((1-methylpiperidin-4-yl)oxy)phenylboronic acid pinacol ester (35 mg, 0.11 mmol), $\text{Pd}(\text{PPh}_3)_4$ (6 mg, 0.0055 mmol), satd. aq Na_2CO_3 (0.5 mL), and 1.5 mL of PhMe:EtOH (1:1). The vial was charged with Ar and heated in the microwave reactor at 125° C. for 2 h. Purification by RPHPLC gave the title compound as a TFA salt (white solid, 24 mg, 34%). ^1H NMR (400 MHz, CD_3OD) δ ppm 8.19 (s, 1H), 7.85 (t, $J=8.3$ Hz, 2H), 7.64 (d, $J=8.8$ Hz, 1H), 7.51 (d, $J=8.8$ Hz, 1H), 7.21-7.31 (m, 4H), 7.11-7.21 (m, 3H), 4.63-4.73 (m, 0.3H), 3.85-3.93 (m, 1H), 3.62-3.69 (m, 0.7H), 3.34-3.56 (m, 4H), 3.15-3.27 (m, 1H), 2.91-2.97 (m, 3H), 2.75-2.86 (m, 1H), 2.40-2.48 (m, 0.7H), 2.23-2.37 (m, 1.3H), 2.010-2.20 (m, 3.3H), 1.87-2.00 (m, 0.7H), 1.35-1.77 (m, 6H), 0.96-1.10 (m, 1H); MS ESI 523.4 $[\text{M}+\text{H}]^+$, calcd for $[\text{C}_{33}\text{H}_{38}\text{N}_4\text{O}_2+\text{H}]^+$ 523.3.

Example A208

N-(cyclopentyl(pyridin-2-yl)methyl)-3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazole-5-carboxamide

[0964]



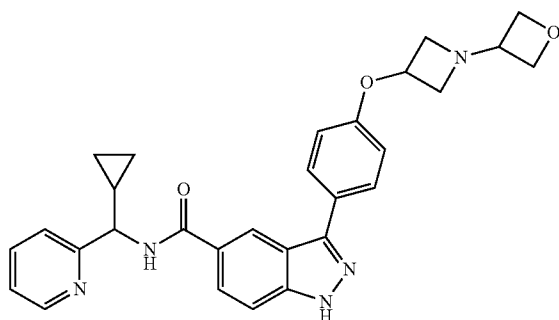
[0965] The title compound was synthesized according to the General Method C, utilizing N-(cyclopentyl(pyridin-2-

yl)methyl)-3-iodo-1H-indazole-5-carboxamide (100 mg, 0.22 mmol), (4-((1-methylpiperidin-4-yl)oxy)phenyl)boronic acid pinacol ester (70 mg, 0.22 mmol), Pd(PPh₃)₄ (13 mg, 0.011 mmol), satd. aq Na₂CO₃ (1.25 mL), and 3.75 mL of PhMe:EtOH (1:1). The vial was charged with Ar and heated in the microwave reactor at 125° C. for 2 h. Purification by RPHPLC followed by flash chromatography (SiO₂, Biotage 25 g, 0-30% MeOH in CH₂Cl₂) gave the title compound (white solid, 43 mg, 38%). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.57 (s, 1H), 8.51 (d, J=4.3 Hz, 1H), 7.86-7.94 (m, 3H), 7.79 (t, J=7.6 Hz, 1H), 7.59 (d, J=8.8 Hz, 1H), 7.49 (d, J=7.8 Hz, 1H), 7.29 (dd, J=7.0, 5.0 Hz, 1H), 7.10 (d, J=8.5 Hz, 2H), 5.01 (d, J=10.3 Hz, 1H), 4.52 (br. s, 1H), 2.82 (br. s, 2H), 2.46-2.58 (m, 3H), 2.39 (s, 3H), 1.81-2.12 (m, 5H), 1.45-1.76 (m, 5H), 1.20-1.41 (m, 2H); MS ESI 510.2 [M+H]⁺, calcd for [C₃₁H₃₅N₅O₂+H]⁺ 510.3.

Example A209

N-(cyclopropyl(pyridin-2-yl)methyl)-3-(4-((1-(oxetan-3-yl)azetidin-3-yl)oxy)phenyl)-1H-indazole-5-carboxamide

[0966]



[0967] To a 20 mL microwave vial charged with Mg powder (240 mg, 10 mmol), THF (10 mL) was added bromocyclopropane (1.21 g, 10 mmol). The resulting mixture was stirred for 30 min at rt before a solution of picolinonitrile (520 mg, 5 mmol) in THF (3 mL) was added. It was microwaved 10 min at 100° C., cooled to rt and added dropwise to a cold solution of NaBH₄ (380 mg, 10 mmol) in MeOH (30 mL) at 0° C. The resulting mixture was stirred for 15 min at rt, quenchd with H₂O, extracted with DCM and purified by flash chromatography (MeOH/DCM 0-30%) to give cyclopropyl (pyridin-2-yl)methanamine (light brown oil, 590 mg). ¹H NMR (400 MHz, CDCl₃) δ 8.52 (d, J=4.0 Hz, 1H), 7.82 (dt, J=7.6 Hz, 1.6 Hz, 1H), 7.50 (d, J=8.0 Hz, 1H), 7.34-7.39 (m, 1H), 3.25 (d, J=8.8 Hz, 1H), 1.18-1.10 (m, 1H), 0.70-0.62 (m, 1H), 0.54-0.42 (m, 2H), 0.40-0.34 (m, 1H); MS ESI 132.0 [M+H]⁺, calcd for [C₉H₁₂N₂—NH₃+H]⁺ 132.1.

[0968] To a solution of cyclopropyl(pyridin-2-yl)methanamine (575 mg, 3.94 mmol), 3-iodo-1H-indazole-5-carboxamide (1.14 g, 3.94 mmol) in DMF (15 mL) at 0° C. was added TBTU (1.27 g, 3.94 mmol), followed by ^tPr₂NEt (1.37 mL, 7.88 mmol). The resulting mixture was stirred at rt for 30 min, quenched with H₂O till total volume about 100 mL and stirred for 10 min at rt. Suction filtration gave crude N-(cyclopropyl(pyridin-2-yl)methyl)-3-iodo-1H-indazole-5-car-

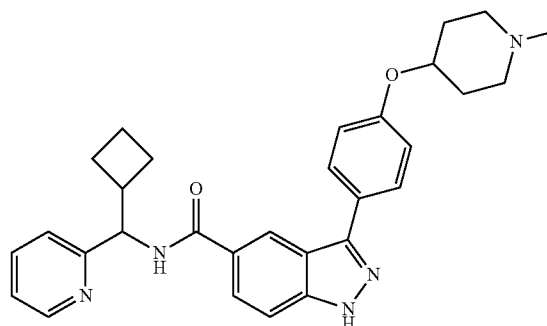
boxamide (off white solid, 1.290 g). MS ESI 419.0 [M+H]⁺, calcd for [C₁₇H₁₅IN₄O+H]⁺ 419.0.

[0969] To a mixture of crude N-(cyclopropyl(pyridin-2-yl)methyl)-3-iodo-1H-indazole-5-carboxamide (209 mg, 0.5 mmol) and 1-(oxetan-3-yl)-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)azetidine (166 mg, 0.5 mmol) in EtOH (12 mL) was added 1 M aq Na₂CO₃ (1 mL, 1 mmol), followed by Pd(PPh₃)₄ (29 mg, 0.025 mmol). The resulting mixture was purged with Ar and microwaved 4 h at 125° C. After removal of solvents, it was purified by flash chromatography (MeOH/DCM 0-20%), prep-HPLC and PoraPak to give the title compound (white solid, 40.0 mg, 16%). ¹H NMR (400 MHz, CD₃OD) δ 8.64 (s, 1H), 8.51 (d, J=4.4 Hz, 1H), 7.96 (dd, J=9.0 Hz, 1.4 Hz, 1H), 7.92 (d, J=8.8 Hz, 2H), 7.80 (dt, J=7.8 Hz, 1.6 Hz, 1H), 7.60 (d, J=8.8 Hz, 1H), 7.52 (d, J=8.0 Hz, 1H), 7.32-7.27 (m, 1H), 6.96 (d, J=8.8 Hz, 2H), 4.96-4.90 (m, 1H, partially buried under H₂O peak), 4.75 (t, J=6.6 Hz, 2H), 4.53-4.47 (m, 3H), 3.90-3.83 (m, 3H), 3.38-3.33 (m, 2H, partially overlapped with CD₃OD solvent residue), 1.45-1.35 (m, 1H), 0.72-0.65 (m, 1H), 0.62-0.50 (m, 3H); MS ESI 496.2 [M+H]⁺, calcd for [C₂₉H₂₉N₅O₃+H]⁺ 496.2.

Example A210

N-(cyclobutyl(pyridin-2-yl)methyl)-3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazole-5-carboxamide

[0970]

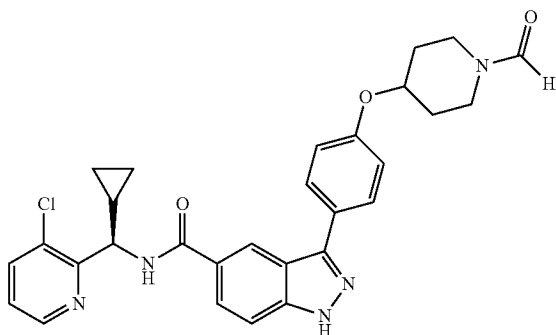


[0971] The title compound was synthesized according to the General Method C, utilizing N-(cyclobutyl(pyridin-2-yl)methyl)-3-iodo-1H-indazole-5-carboxamide (200 mg, 0.46 mmol), (4-((1-methylpiperidin-4-yl)oxy)phenyl)boronic acid pinacol ester (147 mg, 0.46 mmol), Pd(PPh₃)₄ (27 mg, 0.023 mmol), satd. aq Na₂CO₃ (1.25 mL), and 3.75 mL of PhMe:EtOH (1:1). The vial was charged with Ar and heated in the microwave reactor at 125° C. for 3 h. Purification by RPHPLC followed by flash chromatography (SiO₂, Biotage 25 g, 0-30% MeOH in CH₂Cl₂) gave the title compound (white solid, 70 mg, 31%). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.58 (s, 1H), 8.51 (d, J=4.3 Hz, 1H), 7.93 (d, J=8.5 Hz, 3H), 7.80 (td, J=7.8, 1.5 Hz, 1H), 7.60 (d, J=8.8 Hz, 1H), 7.48 (d, J=8.0 Hz, 1H), 7.27-7.33 (m, 1H), 7.14 (d, J=8.5 Hz, 2H), 5.19 (d, J=10.3 Hz, 1H), 4.60 (br. s, 1H), 2.86-2.98 (m, 3H), 2.65 (br. s, 2H), 2.48 (s, 3H), 2.16-2.25 (m, 1H), 2.05-2.16 (m, 2H), 1.86-2.04 (m, 6H), 1.76-1.86 (m, 1H); MS ESI 496.2 [M+H]⁺, calcd for [C₃₀H₃₃N₅O₂+H]⁺ 496.3.

Example A211

(R)—N-((3-chloropyridin-2-yl)(cyclopropyl)methyl)-3-(4-(((1-formylpiperidin-4-yl)oxy)phenyl)-1H-indazole-5-carboxamide

[0972]

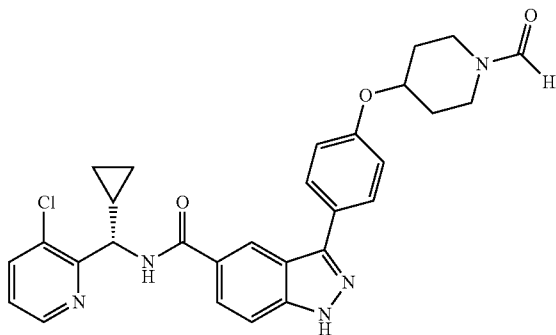


[0973] A TFA salt of the title compound was synthesized according to Method C3 utilizing (R)-2-(3-chloropyridin-2-yl)-2-cyclopropyl-N-(3-iodo-1H-indazol-5-yl)acetamide and 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine-1-carbaldehyde obtained as a light yellow solid (42 mg, 48% yield). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.64 (s, 1H), 8.53 (d, J=3.51 Hz, 1H), 8.04 (s, 1H), 7.93 (t, J=9.16 Hz, 4H), 7.59 (d, J=9.03 Hz, 1H), 7.36 (dd, J=8.16, 4.89 Hz, 1H), 7.10 (d, J=8.78 Hz, 2H), 5.13 (d, J=9.03 Hz, 1H), 4.71 (br. s., 1H), 3.62-3.80 (m, 2H), 3.46-3.58 (m, 1H), 3.36-3.46 (m, 1H), 1.97 (d, J=13.30 Hz, 2H), 1.69-1.86 (m, 2H), 1.51 (d, J=6.27 Hz, 1H), 0.46-0.74 (m, 4H); MS ESI [M+H]⁺ 530.4, calcd for [C₂₉H₂₈ClN₅O₃+H]⁺ 530.20.

Example A212

(S)—N-((3-chloropyridin-2-yl)(cyclopropyl)methyl)-3-(4-(((1-formylpiperidin-4-yl)oxy)phenyl)-1H-indazole-5-carboxamide

[0974]



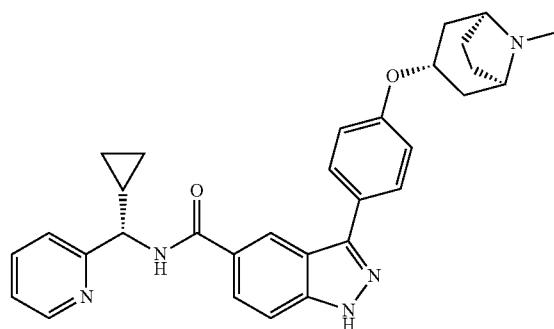
[0975] The title compound was synthesized according to Method C3 utilizing (S)-2-(3-chloropyridin-2-yl)-2-cyclopropyl-N-(3-iodo-1H-indazol-5-yl)acetamide and 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine-1-carbaldehyde and obtained as a light yellow solid (36 mg, 49% yield). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.63 (s,

1H), 8.46 (d, J=4.52 Hz, 1H), 8.00 (s, 1H), 7.93 (dd, J=8.78, 1.25 Hz, 1H), 7.87 (d, J=8.28 Hz, 2H), 7.79 (d, J=8.28 Hz, 1H), 7.56 (d, J=8.78 Hz, 1H), 7.20-7.28 (m, 1H), 6.97-7.06 (m, 2H), 5.19 (d, J=9.03 Hz, 1H), 4.62 (m, J=3.30 Hz, 1H), 3.65-3.75 (m, 1H), 3.55-3.65 (m, 1H), 3.41-3.51 (m, 1H), 3.28-3.39 (m, 1H), 1.92 (br. s., 2H), 1.71 (br. s., 2H), 1.40-1.53 (m, 1H), 0.54-0.66 (m, 2H), 0.50 (d, J=6.02 Hz, 2H); MS ESI [M+H]⁺ 530.4, calcd for [C₂₉H₂₈ClN₅O₃+H]⁺ 530.20.

Example A213

N-((S)-cyclopropyl(pyridin-2-yl)methyl)-3-(4-(((1R,3r,5S)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)phenyl)-1H-indazole-5-carboxamide

[0976]

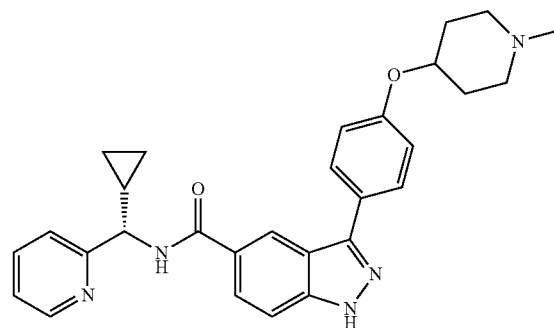


The title compounds was synthesized according to the General Method C2 utilizing (S)—N-(cyclopropyl(pyridin-2-yl)methyl)-3-iodo-1H-indazole-5-carboxamide (60 mg, 0.14 mmol) and (1R,3r,5S)-8-methyl-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)-8-azabicyclo[3.2.1]octane (33 mg, 0.099 mmol) to afford N-((S)-cyclopropyl(pyridin-2-yl)methyl)-3-(4-(((1R,3r,5S)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)phenyl)-1H-indazole-5-carboxamide as a white powder (14.3 mg, 28%). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.66 (s, 1H), 8.53 (d, J=4.02 Hz, 1H), 7.89-8.01 (m, 3H), 7.79-7.87 (m, 1H), 7.61 (d, J=8.78 Hz, 1H), 7.54 (s, 1H), 7.32 (dd, J=6.90, 5.40 Hz, 1H), 7.04 (d, J=8.53 Hz, 2H), 4.61-4.72 (m, 1H), 4.50 (d, J=9.54 Hz, 1H), 3.21 (br. s., 2H), 2.34 (s, 3H), 1.98-2.26 (m, 8H), 1.34-1.48 (m, 1H), 0.67-0.77 (m, 1H), 0.46-0.65 (m, 3H); MS ESI 508.2 [M+H]⁺, calcd for [C₃₁H₃₃N₅O₂+H]⁺ 508.2.

Example A214

(S)—N-(cyclopropyl(pyridin-2-yl)methyl)-3-(4-(((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazole-5-carboxamide

[0977]

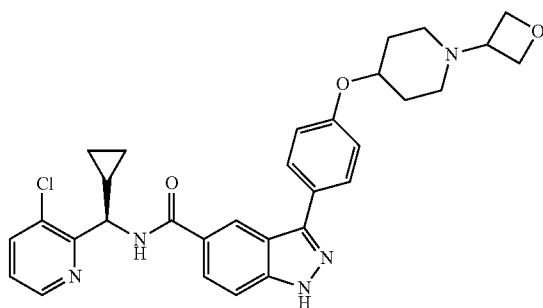


[0978] The title compound was synthesized according to the General Method C, utilizing (S)—N-(cyclopropyl(pyridin-2-yl)methyl)-3-iodo-1H-indazole-5-carboxamide (50 mg, 0.12 mmol), 4-(((1-methylpiperidin-4-yl)oxy)phenyl)boronic acid pinacol ester (38 mg, 0.12 mmol), Pd(PPh₃)₄ (7 mg, 0.006 mmol), satd. aq Na₂CO₃ (1.25 mL), and 3.75 mL of PhMe:EtOH (1:1). The vial was charged with Ar and heated in the microwave reactor at 125° C. for 3 h. Purification by RPHPLC followed by flash chromatography (SiO₂, Biotage 25 g, 0-30% MeOH in CH₂Cl₂) gave the title compound (white solid, 21 mg, 36%). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.64 (s, 1H), 8.52 (d, J=4.8 Hz, 1H), 7.94 (s, 3H), 7.82 (td, J=7.6, 1.8 Hz, 1H), 7.60 (d, J=8.8 Hz, 1H), 7.54 (d, J=7.8 Hz, 1H), 7.29-7.35 (m, 1H), 7.12 (d, J=8.8 Hz, 2H), 4.53 (br. s, 1H), 4.50 (d, J=9.5 Hz, 1H), 2.76 (br. s, 2H), 2.43 (br. s, 2H), 2.33 (s, 3H), 2.02-2.11 (m, 2H), 1.81-1.91 (m, 2H), 1.35-1.46 (m, 1H), 0.65-0.74 (m, 1H), 0.49-0.62 (m, 3H); MS ESI 482.2 [M+H]⁺, calcd for [C₂₉H₃₁N₅O₂+H]⁺ 482.3.

Example A215

(R)—N-((3-chloropyridin-2-yl)(cyclopropyl)methyl)-3-(4-(((1-(oxetan-3-yl)piperidin-4-yl)oxy)phenyl))-1H-indazole-5-carboxamide

[0979]

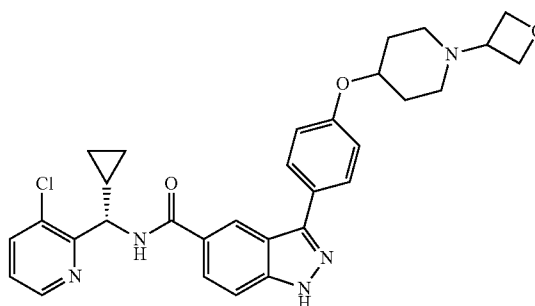


[0980] The title compound was synthesized according to Method C3 utilizing (R)-2-(3-chloropyridin-2-yl)-2-cyclopropyl-N-(3-iodo-1H-indazol-5-yl)acetamide and 1-(oxetan-3-yl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine and obtained as a white solid (30 mg, 48% yield). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.65 (s, 1H), 8.47 (dd, J=4.64, 1.38 Hz, 1H), 7.94 (dd, J=8.78, 1.51 Hz, 1H), 7.88 (d, J=8.53 Hz, 2H), 7.81 (dd, J=8.16, 1.38 Hz, 1H), 7.57 (d, J=8.78 Hz, 1H), 7.25 (dd, J=8.16, 4.64 Hz, 1H), 7.01 (d, J=8.78 Hz, 2H), 5.19 (d, J=9.03 Hz, 1H), 4.60-4.68 (m, 2H), 4.56 (t, J=6.27 Hz, 2H), 4.35-4.45 (m, 1H), 3.44 (quin, J=6.46 Hz, 1H), 2.53 (br. s., 2H), 2.15 (br. s., 2H), 1.97 (br. s., 2H), 1.78 (d, J=8.53 Hz, 2H), 1.40-1.53 (m, 1H), 0.55-0.66 (m, 2H), 0.43-0.55 (m, 2H); MS ESI [M+H]⁺ 558.4, calcd for [C₃₁H₃₂ClN₅O₃+H]⁺ 558.23.

Example A216

(S)—N-((3-chloropyridin-2-yl)(cyclopropyl)methyl)-3-(4-(((1-(oxetan-3-yl)piperidin-4-yl)oxy)phenyl))-1H-indazole-5-carboxamide

[0981]



[0982] The title compound was synthesized according to Method C3 utilizing (S)-2-(3-chloropyridin-2-yl)-2-cyclopropyl-N-(3-iodo-1H-indazol-5-yl)acetamide and 1-(oxetan-3-yl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine and obtained as a white solid (26 mg, 42% yield). ¹H NMR (400 MHz, CD₃OD) δ ppm 8.65 (s, 1H), 8.47 (dd, J=4.64, 1.38 Hz, 1H), 7.94 (dd, J=8.78, 1.51 Hz, 1H), 7.88 (d, J=8.53 Hz, 2H), 7.81 (dd, J=8.16, 1.38 Hz, 1H), 7.57 (d, J=8.78 Hz, 1H), 7.25 (dd, J=8.16, 4.64 Hz, 1H), 7.01 (d, J=8.78 Hz, 2H), 5.19 (d, J=9.03 Hz, 1H), 4.60-4.68 (m, 2H), 4.56 (t, J=6.27 Hz, 2H), 4.35-4.45 (m, 1H), 3.44 (quin, J=6.46 Hz, 1H), 2.53 (br. s., 2H), 2.15 (br. s., 2H), 1.97 (br. s., 2H), 1.78 (d, J=8.53 Hz, 2H), 1.40-1.53 (m, 1H), 0.55-0.66 (m, 2H), 0.43-0.55 (m, 2H); MS ESI [M+H]⁺ 558.4, calcd for [C₃₁H₃₂ClN₅O₃+H]⁺ 558.23.

Example B

TTK Inhibition Assay

[0983] Active TTK was purchased from Invitrogen as an amino terminal GST fusion of full length human TTK. Amino terminal 6 histidine, sumo tagged human TTK (residues 1-275) was expressed in *E. coli*, and purified to >95% homogeneity by Ni²⁺ agarose, gel filtration, and ion exchange chromatography.

[0984] TTK activity was measured using an indirect ELISA detection system. GST-TTK (0.68 nM) was incubated in the presence of 16 μM ATP (Sigma cat#A7699), 50 mM Hepes pH 7.2, 1 mM EGTA, 10 mM MgCl₂, and 0.1% Pluronic in a 96 well microtitre plate pre-coated with amino terminal 6 histidine, sumo tagged TTK (amino acid residues 1-275). The reaction was allowed to proceed for 30 minutes, followed by 5 washes of the plate with Wash Buffer (phosphate buffered saline supplemented with 0.2% Tween 20), and incubation for 30 minutes with a 1:3000 dilution of primary antibody (Cell Signaling cat#9381). The plate was washed 5 times with Wash Buffer, incubated for 30 minutes in the presence of secondary antibody coupled to horseradish peroxidase (BioRad cat#1721019, 1:3000 concentration), washed an additional 5 times with Wash Buffer, and incubated in the presence of TMB substrate (Sigma cat#T0440). The colourimetric reaction was allowed to continue for 5 minutes, followed by addition of stop solution (0.5 N sulphu-

ric acid), and quantified by detection at 450 nm with either a monochromatic or filter based plate reader (Molecular Devices M5 or Beckman DTX880, respectively).

[0985] Compound inhibition was determined at either a fixed concentration (10 μ M) or at a variable inhibitor concentration (typically 0.5 μ M to 0.001 μ M in a 10 point dose response titration). Compounds were pre-incubated in the presence of enzyme for 5 minutes prior to addition of ATP and the activity remaining quantified using the above described activity assay. The % Inhibition of a compound was determined using the following formula; % Inhibition=100 $\times$ (1-(experimental value-background value)/(high activity control-background value)). The IC₅₀ value was determined using a non-linear 4 point logistic curve fit (XLfit4, IDBS) with the formula; $(A+(B/(1+((x/C)^D))))$, where A=background value, B=range, C=inflection point, D=curve fit parameter.

Example C

PLK4 Inhibition Assay

[0986] Active PLK4 was purified from an *E. coli* expression system as an amino terminal GST fusion of residues 1-391 of human PLK4. The protein was purified from clarified cell extracts after induction at 15° C. overnight using glutathione sepharose, gel permeation chromatography, and ion exchange (Resource Q). The resulting protein was dephosphorylated with lambda phosphatase (NEB cat#P0753), and resolved from the phosphatase using glutathione sepharose. The dephosphorylated GST-PLK4 was stored in aliquots at -80° C. until use.

[0987] PLK4 activity was measured using an indirect ELISA detection system. GST-PLK4 (4 nM) was incubated in the presence of 15 μ M ATP (Sigma cat#A7699), 50 mM HEPES-Na²⁺ pH 7.5, 10 mM MgCl₂, 0.01% Brij 35 (Sigma cat#03-3170), in a 96 well microtitre plate pre-coated with MBP (Millipore cat#30-011). The reaction was allowed to proceed for 30 minutes, followed by 5 washes of the plate with Wash Buffer (phosphate buffered saline supplemented with 0.2% Tween 20), and incubation for 30 minutes with a 1:3000 dilution of primary antibody (Cell Signaling cat#9381). The plate was washed 5 times with Wash Buffer, incubated for 30 minutes in the presence of secondary antibody coupled to horse radish peroxidase (BioRad cat#1721019, 1:3000 concentration), washed an additional 5 times with Wash Buffer, and incubated in the presence of TMB substrate (Sigma cat#T0440). The colourimetric reaction was allowed to continue for 5 minutes, followed by addition of stop solution (0.5 N sulphuric acid), and quantified by detection at 450 nm with either a monochromatic or filter based plate reader (Molecular Devices M5 or Beckman DTX880, respectively).

[0988] Compound inhibition was determined at either a fixed concentration (10 μ M) or at a variable inhibitor concentration (typically 0.5 μ M to 0.001 μ M in a 10 point dose response titration). Compounds were pre-incubated in the presence of enzyme for 15 minutes prior to addition of ATP and the activity remaining quantified using the above described activity assay. The % Inhibition of a compound was determined using the following formula; % Inhibition=100 $\times$ (1-(experimental value-background value)/(high activity control-background value)). The IC₅₀ value was determined using a non-linear 4 point logistic curve fit (XLfit4, IDBS)

with the formula; $(A+(B/(1+((x/C)^D))))$, where A=background value, B=range, C=inflection point, D=curve fit parameter.

Example D

Aurora B Inhibition Assay

[0989] Aurora B inhibition was determined using the Z-Lyte assay kit from Invitrogen. The assay was performed using the recommended manufacturer's instructions with 128 μ M ATP and 28 nM Aurora B (Invitrogen cat #PV3970). The % inhibition values were determined according to the manufacturer's directions and IC₅₀ values were obtained using a non-linear 4 point logistic curve fit (XLfit4, IDBS)

[0990] In Table 1, IC₅₀ values for PLK4, TTK and Aurora B Kinases are indicated as "A," "B," and "C," for those less than or equal to 5 μ M; those greater than 5 μ M and less than or equal to 50 μ M; and those greater than 50 μ M, respectively. As shown in Table 1, numerous compounds described herein are effective TTK inhibitors. In addition, a number of compounds described herein also inhibit other kinases, including for instance, PLK4 and Aurora B kinases.

TABLE 1

Inhibition Data of PLK4, TTK, Aurora A and Aurora B Kinases			
Example #	IC50 Ranges		
	TTK	PLK4	Aurora B
Example A1	A	A	B
Example A2	A	A	A
Example A3	A	A	A
Example A4	A	A	A
Example A5	A	A	B
Example A6	A	A	A
Example A7	A	A	A
Example A8	A	A	A
Example A9	A	A	A
Example A10	A	A	A
Example A11	A	A	A
Example A12	A	A	A
Example A13	A	A	A
Example A14	A	A	A
Example A15	A	A	A
Example A16	A	A	A
Example A17	A	A	A
Example A18	A	A	A
Example A19	A	A	A
Example A20	A	A	A
Example A21	A	A	A
Example A22	A	A	B
Example A23	A	A	A
Example A24	A	A	A
Example A25	A	A	A
Example A26	A	A	A
Example A27	A	A	A
Example A28	A	A	A
Example A29	A	A	A
Example A30	A	A	A
Example A31	A	A	A
Example A32	A	A	A
Example A33	A	A	A
Example A34	A	A	A
Example A35	A	A	A
Example A36	A	A	A
Example A37	A	A	A
Example A38	A	A	A
Example A39	A	A	A
Example A40	A	A	A
Example A41	A	A	A
Example A42	A	A	A

TABLE 1-continued

Inhibition Data of PLK4, TTK, Aurora A and Aurora B Kinases			
Example #	IC50 Ranges		
	TTK	PLK4	Aurora B
Example A43	A	A	A
Example A44	A	A	A
Example A45	A	A	A
Example A46	A	A	A
Example A47	A	A	A
Example A48	A	A	A
Example A49	A	A	A
Example A50	A	A	A
Example A51	A	A	A
Example A53	A	A	A
Example A55	A	A	A
Example A56	A	A	A
Example A57	A	A	A
Example A58	A	A	A
Example A59	A	A	A
Example A60	A	A	A
Example A61	A	A	A
Example A62	A	A	A
Example A63	A	A	A
Example A64	A	A	A
Example A65	A	A	A
Example A66	A	A	A
Example A67	A	A	A
Example A68	A	A	A
Example A69	A	A	A
Example A70	A	A	A
Example A71	A	A	A
Example A72	A	A	A
Example A73	A	A	A
Example A74	A	A	A
Example A75	A	A	A
Example A76	A	A	A
Example A77	A	A	A
Example A78	A	A	A
Example A79	A	A	A
Example A80	A	A	A
Example A81	A	A	A
Example A82	A	A	A
Example A83	A	A	A
Example A84	A	A	A
Example A85	A	A	A
Example A86	A	A	A
Example A87	A	A	A
Example A88	A	A	A
Example A89	A	A	A
Example A90	A	A	A
Example A91	A	A	A
Example A92	A	A	A
Example A93	A	A	A
Example A94	A	A	A
Example A95	A	A	A
Example A96	A	A	B
Example A97	A	A	A
Example A98	A	A	A
Example A99	A	A	A
Example A100	A	A	A
Example A101	A	A	A
Example A102	A	A	A
Example A103	A	A	A
Example A104	A	A	A
Example A105	A	A	A
Example A106	A	A	A
Example A107	A	A	A
Example A108	A	A	A
Example A109	A	A	A
Example A110	A	A	A
Example A111	A	A	A
Example A112	A	A	A
Example A113	A	A	A
Example A114	A	A	A
Example A115	A	A	A

TABLE 1-continued

Inhibition Data of PLK4, TTK, Aurora A and Aurora B Kinases			
Example #	IC50 Ranges		
	TTK	PLK4	Aurora B
Example A116	A	A	A
Example A117	A	A	A
Example A118	A	A	A
Example A119	A	A	A
Example A120	A	A	A
Example A121	A	A	A
Example A122	A	A	A
Example A123	A	A	A
Example A124	A	A	A
Example A125	A	A	A
Example A126	A	A	A
Example A128	A	A	A
Example A129	A	A	A
Example A130	A	A	A
Example A131	A	A	A
Example A132	A	A	A
Example A133	A	A	A
Example A134	A	A	A
Example A135	A	A	A
Example A136	A	A	A
Example A137	A	A	A
Example A138	A	A	A
Example A139	A	A	A
Example A140	A	A	A
Example A141	A	A	A
Example A142	A	A	A
Example A143	A	A	A
Example A144	A	A	A
Example A145	A	A	A
Example A146	A	A	A
Example A147	A	A	A
Example A148	A	A	A
Example A150	A	A	A
Example A151	A	A	A
Example A153	A	A	A
Example A154	A	A	A
Example A155	A	A	A
Example A156	A	A	A
Example A157	A	A	A
Example A158	A	A	A
Example A159	A	A	A
Example A160	A	A	A
Example A161	A	A	A
Example A162	A	A	A
Example A163	A	A	A
Example A164	A	A	A
Example A166	A	A	A
Example A167	A	A	A
Example A169	A	A	A
Example A170	A	A	A
Example A171	A	A	A
Example A172	A	A	A
Example A173	A	A	A
Example A174	A	A	A
Example A175	A	A	A
Example A176	A	A	A
Example A177	A	A	A
Example A178	A	A	A
Example A179	A	A	A
Example A180	A	A	A
Example A181	A	A	A
Example A182	A	A	A
Example A183	A	A	A
Example A184	A	A	A
Example A185	A	A	A
Example A186	A	A	A
Example A187	A	A	A
Example A188	A	A	A
Example A189	A	A	A
Example A190	A	A	A
Example A191	A	A	A

TABLE 1-continued

Inhibition Data of PLK4, TTK, Aurora A and Aurora B Kinases			
Example #	IC50 Ranges		
	TTK	PLK4	Aurora B
Example A192	A	A	A
Example A193	A	A	A
Example A194	A	A	A
Example A195	A	A	A
Example A196	A	A	A
Example A197	A	A	A
Example A198	A	A	A
Example A199	A	A	A
Example A200	A	A	A
Example A201	A	A	A
Example A202	A	A	A
Example A203	A	A	A
Example A204	A	A	A
Example A205	A	A	A
Example A206	A	A	A
Example A207	A	A	A
Example A208	A	A	A
Example A209	A	A	A
Example A210	A	A	A
Example A211	A	A	A
Example A212	A	A	A
Example A213	A	A	A
Example A214	A	A	A
Example A215	A	A	A
Example A216	A	A	A

Example E

Cancer Cell Line Data on Exemplary Compounds of the Invention

[0991] Breast cancer cells (MDA-MB-231, MDA-MB-468), colon cancer cells (HCT116, HT29) and ovarian cancer cells (PA-1, OVCAR-3) were seeded (1000 to 4000 in 80 μ l per well depending on the cell growth rate) into 96 well plates 24 hours before compound overlay. Compounds were prepared as 10 mM stock solutions in 100% DMSO which were diluted with DMEM (Dulbecco's Modified Eagle's Medium) cell growth Medium (Invitrogen, Burlington, ON, Canada) containing 10% FBS (Fetal Bovine Serum) to concentrations ranging from 50 nM to 250 μ M. Aliquots (20 μ l) from each concentration were overlaid to 80 μ l of the pre-seeded cells in the 96 well plates to make final concentrations of 10 nM to 50 μ M. The cells were cultured for 5 days before the Sulforhodamine B assay (SRB) was performed to determine the compound's cell growth inhibition activity.

[0992] Sulforhodamine B (purchased from Sigma, Oakville, ON, Canada) is a water-soluble dye that binds to the basic amino acids of the cellular proteins. Thus, colorimetric measurement of the bound dye provides an estimate of the total protein mass that is related to the cell number. The cells are fixed in situ by gently aspirating off the culture media and adding 50 μ l ice cold 10% Trichloroacetic Acid (TCA) per well and incubate at 4° C. for 30-60 min. The plates are washed with water five times and allowed to air dry for 5 min. Addition of 50 μ l 0.4% (w/v) SRB solution in 1% (v/v) acetic acid to each well and incubation for 30 min at RT completes the staining reaction. Following staining, plates are washed four times with 1% acetic acid to remove unbound dye and then allowed to air dry for 5 min. The stain is solubilized with 100 μ l of 10 mM Tris pH 10.5 per well. Absorbance is read at 570 nm.

[0993] The percentage (%) of relative growth inhibition was calculated by comparing to DMSO treated only cells (100%). GI₅₀'s were determined for compounds with cytotoxic activity. The GI₅₀ was calculated using GraphPad PRISM software (GraphPad Software, Inc., San Diego, Calif., USA). GI₅₀ (growth inhibition) is the compound concentration that causes 50% inhibition of cell growth. In Table 2 below, GI₅₀ value ranges for several compound examples against breast cancer cell lines (MDA-MB-231, MDA-MB-468), colon cancer cell lines (HCT116, HT29) and ovarian cancer cell lines (PA-1, OVCAR-3) are given. The example compounds demonstrated varying growth inhibition/cell killing activity against cells of breast cancer, colon cancer and ovarian cancer. The GI₅₀ ranges are indicated as "A," "B," "C," and "D," for values less than or equal to 5 μ M; those greater than 5 μ M and less than or equal to 20 μ M; those greater than 20 μ M and less than or equal to 50 μ M; and those greater than 50 μ M, respectively.

TABLE 2

Cell Growth Inhibition Data						
Ex. #	Cell Line GI ₅₀ Range					
	MDA-MB-231	MDA-MB-468	HCT116	HT29	PA-1	OVCAR-3
Example A1	A	A	A			
Example A2	A	A	A			
Example A3	A	A	A			
Example A4	A	A	A	A		B
Example A5	A	A	A			
Example A6	A	A	A			
Example A7	A	A	A	A	A	B
Example A8	A	A	A			
Example A9	A	A	A			
Example A10	A	A	A			
Example A11	A	A	A			
Example A12	A	A	A			
Example A13	A	A	A			
Example A14	A	A	A			
Example A15	A	A	A			
Example A16	A	A	A			
Example A17	A	A	A			
Example A18	A	A	A	A	A	A
Example A19	A	A	A			
Example A20	A	A	A			
Example A21	A	A	A			
Example A22	A	A	A			
Example A23	B	A	A			
Example A24	A	A	A	A	A	A
Example A25	A	A	A	A		A
Example A26	A	A	A	A		A
Example A27	B	A	A	A		B
Example A28	A	A	A	A		B
Example A29	B	A	A	A		B
Example A30	A	A	A	A		A
Example A31	A	A	A	A		A
Example A32	C	A	A	A		B
Example A33	A	A	A	A		A
Example A34	A	A	A	A		A
Example A35	A	A	A	A		A
Example A36	A	A	A	A		A
Example A37		A	A	A		
Example A38	A	A	A	A		A
Example A39		A	A	A		
Example A40	A	A	A	A		A
Example A41		A	A	A		A
Example A42	A	A	A	A		A
Example A43	A	A	A	A		A
Example A44	A	A	A	A		A
Example A45	A	A	A	A		B
Example A46	A	A	A	A		A

TABLE 2-continued

Cell Growth Inhibition Data						
Ex. #	Cell Line GI ₅₀ Range					
	MDA-MB-231	MDA-MB-468	HCT116	HT29	PA-1	OVCAR-3
Example A47		A	A	A		
Example A48	A	A	A	A		B
Example A49		A	A	A		
Example A50		A	A	A		
Example A51		A	A	A		
Example A53	A	A	A	A		B
Example A55	A	A	A	A		A
Example A56	A	A	A	A		B
Example A57	A	A	A	A		A
Example A58	A	A	A	A		A
Example A59	A	A	A	A		B
Example A60	A	A	A	A		B
Example A61	B	B	A	A		B
Example A62	A	A	A	A		A
Example A63	A	A	A	A		A
Example A64	B	B	A	A		C
Example A65	A	A	A	A		B
Example A66	B	B	A	A		B
Example A67	A	A	A	A		B
Example A68	A	A	A	A		A
Example A69	A	A	A	A		A
Example A70		A	A	A		A
Example A71		A	A	A		
Example A72						
Example A73	A	A	A	A		B
Example A74	B	A	A	A		C
Example A75	B	A	A	A		B
Example A76		A	A	A		B
Example A77	A	A	A	A		A
Example A78		A	A	A		
Example A79		A	A	A		
Example A80		A	A	A		
Example A81	B	A	A	A	A	
Example A82		A	A	A	A	
Example A83		A	A	A	A	
Example A84		A	A	A	A	
Example A85	A	A	A	A	A	
Example A86	A	A	A	A	A	
Example A87		A	A	A	A	
Example A88		A	A	A	A	
Example A89		A	A	A	A	
Example A90	A	A	A	A	A	
Example A91	A	A	A	A	A	A
Example A92	A	A	A	A	A	A
Example A93	A	A	A	A	A	B
Example A94						
Example A95		A	A	A	A	
Example A96	B	B	B	B	B	B
Example A97		A	A	A	A	
Example A98	A	A	A	A	A	A
Example A99	A	A	A	A	A	A
Example A100	A	A	A	A	A	
Example A101		A	A	A	A	
Example A102		A	A	A	A	B
Example A103	A	A	A	A	A	
Example A104	A	A	A	A	A	A
Example A105		A	A	A	A	
Example A106		A	A	A	A	
Example A107	B	A	A	A	A	
Example A108	A	A	A	A	A	A
Example A109	A	A	A	A	A	A
Example A110	A	A	A	A	A	A
Example A111		A	A	A	A	
Example A112	A	A	A	A	A	A
Example A113	A	A	A	A	A	A
Example A114	A	A	A	A	A	B
Example A115	A	A	A	A	A	A
Example A116	A	A	A	A	A	
Example A117		A	A	A	A	
Example A118		A	A	A	A	

TABLE 2-continued

Cell Growth Inhibition Data						
Ex. #	Cell Line GI ₅₀ Range					
	MDA-MB-231	MDA-MB-468	HCT116	HT29	PA-1	OVCAR-3
Example A119		A	A	A	A	
Example A120		A	A	A	A	
Example A121		A	A	A	A	A
Example A122		A	A	A	A	
Example A123		A	A	A	A	
Example A124	A	A	A	A	A	C
Example A125	A	A	A	A	A	A
Example A126	A	A	A	A	A	A
Example A128	A	A	A	A	A	A
Example A129	A	A	A	A	A	B
Example A130	A	A	A	A	A	A
Example A131	A	A	A	A	A	A
Example A132	A	A	A	A	A	A
Example A133	A	A	A	A	A	A
Example A134	A	A	A	A	A	B
Example A135	A	A	A	A	A	A
Example A136	A	A	A	A	A	A
Example A137	A	A	A	A	A	A
Example A138	A	A	A	A	A	A
Example A139	A	A	A	A	A	A
Example A140	A	A	A	A	A	A
Example A141	A	A	A	A	A	A
Example A142	A	A	A	A	A	B
Example A143	A	A	A	A	A	A
Example A144	A	A	A	A	A	A
Example A145	A	A	A	A	A	A
Example A146	A	A	A	A	A	A
Example A147	A	A	A	A	A	A
Example A148	A	A	A	A	A	A
Example A150	A	A	A	A	A	A
Example A151	A	A	A	A	A	A
Example A153	A	A	A	A	A	A
Example A154	A	A	A	A	A	A
Example A155	A	A	A	A	A	A
Example A156	A	A	A	A	A	A
Example A157	A	A	A	A	A	A
Example A158	A	A	A	A	A	A
Example A159	A	A	A	A	A	A
Example A160		A	A	A	A	
Example A161	A	A	A	A	A	A
Example A162	A	A	A	A	A	A
Example A163	A	A	A	A	A	A
Example A164	A	A	A	A	A	A
Example A166	A	A	A	A	A	A
Example A167		A	A	A	A	
Example A169		A	A	A	A	B
Example A170	A	A	A	A	A	A
Example A171		A	A	A	A	A
Example A172		A	A	A	A	
Example A173	A	A	A	A	A	B
Example A174	A	A	A	A	A	A
Example A175	A	A	A	A	A	A
Example A176	A	A	A	A	A	A
Example A177	A	A	A	A	A	A
Example A178	A	A	A	A	A	A
Example A179	A	A	A	A	A	A
Example A180		A	A		A	
Example A181	A	A	A		A	A
Example A182		A	A		A	
Example A183	A	A	A		A	A
Example A184	A	A	A		A	
Example A185		A	A		A	
Example A186		A	A		A	
Example A187	A	A	A		A	A
Example A188	A	A	A		A	A
Example A189	B	A	A		A	C
Example A190		A	A		A	
Example A191	A	A	A		A	A
Example A192		A	A		A	A
Example A193	A	A	A		A	A

TABLE 2-continued

Cell Growth Inhibition Data						
Ex. #	Cell Line GI ₅₀ Range					
	MDA-MB-231	MDA-MB-468	HCT116	HT29	PA-1	OVCAR-3
Example A194	A	A	A		A	A
Example A195		A	A		A	
Example A196		A	A		A	
Example A197		A	A		A	
Example A198	A	A	A		A	A
Example A199	A	A	A		A	A
Example A200		A	A		A	
Example A201		A	A		A	
Example A202	A	A	A		A	A
Example A203		A	A		A	
Example A204		A	A		A	
Example A205		A	A		A	
Example A206						
Example A207						
Example A208						
Example A209						
Example A210						
Example A211						
Example A212						
Example A213						
Example A214						
Example A215						
Example A216						

Example F

[0994] Colon and Ovarian Cancer Tumor-Initiating Cell Data of Exemplary Compounds

[0995] Materials and Methods: Non-tissue or tissue cultured treated T-75 flask and 96-well plates were purchased from VWR. Vitamin B-27 supplement, MEM NEAA (minimum essential medium non essential amino acids), sodium pyruvate, L-glutamine, N2 supplement, penicillin-streptomycin and fungizone/amphotericin B were obtained from Invitrogen. Lipid mixture, heparin and EGF were purchased from Sigma; bFGF from BD Biosciences. Colon tumor initiating cells (TICs) were routinely maintained using non-tissue cultured treated T-75 flasks in DMEM:F12 medium containing 0.2XB-27 supplement, 4 ug/ml heparin, 1XMEM NEAA, 1x sodium pyruvate, 1 mM glutamine, 10 pg/ul bFGF, 20 pg/ul EGF, 1xN2 supplement, lipid mixture, penicillin-streptomycin and fungizone/amphotericin B. Ovarian TICs were routinely maintained using tissue cultured treated T-75 flasks in DMEM:F12 medium containing 1XB-27 supplement, 4 ug/ml heparin, 20 pg/ul bFGF, 20 pg/ul EGF and penicillin-streptomycin.

[0996] Assay Protocol:

[0997] Compounds described herein were dissolved in DMSO and further diluted in cell culture medium for GI₅₀ determination. Colon TICs were trypsinized and seeded into non-tissue cultured treated 96-well plates with 4,000 cells/well. After 24 h, compound was added into the cell culture at different concentrations, and the final concentration of DMSO was adjusted to 0.1%. Cells were then cultured at 37° C. for 9 days. Ovarian TICs were trypsinized and seeded into tissue cultured treated 96-well plates with 1,000 cells/well. After 24 h, compound was added into the cell culture at different concentrations, and the final concentration of DMSO was adjusted to 0.1%. Cells were then cultured at 37° C. for 6 days. Cell viability was assessed by Alamar Blue

assay: 10 ul of Alamar Blue was added into each well. After 4 hours incubation at 37° C., fluorescence was recorded at excitation 544 and emission 590. GI₅₀ (Growth inhibition) was calculated using GraphPad Prism 4.0 software. Cell growth inhibition data for compounds described herein is tabulated below (Table 3). The GI₅₀ ranges are indicated as “A,” “B,” “C,” and “D,” for values less than or equal to 5 μM; those greater than 5 μM and less than or equal to 20 μM; those greater than 20 μM and less than or equal to 50 μM; and those greater than 50 μM, respectively.

TABLE 3

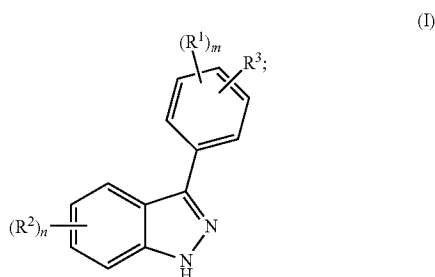
Colon Tumor-Initiating Cell Growth Inhibition Data		
Example #	12 colon	2393A ovarian
Example A4	A	A
Example A7	A	A
Example A9	A	A
Example A12	A	A
Example A24	A	A
Example A25	A	A
Example A27	A	A
Example A29	A	A
Example A33	A	A
Example A35	A	A
Example A41	A	A
Example A46	A	A
Example A89	A	A
Example A91	A	A
Example A98	A	A
Example A110	A	A
Example A118	A	A
Example A128	A	A
Example A130	A	A
Example A131	A	A
Example A132	A	A
Example A133	A	A
Example A134	A	A
Example A136	A	A
Example A137	A	A
Example A138	A	A
Example A144	A	A
Example A147	A	A
Example A150	A	A
Example A151	A	A
Example A154	A	A
Example A157	A	A
Example A160	A	A
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Example A177	A	A
Example A178	A	A
Example A179	A	A
Example A180	A	A
Example A181	A	A
Example A182	A	A
Example A183	A	A
Example A184	A	A
Example A185	A	A
Example A186	A	A
Example A187	A	A
Example A188	A	A

TABLE 3-continued

Colon Tumor-Initiating Cell Growth Inhibition Data		
Example #	12 colon	2393A ovarian
Example A189	A	A
Example A190	A	A
Example A191	A	A
Example A193	A	A

[0998] While this invention has been particularly shown and described with references to example embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

1. A compound represented by the following structural formula:

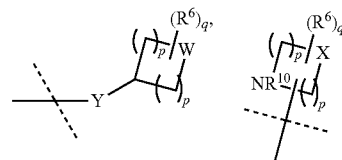


or a pharmaceutically acceptable salt thereof, wherein:

each R^1 is independently selected from $-H$, $-halogen$, $-CN$, $-NO_2$, $-OR^c$, $-NR^aR^b$, $-S(O)_iR^c$, $-NR^dS(O)_iR^c$, $-S(O)_iNR^eR^f$, $-C(=O)OR^c$, $-OC(=O)OR^c$, $-C(=S)OR^c$, $-O(C=S)R^c$, $-C(=O)NR^eR^f$, $-NR^dC(=O)R^c$, $-C(=S)NR^eR^f$, $-NR^dC(=S)R^c$, $-NR^d(C=O)OR^c$, $-O(C=O)NR^eR^f$, $-NR^d(C=S)OR^c$, $-O(C=S)NR^eR^f$, $-NR^d(C=O)NR^eR^f$, $-NR^d(C=S)NR^eR^f$, $-C(=S)R^c$, $-C(=O)R^c$, heterocycloalkyl or alkyl, wherein the heterocycloalkyl or the alkyl is optionally substituted with 1 to 3 substituents independently selected from $-halogen$, $-CN$, $-NO_2$, $-OR^c$, $-NR^aR^b$, $-S(O)_iR^c$, $-NR^dS(O)_iR^c$, $-S(O)_iNR^eR^f$, $-C(=O)OR^c$, $-OC(=O)OR^c$, $-C(=S)OR^c$, $-O(C=S)R^c$, $-C(=O)NR^eR^f$, $-NR^dC(=O)R^c$, $-C(=S)NR^eR^f$, $-NR^dC(=S)R^c$, $-NR^d(C=O)OR^c$, $-O(C=O)NR^eR^f$, $-NR^d(C=S)OR^c$, $-O(C=S)NR^eR^f$, $-NR^d(C=O)NR^eR^f$, $-NR^d(C=S)NR^eR^f$, $-C(=S)R^c$ and $-C(=O)R^c$;

each R^2 is independently selected from: $-(CH_2)_{0-2}C(=O)NR^4(CH_2)_{0-2}Z-R^5$, $-(CH_2)_{0-2}NR^4C(=O)(CH_2)_{0-2}Z-R^5$ and $-(CH_2)_{0-2}NR^4(C=O)NR^4(CH_2)_{0-2}Z-R^5$;

R^3 is



or $-O-(C_1-C_6)alkyl-NR^aR^b$; or R^3 taken together with an instance of R^1 and the phenyl ring to which they are attached form a fused ring heteroaryl or heterocycloalkyl, wherein the heteroaryl or heterocycloalkyl are optionally substituted with 1 to 3 $(C_1-C_3)alkyl$, provided that R^3 is meta or para to the indazole ring;

W is $-O-$, $-NR^7-$, $-S(O)_i-$ or $-CR_8R_9-$;

X is $-O-$, $-CR^8R^9-$, $-NR^{11}-$ or $-S(O)_i-$;

Y is $-O-(CH_2)_r-$, $-NR^{12}-(CH_2)_r-$, $-CH_2-$ or $-S(O)_i-(CH_2)_r-$;

R^4 is $-H$ or an alkyl group optionally substituted with 1 to 3 substituents independently selected from halogen, hydroxy and $(C_1-C_3)alkoxy$;

R^5 is alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl, each of which is optionally substituted with 1 to 3 groups individually represented by R^{15} or R^{16} ;

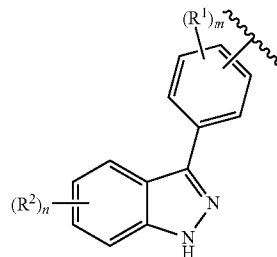
Z is a bond or $-CR^{13}R^{14}-$;

R^6 is halogen, hydroxyl, $(C_1-C_3)alkyl$, $(C_1-C_3)alkoxy$, $(C_1-C_3)alkyl-OR^c$ or $-NR_aR_b$; or two instances of R^6 on the same carbon are taken together form $=O$; or two instances of R^6 on different carbons, together with the ring to which they are attached, form a bridged bicyclic group;

R^7 is $-H$, $(C_1-C_6)alkyl$, cycloalkyl, cycloalkyl(C_1-C_6)alkyl, heterocycloalkyl, heterocycloalkyl(C_1-C_6)alkyl, $-C(=O)R^c$ or $-C(=O)OR^c$, wherein each of the $(C_1-C_6)alkyl$, cycloalkyl, cycloalkyl(C_1-C_6)alkyl, heterocycloalkyl and heterocycloalkyl(C_1-C_6)alkyl groups is optionally substituted with 1 to 3 substituents independently selected from halogen, hydroxy, $(C_1-C_3)alkoxy$ and $-C(=O)NR^eR^f$;

R^8 and R^9 are each independently selected from $-H$, $-OR^c$, and $(C_1-C_6)alkyl$, wherein the $(C_1-C_6)alkyl$ group is optionally substituted with 1 to 3 substituents independently selected from halogen, hydroxy and $(C_1-C_3)alkoxy$;

R^{10} is $-H$ or $(C_1-C_3)alkyl$, or is absent when the nitrogen to which it is attached is attached directly to the



moiety;

R^{11} is $-H$, $(C_1-C_6)alkyl$, cycloalkyl, cycloalkyl(C_1-C_6)alkyl, heterocycloalkyl, heterocycloalkyl(C_1-C_6)alkyl, $-C(=O)R^c$ or $-C(=O)OR^c$, wherein each of the $(C_1-C_6)alkyl$, cycloalkyl, cycloalkyl(C_1-C_6)alkyl, heterocy-

cloalkyl and heterocycloalkyl(C₁-C₆)alkyl groups is optionally substituted with 1 to 3 substituents independently selected from halogen, hydroxy, (C₁-C₃)alkoxy and —C(=O)NR^eR^f;

R¹² is —H or (C₁-C₃)alkyl;

R¹³ and R¹⁴ are each independently selected from —H, alkyl, —OR^c, —NR^aR^b, —(C₁-C₃)alkylene-NR^aR^b, —(C₁-C₃)alkylene-OR^c, —(C₁-C₃)alkylene-OH, cycloalkyl, —O-cycloalkyl and heterocycloalkyl, wherein each of the cycloalkyl or heterocycloalkyl groups is optionally substituted with 1 to 3 substituents independently selected from (C₁-C₃)alkyl and (C₁-C₃)alkoxy, provided that R¹³ and R¹⁴ are not both selected from —OR^c and —NR^aR^b;

each R¹⁵ and R¹⁶ are independently selected from halogen, —CN, —NO₂, =O, —OR^c, —NR^aR^b, —S(O)_iR^c, —NR^dS(O)_iR^c, —S(O)_iNR^eR^f, C(=O)OR^c, —OC(=O)OR^c, —C(=S)OR^c, —O(C=S)R^c, —C(=O)NR^eR^f, —NR^dC(=O)R^c, —C(=S)NR^eR^f, —NR^dC(=S)R^c, —NR^d(C=O)OR^c, —O(C=O)NR^eR^f, —NR^d(C=S)OR^c, —O(C=S)NR^eR^f, —NR^d(C=O)NR^eR^f, —NR^d(C=S)NR^eR^f, —C(=S)R^c, —C(=O)R^c, (C₁-C₆)alkyl, aryl, aryl(C₁-C₃)alkyl, heterocycloalkyl and heteroaryl; wherein each (C₁-C₆)alkyl, aryl, aryl(C₁-C₃)alkyl, heterocycloalkyl and heteroaryl represented by R¹⁵ is optionally substituted with 1 to 3 substituents independently selected from -halogen, —CN, —OR^c, (C₁-C₆)alkyl, halo(C₁-C₆)alkyl, (C₁-C₃)alkoxy, halo(C₁-C₃)alkoxy, (C₁-C₃)alkoxy(C₁-C₆)alkyl, 3 to 8 membered heterocycloalkyl and 3 to 8 membered heteroaryl;

R^a and R^b are each independently selected from —H and (C₁-C₆)alkyl, optionally substituted with 1 to 3 substituents independently selected from halogen, hydroxy, —NR^gR^h and (C₁-C₃)alkoxy;

R^c is —H or (C₁-C₆)alkyl, optionally substituted with 1 to 3 substituents independently selected from halogen, —NR^gR^h, hydroxy and (C₁-C₃)alkoxy;

R^d is —H or (C₁-C₆)alkyl, optionally substituted with 1 to 3 substituents independently selected from halogen, —NR^gR^h, hydroxy and (C₁-C₃)alkoxy;

R^e and R^f are each independently selected from —H and (C₁-C₆)alkyl optionally substituted with 1 to 3 substituents independently selected from halogen, —NR^gR^h, hydroxy and (C₁-C₃)alkoxy;

or R^e and R^f, together with the nitrogen to which they are attached, form a 3-8 membered ring optionally substituted with 1 to 3 substituents independently selected from halogen, —NR^gR^h, —CN, (C₁-C₆)alkyl, halo(C₁-C₆)alkyl, (C₁-C₃)alkoxy, halo(C₁-C₃)alkoxy, and (C₁-C₃)alkoxy(C₁-C₆)alkyl;

R^g and R^h are each independently selected from —H, (C₁-C₆)alkyl, halo(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl and (C₁-C₃)alkoxy(C₁-C₆)alkyl;

i is 0, 1 or 2;

n is an integer from 1 to 4;

m is an integer from 1 to 4;

each p is 1, 2 or 3;

q is 0, 1 or 2; and

r is 0, 1, 2 or 3.

2. The compound of claim 1, wherein:

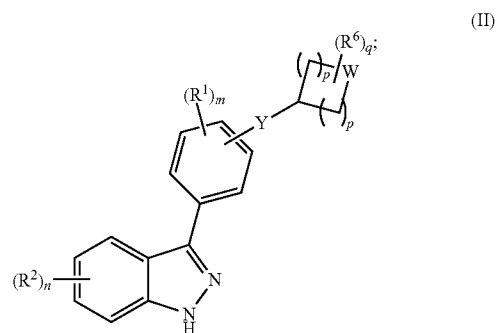
W is —O— or —NR⁷—;

X is —O—, —CR⁸R⁹— or —NR¹¹—; and

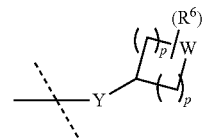
Y is —O—(CH₂)_r—, —NR¹²—(CH₂)_r— or —CH₂—;

3. The compound of claim 2, wherein R⁵ is cycloalkyl, heterocycloalkyl, aryl or heteroaryl, each of which is optionally substituted with 1 to 3 groups individually represented by R¹⁵ or R¹⁶.

4. The compound of claim 3, wherein the compound is represented by structural formula:

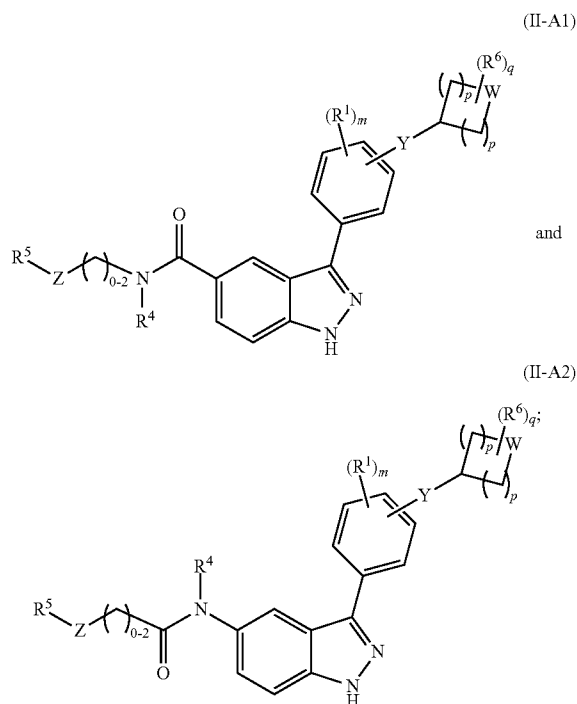


or a pharmaceutically acceptable salt thereof, wherein: the group represented by



is meta or para to the indazole ring.

5. The compound of claim 4, wherein the compound is represented by a structural formula selected from:



or a pharmaceutically acceptable salt thereof.

6-15. (canceled)

16. The compound of claim 5, wherein:

Y is $-\text{O}-(\text{CH}_2)_n$, or $-\text{NR}^{12}-$;

R^4 is $-\text{H}$ or an alkyl group optionally substituted with a substituent selected from halogen, hydroxy and (C_1-C_3) alkoxy;

R^7 is $-\text{H}$, (C_1-C_6) alkyl, cycloalkyl, heterocycloalkyl, $-\text{C}(=\text{O})\text{R}^c$ or $-\text{C}(=\text{O})\text{OR}^c$, wherein each of the (C_1-C_6) alkyl, cycloalkyl, and heterocycloalkyl groups is optionally substituted with a substituent independently selected from halogen, hydroxy, (C_1-C_3) alkoxy and $-\text{C}(=\text{O})\text{NR}^e\text{R}^f$;

R^{13} and R^{14} are each independently selected from $-\text{H}$, alkyl, $-\text{OR}^c$, $-(\text{C}_1-\text{C}_3)$ alkylene- OR^c , $-(\text{C}_1-\text{C}_3)$ alkylene-OH, (C_3-C_8) cycloalkyl, $-\text{O}-(\text{C}_3-\text{C}_8)$ cycloalkyl and 3 to 8 membered heterocycloalkyl, provided that R^{13} and R^{14} are not both $-\text{OR}^c$, wherein each of the cycloalkyl or heterocycloalkyl groups is optionally substituted with a (C_1-C_3) alkyl;

n is an integer from 1 to 2;

m is an integer from 1 to 2; and

each p is 1 or 2.

17. The compound of claim 16, wherein:

each R^1 is independently selected from $-\text{H}$, -halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{OR}^c$, $-\text{NR}^a\text{R}^b$, $-\text{S}(\text{O})\text{R}^c$, $-\text{C}(=\text{O})\text{OR}^c$, $-\text{OC}(=\text{O})\text{OR}^c$, $-\text{C}(=\text{O})\text{NR}^e\text{R}^f$, $-\text{NR}^d\text{C}(=\text{O})\text{R}^c$, $-\text{C}(=\text{O})\text{R}^c$ or (C_1-C_6) alkyl, wherein the alkyl is optionally substituted with a substituent selected from -halogen, $-\text{OR}^c$, $-\text{NR}^a\text{R}^b$, and $-\text{S}(\text{O})\text{R}^c$;

R^5 is (a) cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, morpholinyl, thiomorpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, piperazinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, azetidiny, dihydroimidazole, dihydrofuran, dihydropyran, dihydropyridinyl, dihydropyrimidinyl, dihydrothienyl, dihydrothiophenyl, dihydrothiopyran, tetrahydroimidazole, tetrahydrofuran, tetrahydropyran, tetrahydrothienyl, tetrahydropyridinyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyran, phenyl, furanyl, imidazolyl, oxazolyl, isoxazolyl, oxadiazolyl, pyrazolyl, pyrrolyl, pyridyl, pyrimidinyl, pyridazinyl, thiazolyl, isothiazolyl, triazolyl, tetrazolyl or thienyl, each of which is optionally substituted with 1 to 3 groups represented by R^{15} or (b) bicyclooctanyl, decahydronaphthyl, octahydroindenyl, dihydronaphthalenyl, tetrahydronaphthalenyl, dihydroindolyl, dihydroisindolyl, dihydrobenzimidazolyl, dihydrobenzothienyl, dihydrobenzofuran, dihydroisobenzofuran, dihydrobenzotriazolyl, dihydrobenzothiazolyl, dihydrobenzoxazolyl, dihydrobenzisoxazolyl, dihydroquinolinyl, tetrahydroquinolinyl, dihydroisoquinolinyl, tetrahydroisoquinolinyl, dihydroindazolyl, dihydroacridinyl, tetrahydroacridinyl, chromanyl, isochromanyl, chromenyl, isochromenyl, naphthyl, anthracenyl, fluorenyl, indanyl, indenyl, carbazolyl, benzimidazolyl, benzothienyl, benzofuran, isobenzofuran, indolyl, isoindolyl, benzotriazolyl, benzothiazolyl, benzoxazolyl, benzisoxazolyl, quinolinyl, isoquinolinyl, indazolyl or acridinyl, each of which is optionally substituted with 1 to 3 groups represented by R^{16} ;

R^6 is absent, halogen or (C_1-C_4) alkyl; or two instances of R^6 on different carbons, together with the ring to which they are attached, form an azabicyclooctanyl, a diazabi-

cyclooctanyl, an oxabicyclooctanyl, a dioxabicyclooctanyl, an oxa-azabicyclooctanyl, an azabicyclononanyl, a diazabicyclononanyl, an oxabicyclononanyl, a dioxabicyclononanyl, or an oxa-azabicyclononanyl;

R^7 is $-\text{H}$, (C_1-C_4) alkyl, halo (C_1-C_4) alkyl, hydroxy (C_1-C_4) alkyl, methoxy (C_1-C_4) alkyl, $-(\text{C}_1-\text{C}_4)$ alkyl- $\text{C}(=\text{O})\text{NMe}_2$, $-\text{C}(=\text{O})-(\text{C}_1-\text{C}_4)$ alkyl- NMe_2 , morpholinyl, thiomorpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, piperazinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, azetidiny, dihydroimidazole, dihydrofuran, dihydropyran, dihydropyridinyl, dihydropyrimidinyl, dihydrothienyl, dihydrothiophenyl, dihydrothiopyran, tetrahydroimidazole, tetrahydrofuran, tetrahydropyran, tetrahydrothienyl, tetrahydropyridinyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyran, $-\text{C}(=\text{O})\text{R}^c$ or $-\text{C}(=\text{O})\text{OR}^c$, and wherein each R^c is independently selected from $-\text{H}$, (C_1-C_4) alkyl, amino (C_1-C_4) alkyl or dimethylamino (C_1-C_4) alkyl;

R^{13} is H and R^{14} is $-\text{H}$, (C_1-C_6) alkyl, $-\text{OR}^c$, $-(\text{C}_1-\text{C}_3)$ alkylene- OR^c , $-(\text{C}_1-\text{C}_3)$ alkylene-OH, a cycloalkyl selected from cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl, a $-\text{O}$ -cycloalkyl selected from $-\text{O}$ -cyclopropyl, $-\text{O}$ -cyclobutyl, and $-\text{O}$ -cyclopentyl, $-\text{O}$ -cyclohexyl, or a heterocycloalkyl selected from morpholinyl, thiomorpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, piperazinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, azetidiny, dihydroimidazole, dihydrofuran, dihydropyran, dihydropyridinyl, dihydropyrimidinyl, dihydrothienyl, dihydrothiophenyl, dihydrothiopyran, tetrahydroimidazole, tetrahydrofuran, tetrahydropyran, tetrahydrothienyl, tetrahydropyridinyl, tetrahydropyrimidinyl, tetrahydrothiophenyl and tetrahydrothiopyran, provided that R^{13} and R^{14} are not both $-\text{OR}^c$, wherein each of the $-\text{O}$ -cycloalkyl, cycloalkyl or heterocycloalkyl groups is optionally substituted with a (C_1-C_3) alkyl; and R^c is $-\text{H}$, or (C_1-C_6) alkyl;

each R^{15} is independently selected from halogen, $-\text{CN}$, $-\text{NO}_2$, $=\text{O}$, $-\text{OR}^c$, $-\text{NR}^a\text{R}^b$, $-\text{C}(=\text{O})\text{OR}^c$, $-\text{OC}(=\text{O})\text{OR}^c$, $-\text{C}(=\text{O})\text{NR}^e\text{R}^f$, $-\text{NR}^d\text{C}(=\text{O})\text{R}^c$, $-\text{NR}^d\text{C}(=\text{O})\text{OR}^c$, $-\text{O}(\text{C}(=\text{O})\text{NR}^e\text{R}^f)$, $-\text{NR}^d(\text{C}(=\text{O})\text{NR}^e\text{R}^f)$, $-\text{C}(=\text{O})\text{R}^c$, (C_1-C_6) alkyl, morpholinyl, thiomorpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, piperazinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, azetidiny, dihydroimidazole, dihydrofuran, dihydropyran, dihydropyridinyl, dihydropyrimidinyl, dihydrothienyl, dihydrothiophenyl, dihydrothiopyran, tetrahydroimidazole, tetrahydrofuran, tetrahydropyran, tetrahydrothienyl, tetrahydropyridinyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyran, phenyl, benzyl, furanyl, imidazolyl, oxazolyl, isoxazolyl, oxadiazolyl, pyrazolyl, pyrrolyl, pyridyl, pyrimidinyl, pyridazinyl, thiazolyl, isothiazolyl, triazolyl, tetrazolyl, and thienyl; wherein the (C_1-C_6) alkyl represented by R^{15} is optionally substituted with a substituent selected from -halogen, $-\text{OR}^c$, (C_1-C_6) alkyl, (C_1-C_3) alkoxy, morpholinyl, thiomorpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, piperazinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, azetidiny, dihydroimidazole, dihydrofuran, dihydropyran, dihydropyridinyl, dihydropyrimidinyl, dihydrothienyl, dihydrothiophenyl, dihydrothiopyran, tetrahydroimidazole, tetrahydrofuran, tetrahydropyran,

ranyl, tetrahydrothienyl, tetrahydropyridinyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, furanyl, imidazolyl, oxazolyl, isoxazolyl, oxadiazolyl, pyrazolyl, pyrrolyl, pyridyl, pyrimidinyl, pyridazinyl, thiazolyl, isothiazolyl, triazolyl, tetrazolyl, and thienyl; and

each R^{16} is independently selected from halogen, $-OR^c$, $-NR^aR^b$, $-C(=O)OR^c$, $-C(=O)NR^aR^f$, $-NR^dC(=O)R^c$, $-C(=O)R^c$, (C_1-C_6) alkyl, phenyl, phenyl (C_1-C_3) alkyl, morpholinyl, thiomorpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, piperazinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, azetidiny, dihydroimidazole, dihydrofuranyl, dihydropyranyl, dihydropyridinyl, dihydropyrimidinyl, dihydrothienyl, dihydrothiophenyl, dihydrothiopyranyl, tetrahydroimidazole, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothienyl, tetrahydropyridinyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, furanyl, imidazolyl, oxazolyl, isoxazolyl, oxadiazolyl, pyrazolyl, pyrrolyl, pyridyl, pyrimidinyl, pyridazinyl, thiazolyl, isothiazolyl, triazolyl, tetrazolyl, and thienyl.

18. The compound of claim **17**, wherein:

R^1 is selected from $-H$, -halogen, $-OCH_3$, $-N(CH_3)_2$, $-S(O)_2CH_3$, or methyl;

R^5 is (a) cyclopentyl, cyclohexyl, morpholinyl, pyrrolidinyl, piperidinyl, dihydropyridinyl, tetrahydropyridinyl, dihydropyrimidinyl, tetrahydropyrimidinyl, phenyl, furanyl, imidazolyl, pyrrolyl, pyridyl, pyrimidinyl or thienyl, each of which is optionally substituted with 1 to 3 groups represented by R^{15} or (b) chromanyl, chromenyl, dihydroindolyl, dihydroisindolyl, dihydrobenzothienyl, dihydrobenzofuranyl, dihydroisobenzofuranyl, dihydrobenzotriazolyl, dihydroquinolyl, tetrahydroquinolyl, dihydroisoquinolyl, tetrahydroisoquinolyl, dihydrobenzisoxazolyl, naphthyl, anthracenyl, fluorenyl, indanyl, indenyl, dihydronaphthalene, tetrahydronaphthalene, carbazolyl, benzimidazolyl, benzothienyl, benzofuranyl, isobenzofuranyl, indolyl, quinolyl, isoquinolyl or isoindolyl, each of which is optionally substituted with 1 to 3 groups represented by R^{16} ;

R^6 is absent, halogen or (C_1-C_4) alkyl; or two instances of R^6 on different carbons, together with the ring to which they are attached, form an azabicyclooctanyl, a diazabicyclooctanyl, an oxa-azabicyclooctanyl, an azabicyclononanyl, a diazabicyclononanyl, or an oxa-azabicyclononanyl;

R^7 is $-H$, methyl, ethyl, propyl, isopropyl, methoxyethyl, hydroxyethyl, fluoroethyl, $-C(=O)H$, $-C(=O)CH_2N(CH_3)_2$, $-CH_2-C(=O)N(CH_3)_2$, oxetanyl, tetrahydrofuranyl, $-CH_2C(=O)N(CH_3)_2$, $-C(=O)O(C_1-C_4)$ alkyl;

R^{13} is $-H$ and R^{14} is $-H$, (C_1-C_6) alkyl, $-OR^c$, $-(C_1-C_3)$ alkylene- OR^c , $-(C_1-C_3)$ alkylene-OH, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, $-O$ -cyclopropyl, $-O$ -cyclobutyl, $-O$ -cyclopentyl, $-O$ -cyclohexyl, morpholinyl, thiomorpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, piperazinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, azetidiny, dihydroimidazole, dihydrofuranyl, dihydropyranyl, dihydropyridinyl, dihydropyrimidinyl, dihydrothienyl, dihydrothiophenyl, dihydrothiopyranyl, tetrahydroimidazole, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothienyl, tetra-

rahydropyridinyl, tetrahydropyrimidinyl, tetrahydrothiophenyl or tetrahydrothiopyranyl; and R^c is $-H$, or (C_1-C_6) alkyl;

each R^{15} is independently selected from halogen, $-OR^c$, $-NR^aR^b$, (C_1-C_6) alkyl, morpholinyl, thiomorpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, piperazinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, azetidiny, dihydroimidazole, dihydrofuranyl, dihydropyranyl, dihydropyridinyl, dihydropyrimidinyl, dihydrothienyl, dihydrothiophenyl, dihydrothiopyranyl, tetrahydroimidazole, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothienyl, tetrahydropyridinyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, furanyl, imidazolyl, isoxazolyl, oxadiazolyl, oxazolyl, pyrazolyl, pyrrolyl, pyridyl, pyrimidinyl, pyridazinyl, thiazolyl, isothiazolyl, triazolyl, tetrazolyl and thienyl; wherein the (C_1-C_6) alkyl represented by R^{15} is optionally substituted with a substituent selected from -halogen, $-OR^c$, (C_1-C_3) alkoxy, morpholinyl, thiomorpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, piperazinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, azetidiny, dihydroimidazole, dihydrofuranyl, dihydropyranyl, dihydropyridinyl, dihydropyrimidinyl, dihydrothienyl, dihydrothiophenyl, dihydrothiopyranyl, tetrahydroimidazole, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothienyl, tetrahydropyridinyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, furanyl, imidazolyl, isoxazolyl, oxadiazolyl, oxazolyl, pyrazolyl, pyrrolyl, pyridyl, pyrimidinyl, pyridazinyl, thiazolyl, isothiazolyl, triazolyl, tetrazolyl and thienyl;

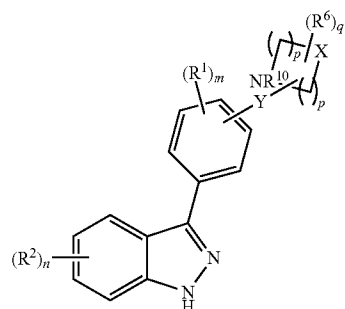
each R^{16} is independently selected from halogen, $-OR^c$, $-NR^aR^b$, and (C_1-C_6) alkyl; and

m is 1.

19. (canceled)

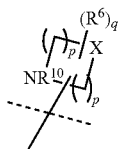
20. The compound of claim **18**, wherein two instances of R^6 on different carbons, together with the ring to which they are attached, form an 8-azabicyclo[3.2.1]octanyl, a 9-azabicyclo[3.3.1]nonanyl, a 3-oxa-9-azabicyclo[3.3.1]nonanyl or a 3,9-diazabicyclo[3.3.1]nonanyl

21. The compound of claim **1**, wherein the compound is represented by structural formula



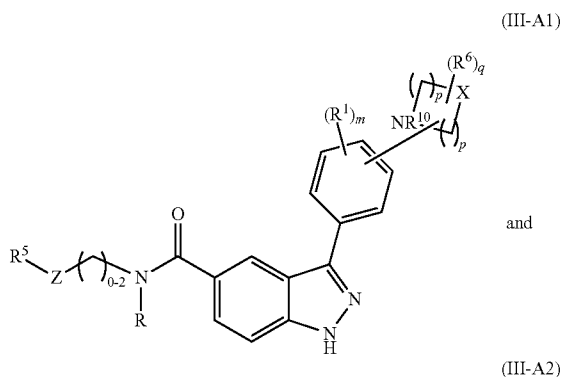
(III)

or a pharmaceutically acceptable salt thereof; wherein:
the group represented by



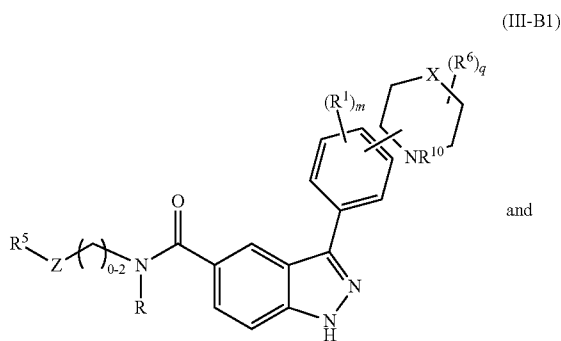
is meta or para to the indazole ring.

22. The compound of claim **21**, wherein the compound is represented by a structural formula selected from:

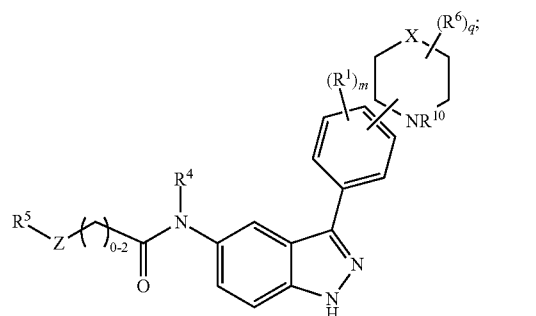


or a pharmaceutically acceptable salt thereof.

23. The compound of claim **22**, wherein the compound is represented by a structural formula selected from:

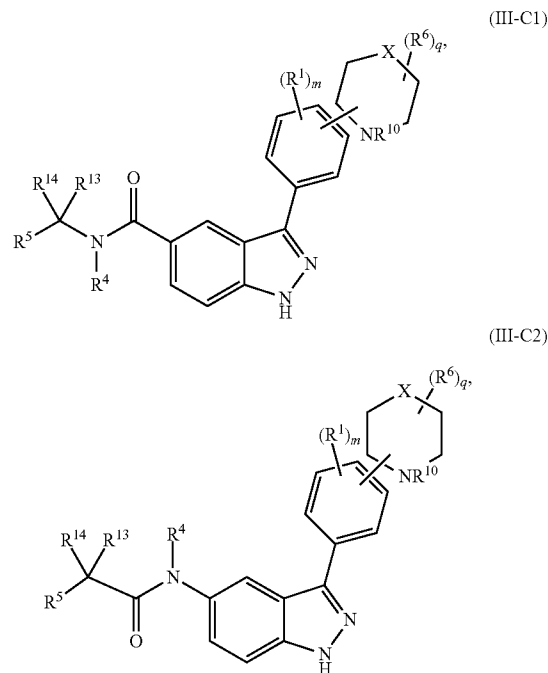


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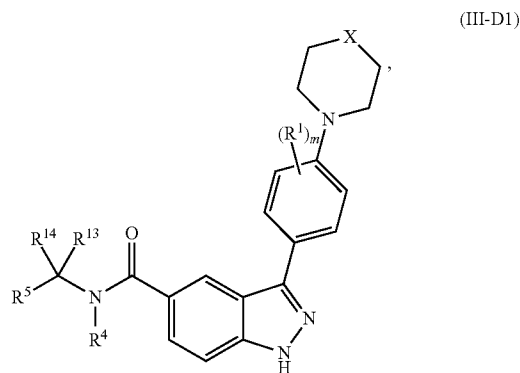
or a pharmaceutically acceptable salt thereof.

24. The compound of claim **23**, wherein the compound is represented by a structural formula selected from:

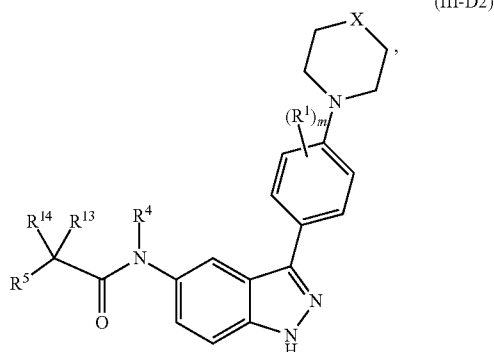


or a pharmaceutically acceptable salt thereof.

25. The compound of claim **24**, wherein the compound is represented by a structural formula selected from:

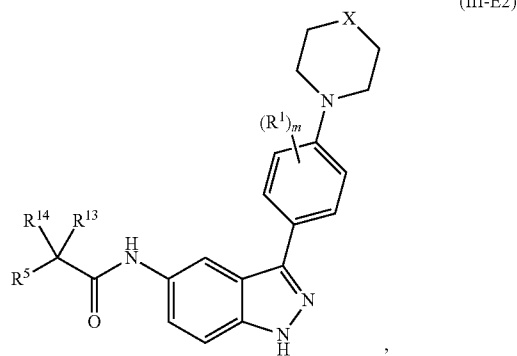
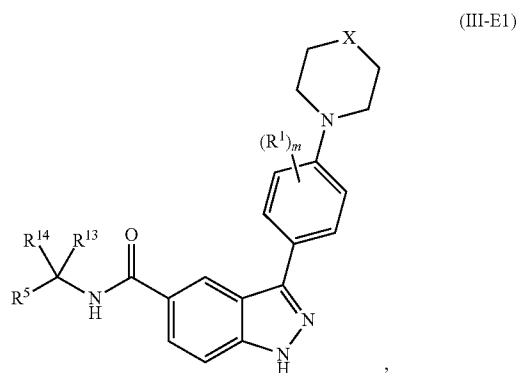


-continued



or a pharmaceutically acceptable salt thereof.

26. The compound of claim **25**, wherein the compound is represented by a structural formula selected from:



or a pharmaceutically acceptable salt thereof.

27-28. (canceled)**29.** The compound of claim **26**, wherein:X is —O—, —CR⁸R⁹— or —NR¹¹—;R⁴ is —H or an alkyl group optionally substituted with a substituent selected from halogen, hydroxy and (C₁-C₃)alkoxy;R⁸ and R⁹ are each independently selected from —H, —OR^c, and (C₁-C₆)alkyl, wherein the (C₁-C₆)alkyl group is optionally substituted with a substituent selected from halogen, hydroxy and (C₁-C₃)alkoxy;

R¹ is —H, (C₁-C₆)alkyl, wherein the (C₁-C₆)alkyl is optionally substituted with a substituent selected from halogen, hydroxy, (C₁-C₃)alkoxy and —C(=O)NR^eR^f; R¹³ and R¹⁴ are each independently selected from —H, alkyl, —OR^c, —(C₁-C₃)alkylene-OR^c, —(C₁-C₃)alkylene-OH, (C₃-C₈)cycloalkyl, —O—(C₃-C₈)cycloalkyl and 3 to 8 membered heterocycloalkyl, provided that R¹³ and R¹⁴ are not both —OR^c, wherein each of the cycloalkyl or heterocycloalkyl groups is optionally substituted with a (C₁-C₃)alkyl;

n is an integer from 1 to 2;

m is an integer from 1 to 2; and

each p is 1 or 2.

30. The compound of claim **29**, wherein:

each R¹ is independently selected from —H, -halogen, —CN, —NO₂, —OR^c, —NR^aR^b, —S(O)_pR^c, —C(=O)OR^c, —OC(=O)OR^c, —C(=O)NR^eR^f, —NR^dC(=O)R^c, —C(=O)R^c or alkyl, wherein the alkyl is optionally substituted with a substituent selected from -halogen, —OR^c, —NR^aR^b, and —S(O)_pR^c;

R⁵ is (a) cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, morpholinyl, thiomorpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, piperazinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, azetidiny, dihydroimidazole, dihydrofuranyl, dihydropyranyl, dihydropyridinyl, dihydropyrimidinyl, dihydrothienyl, dihydrothiophenyl, dihydrothiopyranyl, tetrahydroimidazole, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothienyl, tetrahydropyridinyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, phenyl, furanyl, imidazolyl, oxazolyl, isoxazolyl, oxadiazolyl, pyrazolyl, pyrrolyl, pyridyl, pyrimidinyl, pyridazinyl, thiazolyl, isothiazolyl, triazolyl, tetrazolyl or thienyl, each of which is optionally substituted with 1 to 3 groups represented by R¹⁵ or (b) bicyclooctanyl, decahydronaphthyl, octahydroindenyl, dihydronaphthalenyl, tetrahydronaphthalenyl, dihydroindolyl, dihydroisindolyl, dihydrobenzimidazolyl, dihydrobenzothienyl, dihydrobenzofuranyl, dihydroisobenzofuranyl, dihydrobenzotriazolyl, dihydrobenzothiazolyl, dihydrobenzoxazolyl, dihydrobenzisoxazolyl, dihydroquinolinyl, tetrahydroquinolinyl, dihydroisoquinolinyl, tetrahydroisoquinolinyl, dihydroindazolyl, dihydroacridinyl, tetrahydroacridinyl, chromanyl, isochromanyl, chromenyl, isochromenyl, naphthyl, anthracenyl, fluorenyl, indanyl, indenyl, carbazolyl, benzimidazolyl, benzothienyl, benzofuranyl, isobenzofuranyl, indolyl, isoindolyl, benzotriazolyl, benzothiazolyl, benzoxazolyl, benzisoxazolyl, quinolinyl, isoquinolinyl, indazolyl or acridinyl, each of which is optionally substituted with 1 to 3 groups represented by R¹⁶;

R¹³ is H and R¹⁴ is —H, (C₁-C₆)alkyl, —OR^c, —(C₁-C₃)alkylene-OR^c, —(C₁-C₃)alkylene-OH, a cycloalkyl selected from cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl, a —O-cycloalkyl selected from —O-cyclopropyl, —O-cyclobutyl, and —O-cyclopentyl, —O-cyclohexyl, or a heterocycloalkyl selected from morpholinyl, thiomorpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, piperazinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, azetidiny, dihydroimidazole, dihydrofuranyl, dihydropyranyl, dihydropyrimidinyl, dihydrothienyl, dihydrothiophenyl, dihydrothiopyranyl, tetrahydroimidazole, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothienyl, tetrahydropyridi-

nyl, tetrahydropyrimidinyl, tetrahydrothiophenyl and tetrahydrothiopyranyl, provided that R^{13} and R^{14} are not both $—OR^c$, wherein each of the $—O$ -cycloalkyl, cycloalkyl or heterocycloalkyl groups is optionally substituted with a (C_1-C_3) alkyl; and R^c is $—H$, or (C_1-C_6) alkyl;

each R^{15} is independently selected from halogen, $—CN$, $—NO_2$, $=O$, $—OR^c$, $—NR^aR^b$, $—C(=O)OR^c$, $—OC(=O)OR^c$, $—C(=O)NR^cR^f$, $—NR^dC(=O)R^c$, $—NR^d(C=O)OR^c$, $—O(C=O)NR^cR^f$, $—NR^d(C=O)NR^cR^f$, $—C(=O)R^c$, (C_1-C_6) alkyl, morpholinyl, thiomorpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, piperazinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, azetidiny, dihydroimidazole, dihydrofuranyl, dihydropyranyl, dihydropyridinyl, dihydropyrimidinyl, dihydrothienyl, dihydrothiophenyl, dihydrothiopyranyl, tetrahydroimidazole, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothienyl, tetrahydropyridinyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, phenyl, benzyl, furanyl, imidazolyl, oxazolyl, isoxazolyl, oxadiazolyl, pyrazolyl, pyrrolyl, pyridyl, pyrimidinyl, pyridazinyl, thiazolyl, isothiazolyl, triazolyl, tetrazolyl, and thienyl; wherein the (C_1-C_6) alkyl represented by R^{15} is optionally substituted with a substituent selected from -halogen, $—OR^c$, (C_1-C_6) alkyl, (C_1-C_3) alkoxy, morpholinyl, thiomorpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, piperazinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, azetidiny, dihydroimidazole, dihydrofuranyl, dihydropyranyl, dihydropyridinyl, dihydropyrimidinyl, dihydrothienyl, dihydrothiophenyl, dihydrothiopyranyl, tetrahydroimidazole, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothienyl, tetrahydropyridinyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, furanyl, imidazolyl, oxazolyl, isoxazolyl, oxadiazolyl, pyrazolyl, pyrrolyl, pyridyl, pyrimidinyl, pyridazinyl, thiazolyl, isothiazolyl, triazolyl, tetrazolyl, and thienyl; and

each R^{16} is independently selected from halogen, $—OR^c$, $—NR^aR^b$, $—C(=O)OR^c$, $—C(=O)NR^cR^f$, $—NR^dC(=O)R^c$, $—C(=O)R^c$, (C_1-C_6) alkyl, phenyl, phenyl (C_1-C_3) alkyl, morpholinyl, thiomorpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, piperazinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, azetidiny, dihydroimidazole, dihydrofuranyl, dihydropyranyl, dihydropyridinyl, dihydropyrimidinyl, dihydrothienyl, dihydrothiophenyl, dihydrothiopyranyl, tetrahydroimidazole, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothienyl, tetrahydropyridinyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, furanyl, imidazolyl, oxazolyl, isoxazolyl, oxadiazolyl, pyrazolyl, pyrrolyl, pyridyl, pyrimidinyl, pyridazinyl, thiazolyl, isothiazolyl, triazolyl, tetrazolyl, and thienyl.

31. The compound of claim 30, wherein:

R^1 is selected from $—H$, -halogen, $—OCH_3$, $—N(CH_3)_2$, $—S(O)_2CH_3$, or methyl;

R^5 is cyclopentyl, cyclohexyl, morpholinyl, pyrrolidinyl, piperidinyl, dihydropyridinyl, tetrahydropyridinyl, dihydropyrimidinyl, tetrahydropyrimidinyl, phenyl, furanyl, imidazolyl, pyrrolyl, pyridyl, pyrimidinyl or

thienyl, each of which is optionally substituted with 1 to 3 groups represented by R^{15} or (b) chromanyl, chromenyl, dihydroindolyl, dihydroisindolyl, dihydrobenzothienyl, dihydrobenzofuranyl, dihydroisobenzofuranyl, dihydrobenzotriazolyl, dihydroquinolinyl, tetrahydroquinolinyl, dihydroisoquinolinyl, tetrahydroisoquinolinyl, dihydrobenzoxazolyl, naphthyl, anthracenyl, fluorenyl, indanyl, indenyl, dihydronaphthalene, tetrahydronaphthalene, carbazolyl, benzimidazolyl, benzothienyl, benzofuranyl, isobenzofuranyl, indolyl, quinolinyl, isoquinolinyl or isindolyl, each of which is optionally substituted with 1 to 3 groups represented by R^{16} ;

R^{13} is $—H$ and R^{14} is $—H$, (C_1-C_6) alkyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, $—O$ -cyclopropyl, $—O$ -cyclobutyl, $—O$ -cyclopentyl, $—O$ -cyclohexyl, morpholinyl, thiomorpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, piperazinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, azetidiny, dihydroimidazole, dihydrofuranyl, dihydropyranyl, dihydropyridinyl, dihydropyrimidinyl, dihydrothienyl, dihydrothiophenyl, dihydrothiopyranyl, tetrahydroimidazole, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothienyl, tetrahydropyridinyl, tetrahydropyrimidinyl, tetrahydrothiophenyl or tetrahydrothiopyranyl;

R^{15} is independently selected from halogen, $—OR^c$, $—NR^aR^b$, and (C_1-C_6) alkyl;

each R^{16} is independently selected from (C_1-C_6) alkyl; and m is 1.

32. (canceled)

33. The compound of claim 26, wherein X is $—NR^{11}—$ and wherein R^{11} is (C_1-C_4) alkyl.

34. The compound of claim 33, wherein R^5 is cyclohexyl, phenyl, pyridyl, or thienyl, each of which is optionally substituted with 1 to 3 groups selected from methyl, ethyl, propyl, halogen, hydroxymethyl, hydroxyethyl, methoxy, ethoxy, and $—(CH_2)_{0-2}$ -morpholinyl.

35. The compound of claim 34, wherein R^5 is cyclohexyl, phenyl, pyridyl, or thienyl, each of which is optionally substituted with 1 to 3 groups selected from methyl, ethyl, propyl and halogen.

36. The compound of claim 35, wherein R^{14} is $—H$, methyl, ethyl, propyl, hydroxymethyl, hydroxyethyl, hydroxypropyl, methoxy, ethoxy, propoxy, methoxymethyl, methoxyethyl, methoxypropyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, $—O$ -cyclopropyl, $—O$ -cyclobutyl, $—O$ -cyclopentyl, $—O$ -cyclohexyl, morpholinyl, oxetanyl, tetrahydrofuryl, tetrahydropyranyl, azetidiny, pyrrolidinyl, piperidyl, wherein the morpholinyl, tetrahydrofuryl, tetrahydropyranyl, pyrrolidinyl or piperidyl are optionally substituted with methyl.

37. The compound of claim 36, wherein R^3 is piperidyloxy, N -methylpiperidyloxy, morpholinyl or hydroxypiperidyl.

38. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier or diluent.

39. A method for treating cancer, the method comprising: administering to a subject in need thereof an effective amount of a compound of claim 1, such that the cancer is treated.

* * * * *