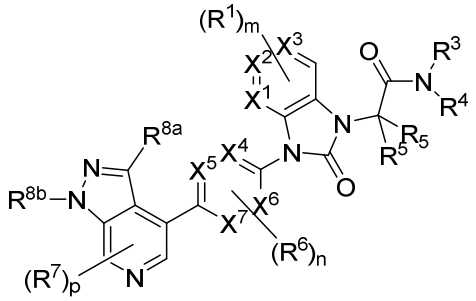
BRIEF SUMMARY OF THE DISCLOSURE

[0008] In one aspect, the present disclosure relates to a compound of formula (**I**) or a pharmaceutically acceptable salt thereof:



(**I**); wherein

X^1, X^2 and X^3 are each independently selected from carbon and nitrogen, wherein at least two of X^1, X^2 and X^3 are carbon;

X^4, X^5 , X^6 and X^7 are each independently selected from carbon and nitrogen, wherein at least two of X^4, X^5, X^6 and X^7 are carbon;

R^1 is independently selected at each occurrence from halo, nitro, cyano, NR^9R^{10}, OR^{11}, SR^9, $SO_2NR^9R^9$, SO_2R^9, CO_2R^9, $C(O)R^9$, $CONR^9R^9$, C_1-C_4-alkyl, C_1-C_4-alkyl substituted with NR^9R^{10}, C_1-C_4-alkyl substituted with OR^{11}, C_2-C_4-alkenyl, C_2-C_4-alkynyl, C_1-C_4-haloalkyl and cyclopropyl;

R^3 is independently selected from H and C_1-C_4-alkyl;

R^4 is independently selected from C_1-C_6-alkyl, C_1-C_6-haloalkyl, C_0-C_4-alkylene-R^{4a}; wherein R^{4a} is independently selected from: C_3-C_8-cycloalkyl, phenyl, 5-, 6-, 9- or 10-membered heteroaryl and 4- to 10-membered heterocycloalkyl; wherein said heterocycloalkyl or heteroaryl group may be monocyclic or bicyclic; wherein said cycloalkyl or heterocycloalkyl group is optionally substituted with a single R^{12} group and/or from 1 to 4 R^{13} groups and wherein said phenyl or heteroaryl group is optionally substituted with a single R^{12} group and/or from 1 to 3 R^{14} groups;

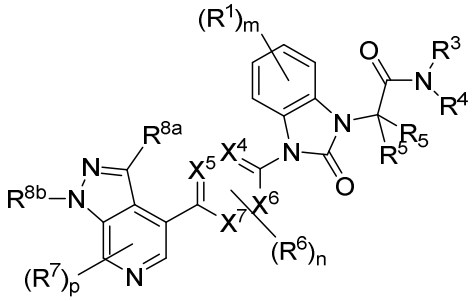
or R^3 and R^4, together with the nitrogen atom to which they are attached together form a 4- to 10-membered heterocycloalkyl group or a 5-, or 9-membered heteroaryl group; wherein said heterocycloalkyl or heteroaryl group may be monocyclic or bicyclic; wherein said heterocycloalkyl group is optionally substituted with a single R^{12} group and/or from 1 to 4 R^{13} groups and wherein said heteroaryl group is optionally substituted with a single R^{12} group and/or from 1 to 3 R^{14} groups;

R^5 is independently at each occurrence selected from H, halo and C_1-C_4-alkyl, or the two R^5 groups and the carbon atom to which they are attached may together form a C_3-C_6 cycloalkyl ring;

R^6 is independently at each occurrence selected from halo, nitro, cyano, NR^9R^{10}, OR^{11}, SR^9, $SO_2NR^9R^9$, SO_2R^9, CO_2R^9, $C(O)R^9$, $CONR^9R^9$, C_1-C_4-alkyl, C_1-C_4-alkyl substituted with NR^9R^{10}, C_1-C_4-alkyl substituted with OR^{11}, C_2-C_4-alkenyl, C_2-C_4-alkynyl, C_1-C_4-haloalkyl and cyclopropyl;

from the group consisting of: halo, oxo, fluoro, nitro, cyano, NR^aR^b, OR^a, SR^a, CO_2R^a, $C(O)R^a$, $CONR^aR^a$, C_1-C_4-alkyl, C_1-C_4-haloalkyl and cyclopropyl; wherein R^a is independently at each occurrence selected from H, C_1-C_4-alkyl and C_1-C_4-haloalkyl; and R^b is independently at each occurrence selected from H, C_1-C_4-alkyl, $C(O)$-C_1-C_4-alkyl and $S(O)_2$-C_1-C_4-alkyl.

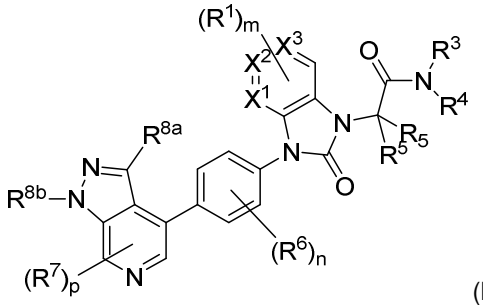
[0009] In an example, the compound of formula (**I**) is a compound of formula (**II**):



(**II**)

wherein X^4, X^5, X^6, X^7, R^1, R^3, R^4, R^5, R^6, R^7, R^{8a}, R^{8b}, m, n and p are as described above for compounds of formula (**I**).

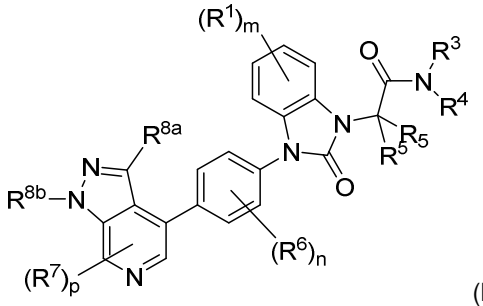
[0010] In an example, the compound of formula (**I**) is a compound of formula (**III**):



(**III**)

wherein X^1, X^2, X^3, R^1, R^3, R^4, R^5, R^6, R^7, R^{8a}, R^{8b}, m, n and p are as described above for compounds of formula (**I**).

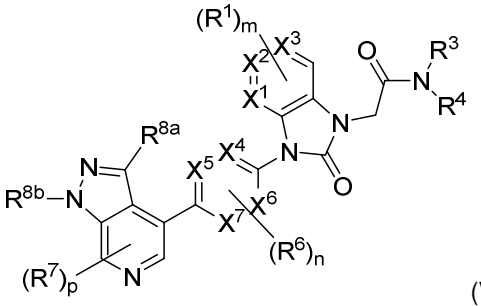
[0011] In an example, the compound of formula (**I**) is a compound of formula (**IV**):



(**IV**)

wherein R^1, R^3, R^4, R^5, R^6, R^7, R^{8a}, R^{8b}, m, n and p are as described above for compounds of formula (**I**).

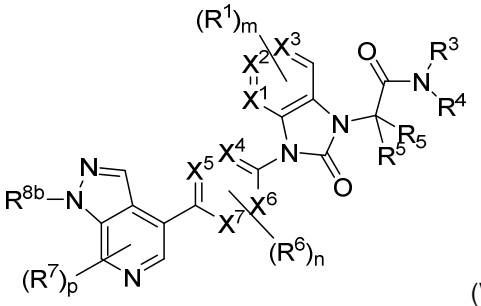
[0012] In an example, the compound of formula (**I**) is a compound of formula (**V**):



(**V**)

wherein X^1, X^2, X^3, X^4, X^5, X^6, X^7, R^1, R^3, R^4, R^6, R^7, R^{8a}, R^{8b}, m, n and p are as described above for compounds of formula (**I**).

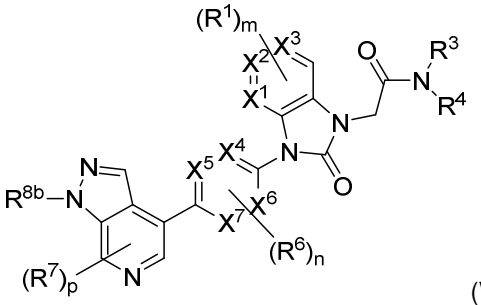
[0013] In an example, the compound of formula (**I**) is a compound of formula (**VI**):



(**VI**)

wherein X^1, X^2, X^3, X^4, X^5, X^6, X^7, R^1, R^3, R^4, R^5, R^6, R^7, R^{8b}, m, n and p are as described above for compounds of formula (**I**).

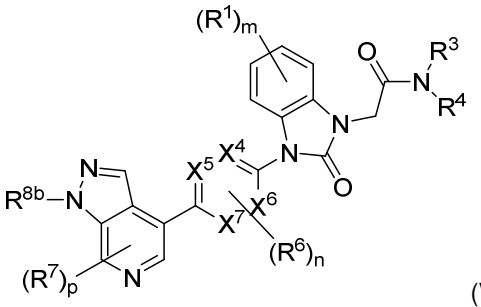
[0014] In an example, the compound of formula (**I**) is a compound of formula (**VII**):



(**VII**)

wherein X^1, X^2, X^3, X^4, X^5, X^6, X^7, R^1, R^3, R^4, R^6, R^7, R^{8b}, m, n and p are as described above for compounds of formula (**I**).

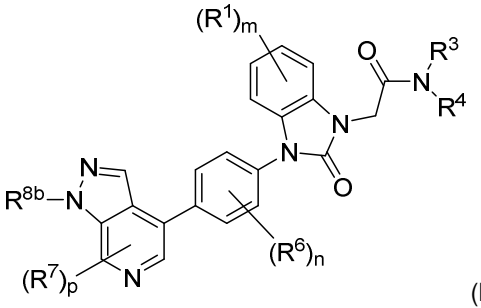
[0015] In an example, the compound of formula (**I**) is a compound of formula (**VIII**):



(**VIII**)

wherein X^4, X^5, X^6, X^7, R^1, R^3, R^4, R^6, R^7, R^{8b}, m, n and p are as described above for compounds of formula (**I**).

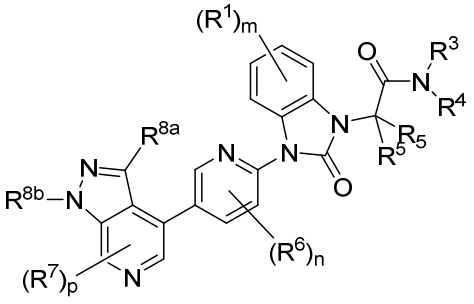
[0016] In an example, the compound of formula (**I**) is a compound of formula (**IX**):



(**IX**)

wherein R^1, R^3, R^4, R^6, R^7, R^{8b}, m, n and p are as described above for compounds of formula (**I**).

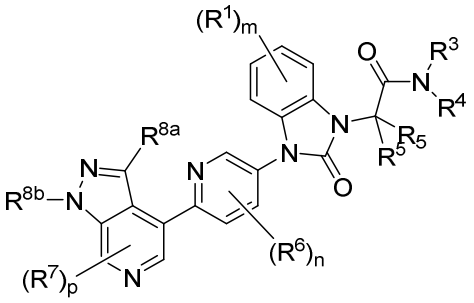
[0017] In an example, the compound of formula (**I**) is a compound of formula (**X**):



(**X**)

wherein R^1, R^3, R^4, R^5, R^6, R^7, R^{8a}, R^{8b}, m and p are as described above for compounds of formula (**I**), and n is an integer selected from 0, 1, 2 and 3.

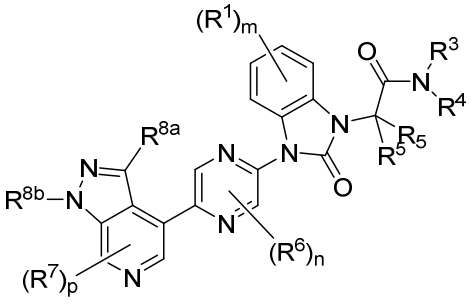
[0018] In an example, the compound of formula (**I**) is a compound of formula (**XI**):



(**XI**)

wherein R^1, R^3, R^4, R^5, R^6, R^7, R^{8a}, R^{8b}, m and p are as described above for compounds of formula (**I**), and n is an integer selected from 0, 1, 2 and 3.

[0019] In an example, the compound of formula (**I**) is a compound of formula (**XII**):



(**XII**)

wherein R^1, R^3, R^4, R^5, R^6, R^7, R^{8a}, R^{8b}, m and p are as described above for compounds of formula (**I**), and n is an integer selected from 0, 1 and 2.

[0020] The following examples apply to compounds of any of formulae (**I**)-(**XII**). These examples are independent and interchangeable. Any one example may be combined with any other example, where chemically allowed. In other words, any of the features described in the following examples may (where chemically allowable) be combined with the features described in one or more other examples. In particular, where a compound is exemplified or illustrated in this specification, any two or more of the examples listed below, expressed at any level of generality, which encompass that compound may be combined to provide a further example which forms part of the present disclosure.

[0021] It may be that X^1 is carbon. It may be that X^2 is carbon. It may be that X^3 is carbon It may be that X^1 and X^2 are both carbon. It may be that X^2 and X^3 are both carbon. It may be that X^1 and X^3 are both carbon. It may be that X^1, X^2 and X^3 are each carbon.

[0022] It may be that a single one of X^1, X^2 and X^3 is nitrogen. It may be that X^1 is nitrogen. It may be that X^2 is nitrogen. It may be that X^3 is nitrogen.

[0023] It may be that X^4 is carbon. It may be that X^5 is carbon. It may be that X^6 is carbon. It may be that X^7 is carbon. It may be that X^4 and X^5 are both carbon. It may be that X^4 and X^6 are both carbon. It may be that X^4 and X^7 are both carbon. It may be that X^5 and X^6 are both carbon. It may be that X^5 and X^7 are both carbon. It may be that X^6 and X^7 are both carbon. It may be that X^4, X^5 and X^6 are each

carbon. It may be that X^4, X^5 and X^7 are each carbon. It may be that X^4, X^6 and X^7 are each carbon. It may be that X^5, X^6 and X^7 are each carbon. It may be that X^4, X^5, X^6 and X^7 are each carbon.

[0024] It may be that at least one of X^4, X^5, X^6, and X^7 is nitrogen. It may be that a single one of X^4, X^5, X^6, and X^7 is nitrogen. It may be that X^5 is nitrogen. It may be that X^4 is nitrogen. It may be that two of X^4, X^5, X^6, and X^7 are nitrogen. It may be that X^4 and X^5 are each nitrogen. It may be that X^4 and X^7 are each nitrogen. It may be that X^5 and X^7 are each nitrogen. It may be that X^4 and X^6 are each nitrogen.

[0025] m may be selected from 0 and 1. m may be 0. m may be 1. m may be 2. m may be 3. m may be 4.

[0026] R^1 may be independently at each occurrence selected from halo, nitro, cyano, OR^{11}, C_1-C_4-alkyl, C_1-C_4-alkyl substituted with NR^9R^{10}, C_1-C_4-alkyl substituted with OR^{11}, C_1-C_4-haloalkyl and cyclopropyl. R^1 may be independently at each occurrence selected from halo, OR^{11}, NR^9R^{10}, cyano, C_1-C_4-alkyl and C_1-C_4-haloalkyl. R^1 may be independently at each occurrence selected from halo, OR^{11}, C_1-C_4-alkyl, C_1-C_4-haloalkyl and cyclopropyl. R^1 may be independently at each occurrence selected from halo and C_1-C_4-alkyl. R^1 may be independently at each occurrence halo, e.g. fluoro. R^1 may be independently at each occurrence C_1-C_4-alkyl, e.g. methyl.

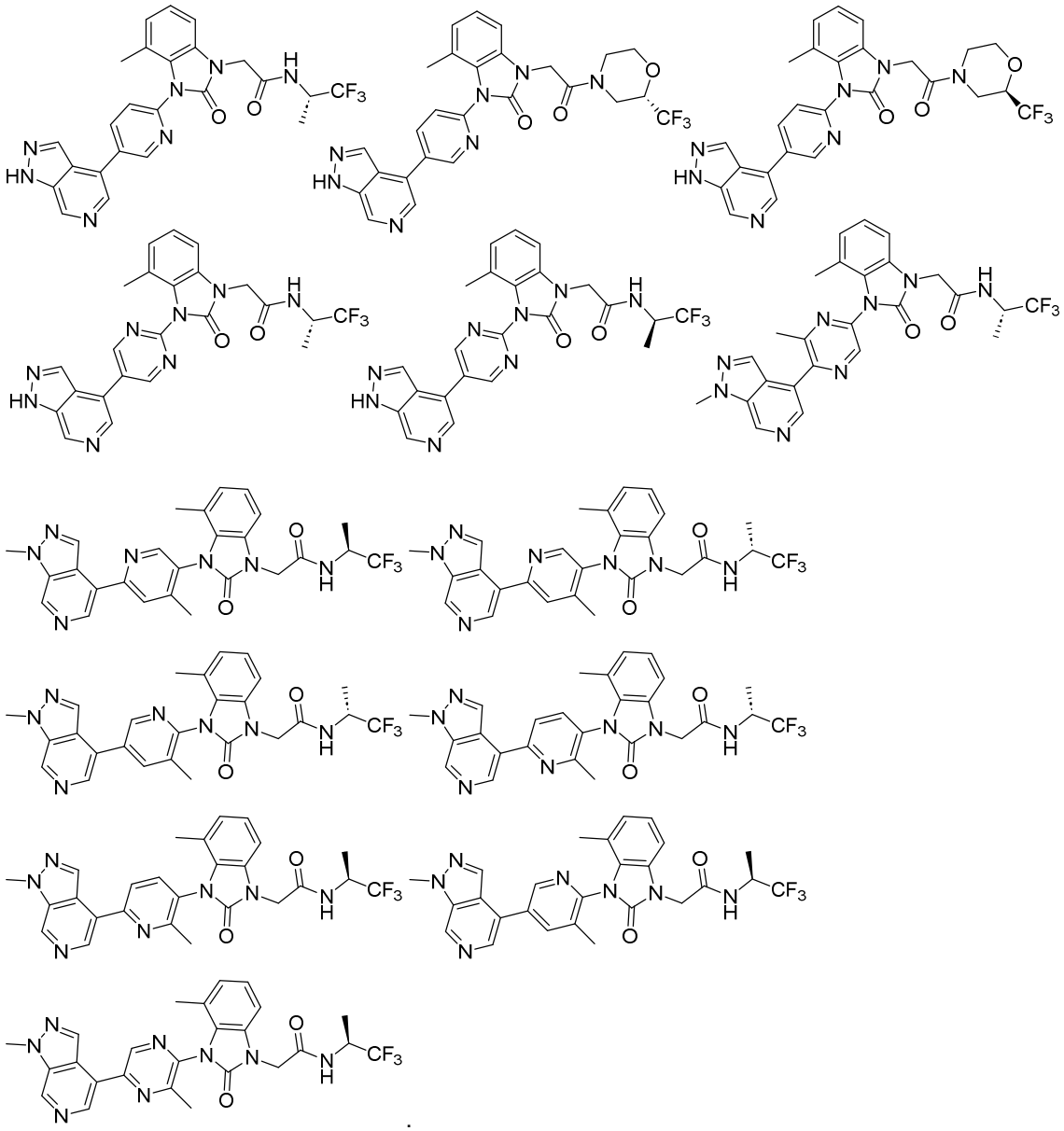
[0027] It may be that X^1 is not CH. It may be that X^1 is selected from nitrogen and a carbon substituted with R^1. It may be that m is at least 1, X^1 is carbon and an R^1 group is attached to the X^1 carbon. It may be that m is 1, X^1 is carbon and the R^1 group is attached to the X^1 carbon. Compounds having an R^1 group attached to the X^1 carbon can show increased activity relative to compounds without an R^1 group attached to the X^1 carbon. In these examples, the R^1 group attached to X^1 may be C_1-C_4-alkyl, e.g. methyl.

[0028] R^5 may be independently at each occurrence selected from H, fluoro and C_1-C_4-alkyl. R^5 may be independently at each occurrence selected from H, fluoro and C_1-C_4-alkyl, or the two R^5 groups and the carbon atom to which they are attached may together form a C_3-C_6 cycloalkyl ring. R^5 may be independently at each occurrence selected from H and C_1-C_4-alkyl, or the two R^5 groups and the carbon atom to which they are attached may together form a C_3-C_6 cycloalkyl ring. R^5 may be independently at each occurrence selected from H and C_1-C_4-alkyl, e.g. methyl.

[0029] It may be that R^5 is at each occurrence H. It may be that R^5 is at one occurrence H and at the other occurrence C_1-C_4-alkyl, e.g. methyl. It may be that R^5 is at each occurrence C_1-C_4-alkyl, e.g. methyl.

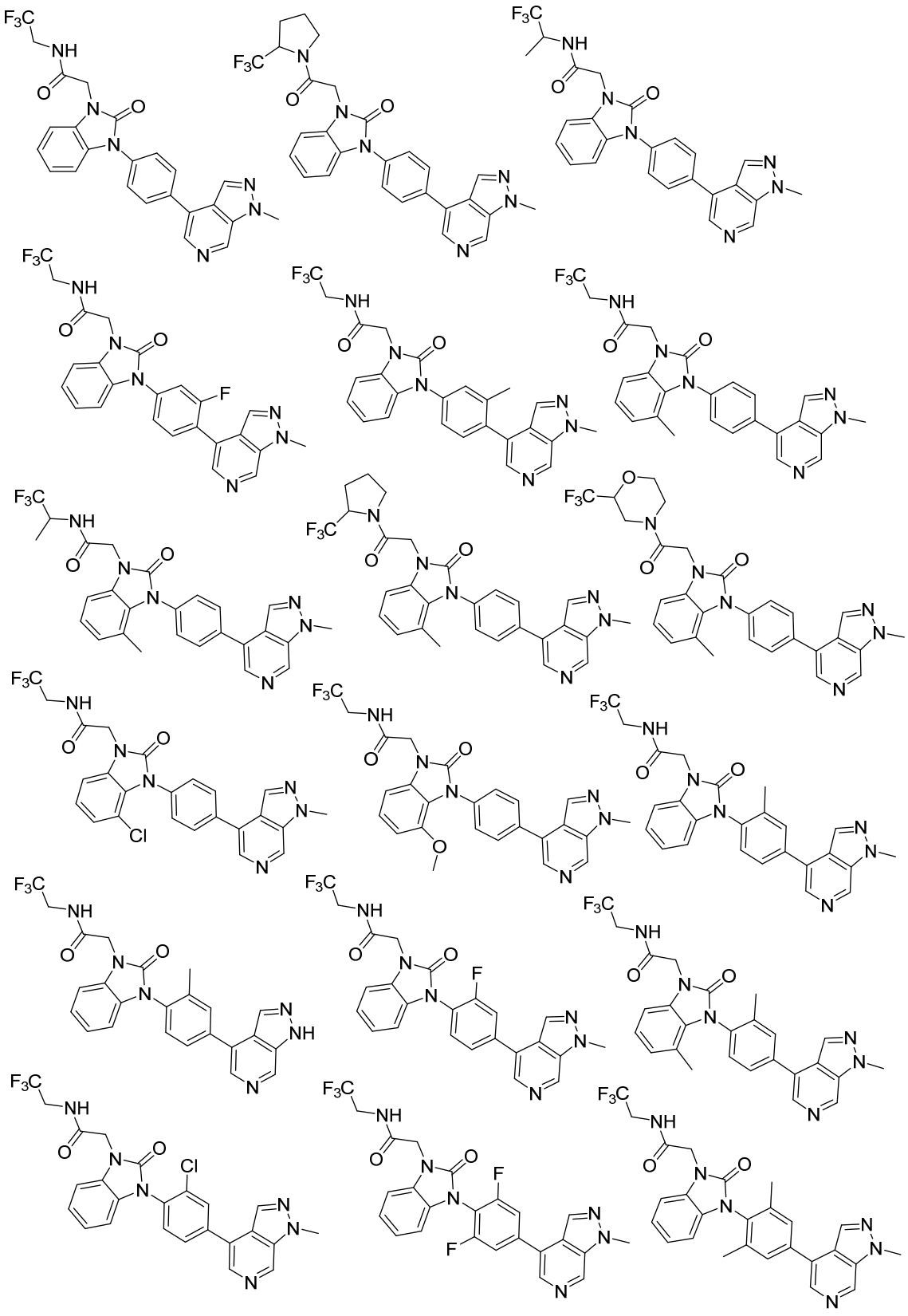
[0030] n may be selected from 0 and 1. n may be 0. n may be 1. n may be 2. n may be 3. n may be 4.

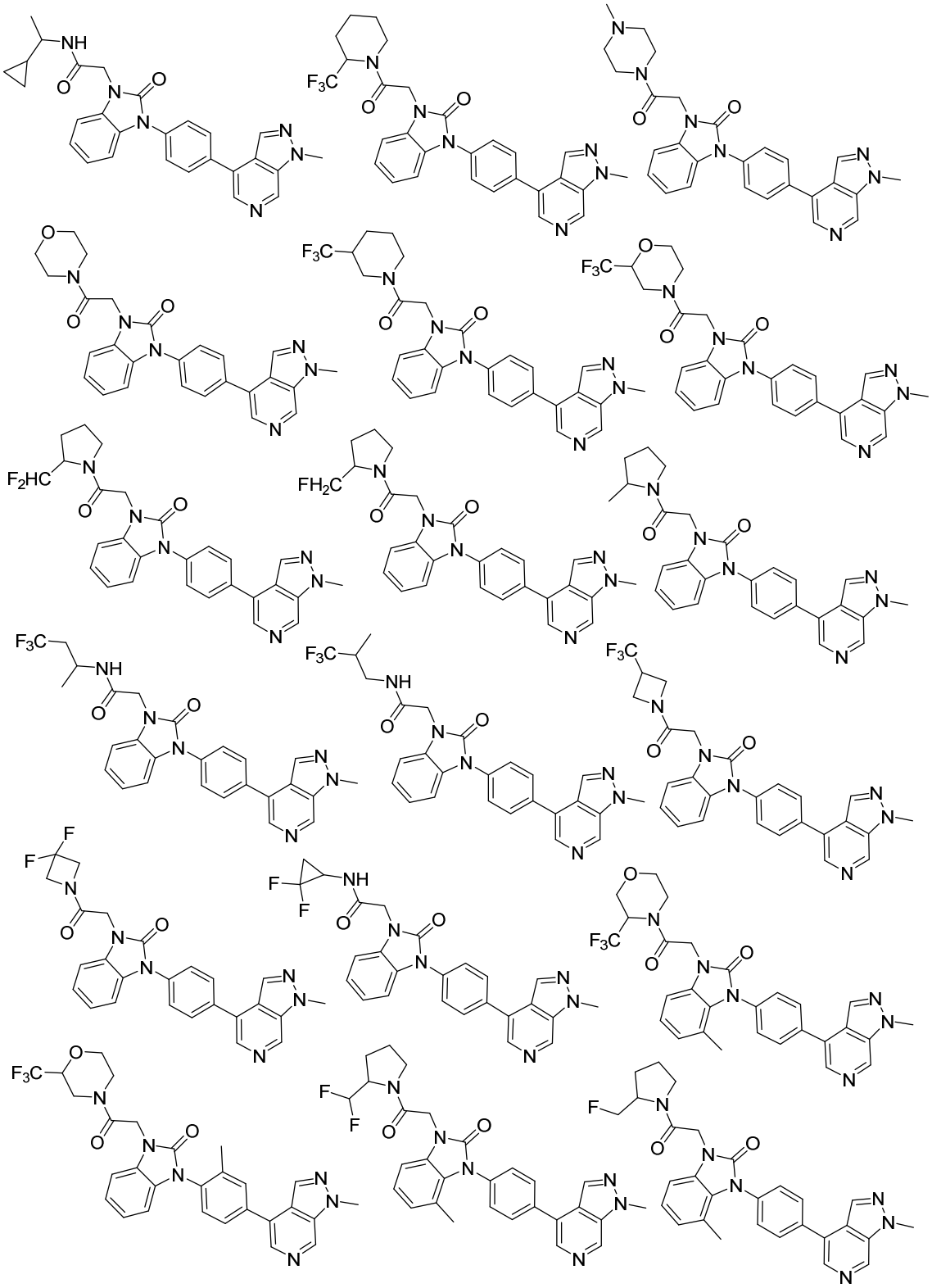
[0031] R^6 may be independently selected from halo, nitro, cyano, OR^{11}, C_1-C_4-alkyl, C_1-C_4-alkyl substituted with NR^9R^{10}, C_1-C_4-alkyl substituted with OR^{11}, C_1-C_4-haloalkyl and cyclopropyl. R^6 may be independently selected from halo, OR^{11}, C_1-C_4-alkyl, C_1-C_4-haloalkyl and cyclopropyl. R^6 may be

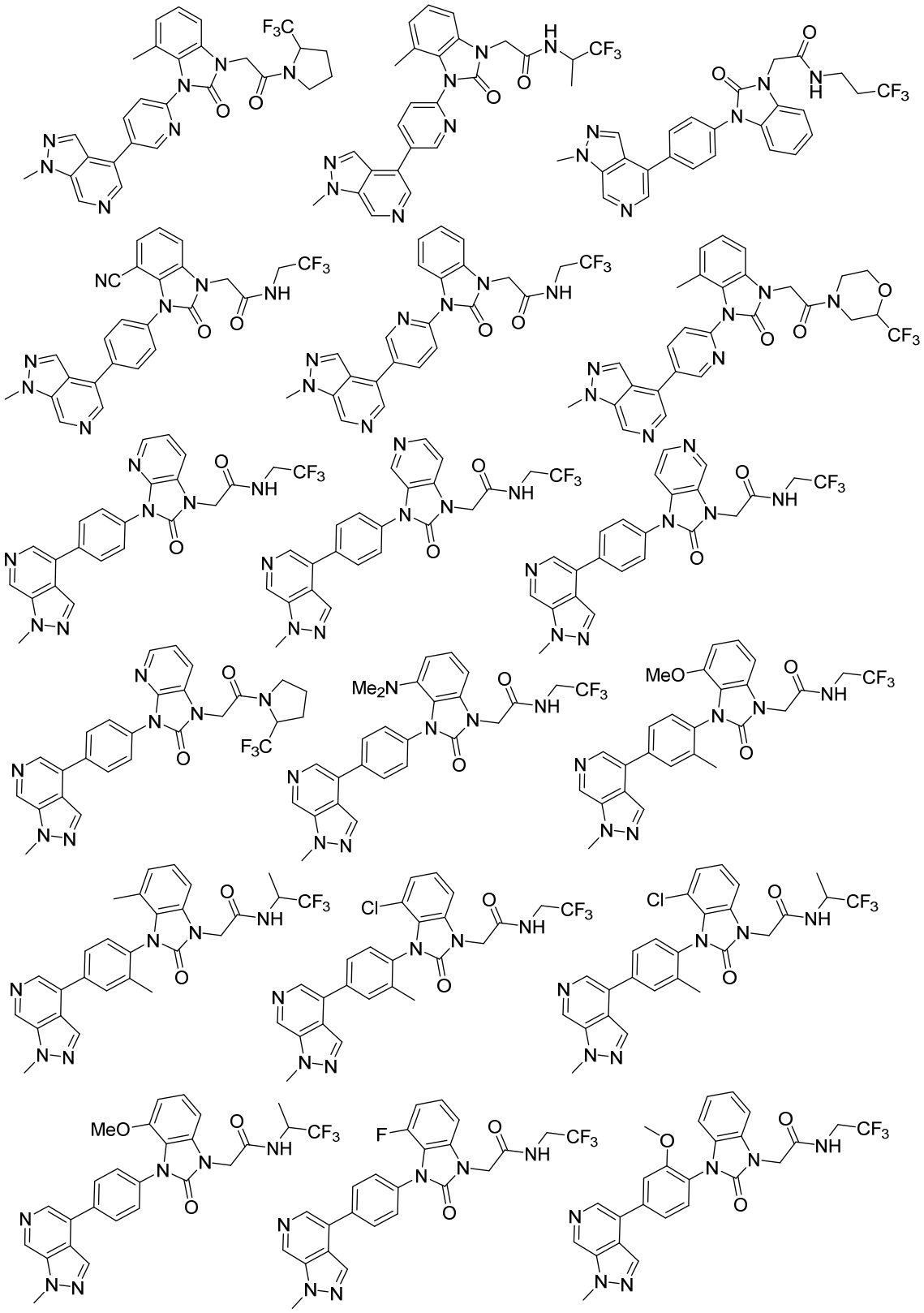


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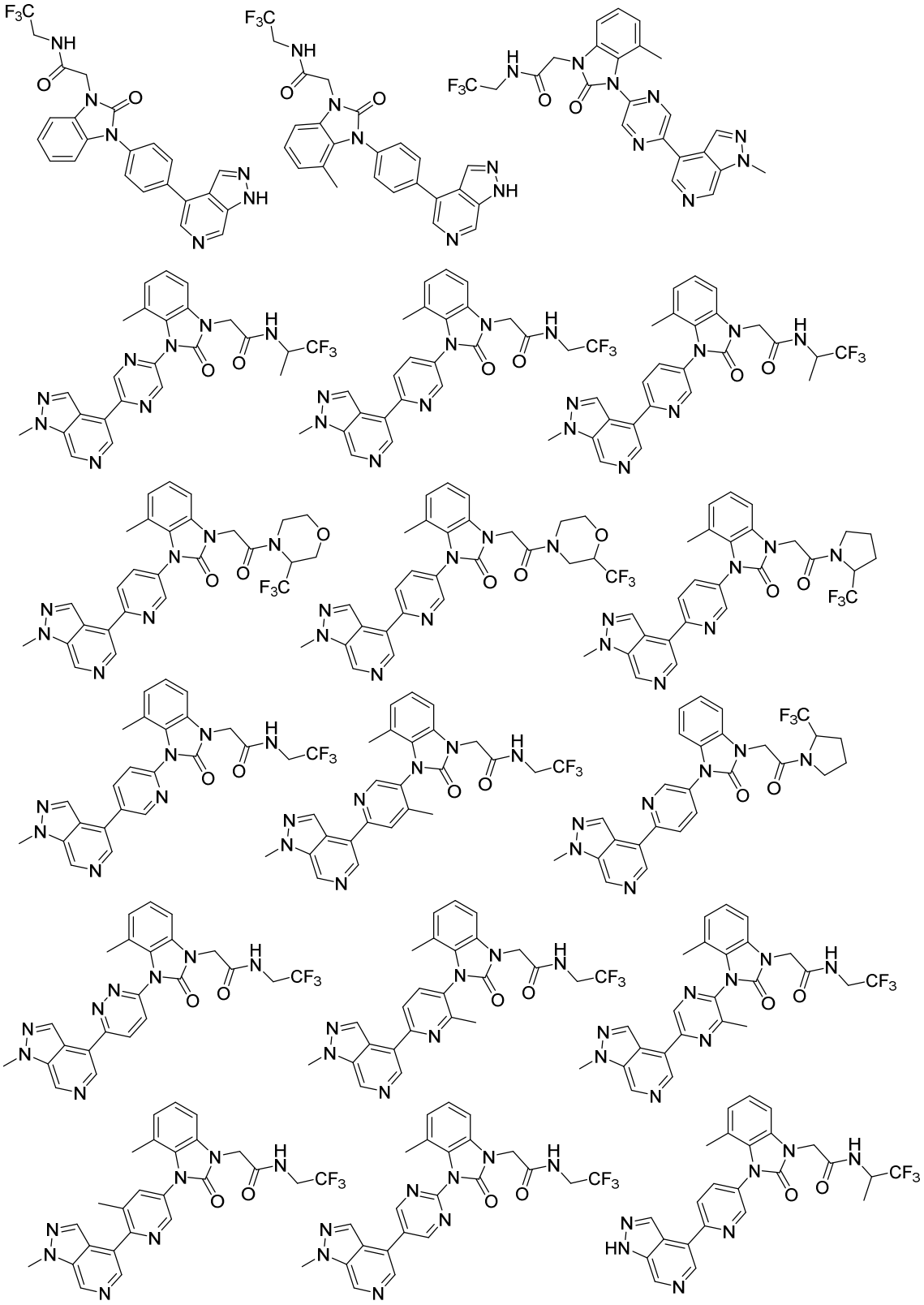
[0077a] In one aspect, the present disclosure relates to a compound of formula (**I**) selected from:



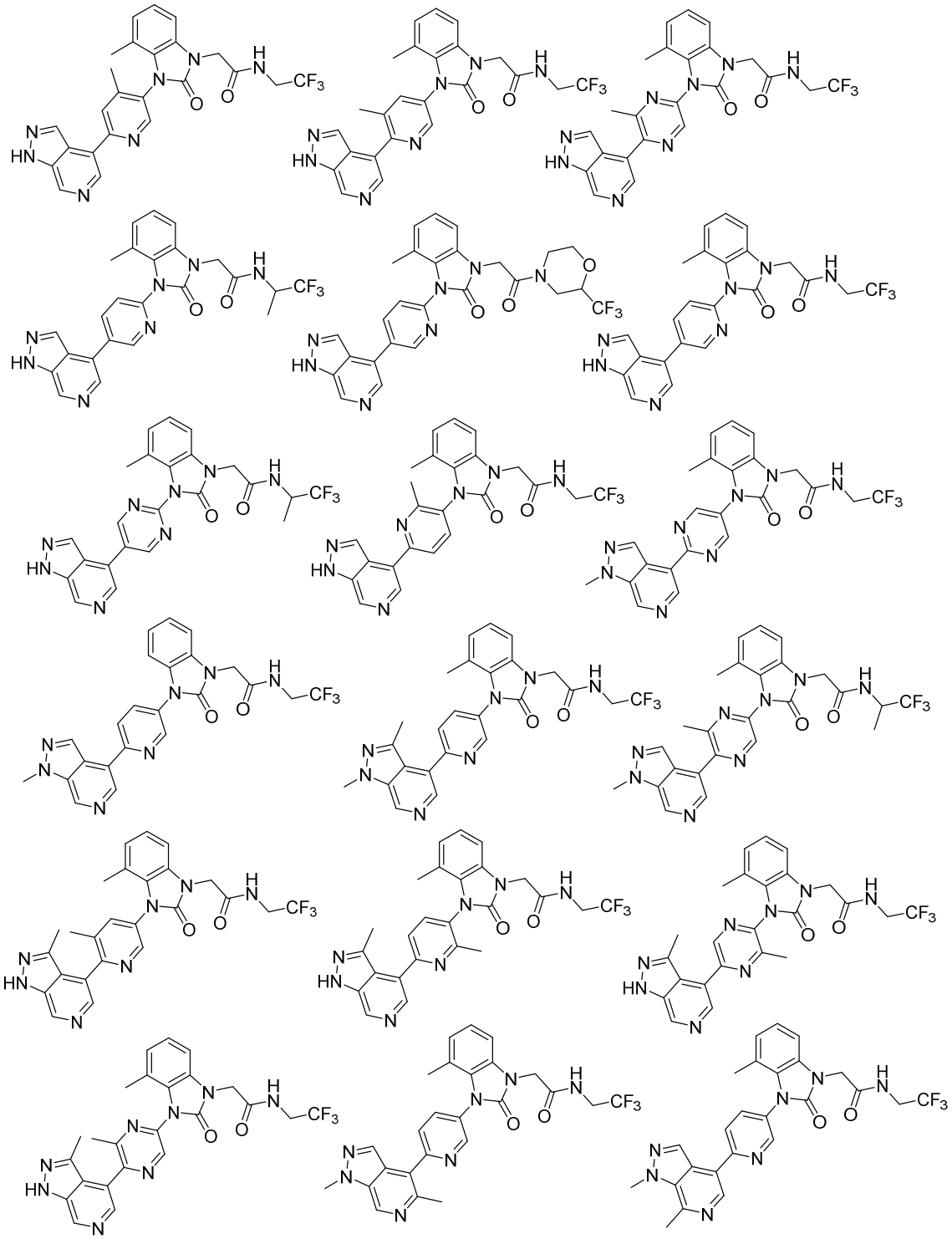


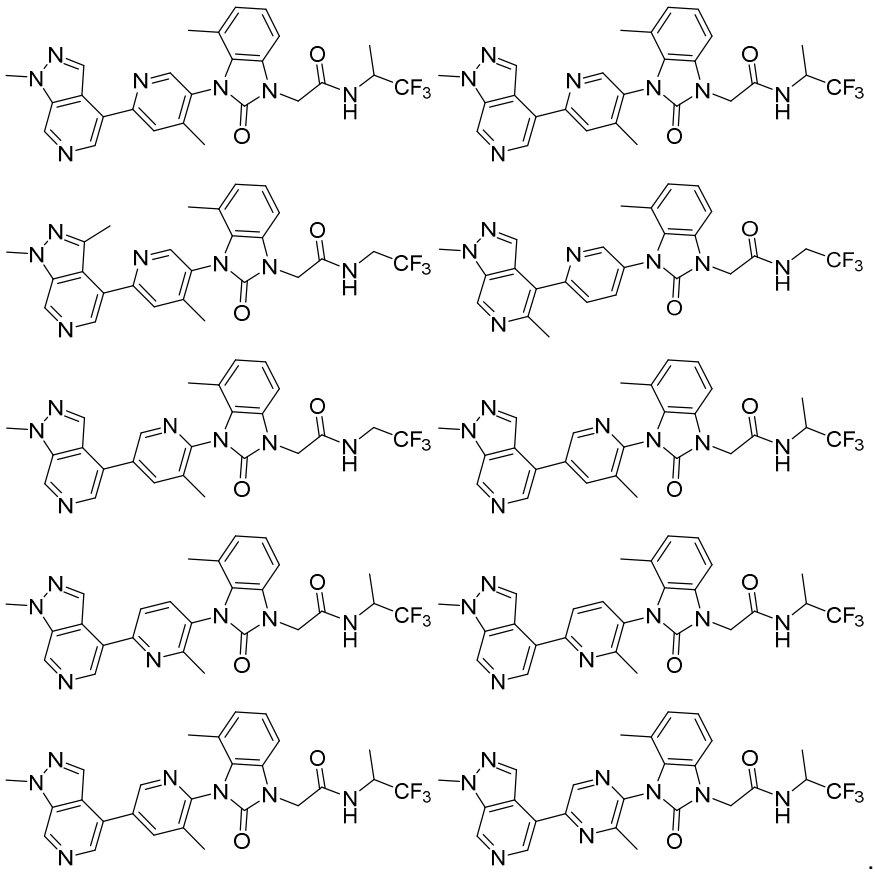


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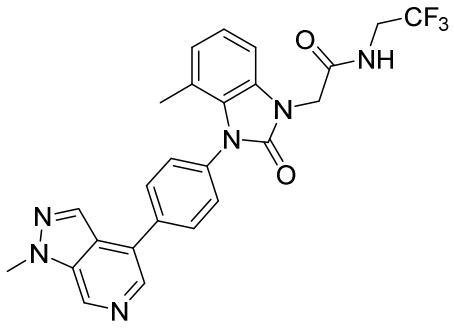
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[0078] It may be that the compound of formula (I) is not



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[0079] In an example of the disclosure there is provided the compounds of the present disclosure for use as a medicament. In one aspect, the present disclosure relates to a compound disclosed herein for use as a medicament.

[0080] In accordance with another example, there is provided a compound of the present disclosure for use in the treatment of a condition which is modulated by DDR1 and/or DDR2. A compound of any formula disclosed herein may be for use in the treatment of a condition treatable by the inhibition of DDR1 and/or DDR2.

[0081] In another example of the disclosure, there is provided a compound of the present disclosure for use in the treatment of a disease or disorder selected from: renal conditions, liver conditions, inflammatory conditions, cardiovascular conditions, acute and chronic organ transplant rejection, fibrotic diseases and cancer.

[0082] In an example of the disclosure there is provided a method of treating a disease or disorder which is modulated by DDR1 and/or DDR2 wherein the method comprises administering a therapeutic amount of a compound of the disclosure, to a patient in need thereof.

[0083] The method of treatment may be a method of treating a condition treatable by the inhibition of DDR1 and/or DDR2.

[0084] The disclosure also provides a method of treating a disease or disorder selected from: renal conditions, liver conditions, inflammatory conditions, cardiovascular conditions, acute and chronic organ transplant rejection, fibrotic diseases and cancer wherein the method comprises administering a therapeutic amount of a compound of any formula disclosed herein, to a patient in need thereof.

[0085] Renal conditions include, acute kidney injury and chronic renal disease with and without proteinuria including end-stage renal disease (ESRD). This includes decreased creatinine clearance and decreased glomerular filtration rate, micro albuminuria, albuminuria and proteinuria, glomerulosclerosis with expansion of reticulated mesangial matrix with or without significant hypercellularity (particularly diabetic nephropathy and amyloidosis), focal thrombosis of glomerular capillaries (particularly thrombotic microangiopathies), global fibrinoid necrosis, ischemic lesions, malignant nephrosclerosis (such as ischemic retraction, reduced renal blood flow and renal arteriopathy), swelling and proliferation of intracapillary (endothelial and mesangial) and/or extracapillary cells (crescents) like in glomerular nephritis entities, focal segmental glomerular sclerosis, IgA nephropathy, vasculitis / systemic diseases as well as acute and chronic kidney transplant rejection. Early and advanced Alport syndrome are also included amongst renal conditions.

[0086] Inflammatory conditions include, arthritis, osteoarthritis, multiple sclerosis, systemic lupus erythematodes, inflammatory bowel disease, abnormal evacuation disorder and the like as well as inflammatory airways diseases such as idiopathic pulmonary fibrosis (IPF), chronic obstructive pulmonary disease (COPD) or chronic asthma. Further conditions of the respiratory system include other diffuse parenchymal lung diseases of different etiologies including iatrogenic drug-induced fibrosis, occupational and/or environmental induced fibrosis, systemic diseases and vasculitis, granulomatous diseases (sarcoidosis, hypersensitivity pneumonia), collagen vascular disease, radiation induced fibrosis.

[0087] Vascular conditions include atherosclerosis, thrombotic vascular disease as well as thrombotic microangiopathies, proliferative arteriopathy (such as swollen myointimal cells surrounded by mucinous extracellular matrix and nodular thickening), atherosclerosis, decreased vascular compliance (such as stiffness, reduced ventricular compliance and reduced vascular compliance), endothelial dysfunction and the like.

[0088] Cardiovascular conditions include acute coronary syndrome, coronary heart disease, myocardial infarction, arterial and pulmonary hypertension, cardiac arrhythmia such as atrial fibrillation, stroke and other vascular damage.

[0089] Fibrotic diseases include, but are not limited to myocardial and vascular fibrosis, renal fibrosis, liver fibrosis, pulmonary fibrosis, skin fibrosis, scleroderma and encapsulating peritonitis, systemic sclerosis, Alport syndrome, Chronic kidney disease, NASH, Interstitial lung diseases and Systemic Sclerosis.

[0090] In certain examples compounds of the disclosure are for use in the treatment of or are used in a method of treatment of cancer. Examples include but are not limited to: liver cancer, bladder cancer, hepatoma, squamous carcinoma of the lung, non-small cell lung cancer, adenocarcinoma of the lung, small-cell lung cancer, various types of head and neck cancer, breast cancer, colon cancer, colorectal cancer, cancer of the peritoneum, hepatocellular cancer, gastrointestinal cancer, esophageal cancer, endometrial or uterine carcinoma, salivary gland carcinoma, squamous cell cancer, pituitary cancer, astrocytoma, soft tissue sarcoma, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, kidney cancer, liver cancer, prostate cancer, vulval cancer, thyroid cancer, hepatic carcinoma, brain cancer, endometrial cancer, testis cancer, cholangiocarcinoma, gallbladder carcinoma, gastric cancer and melanoma. In certain examples, the cancer is selected from bladder cancer, pancreatic cancer, breast cancer, lung cancer, ovarian cancer and glioblastoma.

[0091] In one aspect, the present disclosure relates to a pharmaceutical formulation comprising a compound disclosed herein and a pharmaceutically acceptable excipient. In another example of the disclosure there is provided a pharmaceutical composition, wherein the composition comprises a compound of the disclosure and pharmaceutically acceptable excipients.

[0092] In an example the pharmaceutical composition may be a combination product comprising an additional pharmaceutically active agent.

[0093] In an example of the present disclosure there is provided the use of a compound of the disclosure in the manufacture of a medicament for use in the treatment of any condition disclosed herein. In one aspect, the present disclosure relates to use of a compound disclosed herein in the manufacture of a medicament for treating a disease or disorder selected from renal conditions, liver conditions, inflammatory conditions, cardiovascular conditions, acute and chronic organ transplant rejection, fibrotic diseases and cancer.

DETAILED DESCRIPTION

[0094] Given below are definitions of terms used in this application. Any term not defined herein takes the normal meaning as the skilled person would understand the term.

[0095] The term “halo” refers to one of the halogens, group 17 of the periodic table. In particular, the term refers to fluorine, chlorine, bromine and iodine. Preferably, the term refers to chlorine or fluorine.

[0096] The term “alkyl” refers to a linear or branched hydrocarbon chain. For example, the term “C_{1-6} alkyl” refers to a linear or branched hydrocarbon chain containing 1, 2, 3, 4, 5 or 6 carbon atoms, for