DDR1 AND DDR2 INHIBITORS FOR THE TREATEMENT OF CANCER AND FIBROTIC DISEASES

[0001] This invention relates to novel compounds and pharmaceutical compositions comprising the novel compounds. More specifically, the invention relates to compounds useful as inhibitors of discoidin domain receptor 1 (DDR1) and discoidin domain receptor 2 (DDR2). The compounds are particularly useful in the treatment of cancer and fibrotic diseases

BACKGROUND

[0002] Discoidin Domain Receptors (DDRs) DDR1 and DDR2 are type 1 transmembrane Receptor Tyrosine Kinases (RTKs) with collagen receptor functionality (Vogel et al, Mol. Cell, 1997). DDRs contain characteristic collagen binding discoidin domains in the N-terminal extracellular domain. These domains are proceeded by an extracellular juxtamembrane domain, a single transmembrane domain, a cytosolic juxtamembrane domain and a catalytic kinase domain prior to a short C-terminal tail. Five isoforms of DDR1 (DRR1a-e) have been identified which arise from alternative splicing of the cytoplasmic region. No alternative isoforms of DDR2 have been identified. DDR1 and DDR2 have broadly (but not completely) mutually exclusive expression profiles in epithelial cell and stroma respectively. DDRs are activated by binding to collagens with broad specificity but with distinct preference for certain collagen types. Upon activation DDRs are known to regulate cell adhesion, proliferation and remodelling of the extracellular matrix. It is recognised that DDRs are upregulated in response to cellular activity and many forms of tissue injury and as such DDRs are implicated in diseases including cancer, atherosclerosis as well as diseases characterised by fibrosis and inflammation. Inhibitors of DDR kinase activity may be of benefit as therapeutic agents in these disease areas.

[0003] DDR1 and DDR2 overexpression and/or activation has been linked to multiple forms of cancer as summarised in a recent review (Elkamhawy et al, Int. J. Mol. Sci., 2021). Studies have shown that elevated DDR expression levels and/or mutations can be found in a number of cancer cell lines as well as primary tumour tissues including lung, pancreas, prostate, breast, brain, ovary, liver and others. DDR1 was found to be a prognostic marker for non-small-cell lung carcinoma (NSCLC) patients. A recent study demonstrated that siRNA-mediated downregulation of DDR1 suppressed melanoma cell malignancy, migration, invasion, and survival. DDR1 protein was also found to be expressed in 63% of serous ovarian cancer tissue, but not in normal ovarian surface epithelium. Involvement of DDR1 in glioblastoma cell invasion and epithelial-mesenchymal transition (EMT) has also been demonstrated. DDR1 expression was found in 50.5% of gastric cancer tissues . DDR1 was found to control triple-negative breast cancer growth by modulating tumuor-infiltrating CD4+ and CD8+ T cells . There is also strong evidence indicating that DDR2 could be a potential biomarker and a molecular target for a variety of cancers. For instance, DDR2 overexpression was reported to contribute to NSCLC, thyroid carcinoma, Hodgkin's lymphoma, nasopharyngeal carcinomas, prostate cancer, as well as to head and neck squamous cell carcinoma. According to studies DDR2 contributes to breast cancer metastasis by stabilizing the SNAIL1 protein. DDR2 has also been shown to be a favourable independent predictor of recurrence and outcome in primary breast cancers. In addition to the essential roles of the wild type of DDR in cancer pathology and prognosis, various mutations of DDR1 and/or DDR2 have also been reported in numerous types of cancer cells, for instance, G1486T(DDR1) and A496S(DDR1) in lung

cancer, N502S(DDR1), A533S(DDR1), and A803V(DDR1) in acute myeloid leukemia (AML), and S768R(DDR2) in squamous cell carcinoma. DDRs also play a role in cancer growth by controlling how tumour cells interact with their surrounding collagen matrix. This role of DDRs becomes more prominent when considering their role as extracellular matrix receptors. The extracellular matrix (ECM) confers structural properties to tissues around the tumour, as well as regulating cell proliferation, survival, migration, and invasion. The physiological interactions between tumour cells and their immediate microenvironment, represented by the extracellular matrix, are disrupted in metastatic cancers. As a key component of the tumour extracellular matrix, type I collagen shows high density and distorted architecture in malignant cancer, linking it to tumour formation and metastasis. Therefore, the discovery of DDRs as collagen receptors represents a new target in the regulation of tumour progression.

[0004] DDRs also appear to play a central role in the modulation of inflammation and fibrosis. Modulation of fibrosis and inflammation has been demonstrated in several organs including lung and kidney. In lung DDR-1 deficient mice show reduced bleomycin induced pulmonary injury (Vogel et al, Am. J. Respir. Crit. Care Med., 2006) and both DDR1 and DDR2 have been demonstrated to have increased expression in patients with fibrotic lung disease (Bian et al, ERJ Open Res., 2016). In kidney, DDR1 expression is elevated in patients with lupus nephritis and Goodpasture's syndrome as well as mouse models of glomerulonephritis (Kerroch et al, FASEB journal, 2012) and in the tubules of mice that have undergone unilatereal ureteral obstruction (UUO) (Guerrot et al, Am. J. Pathol., 2011). Several studies have demonstrated that DDR1-null mice are protected from angiotensin II-mediated proteinuria, glomerular fibrosis and inflammation as well as showing reduced collagen deposition, tubular macrophage infiltration and pro-inflamatory cytokine levels following the UUO procedure.. Finally, COL3A3 KO mice (the mouse model for human Alport syndrome, crossed on to DDR1-null mice have mice have reduced renal fibrosis and inflammation as a consequence of reduced TGF-β mediated signalling and reduced levels of the pro-inflammatory cytokine IL-6 (Dorison, Cell Adhesion and Migration, 2018).

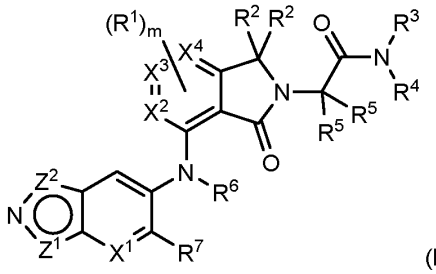
[0005] Small molecule inhibitors of DDR1 and DDR2 kinase activity have been disclosed in the prior art and inhibitory activity of DDR1 and/or DDR2 has been demonstrated to give rise to efficacious effects in mouse models of cancer and fibrotic disease (Richter et al, ACS Chem. Biol., 2019; Wang et al, J. Med. Chem., 2018; Zhu et al, J. Med. Chem., 2019). Such reports support the hypothesis that inhibitors of DDR kinase activity may be of benefit as therapeutic agents for the treatment of human cancer and fibrotic disease.

[0006] Furthermore, it is an aim of certain embodiments of this invention to provide new compounds useful in treating diseases such as cancer and fibrotic diseases. The compounds may be inhibitors of DDR1 and/or DDR2. It is an aim of certain embodiments of this invention to provide compounds which have comparable activity to existing DDR1 and/or DDR2 inhibitors. It is an aim of certain embodiments of this invention to provide compounds which have increased activity relative to existing DDR1 and/or DDR2 inhibitors.

[0007] Certain embodiments of the present invention satisfy some or all of the above aims.

BRIEF SUMMARY OF THE DISCLOSURE

[0008] The present invention provides a compound of formula (I) and pharmaceutically acceptable salts thereof:



(I); wherein

Z^1 and Z^2 are each selected from $-CR^{8a}-$ and $-NR^{8b}-$, wherein one of Z^1 and Z^2 is $-CR^{8a}-$ and the other is $-NR^{8b}-$; and wherein the ring comprising Z^1 and Z^2 is a pyrazole;

X^1 is independently selected from CR^{7a} and N;

X^2, X^3 and X^4 are each independently selected from carbon and nitrogen, wherein at least one of X^2, X^3 and X^4 is 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^2 is independently selected at each occurrence from H, fluoro, C_1-C_4-alkyl, C_1-C_4-haloalkyl and cyclopropyl, or the two R^2 groups and the carbon atom to which they are attached together form a C_3-C_6-cycloalkyl ring;

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 selected from H, C_1-C_4-alkyl, C_1-C_4-haloalkyl and cyclopropyl;

R^7 and R^{7a} are each independently selected from H, 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^{8a} is independently selected from H, 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 C_0-C_4-alkylene-R^{8c};

R^{8b} is independently selected from H, C_1-C_4-alkyl, C_2-C_4-alkyl substituted with NR^9R^{10}, C_2-C_4-alkyl substituted with OR^{11}, C_3-C_4-alkenyl, C_3-C_4-alkynyl, C_1-C_4-haloalkyl and C_0-C_4-alkylene-R^{8c};

R^{8c} is independently selected from C_3-C_6-cycloalkyl and 3- to 7-membered heterocycloalkyl; wherein said heterocycloalkyl group is attached to the C_0-C_4-alkylene via a carbon atom in the heterocycloalkyl ring; wherein said cycloalkyl or heterocycloalkyl group is optionally substituted with from 1 to 4 R^{13} groups;

R^9 is independently at each occurrence selected from H and C_1-C_4-alkyl; or two R^9 groups, together with the nitrogen atom to which they are attached together form a C_5-C_8-heterocycloalkyl group optionally substituted with from 0 to 4 R^{13} groups;

R^{10} 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; or R^9 and R^{10}, together with the nitrogen atom to which they are attached together form a C_5-C_8-heterocycloalkyl group optionally substituted with from 0 to 4 R^{13} groups;

R^{11} is independently at each occurrence selected from H, C_1-C_4-alkyl, C(O)-C_1-C_4-alkyl and C_1-C_4-haloalkyl;

R^{12} is independently selected from C_3-C_6-cycloalkyl, phenyl, 5- or 6- membered heteroaryl and 3- to 6-membered-heterocycloalkyl; wherein said cycloalkyl or heterocycloalkyl group is optionally substituted with from 1 to 4 R^{13} groups and wherein said phenyl or heteroaryl group is optionally substituted with from 1 to 3 R^{14} groups;

R^{13} is independently at each occurrence selected from =O, halo, nitro, cyano, NR^8R^9, OR^{14}, SR^8, $SO_2NR^8R^8$, CO_2R^8, $C(O)R^8$, $CONR^8R^8$, C_1-C_4-alkyl, C_1-C_4-alkyl substituted with OR^{11}, C_1-C_4-alkyl substituted with NR^9R^{10}, C_2-C_4-alkenyl, C_2-C_4-alkynyl, C_1-C_4-haloalkyl, C_6-C_{10}-aryl, and C_3-C_6-cycloalkyl;

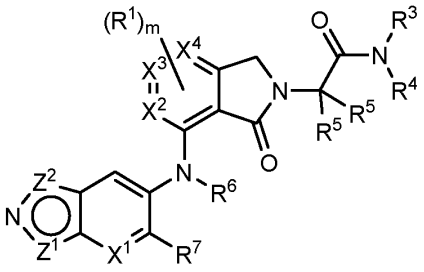
R^{14} is independently at each occurrence selected from halo, nitro, cyano, NR^8R^9, OR^{10}, SR^8, SO_2R^8, $SO_2NR^8R^8$, CO_2R^8, $C(O)R^8$, $CONR^8R^8$, C_1-C_4-alkyl, C_2-C_4-alkenyl, C_2-C_4-alkynyl, C_1-C_4-haloalkyl, C_1-C_4--alkyl substituted with OR^{11}, C_1-C_4-alkyl substituted with NR^8R^9 and cyclopropyl;

m is an integer selected from 0, 1, 2 and 3;

wherein any of the aforementioned alkyl, alkylene or cyclopropyl groups is optionally substituted, where chemically possible, by 1 to 5 substituents which are each independently at each occurrence selected 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.

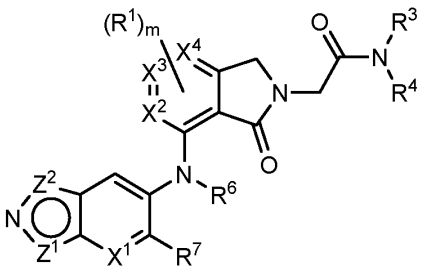
[0009] In an embodiment, the compound of formula (**I**) is a compound of formula (**II**):



(**II**)

wherein Z^1, Z^2, X^1, X^2, X^3, X^4, R^1, R^3, R^4, R^5, R^6, R^7 and m are as described above for compounds of formula (**I**).

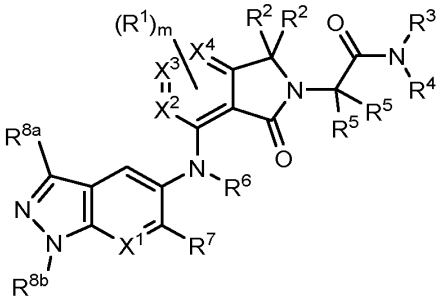
[0010] In an embodiment, the compound of formula (**I**) is a compound of formula (**III**):



(**III**)

wherein Z^1, Z^2, X^1, X^2, X^3, X^4, R^1, R^3, R^4, R^7 and m are as described above for compounds of formula (**I**).

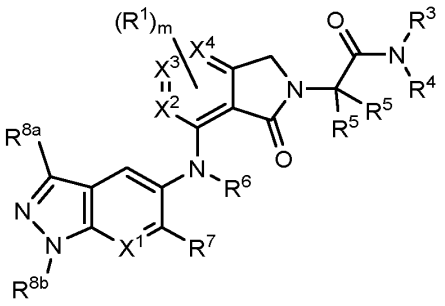
[0011] In an embodiment, the compound of formula (**I**) is a compound of formula (**IV**):



(**IV**)

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

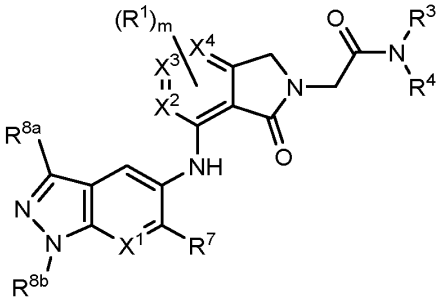
[0012] In an embodiment, the compound of formula (**I**) is a compound of formula (V):



(**V**)

[0013] wherein X^1, X^2, X^3, X^4, R^1, R^3, R^4, R^5, R^6, R^7, R^{8a}, R^{8b} and m are as described above for compounds of formula (**I**).

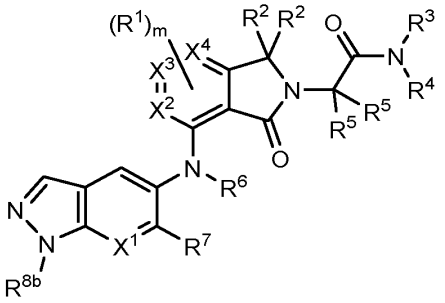
[0014] In an embodiment, the compound of formula (**I**) is a compound of formula (**VI**):



(**VI**)

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

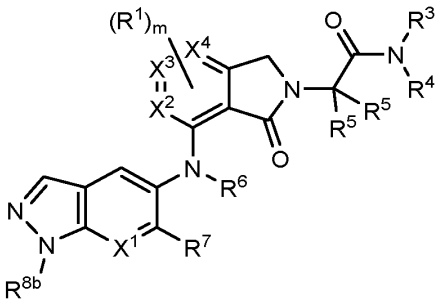
[0015] In an embodiment, the compound of formula (**I**) is a compound of formula (**VII**):



(**VII**)

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

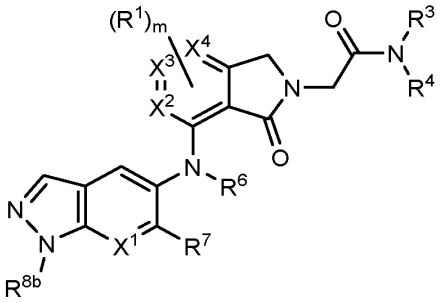
[0016] In an embodiment, the compound of formula (**I**) is a compound of formula (**VIII**):



(**VIII**)

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

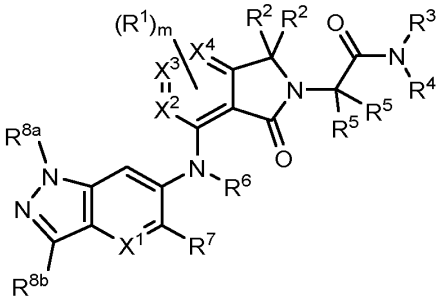
[0017] In an embodiment, the compound of formula (**I**) is a compound of formula (**IX**):



(**IX**)

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

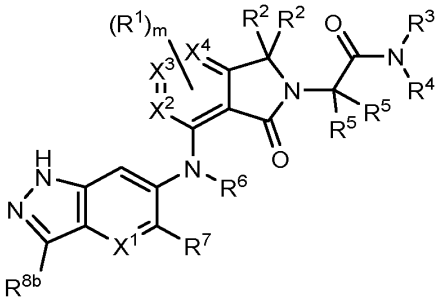
[0018] In an embodiment, the compound of formula (**I**) is a compound of formula (**X**):



(**X**)

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

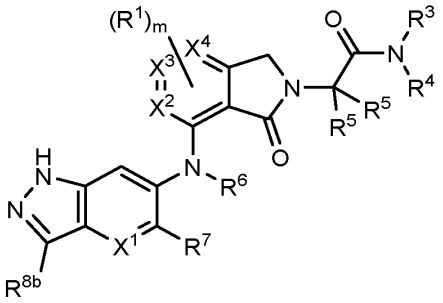
[0019] In an embodiment, the compound of formula (**I**) is a compound of formula (**XI**):



(**XI**)

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

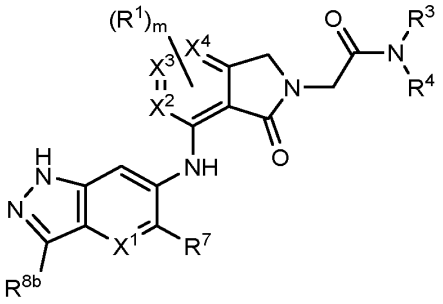
[0020] In an embodiment, the compound of formula (**I**) is a compound of formula (**XII**):



(**XII**)

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

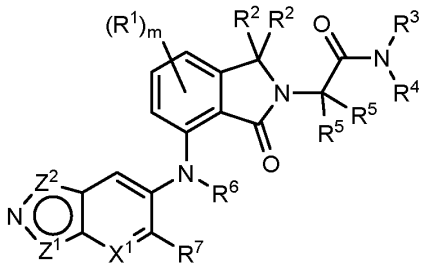
[0021] In an embodiment, the compound of formula (**I**) is a compound of formula (**XIII**):



(**XIII**)

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

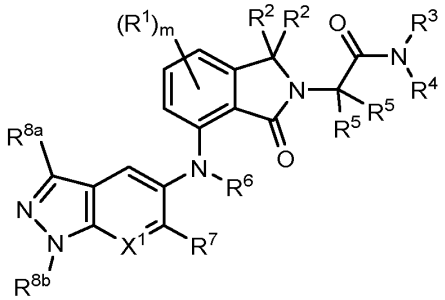
[0022] In an embodiment, the compound of formula (**I**) is a compound of formula (**XIV**):



(**XIV**)

wherein Z^1, Z^2, X^1, R^1, R^2, R^3, R^4, R^5, R^6, R^7 and m are as described above for compounds of formula (**I**).

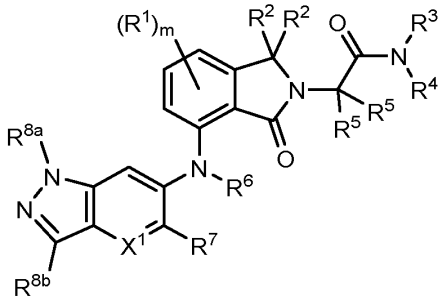
[0023] In an embodiment, the compound of formula (**I**) is a compound of formula (**XV**):



(**XV**)

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

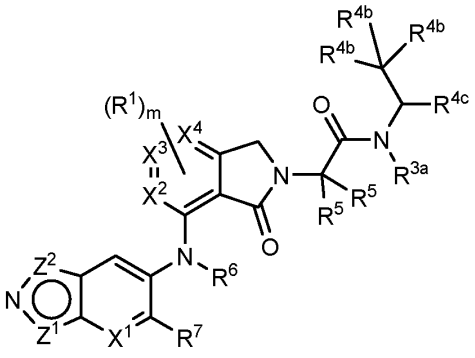
[0024] In an embodiment, the compound of formula (**I**) is a compound of formula (**XVI**):



(**XVI**)

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

[0025] In an embodiment, the compound of formula (**I**) is a compound of formula (**XVII**):



(**XVII**)

wherein Z^1, Z^2, X^1, X^2, X^3, X^4, R^1, R^5, R^6, R^7 and m are as described above for compounds of formula (**I**) and wherein

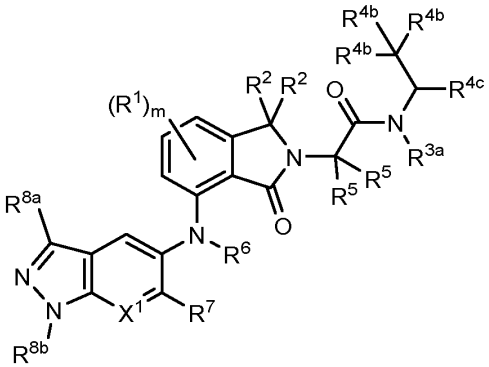
R^{4b} is at each occurence selected from H and F; wherein at least two R^{4b} groups are F;

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

R^{4c} is independently selected from H, C_1-C_4-alkyl and C_4-C_6-cycloalkyl; or

R^{3a} and R^{4c}, together with the carbon and nitrogen to which they are attached, form a 4- to 6-membered heterocycloalkyl group

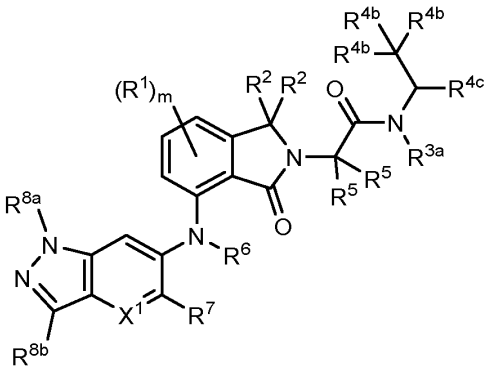
[0026] In an embodiment, the compound of formula (**I**) is a compound of formula (**XVIII**):



(**XVIII**)

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

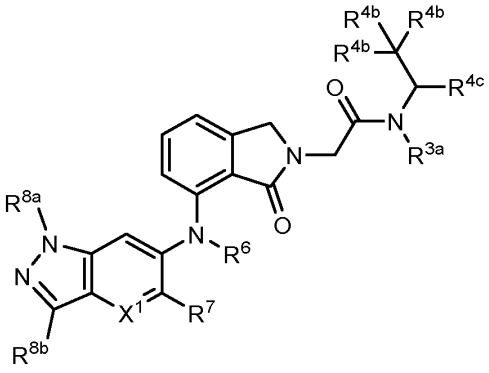
[0027] In an embodiment, the compound of formula (**I**) is a compound of formula (**XIX**):



(**XIX**)

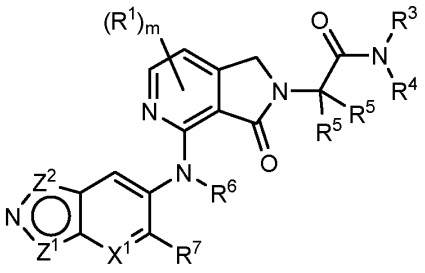
wherein X^1, R^1, R^2, R^5, R^6, R^7, R^{8a}, R^{8b} and m are as described above for compounds of formula (**I**); and wherein R^{3a}, R^{4b} and R^{4c} are as described above for formula (**XVII**).

[0028] In an embodiment, the compound of formula (**I**) is a compound of formula (**XX**):



(**XX**)

[0029] wherein X^1, R^6, R^7, R^{8a} and R^{8b} are as described above for compounds of formula (**I**); and wherein R^{3a}, R^{4b} and R^{4c} are as described above for formula (**XVII**).In an embodiment, the compound of formula (**I**) is a compound of formula (**XXI**):



(**XXI**)

wherein Z^1, Z^2, X^1, R^1, R^3, R^4, R^5, R^6, R^7 and m are as described above for compounds of formula (**I**).

[0030] The following embodiments apply to compounds of any of formulae (**I**)-(**XXI**). These embodiments are independent and interchangeable. Any one embodiment may be combined with any other embodiment, where chemically allowed. In other words, any of the features described in the following embodiments may (where chemically allowable) be combined with the features described in

one or more other embodiments. In particular, where a compound is exemplified or illustrated in this specification, any two or more of the embodiments listed below, expressed at any level of generality, which encompass that compound may be combined to provide a further embodiment which forms part of the present disclosure.

[0031] It may be either that Z^1 is NR^{8b} and Z^2 is CH or that Z^1 is CR^{8a} and Z^2 is NH.

[0032] It may be that Z^1 is NR^{8b} and Z^2 is CR^{8a}. It may be that Z^1 is NR^{8b} and Z^2 is CH. It may be that Z^1 is NMe and Z^2 is CR^{8a}. It may be that Z^1 is NMe and Z^2 is CH.

[0033] It may be that Z^1 is CR^{8a} and Z^2 is NR^{8b}. It may be that Z^1 is CR^{8a} and Z^2 is NH.

[0034] It may be that X^1 is N. It may be that X^1 is CR^{7a}.

[0035] It may be that X^2 is carbon. It may be that X^3 is carbon. It may be that X^4 is carbon. It may be that X^2 and X^3 are both carbon. It may be that X^3 and X^4 are both carbon. It may be that X^2 and X^4 are both carbon. It may be that X^2, X^3 and X^4 are each carbon.

[0036] It may be that no more than one of X^2, X^3 and X^4 are nitrogen. It may be that a single one of X^2, X^3 and X^4 is nitrogen. It may be that X^2 is nitrogen. It may be that X^3 is nitrogen. It may be that X^4 is nitrogen. It may be that X^2 is nitrogen, X^3 is carbon and X^4 is carbon.

[0037] m may be 0.

[0038] m may be 1. Where m is 1, it may be that the single R^1 group is situated ortho to NR^6. Where m is 1, it may be that the single R^1 group is situated para to NR^6. Where m is 1, it may be that the single R^1 group is situated para to NR^6.

[0039] m may be 2.

[0040] 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}, 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. R^1 may be H.

[0041] It may be that m is 1, the single R^1 group is F and is situated ortho to NR^6.

[0042] It may be that m is 0, R^2 at each occurrence is H and R^5 at each occurrence is H.

[0043] R^2 may be independently at each occurrence selected from H, fluoro, 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^2 may be independently at each occurrence selected from H, fluoro, OR^{11}, C_1-C_4-alkyl, C_1-C_4-haloalkyl and cyclopropyl. R^2 may be independently at each occurrence selected from H, fluoro and C_1-C_4-alkyl. R^2 may be independently at each occurrence selected from fluoro and C_1-C_4-alkyl. R^2 may be independently at each occurrence selected from H and C_1-C_4-alkyl. R^2 may be at each occurrence H. R^2 may be at each occurrence fluoro. R^2 may be at each occurrence C_1-C_4-alkyl, e.g.

methyl. It may be that the R^2 groups and the carbon atom to which they are attached together form a C_3-C_6-cycloalkyl ring, e.g. cyclopropyl.

[0044] 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.

[0045] 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.

[0046] R^6 may be H. R^6 may be C_1-C_4-alkyl, e.g. methyl.

[0047] It may be that R^7 is H. R^7 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^7 may be independently selected from halo, OR^{11}, C_1-C_4-alkyl, C_1-C_4-haloalkyl and cyclopropyl. R^7 may be independently selected from halo and C_1-C_4-alkyl. If present, R^7 may be halo, e.g. fluoro. R^7 may be C_1-C_4-alkyl, e.g. methyl.

[0048] It may be that R^{7a} is H. R^{7a} may be independently selected from halo, nitro, cyano, OR^{11}, CO_2R^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_1-C_4-haloalkyl and cyclopropyl. R^{7a} may be independently selected from halo, OR^{11}, C_1-C_4-alkyl, C_1-C_4-haloalkyl and cyclopropyl.

[0049] It may be that R^7 is H and X^1 is N. It may be that R^7 is H and X^1 is CR^{7a}. It may be that R^7 is H and X^1 is CH. It may be that R^7 is H and X^1 is CR^{7a}, wherein R^{7a} is independently selected from halo, nitro, cyano, OR^{11}, CO_2R^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_1-C_4-haloalkyl and cyclopropyl.

[0050] R^{8a} may be H. R^{8a} may be selected from halo, 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 C_0-C_4-alkylene-R^{8c}. R^{8a} may be selected from H, halo, C_1-C_4-alkyl, C_1-C_4-haloalkyl and cyclopropyl. R^{8a} may be selected from H, C_1-C_4-alkyl, C_1-C_4-haloalkyl and cyclopropyl. R^{8a} may be selected from C_1-C_4-alkyl (e.g. methyl) and C_1-C_4-haloalkyl (e.g. CF_3). R^{8a} may be C_1-C_4-alkyl (e.g. methyl). R^{8a} may be halo e.g., F.

[0051] R^{8b} may be H. R^{8b} may be selected from C_1-C_4-alkyl, C_2-C_4-alkyl substituted with NR^9R^{10}, C_2-C_4-alkyl substituted with OR^{11}, C_1-C_4-haloalkyl and C_0-C_4-alkylene-R^{8c}. R^{8b} may be selected from H, C_1-C_4-alkyl and cyclopropyl. R^{8b} may be C_1-C_4-alkyl (e.g. methyl).

[0052] R^{8b} is independently selected from H, C_1-C_4-alkyl, C_2-C_4-alkyl substituted with NR^9R^{10}, C_2-C_4-alkyl substituted with OR^{11}, C_3-C_4-alkenyl, C_3-C_4-alkynyl, C_1-C_4-haloalkyl and C_0-C_4-alkylene-R^{8c}.

[0053] It may be that R^{8a} is H and R^{8b} is C_1-C_4-alkyl (e.g. methyl). It may be that R^{8a} is C_1-C_4-alkyl (e.g. methyl) and R^{8b} is C_1-C_4-alkyl (e.g. methyl). It may be that R^{8a} and R^{8b} are both methyl.

[0054] It may be that R^9 is independently at each occurrence selected from H and C_1-C_4-alkyl.

[0055] It may be that R^{10} 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. It may be that R^{10} is independently at each occurrence selected from H and C_1-C_4-alkyl.

[0056] It may be that R^{11} is independently at each occurrence selected from H, C_1-C_4-alkyl and C_1-C_4-haloalkyl. It may be that R^{11} is independently at each occurrence selected from H and C_1-C_4-alkyl. It may be that R^{11} is independently at each occurrence C_1-C_4-alkyl, e.g. methyl.

[0057] R^{12} may be independently selected from 5- or 6- membered heteroaryl, wherein said heteroaryl group is optionally substituted with from 1 to 3 R^{14} groups. R^{12} may be independently selected from 5-membered heteroaryl, e.g. imidazole, wherein said heteroaryl group is optionally substituted with from 1 to 3 R^{14} groups.

[0058] R^{13} may be independently at each occurrence selected from oxo, fluoro, OR^{11}, CO_2R^9, $CO_2NR^9R^9$, 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_1-C_4-haloalkyl and cyclopropyl. R^{13} may be independently at each occurrence selected from oxo, OR^{11}, C_1-C_4-alkyl and cyclopropyl. R^{13} may be independently at each occurrence selected from oxo and C_1-C_4-alkyl. R^{13} may be independently at each occurrence C_1-C_4-alkyl, e.g. methyl.

[0059] R^{14} 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^8R^9, C_1-C_4-alkyl substituted with OR^{11}, C_1-C_4-haloalkyl and cyclopropyl. R^{14} may be independently at each occurrence selected from halo, OR^{11}, C_1-C_4-alkyl, C_1-C_4-haloalkyl and cyclopropyl. R^{14} may be independently at each occurrence selected from halo and C_1-C_4-alkyl. R^{14} may be independently at each occurrence halo, e.g. fluoro. R^{14} may be independently at each occurrence C_1-C_4-alkyl, e.g. methyl.

[0060] It may be that:

R^3 is H; and

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 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.

[0061] It may be that:

R^3 is H; and

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 from 1 to 4 R^{13} groups and wherein said phenyl or heteroaryl group is optionally substituted with from 1 to 3 R^{14} groups;

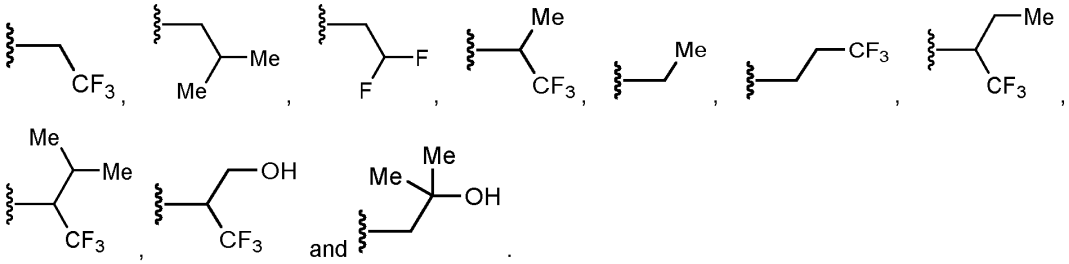
or R^3 and R^4, together with the nitrogen atom to which they are attached together form a 4- to 10-membered heterocycloalkyl group or a 5-, or 9-membered heteroaryl group; wherein said heterocycloalkyl group is optionally substituted with from 1 to 4 R^{13} groups and wherein said heteroaryl group is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

[0062] It may be that R^3 is H.

[0063] It may be that R^4 is selected from C_1-C_6-alkyl, C_1-C_6-haloalkyl and C_0-C_4-alkylene-R^{4a}.

[0064] It may be that R^4 is selected from C_1-C_6-alkyl and C_1-C_6-haloalkyl. It may be that R^4 is selected from C_2-C_3-alkyl and C_2-C_3-haloalkyl. It may be that R^4 is C_1-C_4-haloalkyl. It may be that R^4 is C_2-C_3-haloalkyl. It may be that R^4 is 2,2,2-trifluoroethyl.

[0065] Illustrative R^4 groups include:



[0066] It may be that R^4 is C_0-C_4-alkylene-R^{4a}. It may be that R^4 is CH_2-R^{4a}. It may be that R^4 is R^{4a}.

[0067] It may be that R^{4a} is independently selected from C_3-C_8-cycloalkyl, phenyl, 5-, 6-, 9- or 10-membered heteroaryl, 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 from 1 to 4 R^{13} groups and wherein said phenyl or heteroaryl group is optionally substituted with from 1 to 3 R^{14} groups.

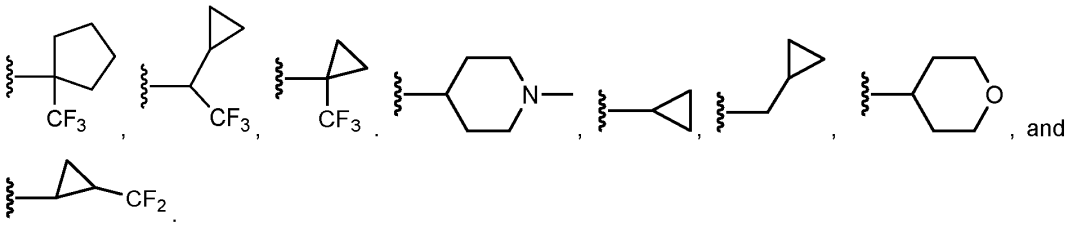
[0068] It may be that R^{4a} is selected from C_3-C_8-cycloalkyl and 4- to 10-membered heterocycloalkyl, wherein said cycloalkyl or heterocycloalkyl group is optionally substituted with a single R^{12} group and/or from 1 to 4 R^{13} groups. It may be that R^{4a} is selected from C_3-C_8-cycloalkyl and 4- to 10-membered

heterocycloalkyl, wherein said cycloalkyl or heterocycloalkyl group is optionally substituted with from 1 to 4 R^{13} groups.

[0069] It may be that R^4 is selected from CH_2-C_3-C_8-cycloalkyl and CH_2-4- to 10-membered heterocycloalkyl, wherein said cycloalkyl or heterocycloalkyl group is optionally substituted with a single R^{12} group and/or from 1 to 4 R^{13} groups. It may be that R^4 is selected from CH_2-C_3-C_8-cycloalkyl and CH_2-4- to 10-membered heterocycloalkyl, wherein said cycloalkyl or heterocycloalkyl group is optionally substituted with from 1 to 4 R^{13} groups.

[0070] It may be that R^4 is selected from C_3-C_8-cycloalkyl and 4- to 10-membered heterocycloalkyl, wherein said cycloalkyl or heterocycloalkyl group is optionally substituted with a single R^{12} group and/or from 1 to 4 R^{13} groups. It may be that R^4 is selected from C_3-C_8-cycloalkyl and 4- to 10-membered heterocycloalkyl, wherein said cycloalkyl or heterocycloalkyl group is optionally substituted with from 1 to 4 R^{13} groups.

[0071] Illustrative R^4 groups include:



, and .

[0072] It may be that R^{4a} is independently selected from: phenyl and 5- or 6- membered heteroaryl; wherein said phenyl or heteroaryl group is optionally substituted with a single R^{12} group and/or from 1 to 3 R^{14} groups. It may be that R^{4a} is independently selected from: phenyl and 5- or 6- membered heteroaryl; wherein said phenyl or heteroaryl group is optionally substituted with from 1 to 3 R^{14} groups. It may be that R^{4a} is independently phenyl; wherein said phenyl group is optionally substituted with a single R^{12} group and/or from 1 to 3 R^{14} groups. It may be that R^{4a} is independently phenyl; wherein said phenyl group is optionally substituted with from 1 to 3 R^{14} groups. It may be that R^{4a} is independently 5- or 6- membered heteroaryl; wherein said heteroaryl group is optionally substituted with a single R^{12} group and/or from 1 to 3 R^{14} groups. It may be that R^{4a} is independently 5- or 6- membered heteroaryl; wherein said heteroaryl group is optionally substituted with from 1 to 3 R^{14} groups.

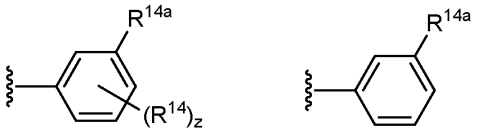
[0073] It may be that R^4 is independently selected from CH_2-phenyl or CH_2-5- or 6- membered heteroaryl wherein said phenyl or heteroaryl group is optionally substituted with a single R^{12} group and/or from 1 to 3 R^{14} groups. It may be that R^4 is independently selected from CH_2-phenyl or CH_2-5- or 6-membered heteroaryl wherein said phenyl or heteroaryl group is optionally substituted with from 1 to 3 R^{14} groups. It may be that R^4 is independently CH_2-phenyl wherein said phenyl is optionally substituted with a single R^{12} group and/or from 1 to 3 R^{14} groups. It may be that R^4 is independently CH_2-phenyl wherein said phenyl group is optionally substituted with from 1 to 3 R^{14} groups. It may be that R^4 is independently CH_2-5- or 6- membered heteroaryl wherein said heteroaryl group is optionally substituted

with a single R^{12} group and/or from 1 to 3 R^{14} groups. It may be that R^4 is independently CH_2-5- or 6-membered heteroaryl wherein said heteroaryl group is optionally substituted with from 1 to 3 R^{14} groups.

[0074] It may be that R^4 is independently selected from phenyl or 5- or 6- membered heteroaryl wherein said phenyl or heteroaryl group is optionally substituted with a single R^{12} group and/or from 1 to 3 R^{14} groups. It may be that R^4 is independently selected from phenyl or 5- or 6- membered heteroaryl wherein said phenyl or heteroaryl group is optionally substituted with from 1 to 3 R^{14} groups. It may be that R^4 is independently phenyl wherein said phenyl group is optionally substituted with a single R^{12} group and/or from 1 to 3 R^{14} groups. It may be that R^4 is independently phenyl wherein said phenyl group is optionally substituted with from 1 to 3 R^{14} groups. It may be that R^4 is independently 5- or 6-membered heteroaryl wherein said heteroaryl group is optionally substituted with a single R^{12} group and/or from 1 to 3 R^{14} groups. It may be that R^4 is independently 5- or 6- membered heteroaryl wherein said heteroaryl group is optionally substituted with from 1 to 3 R^{14} groups.

[0075] It may be that R^4 is independently selected from phenyl or 6-membered heteroaryl wherein said phenyl or 6-membered heteroaryl group is substituted at the meta position with 1 R^{14} group. It may be that the R^{14} group is selected from C_1-C_4-alkyl substituted with OR^{11}, C_1-C_4-alkyl and C_1-C_4-haloalkyl. It may be that the R^{14} group at the meta position is C_1-C_4-alkyl substituted with OR^{11} e.g. $-(CH_3)_2$-OH. It may be that the R^{14} group at the meta position is C_1-C_4-haloalkyl e.g. CF_3.

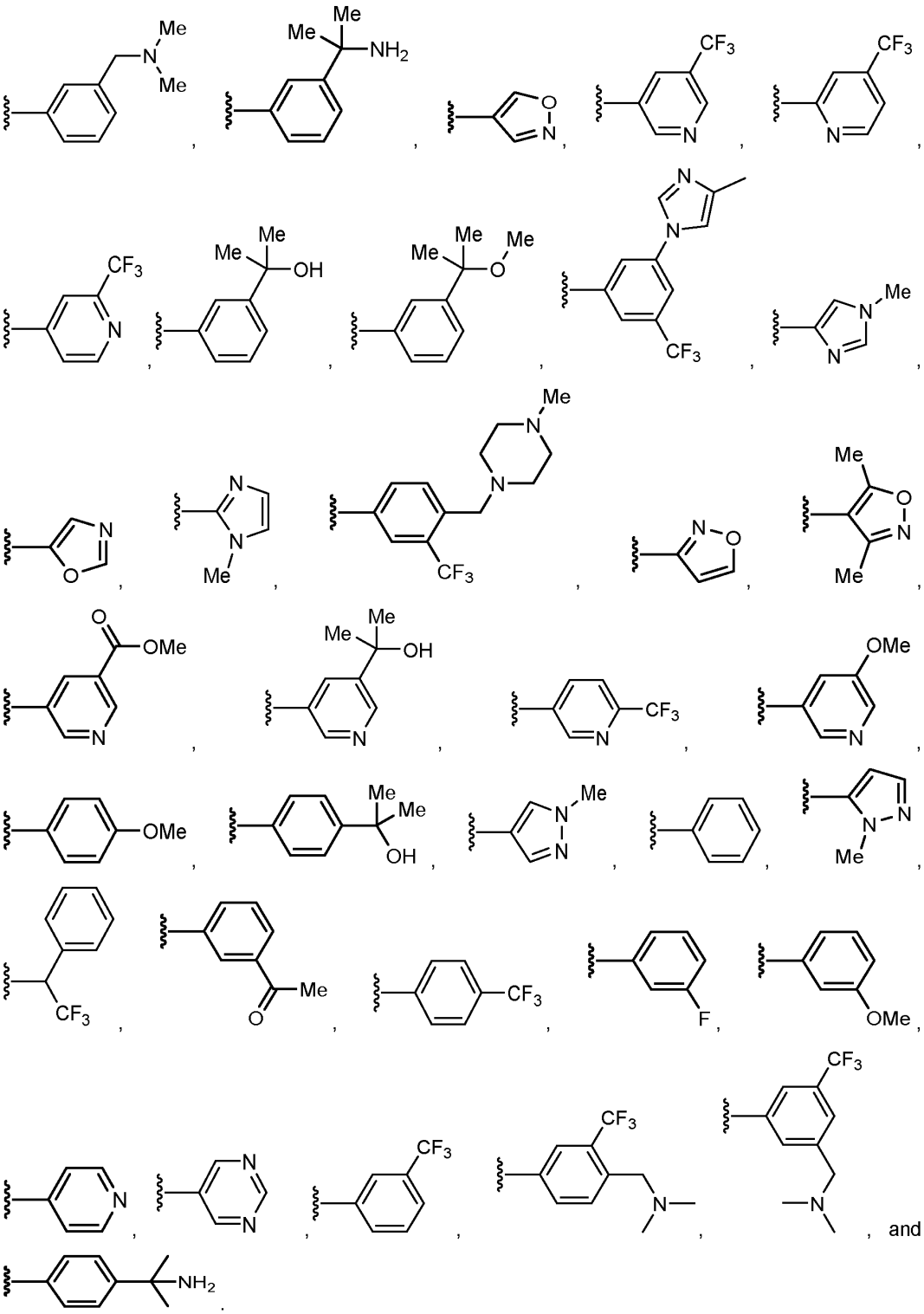
[0076] It may be that R^4 is a 6-membered heteroaryl group. It may be that R^4 is phenyl. It may be that R^4 is phenyl substituted at the meta position with 1 R^{14} group. It may be that R^{14} is R^{14a}. Illustrative R^4 groups include:



;

wherein R^{14a} is selected from halo, nitro, cyano, NR^8R^9, OR^{10}, SR^8, SO_2R^8, $SO_2NR^8R^8$, CO_2R^8, $C(O)R^8$, $CONR^8R^8$, C_1-C_4-alkyl, C_2-C_4-alkenyl, C_2-C_4-alkynyl, C_1-C_4-haloalkyl, C_1-C_4-alkyl substituted with OR^{11}, C_1-C_4-alkyl substituted with NR^8R^9 and cyclopropyl; and wherein z is an integer selected from 1 and 2.

[0077] Illustrative R^4 groups include:

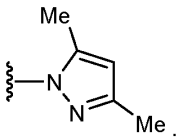


[0078] It may be that R^3 and R^4, together with the nitrogen atom to which they are attached together form a 4- to 10-membered heterocycloalkyl group or a 5-, or 9-membered heteroaryl group; wherein

said heterocycloalkyl 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. It may be that 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 group is optionally substituted with from 1 to 4 R^{13} groups and wherein said heteroaryl group is optionally substituted with from 1 to 3 R^{14} groups.

[0079] It may be that R^3 and R^4, together with the nitrogen atom to which they are attached together form a 5-, or 9-membered heteroaryl group; wherein heteroaryl group is optionally substituted with a single R^{12} group and/or from 1 to 3 R^{14} groups. It may be that R^3 and R^4, together with the nitrogen atom to which they are attached together form a 5-, or 9-membered heteroaryl group; wherein said heteroaryl group is optionally substituted with from 1 to 3 R^{14} groups. It may be that R^3 and R^4, together with the nitrogen atom to which they are attached together form a 5- membered heteroaryl group; wherein heteroaryl group is optionally substituted with a single R^{12} group and/or from 1 to 3 R^{14} groups. It may be that R^3 and R^4, together with the nitrogen atom to which they are attached together form a 5-membered heteroaryl group; wherein said heteroaryl group is optionally substituted with from 1 to 3 R^{14} groups.

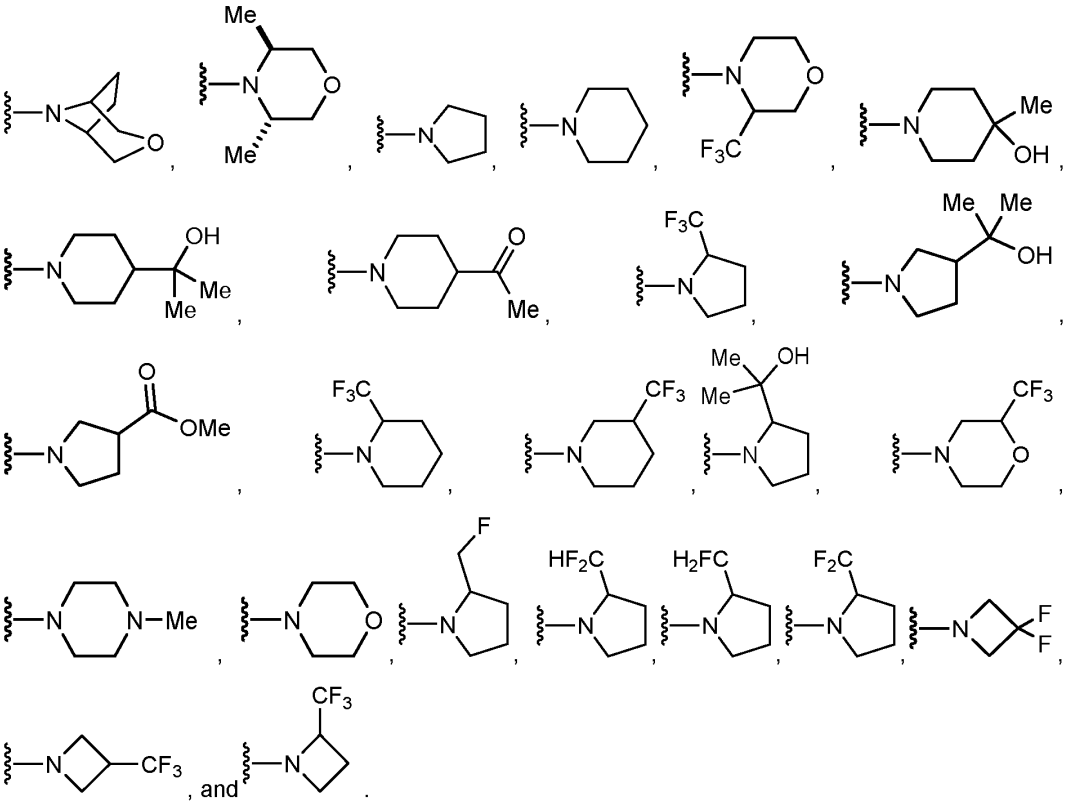
[0080] Illustrative NR^3R^4 groups include:



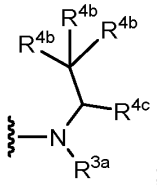
[0081] It may be that R^3 and R^4, together with the nitrogen atom to which they are attached together form a 4- to 10-membered heterocycloalkyl group; wherein said heterocycloalkyl group is optionally substituted with a single R^{12} group and/or from 1 to 4 R^{13} groups. It may be that R^3 and R^4, together with the nitrogen atom to which they are attached together form a 4- to 10-membered heterocycloalkyl group; wherein said heterocycloalkyl group is optionally substituted with from 1 to 4 R^{13} groups. It may be that said heterocycloalkyl group is 7- to 10-membered bicyclic heterocycloalkyl group. It may be that said heterocyclic group is 7- to 10-membered bridged bicyclic heterocycloalkyl group. It may be that said heterocyclic group is a monocyclic 4- to 7- membered heterocycloalkyl group. It may be that said heterocyclic group is a monocyclic 5- to 6- membered heterocycloalkyl group. It may be that said heterocyclic group is pyrrolidine. It may be that said heterocyclic group is piperidine. It may be that said heterocyclic group is morpholine. It may be that said heterocyclic group is piperazine. For the absence of doubt the heterocycloalkyl groups mentioned in this paragraph are optionally substituted with a single R^{12} group and/or from 1 to 4 R^{13} groups. It may be that the heterocycloalkyl groups mentioned in this paragraph are optionally substituted with from 1 to 4 R^{13} groups. It may be that said heterocyclic group is pyrrolidine and is substituted at the 2 position with 1 R^{13} group. It may be that said heterocyclic group is pyrrolidine and is substituted at the 3 position with 1 R^{13} group. It may be that said heterocyclic group is piperidine and is substituted at the 2 position with 1 R^{13} group. It may be that said heterocyclic group is piperidine and is substituted at the 3 position with 1 R^{13} group. It may be that said heterocyclic group

is piperidine and is substituted at the 4 position with 1 R^{13} group. It may be that said heterocyclic group is morpholine and is substituted at the 2 position with 1 R^{13} group. It may be that said heterocyclic group is morpholine and is substituted at the 3 position with 1 R^{13} group.. It may be that the R^{13} group is selected from C_1-C_4-alkyl, C_1-C_4-alkyl substituted with OR^{11} e.g. -$(CH_3)_2$-OH, and C_1-C_4-haloalkyl, e.g. -CF_3. It may be that the R^{13} group is C_1-C_4-haloalkyl, e.g. -CHF_2 or -CF_3.

[0082] Illustrative NR^3R^4 groups include:



[0083] It may be that R^3 and R^4 are selected such that NR^3R^4 comprises a CHF_2 group or a CF_3 group.

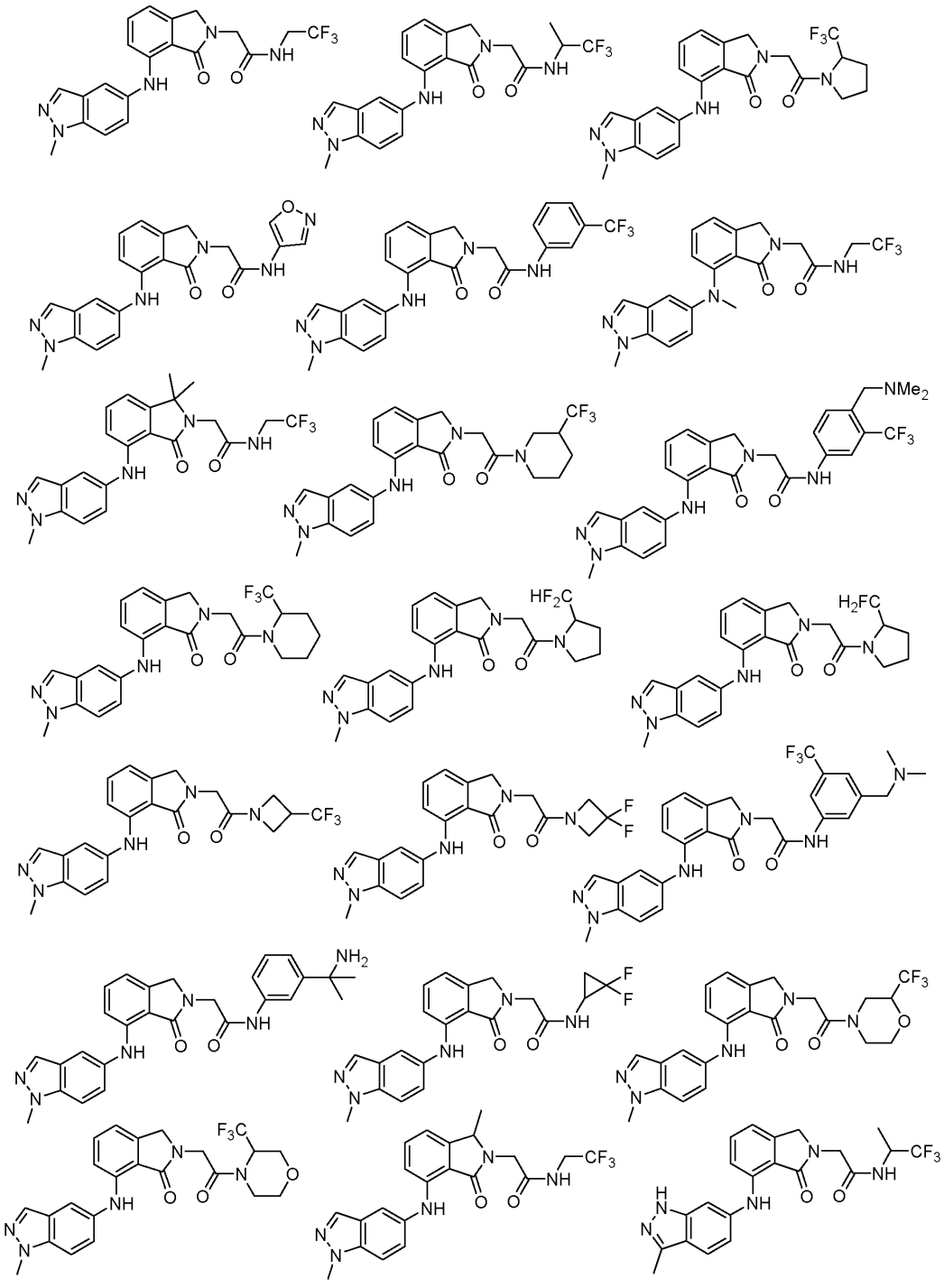
[0084] It may be that NR^3R^4 has the formula  ; wherein R^{4b} is at each occurence selected from H and F; wherein at least one R^{4b} group is F; R^{3a} is independently selected from H and C_1-C_4-alkyl; R^{4c} is independently selected from H, C_1-C_4-alkyl and C_4-C_6-cycloalkyl; or R^{3a} and R^{4c}, together with the carbon and nitrogen to which they are attached, form a 4- to 6-membered heterocycloalkyl group.

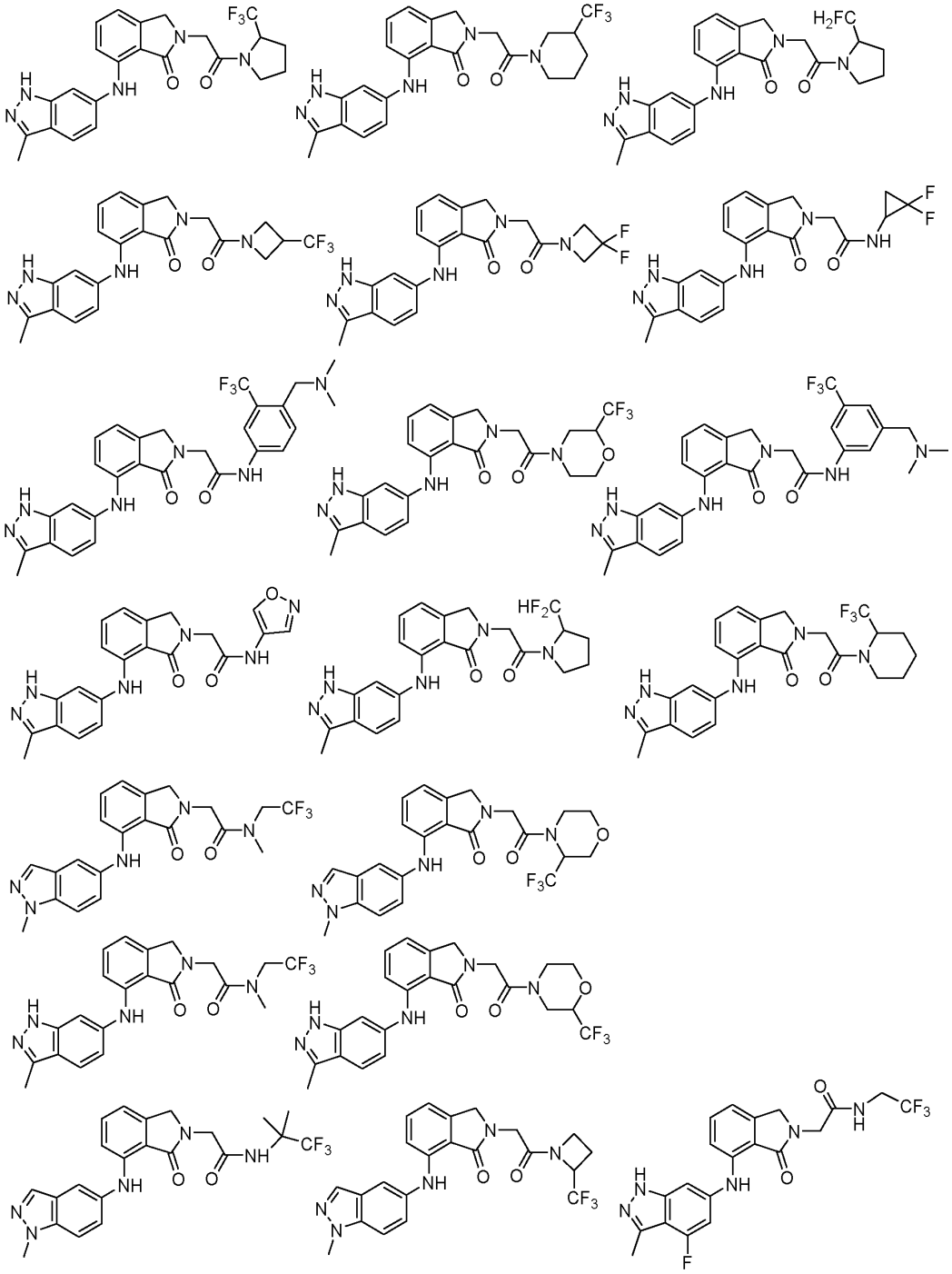
[0085] It may be that at least two R^{4b} groups are F. It may be that two R^{4b} groups are F and one R^{4b} group is H. It may be that each R^{4b} group is F.

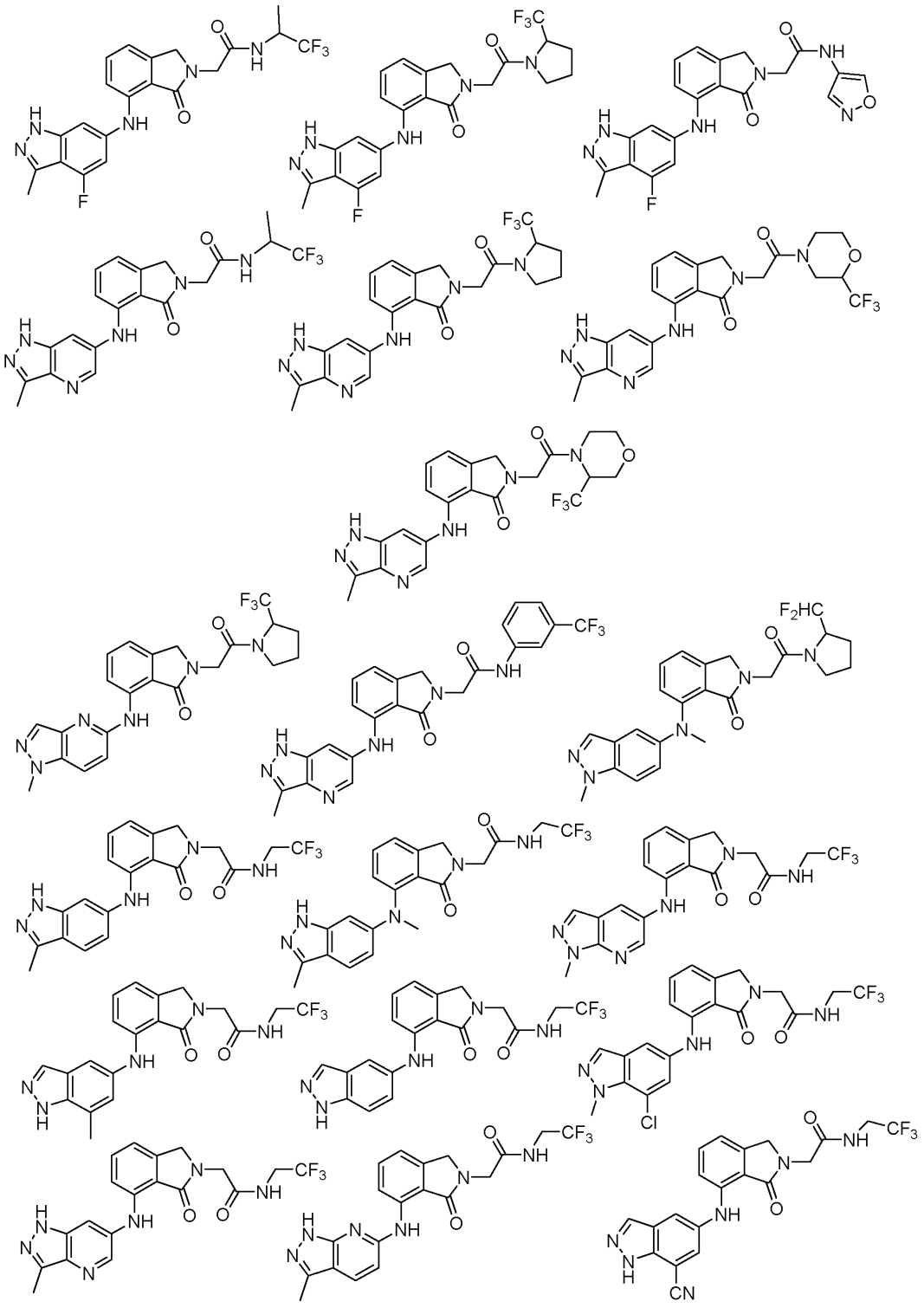
[0086] It may be that R^{3a} is independently selected from H and C_1-C_4-alkyl; and R^{4c} is independently selected from H, C_1-C_4-alkyl and C_4-C_6-cycloalkyl. It may be that R^{3a} is H; and R^{4c} is independently selected from H, C_1-C_4-alkyl and C_4-C_6-cycloalkyl. Said alkyl or cycloalkyl group may be unsubstituted.

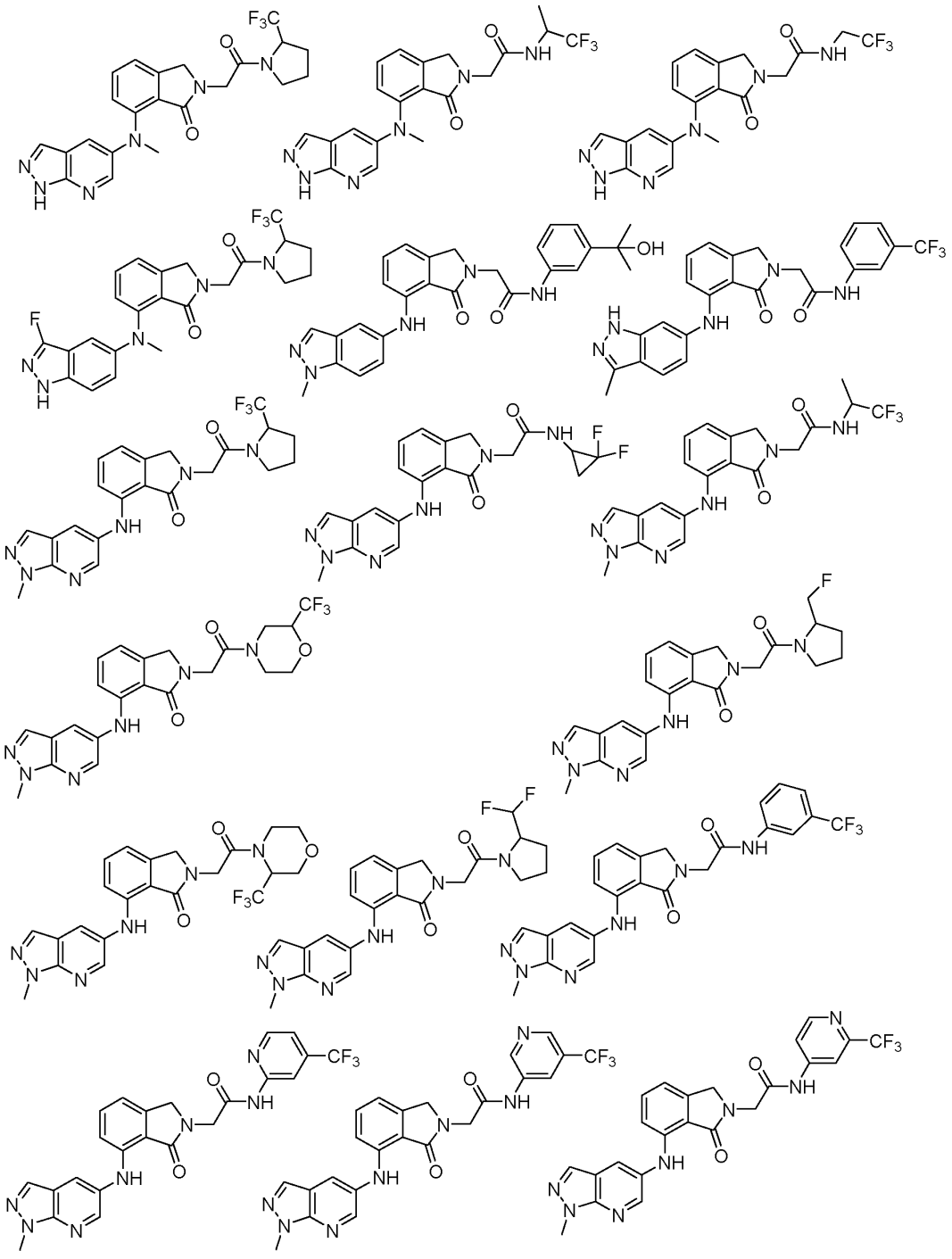
[0087] It may be that R^{3a} and R^{4c}, together with the carbon and nitrogen to which they are attached, form a 4- to 6-membered heterocycloalkyl group. It may be that R^{3a} and R^{4c}, together with the carbon and nitrogen to which they are attached, form a 5-membered heterocycloalkyl group. Said heterocycloalkyl group may be unsubstituted.

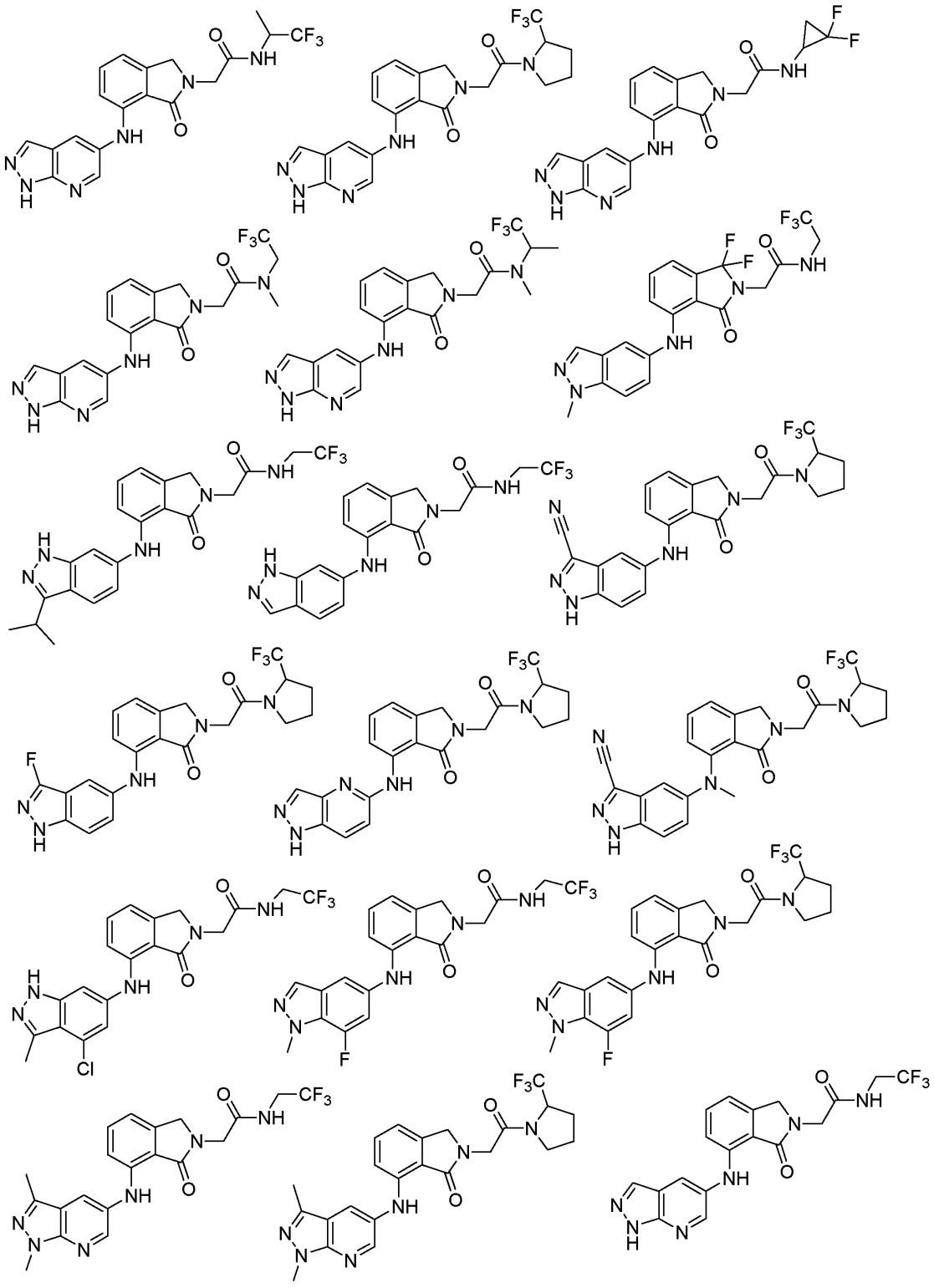
[0088] The compound of formula (**I**) may be selected from:

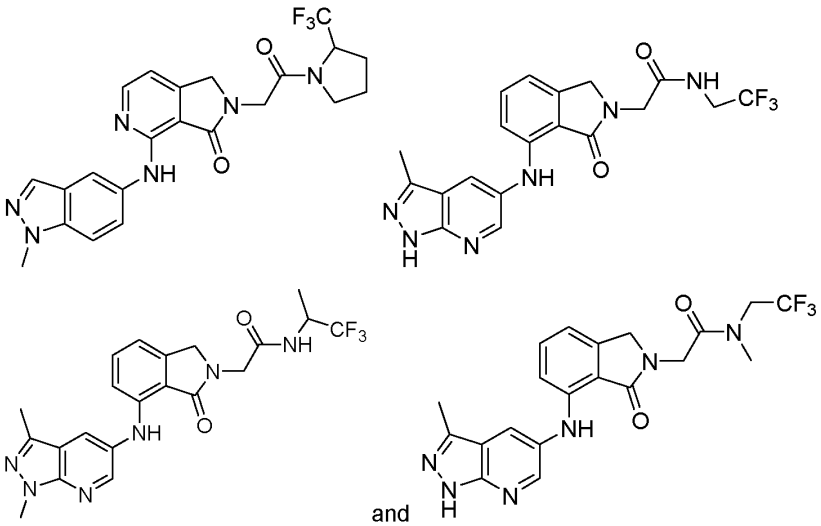






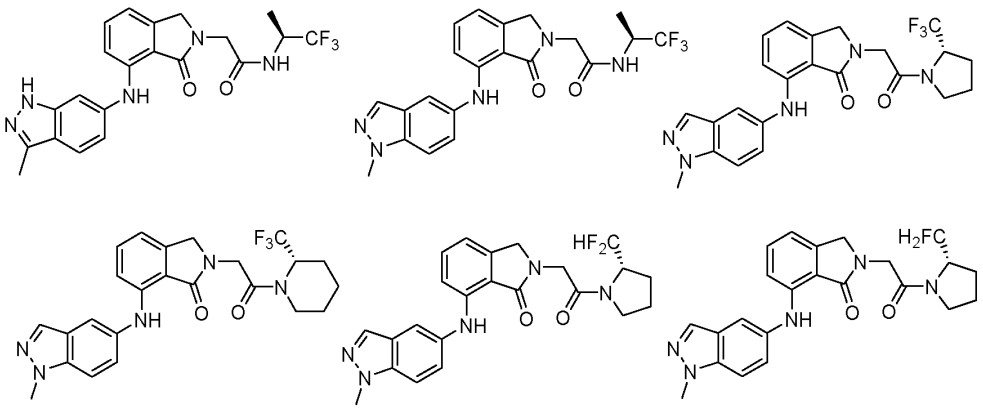




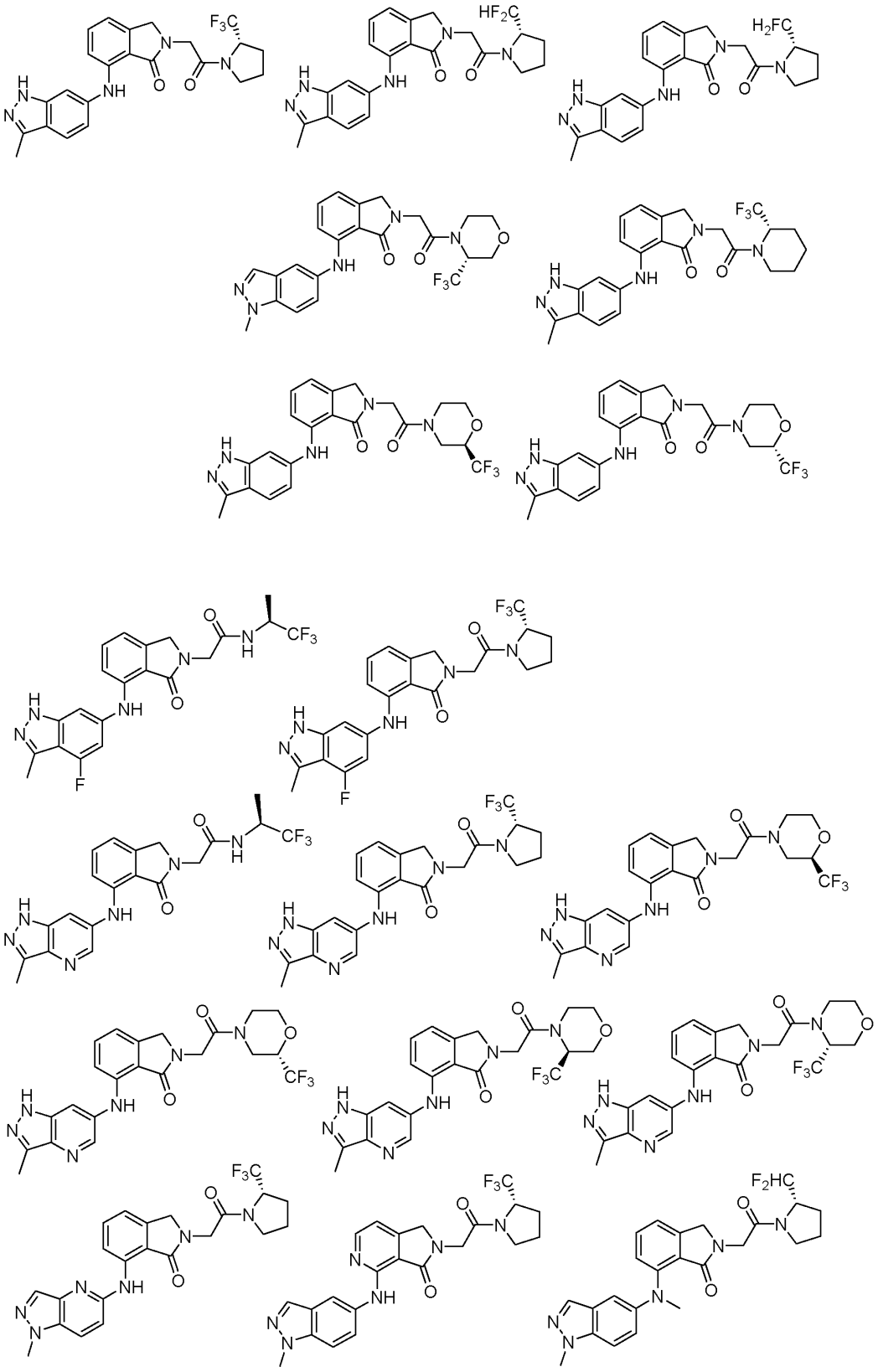


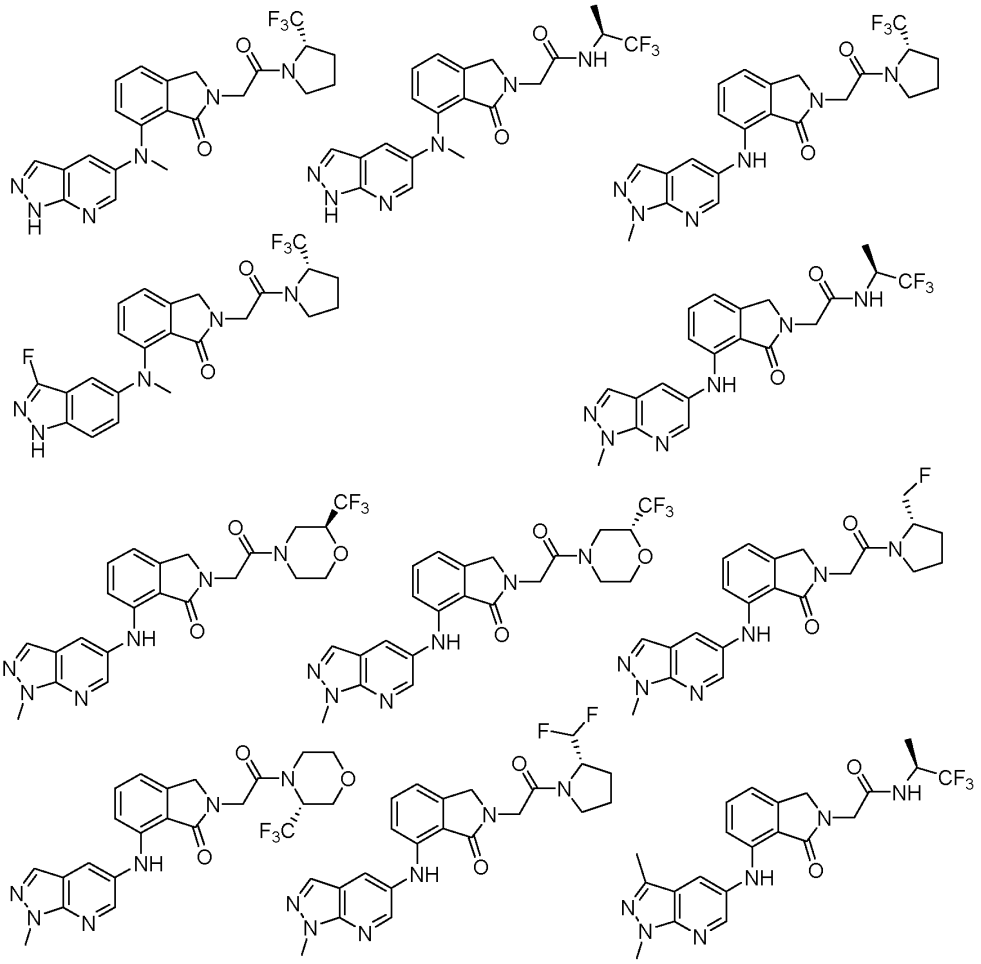
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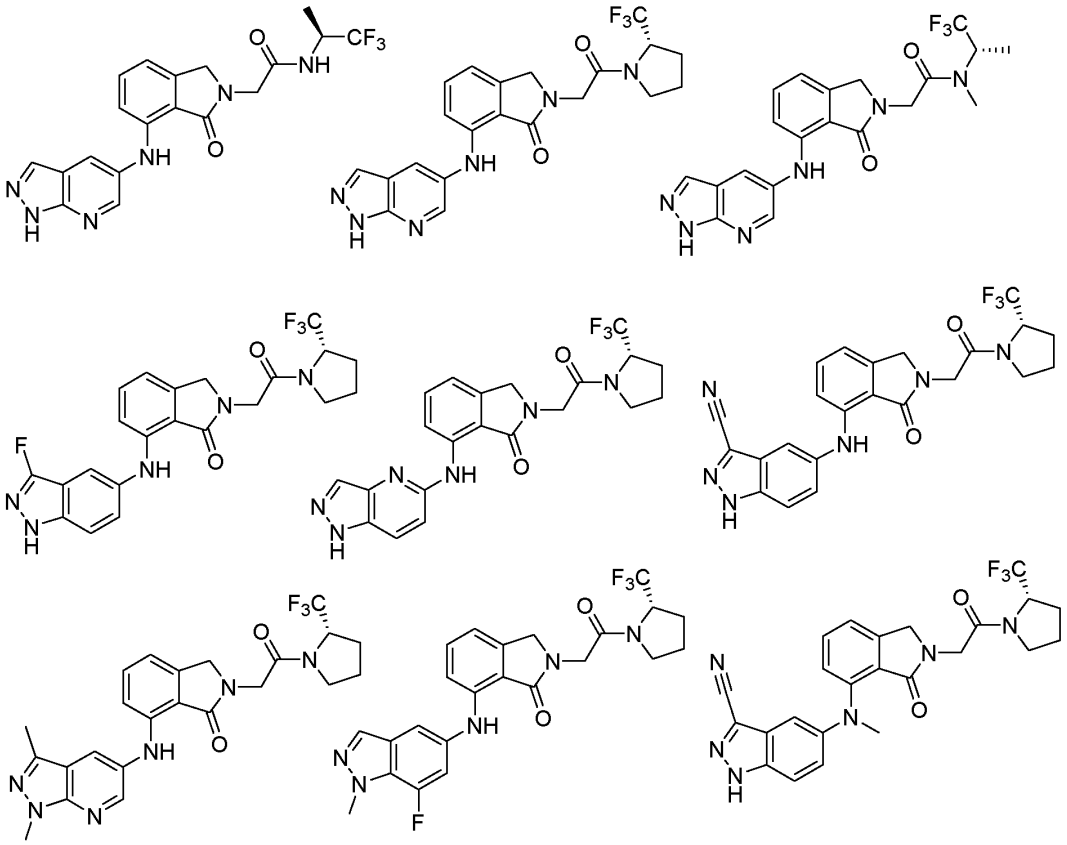
[0089] The compound of formula (I) may be selected from:



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[0090] In an aspect of the invention there is provided the compounds of the present invention for use as a medicament.

[0091] In accordance with another aspect, there is provided a compound of the present invention 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.

[0092] In another aspect of the invention, there is provided a compound of the present invention 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.

[0093] In an aspect of the invention 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 invention, to a patient in need thereof.

[0094] The method of treatment may be a method of treating a condition treatable by the inhibition of DDR1 and/or DDR2.

[0095] The invention 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.

[0096] 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.

[0097] 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.

[0098] 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.

[0099] 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.

[00100] 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.

[00101] In certain embodiments compounds of the invention 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 embodiments, the cancer is selected from bladder cancer, pancreatic cancer, breast cancer, lung cancer, ovarian cancer and glioblastoma.

[00102] In another aspect of the invention there is provided a pharmaceutical composition, wherein the composition comprises a compound of the invention and pharmaceutically acceptable excipients.

[00103] In an embodiment the pharmaceutical composition may be a combination product comprising an additional pharmaceutically active agent.

[00104] In an aspect of the present invention there is provided the use of a compound of the invention in the manufacture of a medicament for use in the treatment of any condition disclosed herein.

DETAILED DESCRIPTION

[00105] 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.

[00106] 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.

[00107] 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 example methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *tert*-butyl, *n*-pentyl and *n*-hexyl. "Alkylene" groups may likewise be linear or branched and is divalent, i.e. it attached at two positions to other portions of the molecule. Furthermore, an alkylene group may, for example, correspond to one of those alkyl groups listed in this paragraph. The alkyl and alkylene groups may be unsubstituted or substituted by one or more substituents.

[00108] The term "haloalkyl" refers to a hydrocarbon chain substituted with at least one halogen atom independently chosen at each occurrence, for example fluorine, chlorine, bromine and iodine. For example, the term "C_{1-6} haloalkyl" refers to a linear or branched hydrocarbon chain containing 1, 2, 3, 4, 5 or 6 carbon atoms substituted with at least one halogen. The halogen atom may be present at any position on the hydrocarbon chain. For example, C_{1-6} haloalkyl may refer to chloromethyl, fluoromethyl, trifluoromethyl, chloroethyl e.g. 1-chloromethyl and 2-chloroethyl, trichloroethyl e.g. 1,2,2-trichloroethyl, 2,2,2-trichloroethyl, fluoroethyl e.g. 1-fluoromethyl and 2-fluoroethyl, trifluoroethyl e.g. 1,2,2-trifluoroethyl and 2,2,2-trifluoroethyl, chloropropyl, trichloropropyl, fluoropropyl, trifluoropropyl. The term "fluoroalkyl" refers to a hydrocarbon chain substituted with at least one fluorine atom..

[00109] The term "alkenyl" refers to a branched or linear hydrocarbon chain containing at least one double bond. For example, the term "C_{2-6} alkenyl" refers to a branched or linear hydrocarbon chain containing at least one double bond and having 2, 3, 4, 5 or 6 carbon atoms. The double bond(s) may be present as the *E* or *Z* isomer. The double bond may be at any possible position of the hydrocarbon chain. For example, the "C_{2-6} alkenyl" may be ethenyl, propenyl, butenyl, butadienyl, pentenyl, pentadienyl, hexenyl and hexadienyl.

[00110] The term "alkynyl" refers to a branched or linear hydrocarbon chain containing at least one triple bond. For example, the term "C_{2-6} alkynyl" refers to a branched or linear hydrocarbon chain containing at least one triple bond and having 2, 3, 4, 5 or 6 carbon atoms. The triple bond may be at any possible position of the hydrocarbon chain. For example, the "C_{2-6} alkynyl" may be ethynyl, propynyl, butynyl, pentynyl and hexynyl.

[00111] The term "heteroalkyl" refers to a branched or linear hydrocarbon chain containing at least one heteroatom selected from N, O and S positioned between any carbon in the chain or at an end of the chain. For example, the term "C_{1-6} heteroalkyl" refers to a branched or linear hydrocarbon chain containing 1, 2, 3, 4, 5, or 6 carbon atoms and at least one heteroatom selected from N, O and S positioned between any carbon in the chain or at an end of the chain. For example, the hydrocarbon chain may contain one or two heteroatoms. The C_{1-6} heteroalkyl may be bonded to the rest of the molecule through a carbon or a heteroatom. For example, the "C_{1-6} heteroalkyl" may be C_{1-6} *N*-alkyl, C_{1-6} *N,N*-alkyl, or C_{1-6} *O*-alkyl.

[00112] The term "heterocycle" refers to a saturated, unsaturated or aromatic ring system containing at least one heteroatom selected from N, O or S. A "heterocyclic" system may contain 1, 2, 3 or 4 heteroatoms, for example 1 or 2. A "heterocyclic" system may be monocyclic or a fused polycyclic ring system, for example, bicyclic or tricyclic. A "heterocyclic" moiety may contain from 3 to 14 carbon atoms, for example, 3 to 8 carbon atoms in a monocyclic system and 7 to 14 carbon atoms in a polycyclic system. "Heterocyclic" encompasses heterocycloalkyl moieties, heterocycloalkenyl moieties and heteroaryl moieties. For example, the heterocyclic group may be: oxirane, aziridine, azetidine, oxetane, tetrahydrofuran, pyrrolidine, imidazolidine, succinimide, pyrazolidine, oxazolidine, isoxazolidine, thiazolidine, isothiazolidine, piperidine, morpholine, thiomorpholine, piperazine, and tetrahydropyran. Heteroaryl includes groups such as pyridones and N-alkyl-pyridones.

[00113] The term "C_{3-8} cycloalkyl" refers to a saturated hydrocarbon ring system containing 3, 4, 5, 6, 7 or 8 carbon atoms. For example, the "C_{3-8} cycloalkyl" may be cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

[00114] The term "C_{3-8} cycloalkenyl" refers to an unsaturated hydrocarbon ring system containing 3, 4, 5, 6, 7 or 8 carbon atoms that is not aromatic. The ring may contain more than one double bond provided that the ring system is not aromatic. For example, the "C_{3-8} cycloalkyl" may be cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclopentadienyl, cyclohexenyl, cyclohexadienly, cycloheptenyl, cycloheptadiene, cyclooctenyl and cycloatadienyl.

[00115] The term "heterocycloalkyl" refers to a saturated hydrocarbon ring system containing carbon atoms and at least one heteroatom within the ring selected from N, O and S. For example, there may be 1, 2 or 3 heteroatoms, optionally 1 or 2. The "heterocycloalkyl" may be bonded to the rest of the molecule through any carbon atom or heteroatom. The "heterocycloalkyl" may have one or more, e.g. one or two, bonds to the rest of the molecule: these bonds may be through any of the atoms in the ring. For example, the "heterocycloalkyl" may be a "C_{3-8} heterocycloalkyl". The term "C_{3-8} heterocycloalkyl" refers to a saturated hydrocarbon ring system containing 3, 4, 5, 6, 7 or 8 atoms at least one of the atoms being a heteroatom within the ring selected from N, O and S. The "heterocycloalkyl" may be oxirane, aziridine, azetidine, oxetane, tetrahydrofuran, pyrrolidine, imidazolidine, succinimide, pyrazolidine, oxazolidine, isoxazolidine, thiazolidine, isothiazolidine, piperidine, morpholine, thiomorpholine, piperazine, and tetrahydropyran.

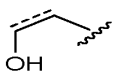
[00116] The term "aromatic" when applied to a substituent as a whole means a single ring or polycyclic ring system with 4n + 2 electrons in a conjugated π system within the ring or ring system where all atoms contributing to the conjugated π system are in the same plane.

[00117] The term "aryl" refers to an aromatic hydrocarbon ring system. The ring system has 4n +2 electrons in a conjugated π system within a ring where all atoms contributing to the conjugated π system are in the same plane. For example, the "aryl" may be phenyl and naphthyl. The aryl system itself may be substituted with other groups.

[00118] The term "heteroaryl" refers to an aromatic hydrocarbon ring system with at least one heteroatom within a single ring or within a fused ring system, selected from O, N and S. The ring or ring system has 4n +2 electrons in a conjugated π system where all atoms contributing to the conjugated π system are in the same plane. For example, the "heteroaryl" may be imidazole, oxazole, isoxazole, thiazole, isothiazole, thiene, furan, thianthrene, pyrrole, benzimidazole, pyrazole, pyrazine, pyridine, pyrimidine and indole.

[00119] A bond terminating in a "" represents that the bond is connected to another atom that is not shown in the structure. A bond terminating inside a cyclic structure and not terminating at an atom of the ring structure represents that the bond may be connected to any of the atoms in the ring structure where allowed by valency.

[00120] A bond drawn as a solid line and a dotted line represents a bond which can be either a single bond or a double bond, where chemically possible. For example, the bond drawn below could be a single bond or a double bond.

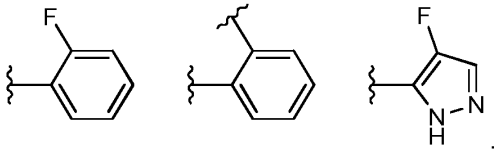


[00121] Where a moiety is substituted, it may be substituted at any point on the moiety where chemically possible and consistent with atomic valency requirements. The moiety may be substituted

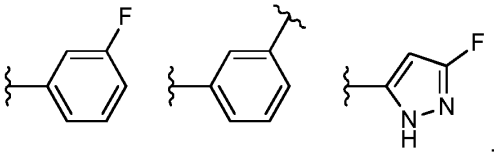
by one or more substituents, e.g. 1, 2, 3 or 4 substituents; optionally there are 1 or 2 substituents on a group. Where there are two or more substituents, the substituents may be the same or different.

[00122] Substituents are only present at positions where they are chemically possible, the person skilled in the art being able to decide (either experimentally or theoretically) without inappropriate effort which substitutions are chemically possible and which are not.

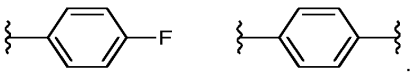
[00123] Ortho, meta and para substitution are well understood terms in the art. For the absence of doubt, "ortho" substitution is a substitution pattern where adjacent carbons possess a substituent, whether a simple group, for example the fluoro group in the example below, or other portions of the molecule, as indicated by the bond ending in " ".



[00124] "Meta" substitution is a substitution pattern where two substituents are on carbons one carbon removed from each other, i.e with a single carbon atom between the substituted carbons. In other words there is a substituent on the second atom away from the atom with another substituent. For example the groups below are meta substituted.



[00125] "Para" substitution is a substitution pattern where two substituents are on carbons two carbons removed from each other, i.e with two carbon atoms between the substituted carbons. In other words there is a substituent on the third atom away from the atom with another substituent. For example the groups below are para substituted.



[00126] Throughout the description the disclosure of a compound also encompasses pharmaceutically acceptable salts, solvates and stereoisomers thereof.

[00127] Where a compound has a stereocentre, both (*R*) and (*S*) stereoisomers are contemplated by the invention, equally mixtures of stereoisomers or a racemic mixture are completed by the present application. Where a compound of the invention has two or more stereocentres any combination of (*R*) and (*S*) stereoisomers is contemplated. The combination of (*R*) and (*S*) stereoisomers may result in a diastereomeric mixture or a single diastereoisomer. The compounds of the invention may be present as a single stereoisomer or may be mixtures of stereoisomers, for example racemic mixtures and other

enantiomeric mixtures, and diasteroemeric mixtures. Where the mixture is a mixture of enantiomers the enantiomeric excess may be any of those disclosed above. Where the compound is a single stereoisomer the compounds may still contain other diasteroisomers or enantiomers as impurities. Hence a single stereoisomer does not necessarily have an enantiomeric excess (e.e.) or diastereomeric excess (d.e.) of 100% but could have an e.e. or d.e. of about at least 85%, at least 60% or less. For example, the e.e. or d.e. may be 90% or more, 90% or more, 80% or more, 70% or more, 60% or more, 50% or more, 40% or more, 30% or more, 20% or more, or 10% or more.

[00128] The invention contemplates pharmaceutically acceptable salts of the compounds of the invention. These may include the acid addition and base salts of the compounds. These may be acid addition and base salts of the compounds. In addition the invention contemplates solvates of the compounds. These may be hydrates or other solvated forms of the compound.

[00129] Suitable acid addition salts are formed from acids which form non-toxic salts. Examples include the acetate, aspartate, benzoate, besylate, bicarbonate/carbonate, bisulfate/sulfate, borate, camsylate, citrate, edisylate, esylate, formate, fumarate, gluceptate, gluconate, glucuronate, hexafluorophosphate, hibenzate, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, isethionate, lactate, malate, maleate, malonate, mesylate, methylsulfate, naphthylate, 1,5-naphthalenedisulfonate, 2-napsylate, nicotinate, nitrate, orotate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, saccharate, stearate, succinate, tartrate, tosylate and trifluoroacetate salts.

[00130] Suitable base salts are formed from bases which form non-toxic salts. Examples include the aluminium, arginine, benzathine, calcium, choline, diethylamine, diolamine, glycine, lysine, magnesium, meglumine, olamine, potassium, sodium, tromethamine and zinc salts. Hemisalts of acids and bases may also be formed, for example, hemisulfate and hemicalcium salts. For a review on suitable salts, see "Handbook of Pharmaceutical Salts: Properties, Selection, and Use" by Stahl and Wermuth (Wiley-VCH, Weinheim, Germany, 2002).

[00131] Pharmaceutically acceptable salts of compounds of formula (**I**) may be prepared by one or more of three methods:

(i) by reacting the compound of the invention with the desired acid or base;

(ii) by removing an acid- or base-labile protecting group from a suitable precursor of the compound of the invention or by ring-opening a suitable cyclic precursor, for example, a lactone or lactam, using the desired acid or base; or

(iii) by converting one salt of the compound of the invention to another by reaction with an appropriate acid or base or by means of a suitable ion exchange column.

[00132] All three reactions are typically carried out in solution. The resulting salt may precipitate out and be collected by filtration or may be recovered by evaporation of the solvent. The degree of ionisation in the resulting salt may vary from completely ionised to almost non-ionised.

[00133] The compounds of the invention may exist in both unsolvated and solvated forms. The term 'solvate' is used herein to describe a molecular complex comprising the compound of the invention and a stoichiometric amount of one or more pharmaceutically acceptable solvent molecules, for example, ethanol. The term 'hydrate' is employed when said solvent is water.

[00134] Included within the scope of the invention are complexes such as clathrates, drug-host inclusion complexes wherein, in contrast to the aforementioned solvates, the drug and host are present in stoichiometric or non-stoichiometric amounts. Also included are complexes of the drug containing two or more organic and/or inorganic components which may be in stoichiometric or non-stoichiometric amounts. The resulting complexes may be ionised, partially ionised, or non- ionised. For a review of such complexes, see J Pharm Sci, 64 (8), 1269-1288 by Haleblian (August 1975).

[00135] Hereinafter all references to compounds of any formula include references to salts, solvates and complexes thereof and to solvates and complexes of salts thereof.

[00136] The compounds of the invention include compounds of a number of formula as herein defined, including all polymorphs and crystal habits thereof, prodrugs and isomers thereof (including optical, geometric and tautomeric isomers) as hereinafter defined and isotopically-labelled compounds of the invention.

[00137] The present invention also includes all pharmaceutically acceptable isotopically-labelled compounds of the invention wherein one or more atoms are replaced by atoms having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number most commonly found in nature.

[00138] Examples of isotopes suitable for inclusion in the compounds of the invention include isotopes of hydrogen, such as ^{2}H and ^{3}H, carbon, such as ^{11}C, ^{13}C and ^{14}C, chlorine, such as ^{36}Cl, fluorine, such as ^{18}F, iodine, such as ^{123}I and ^{125}I, nitrogen, such as ^{13}N and ^{15}N, oxygen, such as ^{15}O, ^{17}O and ^{18}O, phosphorus, such as ^{32}P, and sulphur, such as ^{35}S.

[00139] Certain isotopically-labelled compounds, for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, i.e. ^{3}H, and carbon-14, i.e. ^{14}C, are particularly useful for this purpose in view of their ease of incorporation and ready means of detection.

[00140] Substitution with heavier isotopes such as deuterium, i.e. ^{2}H, may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased in vivo half-life or reduced dosage requirements, and hence may be preferred in some circumstances.

[00141] Before purification, the compounds of the present invention may exist as a mixture of enantiomers depending on the synthetic procedure used. The enantiomers can be separated by conventional techniques known in the art. Thus the invention covers individual enantiomers as well as mixtures thereof.

[00142] For some of the steps of the process of preparation of the compounds of the invention, it may be necessary to protect potential reactive functions that are not wished to react, and to cleave said protecting groups in consequence. In such a case, any compatible protecting radical can be used. In particular methods of protection and deprotection such as those described by T.W. GREENE (Protective Groups in Organic Synthesis, A. Wiley- Interscience Publication, 1981) or by P. J. Kocienski (Protecting groups, Georg Thieme Verlag, 1994), can be used. All of the above reactions and the preparations of novel starting materials used in the preceding methods are conventional and appropriate reagents and reaction conditions for their performance or preparation as well as procedures for isolating the desired products will be well-known to those skilled in the art with reference to literature precedents and the examples and preparations hereto.

[00143] Also, the compounds of the present invention as well as intermediates for the preparation thereof can be purified according to various well-known methods, such as for example crystallization or chromatography.

[00144] One or more compounds of the invention may be combined with one or more pharmaceutical agents, for example anti-inflammatory agents, anti-fibrotic agents, chemotherapeutics, anti cancer agents, immunosuppressants, anti-tumour vaccines, cytokine therapy, or tyrosine kinase inhibitors, for the treatment of conditions modulated by the inhibition of ROCK, for example fibrotic diseases, auto-immune, inflammatory-fibrotic conditions, inflammatory conditions, central nervous system disorders, or cancer.

[00145] The method of treatment or the compound for use in the treatment of renal conditions, liver conditions, inflammatory conditions, cardiovascular conditions, acute and chronic organ transplant rejection, fibrotic diseases and cancer as defined hereinbefore may be applied as a sole therapy or be a combination therapy with an additional active agent.

[00146] The method of treatment or the compound for use in the treatment of renal conditions, liver conditions, inflammatory conditions, cardiovascular conditions, acute and chronic organ transplant rejection, fibrotic diseases and cancer. The additional active agents may be one or more active agents used to treat the condition being treated by the compound of the invention and additional active agent. The additional active agents may include one or more of the following active agents:-

(i) steroids such as corticosteroids, including glucocorticoids and mineralocorticoids, for example aclometasone, aclometasone dipropionate, aldosterone, amcinonide, beclomethasone, beclomethasone dipropionate, betamethasone, betamethasone dipropionate, betamethasone sodium phosphate, betamethasone valerate, budesonide, clobetasone, clobetasone butyrate, clobetasol propionate, cloprednol, cortisone, cortisone acetate, cortivazol, deoxycortone, desonide, desoximetasone, dexamethasone, dexamethasone sodium phosphate, dexamethasone isonicotinate, difluorocortolone, fluclorolone, flumethasone, flunisolide, fluocinolone, fluocinolone acetonide, fluocinonide, fluocortin butyl, fluorocortisone, fluorocortolone, fluocortolone caproate, fluocortolone pivalate, fluorometholone, fluprednidene, fluprednidene acetate, flurandrenolone, fluticasone,

fluticasone propionate, halcinonide, hydrocortisone, hydrocortisone acetate, hydrocortisone butyrate, hydrocortisone aceponate, hydrocortisone buteprate, hydrocortisone valerate, icomethasone, icomethasone enbutate, meprednisone, methylprednisolone, mometasone paramethasone, mometasone furoate monohydrate, prednicarbate, prednisolone, prednisone, tixocortol, tixocortol pivalate, triamcinolone, triamcinolone acetonide, triamcinolone alcohol and their respective pharmaceutically acceptable derivatives. A combination of steroids may be used, for example a combination of two or more steroids mentioned in this paragraph;

(ii) TNF inhibitors for example etanercept; monoclonal antibodies (e.g. infliximab (Remicade), adalimumab (Humira), certolizumab pegol (Cimzia), golimumab (Simponi)); fusion proteins (e.g. etanercept (Enbrel)); and 5-HT_{2A} agonists (e.g. 2,5-dimethoxy-4-iodoamphetamine, TCB-2, lysergic acid diethylamide (LSD), lysergic acid dimethylazetidide);

(iii) anti-inflammatory drugs, for example non-steroidal anti-inflammatory drugs;

(iv) dihydrofolate reductase inhibitors/antifolates, for example methotrexate, trimethoprim, brodimoprim, tetroxoprim, iclaprim, pemetrexed, ralitrexed and pralatrexate; and

(v) immunosuppressants for example cyclosporins, tacrolimus, sirolimus pimecrolimus, angiotensin II inhibitors (e.g. Valsartan, Telmisartan, Losartan, Irbesatan, Azilsartan, Olmesartan, Candesartan, Eprosartan) and ACE inhibitors e.g. sulfhydryl-containing agents (e.g. Captopril, Zofenopril), dicarboxylate-containing agents (e.g. Enalapril, Ramipril, Quinapril, Perindopril, Lisinopril, Benazepril, Imidapril, Zofenopril, Trandolapril), phosphate-containing agents (e.g. Fosinopril), casokinins, lactokinins and lactotripeptides.

(vi)Anti-fibrotic agents for example: Pirfenidone, Nintedanib, Anti-IL-13 monoclonal antibodies (e.g. Tralokinumab, QAX576, Lebrikizumab), simtuzumab, FG-3019, lysophosphatidic acid receptor antagonists (e.g. BMS-986020, AM966), LOXL2 inhibitors, BET bromodomain inhibitors (e.g. JQ1), HDAC inhibitors (e.g. Vorinostat), thrombin inhibitors (e.g. Dabigatran), FactorXa inhibitors (e.g. Apixban, Rivaroxaban) 15PGDH inhibitors, anti-αvβ6 monoclonal antibodies (e.g. BG00011), Anti-CTGF monoclonal antibodies (e.g. FG-3019), PAR1 inhibitors, Nox4 inhibitors and PAI-1 inhibitors.

[00147] The method of treatment or the compound for use in the treatment of cancer may involve, in addition to the compound of the invention, conventional surgery or radiotherapy or chemotherapy. Such chemotherapy may include one or more of the following categories of anti-tumor agents:

(i) antiproliferative/antineoplastic drugs and combinations thereof, such as alkylating agents (for example cis-platin, oxaliplatin, carboplatin, cyclophosphamide, nitrogen mustard, uracil mustard, bendamustin, melphalan, chlorambucil, chlormethine, busulphan, temozolamide, nitrosoureas, ifosamide, melphalan, pipobroman, triethylene-melamine, triethylenethiophoporamine, carmustine, lomustine, stroptozocin and dacarbazine); antimetabolites (for example gemcitabine and antifolates such as fluoropyrimidines like 5-fluorouracil and tegafur, raltitrexed, methotrexate, pemetrexed, cytosine arabinoside, floxuridine, cytarabine, 6-mercaptopurine, 6-thioguanine, fludarabine phosphate, pentostatine, and gemcitabine and hydroxyurea); antibiotics (for example anthracyclines like adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin and

mithramycin); antimitotic agents (for example vinca alkaloids like vincristine, vinblastine, vindesine and vinorelbine and taxoids like taxol and taxotere and polokinase inhibitors); proteasome inhibitors, for example carfilzomib and bortezomib; interferon therapy; and topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan, mitoxantrone and camptothecin); bleomcin, dactinomycin, daunorubicin, doxorubicin, epirubicin, idarubicin, ara-C, paclitaxel (Taxol™), nabpaclitaxel, docetaxel, mithramycin, deoxyco-formycin, mitomycin-C, L-asparaginase, interferons (especially IFN-a), etoposide, and teniposide;

(ii) cytostatic agents such as antiestrogens (for example tamoxifen, fulvestrant, toremifene, raloxifene, droloxifene and iodoxyfene), antiandrogens (for example bicalutamide, flutamide, nilutamide and cyproterone acetate), LHRH antagonists or LHRH agonists (for example goserelin, leuprorelin and buserelin), progestogens (for example megestrol acetate), aromatase inhibitors (for example as anastrozole, letrozole, vorazole and exemestane) and inhibitors of 5α-reductase such as finasteride; and navelbene, CPT-II, anastrazole, letrazole, capecitabine, reloxafme, cyclophosphamide, ifosamide, and droloxafine;

(iii) anti-invasion agents, for example dasatinib and bosutinib (SKI-606), and metalloproteinase inhibitors, inhibitors of urokinase plasminogen activator receptor function or antibodies to Heparanase;

(iv) inhibitors of growth factor function: for example such inhibitors include growth factor antibodies and growth factor receptor antibodies, for example the anti-erbB2 antibody trastuzumab [Herceptin™], the anti-EGFR antibody panitumumab, the anti-erbB1 antibody cetuximab, tyrosine kinase inhibitors, for example inhibitors of the epidermal growth factor family (for example EGFR family tyrosine kinase inhibitors such as gefitinib, erlotinib, 6-acrylamido-*N*-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)-quinazolin-4-amine (CI 1033), erbB2 tyrosine kinase inhibitors such as lapatinib) and antibodies to costimulatory molecules such as CTLA-4, 4-IBB and PD-I, or antibodies to cytokines (IL-I0, TGF-beta); inhibitors of the hepatocyte growth factor family; inhibitors of the insulin growth factor family; modulators of protein regulators of cell apoptosis (for example Bcl-2 inhibitors); inhibitors of the platelet-derived growth factor family such as imatinib and/or nilotinib (AMN107); inhibitors of serine/threonine kinases (for example Ras/Raf signalling inhibitors such as farnesyl transferase inhibitors, for example sorafenib , tipifarnib and lonafarnib), inhibitors of cell signalling through MEK and/or AKT kinases, c-kit inhibitors, abl kinase inhibitors, PI3 kinase inhibitors, Plt3 kinase inhibitors, CSF-1R kinase inhibitors, IGF receptor, kinase inhibitors; aurora kinase inhibitors and cyclin dependent kinase inhibitors such as CDK2 and/or CDK4 inhibitors; and CCR2, CCR4 or CCR6 modulator;

(v) antiangiogenic agents such as those which inhibit the effects of vascular endothelial growth factor, for example the anti-vascular endothelial cell growth factor antibody bevacizumab (Avastin™); thalidomide; lenalidomide; and for example, a VEGF receptor tyrosine kinase inhibitor such as vandetanib, vatalanib, sunitinib, axitinib and pazopanib;

(vi) gene therapy approaches, including for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2;

(vii) immunotherapy approaches, including for example antibody therapy such as alemtuzumab, rituximab, ibritumomab tiuxetan (Zevalin®) and ofatumumab; interferons such as interferon α; interleukins such as IL-2 (aldesleukin); interleukin inhibitors for example IRAK4 inhibitors; cancer vaccines including prophylactic and treatment vaccines such as HPV vaccines, for example Gardasil, Cervarix, Oncophage and Sipuleucel-T (Provenge); gp100;dendritic cell-based vaccines (such as Ad.p53 DC); and toll-like receptor modulators for example TLR-7 or TLR-9 agonists; and

(viii) cytotoxic agents for example fludaribine (fludara), cladribine, pentostatin (Nipent™);

(ix) steroids such as corticosteroids, including glucocorticoids and mineralocorticoids, for example aclometasone, aclometasone dipropionate, aldosterone, amcinonide, beclomethasone, beclomethasone dipropionate, betamethasone, betamethasone dipropionate, betamethasone sodium phosphate, betamethasone valerate, budesonide, clobetasone, clobetasone butyrate, clobetasol propionate, cloprednol, cortisone, cortisone acetate, cortivazol, deoxycortone, desonide, desoximetasone, dexamethasone, dexamethasone sodium phosphate, dexamethasone isonicotinate, difluorocortolone, fluclorolone, flumethasone, flunisolide, fluocinolone, fluocinolone acetonide, fluocinonide, fluocortin butyl, fluorocortisone, fluorocortolone, fluocortolone caproate, fluocortolone pivalate, fluorometholone, fluprednidene, fluprednidene acetate, flurandrenolone, fluticasone, fluticasone propionate, halcinonide, hydrocortisone, hydrocortisone acetate, hydrocortisone butyrate, hydrocortisone aceponate, hydrocortisone buteprate, hydrocortisone valerate, icomethasone, icomethasone enbutate, meprednisone, methylprednisolone, mometasone paramethasone, mometasone furoate monohydrate, prednicarbate, prednisolone, prednisone, tixocortol, tixocortol pivalate, triamcinolone, triamcinolone acetonide, triamcinolone alcohol and their respective pharmaceutically acceptable derivatives. A combination of steroids may be used, for example a combination of two or more steroids mentioned in this paragraph;

(x) targeted therapies, for example PI3Kd inhibitors, for example idelalisib and perifosine; PD-1, PD-L1, PD-L2 and CTL4-A modulators, antibodies and vaccines; other IDO inhibitors (such as indoximod); anti-PD-1 monoclonal antibodies (such as MK-3475 and nivolumab); anti-PD-L1 monoclonal antibodies (such as MEDI-4736 and RG-7446); anti-PD-L2 monoclonal antibodies; and anti-CTLA-4 antibodies (such as ipilimumab);

(xii) chimeric antigen receptors, anticancer vaccines and arginase inhibitors.

[00148] Such combination treatment may be achieved by way of the simultaneous, sequential or separate dosing of the individual components of the treatment. Such combination products employ the compounds of this invention within a therapeutically effective dosage range described hereinbefore and the other pharmaceutically-active agent within its approved dosage range.

[00149] Compounds of the invention may exist in a single crystal form or in a mixture of crystal forms or they may be amorphous. Thus, compounds of the invention intended for pharmaceutical use may be administered as crystalline or amorphous products. They may be obtained, for example, as solid plugs, powders, or films by methods such as precipitation, crystallization, freeze drying, or spray drying, or evaporative drying. Microwave or radio frequency drying may be used for this purpose.

[00150] For the above-mentioned compounds of the invention the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated. For example, if the compound of the invention is administered orally, then the daily dosage of the compound of the invention may be in the range from 0.01 micrograms per kilogram body weight (µg/kg) to 100 milligrams per kilogram body weight (mg/kg).

[00151] A compound of the invention, or pharmaceutically acceptable salt thereof, may be used on their own but will generally be administered in the form of a pharmaceutical composition in which the compounds of the invention, or pharmaceutically acceptable salt thereof, is in association with a pharmaceutically acceptable adjuvant, diluent or carrier. Conventional procedures for the selection and preparation of suitable pharmaceutical formulations are described in, for example, "Pharmaceuticals - The Science of Dosage Form Designs", M. E. Aulton, Churchill Livingstone, 1988.

[00152] Depending on the mode of administration of the compounds of the invention, the pharmaceutical composition which is used to administer the compounds of the invention will preferably comprise from 0.05 to 99 %w (per cent by weight) compounds of the invention, more preferably from 0.05 to 80 %w compounds of the invention, still more preferably from 0.10 to 70 %w compounds of the invention, and even more preferably from 0.10 to 50 %w compounds of the invention, all percentages by weight being based on total composition.

[00153] The pharmaceutical compositions may be administered topically (e.g. to the skin) in the form, e.g., of creams, gels, lotions, solutions, suspensions, or systemically, e.g. by oral administration in the form of tablets, capsules, syrups, powders or granules; or by parenteral administration in the form of a sterile solution, suspension or emulsion for injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion); by rectal administration in the form of suppositories; or by inhalation in the form of an aerosol.

[00154] For oral administration the compounds of the invention may be admixed with an adjuvant or a carrier, for example, lactose, saccharose, sorbitol, mannitol; a starch, for example, potato starch, corn starch or amylopectin; a cellulose derivative; a binder, for example, gelatine or polyvinylpyrrolidone; and/or a lubricant, for example, magnesium stearate, calcium stearate, polyethylene glycol, a wax, paraffin, and the like, and then compressed into tablets. If coated tablets are required, the cores, prepared as described above, may be coated with a concentrated sugar solution which may contain, for example, gum arabic, gelatine, talcum and titanium dioxide. Alternatively, the tablet may be coated with a suitable polymer dissolved in a readily volatile organic solvent.

[00155] For the preparation of soft gelatine capsules, the compounds of the invention may be admixed with, for example, a vegetable oil or polyethylene glycol. Hard gelatine capsules may contain granules of the compound using either the above-mentioned excipients for tablets. Also liquid or semisolid formulations of the compound of the invention may be filled into hard gelatine capsules. Liquid preparations for oral application may be in the form of syrups or suspensions, for example, solutions containing the compound of the invention, the balance being sugar and a mixture of ethanol, water, glycerol and propylene glycol. Optionally such liquid preparations may contain colouring agents,

flavouring agents, sweetening agents (such as saccharine), preservative agents and/or carboxymethylcellulose as a thickening agent or other excipients known to those skilled in art.

[00156] For intravenous (parenteral) administration the compounds of the invention may be administered as a sterile aqueous or oily solution.

[00157] The size of the dose for therapeutic purposes of compounds of the invention will naturally vary according to the nature and severity of the conditions, the age and sex of the animal or patient and the route of administration, according to well-known principles of medicine.

[00158] Dosage levels, dose frequency, and treatment durations of compounds of the invention are expected to differ depending on the formulation and clinical indication, age, and co-morbid medical conditions of the patient.

[00159] Throughout the description and claims of this specification, the words “comprise” and “contain” and variations of them mean “including but not limited to”, and they are not intended to (and do not) exclude other moieties, additives, components, integers or steps. Throughout the description and claims of this specification, the singular encompasses the plural unless the context otherwise requires. In particular, where the indefinite article is used, the specification is to be understood as contemplating plurality as well as singularity, unless the context requires otherwise.

[00160] Features, integers, characteristics, compounds, chemical moieties or groups described in conjunction with a particular aspect, embodiment or example of the invention are to be understood to be applicable to any other aspect, embodiment or example described herein unless incompatible therewith. All of the features disclosed in this specification (including any accompanying claims, abstract and drawings), and/or all of the steps of any method or process so disclosed, may be combined in any combination, except combinations where at least some of such features and/or steps are mutually exclusive. The invention is not restricted to the details of any foregoing embodiments. The invention extends to any novel one, or any novel combination, of the features disclosed in this specification (including any accompanying claims, abstract and drawings), or to any novel one, or any novel combination, of the steps of any method or process so disclosed.

[00161] The reader's attention is directed to all papers and documents which are filed concurrently with or previous to this specification in connection with this application and which are open to public inspection with this specification, and the contents of all such papers and documents are incorporated herein by reference.

[00162] The compounds of the invention may be prepared according to or analogously to the General Schemes 1 – 4 and Examples 1 to 14.

EXAMPLES AND SYNTHESIS

Experimental Procedures

Solvents, reagents and starting materials were purchased from commercial vendors and used as received unless otherwise described. All reactions were performed at room temperature unless otherwise stated. Compound identity and purity confirmations were performed by LCMS. Retention times RT are reported in minutes. The following methods were also used on occasions when described throughout the experimental section, gradients are detailed in table 1. Method 1 utilised a Shimadzu 2020 series spectrometer equipped with a binary pump and diode array detector (acquisition wavelength 214 and 254 nm) and the MS was in positive and negative electrospray mode (*m/z*: 100-900). 2µL Aliquot were injected onto an Agilent Poroshell 120 EC-C18 column (2.7 µm, 4.6×50 mm) maintained at 35°C and eluted at 1.0ml/min using mobile phase consisting of: A: 0.05% Formic acid in water (v/v), B: 0.05% Formic acid in ACN(v/v). Method 2 utilised an Agilent Technologies 1290 series spectrometer equipped with a binary pump and diode array detector (acquisition wavelength 214 and 254 nm) and the MS was in positive electrospray mode (*m/z*: 70-1000). 2µL Aliquots were injected onto an Agilent Eclipse Plus RRHD C18, (1.8µm, 3.0×50 mm) column maintained at 40°C and eluted at 0.8ml/min using mobile phase consisting of: A: 0.05% Formic acid in water (v/v), B: 0.05% Formic acid in ACN(v/v).

Method 1		
Time (min)	%A	%B
0.01	85	15
1.0	85	15
4.0	0	100
4.5	0	100
4.51	85	15
5.0	85	15
Method 2		
Time (min)	%A	%B
0.00	80	20
2.65	20	80
3.00	20	80

Table 1

NMR was also used to characterise final compounds. NMR spectra were obtained on a Bruker AVIII 400 Nanobay with 5mm BBFO probe. Optionally, compound Rf values on silica thin layer chromatography (TLC) plates were measured.

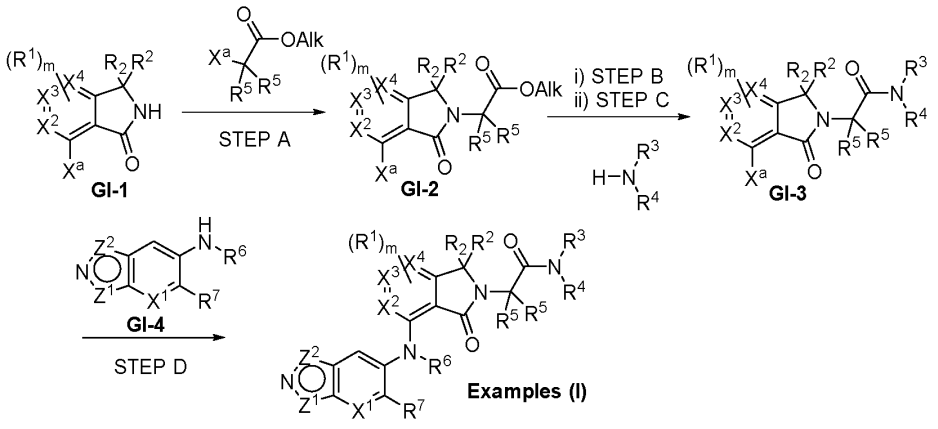
Compound purification was performed by flash column chromatography on silica or by preparative LCMS. LCMS purification was performed using a Waters 3100 Mass detector in positive and negative electrospray mode (*m/z*: 150-800) with a Waters 2489 UV/Vis detector. Samples were eluted at a flow rate of 20mL/min on a XBridge™ prep C18 5µM OBD 19x100mm column with a mobile phase system composed of A (0.1% (v/v) Formic Acid in Water) and B (0.1% (v/v) Formic Acid in Acetonitrile) according to the gradient outlined in Table 2 below.

Time (min)	%A	%B
0	90	10
1.5	90	10
11.7	5	95
13.7	5	95
14	90	10
15	90	10

Table 2

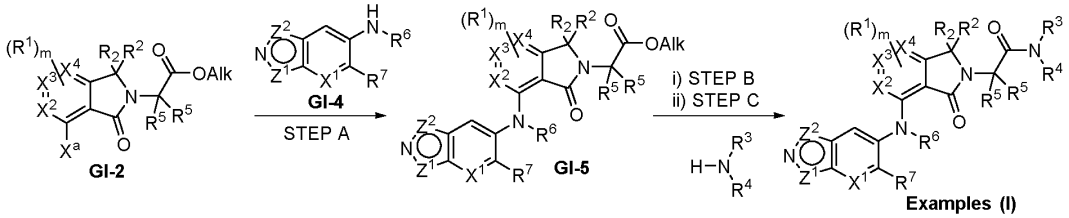
General Syntheitic Routes

Examples conforming to formula (I) can be prepared by one or more of the synthetic routes described in general schemes to 4 below. Starting materials and reagents used in the routes described in gerneral schemes 1 to 4 are either commercially available or prepared using procedures described in chemical literature, as identified using typical chemical structure and reaction searching tools. The order of steps may also be changed. In cases where reactive groups are present, for example amines or alcohols, suitable protecting groups can be used to mask the reactivity of these groups if necessary, for example carbamates, tosylates, hemi-aminals, acteals and esters.



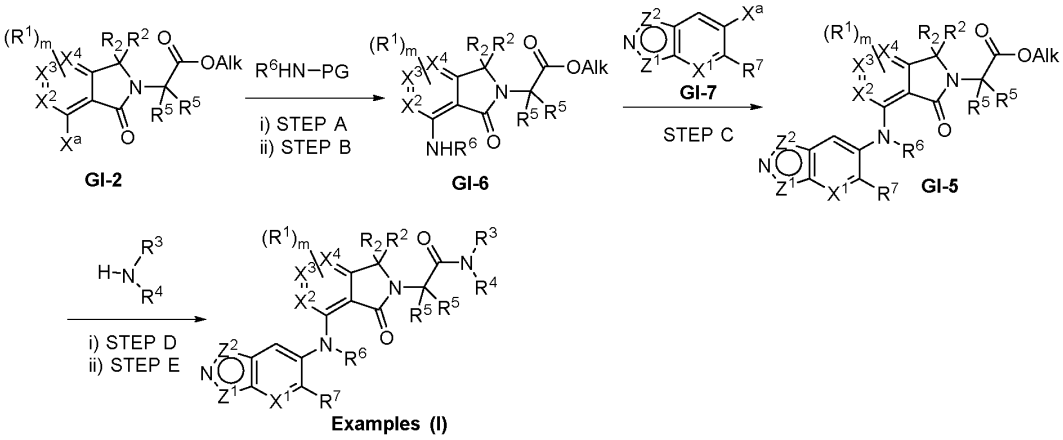
General Scheme 1

In general scheme 1 (where X^a is a halogen, typically bromide but can also be chloride or iodide) a lactam (GI-1) is N-alkylated with an alpha-halo ester such as ethylbromoacetate in the presence of a base such as triethylamine or cesium carbonate in an organic solvent such as acetonitrile or MeCN to afford an intermediate GI-2. The ester group of GI-2 can be hydrolysed in step B using LiOH in MeOH, THG and water and the resulting acid may form an amide bond in step 3 when reacted with an appropriate amine in the presence of an activating agent such as HATU to afford an amide represented by GI-3. In step D GI-3 undergoes a transition metal catalsed amination such a Buchwald-Hartwig reaction with an appropriate amino indazole derivate (GI-4), to afford examples of formula (I). If Z^1 or Z^2 is NH the corresponding NH in GI-4 can be protected with a a suitable group such as THP or tosyl to facilitate step D. In these cases an additional deprotection step (typically using TFA or HCl) is required to ultimately produce examples of formula (I).



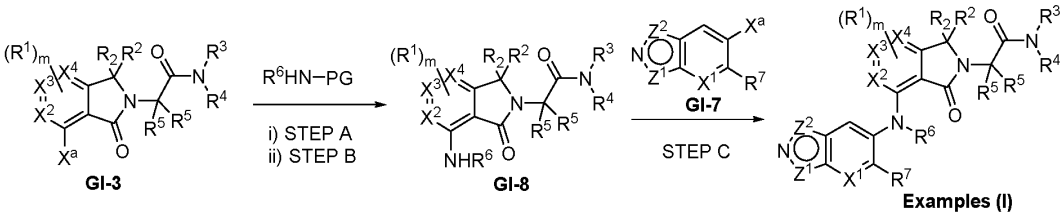
General Scheme 2

General scheme 2 is a variation of general scheme 1 in which N-alklated lactam GI-2 undergoes amination in step A via a Buchwald-Hartwig reaction with an appropriate amino indazole derivate (GI-4) to afford an alkly ester (typically ethyl or t-butyl) of formula GI-5. Steps B and C represent hydrolysis of the ester and amide formation in a similar manner to general scheme 1 to afford examples of formula (I). Once again, if Z^1 or Z^2 is NH the corresponding NH in GI-4 can be protected with a asuitable group such as THP or tosyl to facilitate step A. In these cases an additional deprotection step (typically using TFA or HCl) is required to ultimately produce examples of formula (I).



General Scheme 3

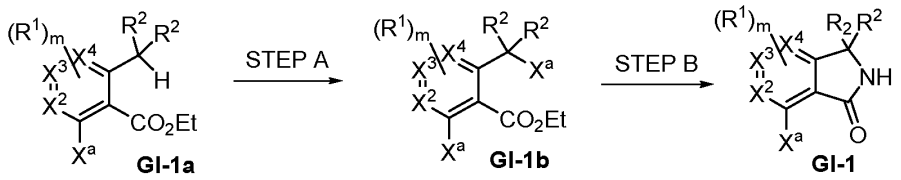
According to general scheme 3, N-alklated lactam GI-2 (where X^a is a halogen, typlically bromide) is converted to an amino lactam of formula GI-6. Step A involves a transition metal catalsed amination such a Buchwald-Hartwig reaction with an appropriate amine bearing an acid labile protecting group (PG) for example t-butyl carbamate and step B is removal of the protecting group using HCl or TFA in an organinc solvent such as DCM or MeOH. GI-6 can then undergoe a second transition metal catalsed amination (step C) such a Buchwald-Hartwig reaction with a halogen bearing indazole derivate (GI-7) in the presence of a palladium catalyst such as $Pd_2(dba)_3$, a ligand such as Xantphos and a base, for example cesium carbonate in 1,4-dioxane as solvent, GI-5 can then undergo hydrolysis and amide formation in steps C and D as previously described in steps B and C in general schemes 1 and 2. As previously described, if Z^1 or Z^2 is NH in examples of formula (I) the corresponding NH in GI-7 can be protected with a suitable group such as THP or tosyl to facilitate step C. In these cases an additional final deprotection step (typically using TFA or HCl) is required to ultimately produce examples of formula (I).



General Scheme 4

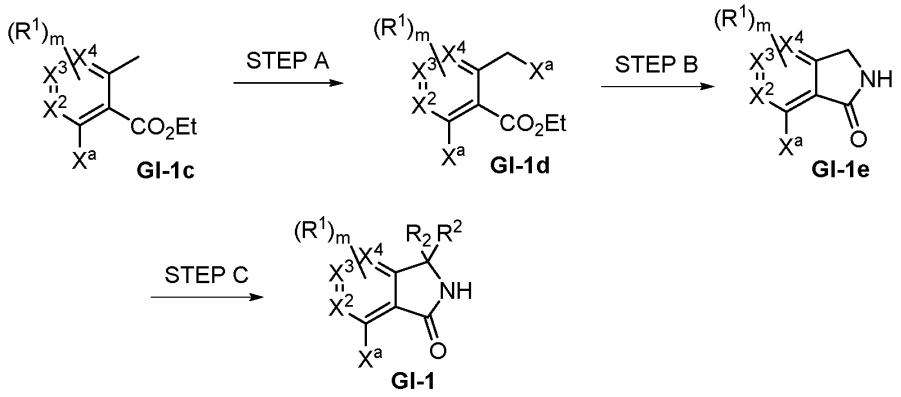
General scheme 4 represents a variation of general scheme 3. In steps A and B GI-3 (described in general scheme 1) undergoes a comparable amination to that described in steps A and B of general scheme 3 to afford GI-8 which then in step C undergoes reaction with GI-7 under conditions described in step C of general scheme 3 to afford examples of formula (I). . As previously described, if Z^1 or Z^2 in examples of formula (I) is NH the corresponding NH in GI-7 can be protected with a asuitable group

such as THP or tosyl to facilitate step C. In these cases an additional deprotection step (typically using TFA or HCl) is required to ultimately produce examples of formula (I).



General Scheme 5

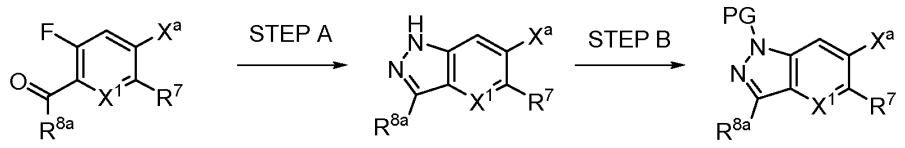
Intermediates of structure GI-1 where not commercially available could be prepared using the methodology outlined in general scheme 5. An appropriately substituted aryl or heteroaryl ethyl ester (where X^a is a halogen, typically a bromide) represented by GI-1a undergoes halogenation in step A, for example with NBS in the presence of a radical initiator such as benzoyl peroxide using CCl_4 as a solvent and is then cyclised in step B with concentrated aqueous ammonia.



General Scheme 6

Alternatively intermediates of structure GI-I (in which one R^2 group is not H) can be prepared according to general scheme 6. GI-1c Is subject to the same steps A and B described in general scheme 5 to afford GI-1e. GI-1e is then alkylated in step C in the presence of a base such as NaHMDS and an appropriate alkyl iodide or bromide in THF as a solvent. If the two R^2 groups are not equivalent and neither are H), step C is repeated with the appropriate alkly iodide or bromide to furnish the second R^2 group.

Where not commercially available or described in the chemical literature halo-indazoles of the formula GI-7 could be prepared by analogy with methods reported in the literature (Gaikwad *et al*. Eur. J. Med. Chem., *90*, **2015**, p707–731). General schemes 7 and 8 describe the methods used herein.

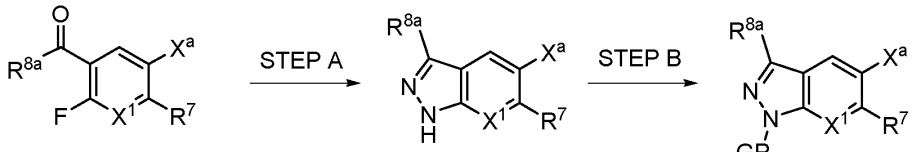


GI-7a **GI-7b** **GI-7(i)**

General Scheme 7

General scheme 7 describes the preparation of halo indazoles (GI-7b and GI-7(i)) used in the synthesis of examples of formula (I) in which Z^1 is CR^{8a} and Z^2 is NH. In step A an appropriate ortho-fluoro carbonyl heteroaryl halide of formula GI-7a (typically halogen X^a is bromide) was reacted with hydrazine hydrate in iPrOH at 80°C. In step B a protecting group could be optionally incorporated to negate any reactivity of the free NH group in subsequent steps. The protecting group used was either a THP group, incorporated using 3,4-dihydropyran with catalytic para-TsOH in THF at 50°C, or a tosyl group, incorporated using tosyl chloride and triethylamine in DCM at room temperature.

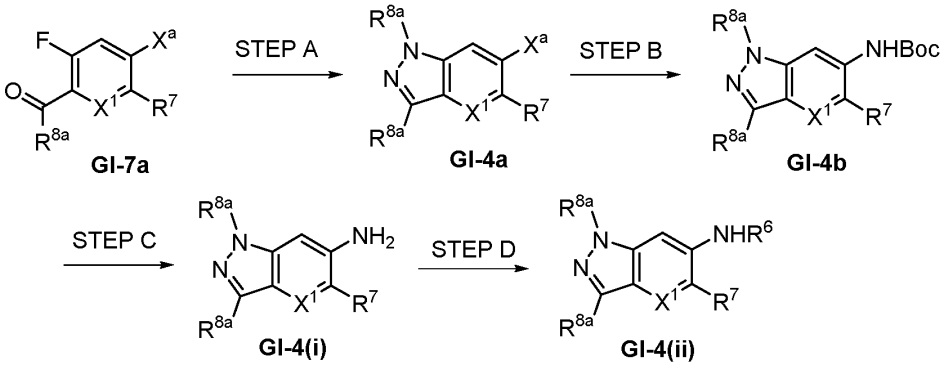
Halo indazoles (GI-7d and GI-7(ii)) used in the synthesis of examples of formula (I) in which Z^2 is CR^{8a} and Z^1 is NH were prepared in an identical fashion starting from the isomeric fluoro carbonyl heteroaryl halides of formula GI-7c, as shown in general scheme 8.



GI-7c **GI-7d** **GI-7(ii)**

General Scheme 8

Where not commercially available or described in the chemical literature amino-indazoles of the formula GI-4 could be prepared by analogy with methods reported in the literature. General schemes 9 and 10 describe the methods used.



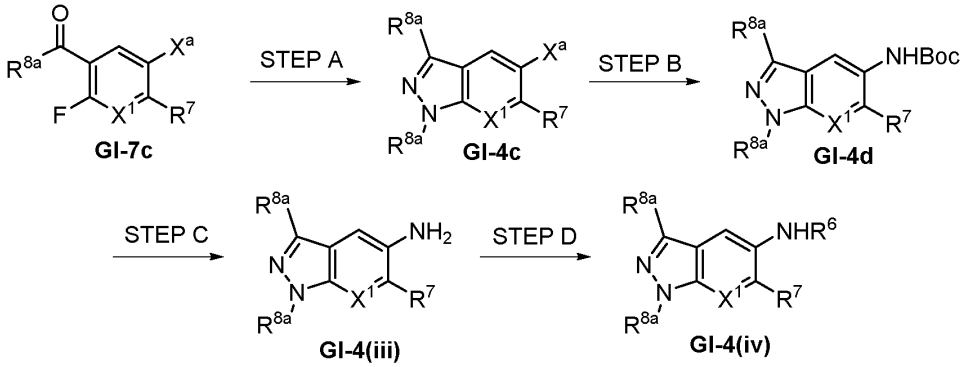
GI-7a **GI-4a** **GI-4b**

GI-4(i) **GI-4(ii)**

General Scheme 9

General scheme 9 describes the preparation of amino indazoles (GI-4(i) and GI-4(ii)) used in the synthesis of examples of formula (I) in which Z^1 is CR^{8a} and Z^2 is not NH. In step A an appropriate ortho-fluoro carbonyl heteroaryl halide of formula GI-7a (typically halogen X^a is bromide) is cyclised with an alkly hydrazine (where the the alkyl substituent of the hydrazine corresponds to R^{8a}) in iPrOH at 80°C affording halo indazoles of formulaGI-4a .In step B halo indazole GI-4a undergoes a Buchwald Hartwig amination with t-butyl carbamate, catalysed by $Pd_2(dba)_3$ and Xantphos (or a comparable catalytic system) in the presence of a base such as cesium carbonate in a solvent such as 1,4-dioxane. GI-4b can be Boc-deprotected in step C with HCl in dioxane or in TFA with or without a cosolvent such as DCM to produce amino indazoles of formula GI-4(i). Finally if R^6 is not H, R^6 can be introduced by reductive amination using an appropriate aldehyde (R^6CHO) and $NaBH_4$ in MeOH or alternatively by alkylation with R^6X^a (where X^a is chloro, bromo or iodo-) in the presence of NaH in THF to produce amino indazoles of formula GI-4(ii) .

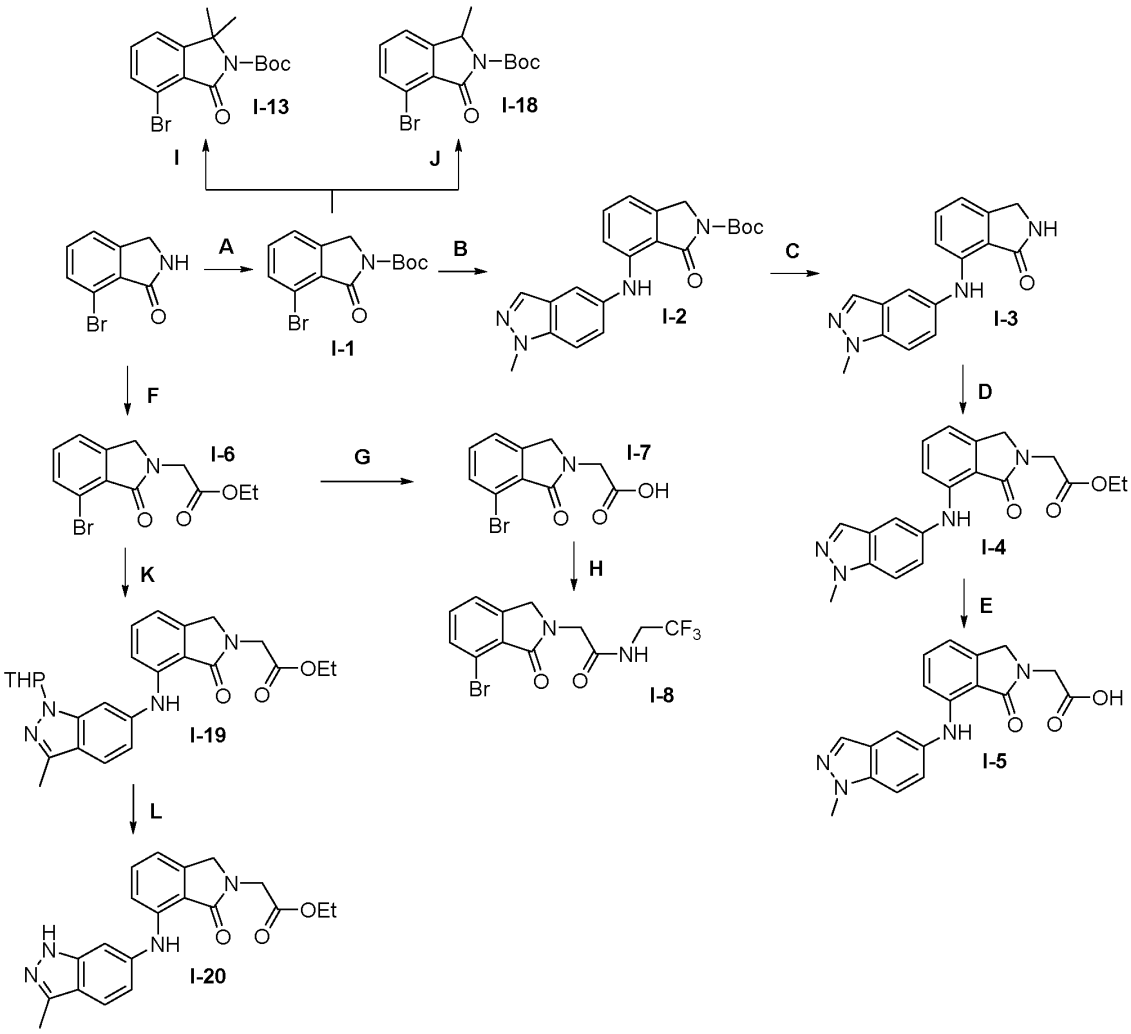
Amino indazoles (GI-4(iii) and GI-4(iv)) used in the synthesis of examples of formula (I) in which Z^2 is CR^{8a} and Z^1 is not NH were prepared in an identical fashion starting from the isomeric fluoro carbonyl heteroaryl halides of formula GI-7c, as shown in general scheme 10.



General Scheme 10

Synthesis of Intermediates

Scheme 1 below describes the synthesis of several intermediates that are common to certain examples and indicates a synthetic approach that could be adopted to prepare other examples by selecting an appropriately functionalised building block in place of one or more of those in Scheme 1, as detailed in the description of the preparation of individual examples.



Scheme 1

STEP A. **Synthesis of Intermediate I-1**, *tert*-butyl 7-bromo-1-oxo-isoindoline-2-carboxylate

A mixture of 7-bromoisoindolin-1-one (1.0 g, 4.7 mmol), Boc_2O (1.5 g, 7.1 mmol) and DMAP (57 mg, 0.47 mmol) in MeCN (20 mL) was stirred at room temperature for 16 h. The mixture was concentrated under reduced pressure and purified by normal phase chromatography (25 g column, 10 to 50% EtOAc in petrol) to give *tert*-butyl 7-bromo-1-oxo-isoindoline-2-carboxylate (Intermediate I-1, 1.4 g, 4.5 mmol, 95% yield) as a white solid.

UPLC-MS (ES^+, Method 1): 4.05 min, m/z 256.0/258.0 $[M\text{-}tBu+H]^+$.

^1H NMR (400 MHz, DMSO-d_6) δ (ppm) 7.75 (d, J=7.2 Hz, 1H), 7.71 - 7.60 (m, 2H), 4.78 (s, 2H), 1.57 (s, 9H).

STEP B. **Synthesis of Intermediate I-2**, *tert*-butyl 7-[(1-methylindazol-5-yl)amino]-1-oxo-isoindoline-2-carboxylate

A mixture of *tert*-butyl 7-bromo-1-oxo-isoindoline-2-carboxylate (Intermediate I-1, 1.0 g, 3.2 mmol), 1-methyl-1H-indazol-5-amine (519 mg, 3.5 mmol), $Pd_2(dba)_3$ (293 mg, 0.32 mmol), XantPhos (185 mg, 0.32 mmol) and Cs_2CO_3 (2.1 g, 6.4 mmol) in 1,4-dioxane (20 mL) was heated to 100 °C and stirred for 16 h. The mixture was allowed to cool to room temperature, concentrated under reduced pressure and purified by normal phase chromatography (25 g column, 5 to 20% EtOAc in petrol) to give *tert*-butyl 7-[(1-methylindazol-5-yl)amino]-1-oxo-isoindoline-2-carboxylate (Intermediate I-2, 1.0 g, 2.6 mmol, 82% yield) as an off-white solid.

UPLC-MS (ES^+, Method 1): 4.39 min, m/z 379.2 $[M+H]^+$.

^1H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.68 (s, 1H), 8.02 (s, 1H), 7.72 - 7.68 (m, 2H), 7.45 (t, J=8.3 Hz, 1H), 7.37 (dd, J=1.7, 8.9 Hz, 1H), 6.98 (d, J=8.3 Hz, 1H), 6.87 (d, J=7.2 Hz, 1H), 4.77 (s, 2H), 4.08 (s, 3H), 1.57 (s, 9H).

STEP C. **Synthesis of Intermediate I-3**, 7-[(1-methylindazol-5-yl)amino]isoindolin-1-one

7-[(1-Methylindazol-5-yl)amino]-1-oxo-isoindoline-2-carboxylate (Intermediate I-2, 150 mg, 0.39 mmol) was dissolved in dichloromethane (2 mL), trifluoroacetic acid (0.5 mL) was added and the mixture was stirred at room temperature for 2 h, then it was concentrated under reduced pressure to give crude 7-[(1-methylindazol-5-yl)amino]isoindolin-1-one (Intermediate I-3, 100 mg, 0.36 mmol, 92% yield) which was used in the next step without further purification.

UPLC-MS (ES^+, Method 2): 1.50 min, m/z 279.2 $[M+H]^+$.

STEP D. **Synthesis of Intermediate I-4**, ethyl 2-[7-[(1-methylindazol-5-yl)amino]-1-oxo-isoindolin-2-yl]acetate

A mixture of 7-[(1-methylindazol-5-yl)amino]isoindolin-1-one (Intermediate I-3, 418 mg, 1.5 mmol), ethyl 2-bromoacetate (276 mg, 1.6 mmol) and Cs_2CO_3 (978 mg, 3.0 mmol) in MeCN (20 mL) was heated to 50 °C and stirred for 16 h. The mixture was concentrated under reduced pressure and purified by normal phase chromatography (12 g column, 10 to 35% EtOAc in petrol) to give ethyl 2-[7-[(1-methylindazol-5-yl)amino]-1-oxo-isoindolin-2-yl]acetate (Intermediate I-4, 428 mg, 78% yield) as an off-white solid.

UPLC-MS (ES^+, Method 1): 4.39 min, m/z 379.2 $[M+H]^+$.

^1H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.62 (s, 1H), 8.02 (s, 1H), 7.71 - 7.69 (m, 2H), 7.42 (t, J=7.8 Hz, 1H), 7.37 (dd, J=1.8, 8.9 Hz, 1H), 7.05 (d, J=8.2 Hz, 1H), 6.93 (d, J=7.2 Hz, 1H), 4.54 (s, 2H), 4.41 (s, 2H), 4.22 (q, J=7.1 Hz, 2H), 4.10 (s, 3H), 1.28 (t, J=7.0 Hz, 3H).

STEP E. **Synthesis of Intermediate I-5**, 2-[7-[(1-methylindazol-5-yl)amino]-1-oxo-isoindolin-2-yl]acetic acid

To a solution of ethyl 2-[7-[(1-methylindazol-5-yl)amino]-1-oxo-isoindolin-2-yl]acetate (428 mg, 1.2 mmol) in THF (8 mL) and MeOH (5 mL) was added a solution of LiOH monohydrate (247 mg, 5.9 mmol) and the mixture was stirred at room temperature for 16 h. The mixture was acidified with 10%

aqueous HCl until pH 6, and the resulting precipitate was collected by filtration, dissolved in MeOH and concentrated under reduced pressure to give 2-[7-[(1-methylindazol-5-yl)amino]-1-oxo-isoindolin-2-yl]acetic acid (Intermediate I-5, 300 mg, 0.89 mmol, 76% yield) as a white solid.

UPLC-MS (ES^+, Method 1): 3.48 min, m/z 337.2 $[M+H]^+$.

^1H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.62 (s, 1H), 8.00 (s, 1H), 7.70 - 7.66 (m, 2H), 7.42 - 7.33 (m, 2H), 7.03 (d, J=9.2 Hz, 1H), 6.90 (d, J=7.3 Hz, 1H), 4.51 (s, 2H), 4.29 (s, 2H), 4.07 (s, 3H).

STEP F. **Synthesis of Intermediate I-6**, ethyl 2-(7-bromo-1-oxo-isoindolin-2-yl)acetate

A solution of 7-bromoisoindolin-1-one (400 mg, 1.9 mmol), ethyl 2-bromoacetate (472 mg, 2.8 mmol) and Cs_2CO_3 (1.8 g, 5.6 mmol) in MeCN (10 mL) was stirred at room temperature for 2 h. The mixture was diluted with water (50 mL), dichloromethane (50 mL) was added and the layers were separated. The aqueous layer was extracted three times with dichloromethane, the organic layers were combined, dried over Na_2SO_4 and concentrated under reduced pressure to give ethyl 2-(7-bromo-1-oxo-isoindolin-2-yl)acetate (Intermediate I-6, 465 mg, 1.6 mmol, 83% yield) as an off-white solid.

UPLC-MS (ES^+, Method 2): 0.95 min, m/z 285.5 $[M+H]^+$ - Me ester (sample run in MeOH, trans-esterified)

^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.62 (d, J=6.0 Hz, 1H), 7.43 - 7.36 (m, 2H), 4.50 (s, 2H), 4.40 (s, 2H), 4.24 (q, J=6.9 Hz, 2H), 1.31 (t, J=7.0 Hz, 3H).

STEP G. **Synthesis of Intermediate I-7**, 2-(7-bromo-1-oxo-isoindolin-2-yl)acetic acid

To a solution of ethyl 2-(7-bromo-1-oxo-isoindolin-2-yl)acetate (Inermediate I-6, 465 mg, 1.6 mmol) in THF (2 mL) and MeOH (2 mL) was added a solution of LiOH monohydrate (197 mg, 4.7 mmol) in water (2mL) and the solution was stirred at room temperature for 2 h. The mixture was acidified with 1 M HCl until pH 5-6, the resulting precipitate was collected by filtration, dissolved in MeOH and concentrated under reduced pressure to give crude 2-(7-bromo-1-oxo-isoindolin-2-yl)acetic acid (Intermediate I-7, 421 mg, quantitative yield) which was used in the next step without further purification.

UPLC-MS (ES^+, Method 2): 0.72 min, m/z 269.7/271.5 $[M+H]^+$.

STEP H. **Synthesis of Intermediate I-8**, 2-(7-bromo-1-oxo-isoindolin-2-yl)-N-(2,2,2-trifluoroethyl) acetamide

A mixture of 2-(7-bromo-1-oxo-isoindolin-2-yl)acetic acid (420 mg, 1.6 mmol), trifluoroethylamine (186 mg, 1.9 mmol), EDCI (292 mg, 1.9 mmol), HOBT (24 mg, 1.9 mmol) and DIPEA (0 mg, 4.7 mmol) in DMF (5 mL) was stirred at room temperature overnight. The mixture was diluted with water (50 mL), dichloromethane (100 mL) was added and the layers were separated. The aqueous layer was extracted with dichloromethane (2 x 100 mL), the organic layers were combined, dried over Na_2SO_4 and concentrated under reduced pressure to give 2-(7-bromo-1-oxo-isoindolin-2-yl)-N-(2,2,2-trifluoroethyl) acetamide (Intermediate I-8, 400 mg, 73% yield) as an off-white solid.

UPLC-MS (ES^+, Method 2): 1.30 min, m/z 350.9/352.9 $[M+H]^+$.

^1H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.81 (t, J=6.2 Hz, 1H), 7.71 - 7.61 (m, 2H), 7.58 - 7.52 (m, 1H), 4.50 (s, 2H), 4.28 (s, 2H), 4.00 - 3.90 (m, 2H).

STEP I. **Synthesis of Intermediate I-13**, *tert*-butyl 4-bromo-1,1-dimethyl-3-oxo-isoindoline-2-carboxylate

A solution of *tert*-butyl 7-bromo-1-oxo-isoindoline-2-carboxylate (Intermediate I-1, 500 mg, 1.6 mmol) in THF (5 mL) was cooled to 0 °C and NaHMDS (2 M in THF, 2.4 mL, 4.8 mmol) was added. The mixture was stirred at 0 °C for 30 min, then methyl iodide (0.3 mL, 4.8 mmol) was added dropwise. The mixture was slowly warmed to room temperature, concentrated under reduced pressure and purified by normal phase chromatography (25 g column, 10% EtOAc in petrol) to give *tert*-butyl 4-bromo-1,1-dimethyl-3-oxo-isoindoline-2-carboxylate (Intermediate I-13, 380 mg, 70% yield) as a clear oil.

UPLC-MS (ES^+, Method 2): 2.10 min, m/z 284.0/286.0 $[M-tBu+H]^+$.

STEP J. **Synthesis of Intermediate I-18**, *tert*-butyl 4-bromo-1-methyl-3-oxo-isoindoline-2-carboxylate

A solution of *tert*-butyl 7-bromo-1-oxo-isoindoline-2-carboxylate (Intermediate I-1, 500 mg, 1.6 mmol) in THF (10 mL) at -60 °C under N_2 was stirred for 5 min, then KHMDS (1.6 mL, 1.6 mmol) was added dropwise and the mixture was stirred for 1 h. MeI (159 mg, 1.12 mmol) in THF (10 mL) was added dropwise and the mixture was stirred for 2 h. The mixture was warmed to room temperature, concentrated *in vacuo* and purified by prep-TLC to give *tert*-butyl 4-bromo-1-methyl-3-oxo-isoindoline-2-carboxylate (Intermediate I-18, 229 mg, 0.7 mmol, 43% yield) as a clear oil.

UPLC-MS (ES^+, Method 1): 4.25 min, m/z 270.0/272.0 $[M-tBu+H]^+$.

^1H NMR (400 MHz, DMSO-d_6) δ (ppm) 7.83 - 7.69 (m, 3H), 5.14 (q, J=6.4 Hz, 1H), 1.66 - 1.62 (m, 12H).

STEP K. **Synthesis of Intermediate I-19**, ethyl 2-[7-[(3-methyl-1-tetrahydropyran-2-yl-indazol-6-yl)amino]-1-oxo-isoindolin-2-yl]acetate

A degassed solution of 3-methyl-1-tetrahydropyran-2-yl-indazol-6-amine (6 g, 26 mmol), Cs_2CO_3 (13 g, 39 mmol), Xantphos (3 g, 5.2 mmol), $Pd_2(dba)_3$ (4.8 g, 5.2 mmol) and ethyl 2-(7-bromo-1-oxo-isoindolin-2-yl)acetate (7.7 g, 26 mmol) in 1,4-dioxane (50 mL) was stirred at 100 °C for 16 h. The mixture was concentrated *in vacuo* and purified by normal phase chromatography (hexane:EtOAc=3:1) to give ethyl 2-[7-[(3-methyl-1-tetrahydropyran-2-yl-indazol-6-yl)amino]-1-oxo-isoindolin-2-yl]acetate (Intermediate I-19, 6.2 g, 14 mmol, 53% yield) as an off-white solid.

UPLC-MS (ES^+, Method 1): 4.32 min, m/z 449.2 $[M+H]^+$.

^1H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.90 (s, 1H), 7.67 (d, J=8.4 Hz, 1H), 7.54 - 7.43 (m, 2H), 7.32 (d, J=8.2 Hz, 1H), 7.09 (d, J=8.2 Hz, 1H), 6.99 (d, J=7.1 Hz, 1H), 5.79 - 5.70 (m, 1H), 4.52 (s, 2H), 4.39 (s, 2H), 4.19 (q, J=7.0 Hz, 2H), 3.93 - 3.83 (m, 1H), 3.78 - 3.69 (m, 1H), 2.47 (s, 3H), 2.44 - 2.33

(m, 1H), 2.08 - 1.99 (m, 2H), 1.96 - 1.89 (m, 1H), 1.81 - 1.67 (m, 1H), 1.62 - 1.52 (m, 2H), 1.25 (t, J=7.0 Hz, 3H).

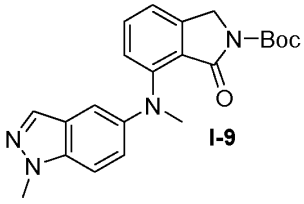
STEP L. **Synthesis of Intermediate I-20**, ethyl 2-[7-[(3-methyl-1H-indazol-6-yl)amino]-1-oxo-isoindolin-2-yl]acetate

A solution of ethyl 2-[7-[(3-methyl-1-tetrahydropyran-2-yl-indazol-6-yl)amino]-1-oxo-isoindolin-2-yl]acetate (Intermediate I-19, 6 g , 13 mmol) in trifluoroacetic acid (30 mL) was stirred under microwave irradiation at 80 °C for 2 h. The mixture was concentrated in vacuo and purified by reverse phase chromatography (MeCN:water=60:40) to give ethyl 2-[7-[(3-methyl-1H-indazol-6-yl)amino]-1-oxo-isoindolin-2-yl]acetate (Intermediate I-20, 1.8 g, 4.9 mmol, 37% yield) as an off-white solid.

UPLC-MS (ES^+, Method 1): 3.65 min, m/z 365.1 $[M+H]^+$.

^1H NMR (400 MHz, DMSO-d_6) δ (ppm) 12.41 (s, 1H), 8.81 (s, 1H), 7.66 (d, J=8.9 Hz, 1H), 7.47 (t, J=7.8 Hz, 1H), 7.33 (s, 1H), 7.29 (d, J=8.4 Hz, 1H), 7.00 - 6.96 (m, 2H), 4.52 (s, 2H), 4.38 (s, 2H), 4.18 (q, J=7.1 Hz, 2H), 2.47 (s, 3H), 1.25 (t, J=7.1 Hz, 3H).

Table 3 describes intermediates which were synthesised in an analogous fashion to I-2, *tert*-butyl 7-[(1-methylindazol-5-yl)amino]-1-oxo-isoindoline-2-carboxylate (Step B, Scheme 1), replacing *tert*-butyl 7-bromo-1-oxo-isoindoline-2-carboxylate (Intermediate I-1) or 1-methyl-1H-indazol-5-amine with the appropriate building block.

Building Block	Structure/Name	LCMS	^1H NMR (400 MHz, DMSO-d_6) δ (ppm)
Intermediate I-1 and N,1-dimethylindazol-5-amine	 **I-9** *tert*-Butyl 7-[methyl-(1-methylindazol-5-yl)amino]-1-oxo-isoindoline-2-carboxylate **Intermediate I-9**	4.18 min, m/z, 393.3 $[M+H]^+$ (Method 1)	7.89 (s, 1H), 7.58 (t, J=7.8 Hz, 1H), 7.46 (d, J=9.0 Hz, 1H), 7.28 (d, J=7.0 Hz, 1H), 7.20 (d, J=1.8 Hz, 1H), 7.05 (d, J=8.2 Hz, 1H), 6.98 (dd, J=2.4, 8.9 Hz, 1H), 4.76 (s, 2H), 4.01 (s, 3H), 1.51 (s, 9H). One CH_3 signal under solvent peak.

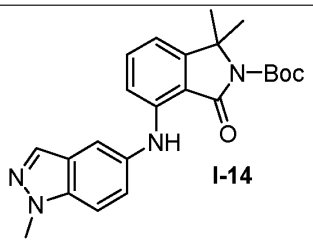
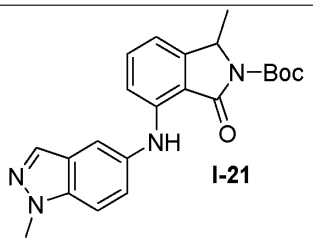
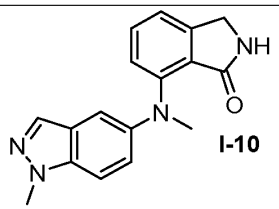
Intermediate I-13 and 1-methyl-1H-indazol-5-amine	 **I-14** *tert*-butyl 1,1-dimethyl-4-[(1-methylindazol-5-yl)amino]-3-oxo-isoindoline-2-carboxylate **Intermediate I-14**	2.39 min, m/z, 307.1 $[M\text{-}Boc+H]^+$ (Method 2)	8.77 (s, 1H), 8.01 (s, 1H), 7.69 (d, J=9.1 Hz, 2H), 7.46 (t, J=7.9 Hz, 1H), 7.37 (dd, J=1.6, 9.0 Hz, 1H), 6.96 – 6.89 (m, 2H), 4.07 (s, 3H), 1.69 (s, 6H), 1.57 (s, 9H).
Intermediate I-18 and 1-methyl-1H-indazol-5-amine	 **I-21** tert-butyl 1-methyl-4-[(1-methylindazol-5-yl)amino]-3-oxo-isoindoline-2-carboxylate **Intermediate I-21**	4.52 min, m/z, 293.2 $[M\text{-}Boc+H]^+$ (Method 1)	

Table 3

Table 4 describes intermediates which were synthesised in an analogous fashion to I-3, 7-[(1-methylindazol-5-yl)amino]isoindolin-1-one (Step C, Scheme 1), replacing 7-[(1-methylindazol-5-yl)amino]-1-oxo-isoindoline-2-carboxylate with the appropriate building block. The intermediates were carried to the next step without further purification.

Building Block	Structure/Name	LCMS
tert-Butyl 7-[methyl-(1-methylindazol-5-yl)amino]-1-oxo-isoindoline-2-carboxylate **Intermediate I-9**	 **I-10** 7-[methyl-(1-methylindazol-5-yl)amino]isoindolin-1-one **Intermediate I-10**	3.28 min, m/z, 293.2 $[M+H]^+$ (Method 1)

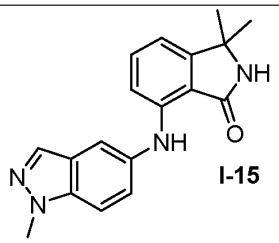
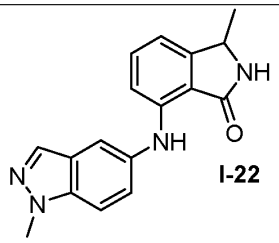
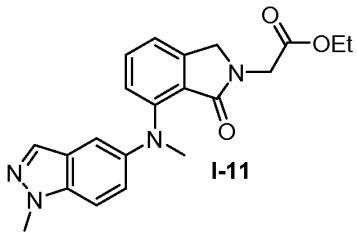
tert-butyl 1,1-dimethyl-4-[(1-methylindazol-5-yl)amino]-3-oxo-isoindoline-2-carboxylate **Intermediate I-14**	 **I-15** 3,3-dimethyl-7-[(1-methylindazol-5-yl)amino]isoindolin-1-one **Intermediate I-15**	1.18 min, m/z, 307.1 $[M+H]^+$ (Method 2)
tert-butyl 1-methyl-4-[(1-methylindazol-5-yl)amino]-3-oxo-isoindoline-2-carboxylate **Intermediate I-21**	 **I-22** Intermediate I-22	Not characterised (used directly in subsequent steps see I-23 for characterisation)

Table 4

Table 5 describes intermediates which were synthesised in an analogous fashion to I-4, ethyl 2-[7-[(1-methylindazol-5-yl)amino]-1-oxo-isoindolin-2-yl]acetate (Step D, Scheme 1), replacing 7-[(1-methylindazol-5-yl)amino]isoindolin-1-one with the appropriate building block.

Building Block	Structure/Name	LCMS	^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm)
7-[methyl-(1-methylindazol-5-yl)amino]isoindolin-1-one **Intermediate I-10**	 **I-11** Ethyl 2-[7-[methyl-(1-methylindazol-5-yl)amino]-1-oxo-isoindolin-2-yl]acetate **Intermediate I-11**	3.78 min, m/z, 379.2 $[M+H]^+$ (Method 1)	7.88 (s, 1H), 7.51 (t, J=7.7 Hz, 1H), 7.44 (d, J=9.2 Hz, 1H), 7.30 (d, J=7.4 Hz, 1H), 7.17 (d, J=1.8 Hz, 1H), 7.04 (d, J=8.2 Hz, 1H), 6.96 (dd, J=2.1, 9.1 Hz, 1H), 4.51 (s, 2H), 4.31 (s, 2H), 4.22 (s, 3H), 4.15 (q, J=7.3

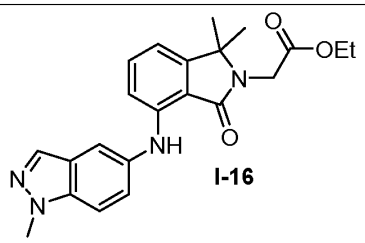
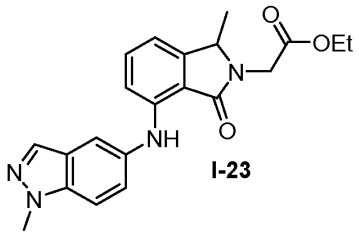
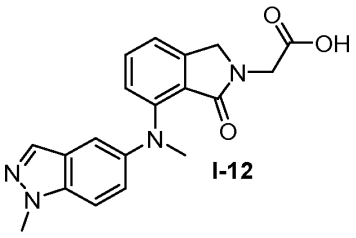
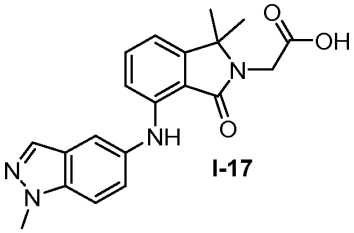
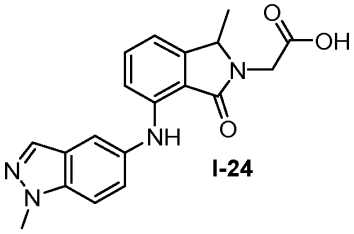
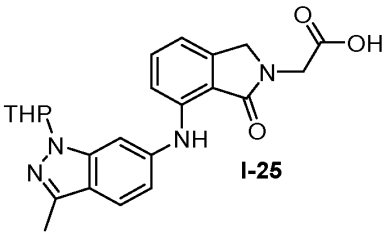
			Hz, 2H), 4.00 (s, 3H), 1.22 (t, J=7.1 Hz, 3H).
3,3-dimethyl-7-[(1-methylindazol-5-yl)amino]isoindolin-1-one **Intermediate I-15**	 **I-16** Ethyl 2-[1,1-dimethyl-4-[(1-methylindazol-5-yl)amino]-3-oxo-isoindolin-2-yl]acetate **Intermediate I-16**	4.15 min, m/z, 393.3 $[M+H]^+$ (Method 1)	N/D
3-methyl-7-[(1-methylindazol-5-yl)amino]isoindolin-1-one **Intermediate I-22**	 **I-23** Ethyl 2-[1-methyl-4-[(1-methylindazol-5-yl)amino]-3-oxo-isoindolin-2-yl]acetate **Intermediate I-23**	4.08 min, m/z, 379.2 $[M+H]^+$ (Method 1)	N/D

Table 5

Table 6 describes intermediates which were synthesised in an analogous fashion to I-5, 2-[7-[(1-methylindazol-5-yl)amino]-1-oxo-isoindolin-2-yl]acetic acid (Step E, Scheme 1), replacing ethyl 2-[7-[(1-methylindazol-5-yl)amino]-1-oxo-isoindolin-2-yl]acetate with the appropriate building block.

Building Block	Structure/Name	LCMS	^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm)
Ethyl 2-[7-[methyl-(1-methylindazol-5-yl)amino]-1-oxo-isoindolin-2-yl]acetate	 **I-12**	3.32 min, m/z, 351.2 $[M+H]^+$ (Method 1)	N/D

Intermediate I-11	2-[7-[methyl-(1-methylindazol-5-yl)amino]-1-oxo-isoindolin-2-yl]acetic acid **Intermediate I-12**		
Ethyl 2-[1,1-dimethyl-4-[(1-methylindazol-5-yl)amino]-3-oxo-isoindolin-2-yl]acetate **Intermediate I-16**	 **I-17** 2-[1,1-dimethyl-4-[(1-methylindazol-5-yl)amino]-3-oxo-isoindolin-2-yl]acetic acid **Intermediate I-17**	3.62 min, m/z, 365.2 $[M+H]^+$ (Method 1)	7.99 (s, 1H), 7.69 – 7.65 (m, 2H), 7.38 (t, J=7.9 Hz, 1H), 7.33 (dd, J=1.9, 9.0 Hz, 1H), 6.99 (d, J=8.2 Hz, 1H), 6.92 (d, J=7.2 Hz, 1H), 4.16 (s, 2H), 4.06 (s, 3H), 1.44 (s, 6H). OH and NH not observed.
2-[1-methyl-4-[(1-methylindazol-5-yl)amino]-3-oxo-isoindolin-2-yl]acetic acid **Intermediate I-23**	 **I-24**	N/D used directly in next step (see example 15 for characterisation)	N/D
ethyl 2-[7-[(3-methyl-1-tetrahydropyran-2-yl-indazol-6-yl)amino]-1-oxo-isoindolin-2-yl]acetate **Intermediate I-19**	 **I-25** 2-[7-[(3-methyl-1-tetrahydropyran-2-yl-indazol-6-yl)amino]-1-oxo-isoindolin-2-yl]acetic acid **Intermediate I-25**	N/D used directly in next step (see example 25 for characterisation)	N/D

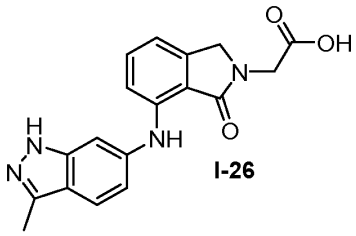
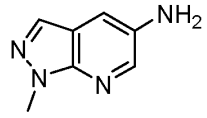
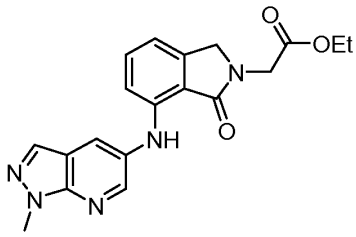
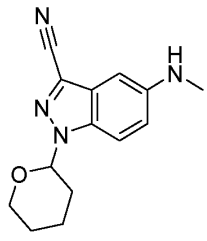
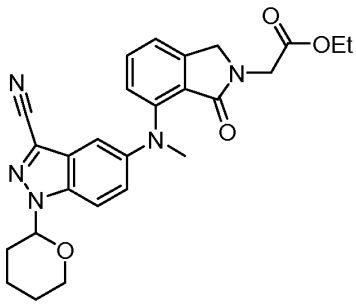
ethyl 2-[7-[(3-methyl-1H-indazol-6-yl)amino]-1-oxo-isoindolin-2-yl]acetate **Intermediate I-20**	 **I-26** 2-[7-[(3-methyl-1H-indazol-6-yl)amino]-1-oxo-isoindolin-2-yl]acetic acid **Intermediate I-26**	3.35 min, m/z, 337.1 $[M+H]^+$ (Method 1)	7.71 (d, J=8.6 Hz, 1H), 7.48 (t, J=7.8 Hz, 1H), 7.37 - 7.29 (m, 2H), 7.04 - 6.99 (m, 2H), 4.52 (s, 2H), 4.29 (s, 2H), 2.53 (s, 3H). 2 x NH and CO2H not observed.

Table 6

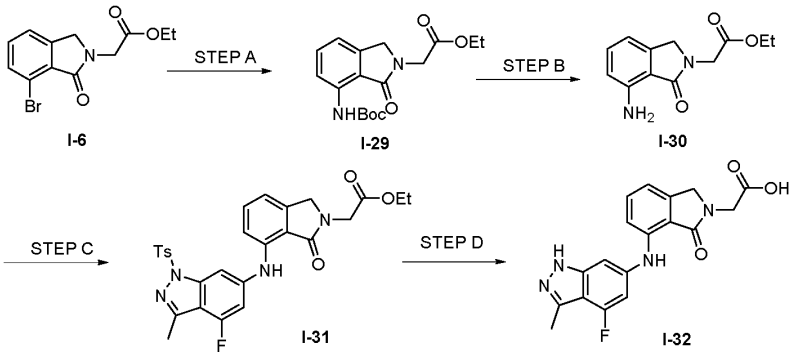
Table 7 describes intermediates prepared from intermediate I-6, ethyl 2-(7-bromo-1-oxo-isoindolin-2-yl)acetate, by analogy with intermediate I-19, ethyl 2-[7-[(3-methyl-1-tetrahydropyran-2-yl-indazol-6-yl)amino]-1-oxo-isoindolin-2-yl]acetate (step K, scheme 1), replacing 3-methyl-1-tetrahydropyran-2-yl-indazol-6-amine with the appropriate amine building block.

Building Block	Structure/Name	LCMS	^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm)
 1-methylpyrazolo[3,4-b]pyridin-5-amine	 ethyl 2-[7-[(1-methylpyrazolo[3,4-b]pyridin-5-yl)amino]-1-oxo-isoindolin-2-yl]acetate Intermediate **I-27**	1.30 min, m/z, 366.0 $[M+H]^+$ (Method 2)	8.59 (s, 1H), 8.52 (s, 1H), 8.17 (s, 1H), 8.08 (s, 1H), 7.38 - 7.34 (m, 1H), 6.92 (d, 2H), 4.50 (s, 2H), 4.36 (s, 2H), 4.17 (q, J=7.0 Hz, 2H), 1.25 (t, J=7.0 Hz, 3H).
 5-(methylamino)-1-tetrahydropyran-2-		4.31 min, m/z, 474.2 $[M+H]^+$ (Method 1)	

yl-indazole-3-carbonitrile	ethyl 2-[7-[(3-cyano-1-tetrahydropyran-2-yl-indazol-5-yl)-methyl-amino]-1-oxo-isoindolin-2-yl]acetate Intermediate **I-41**		

Table 7

Further intermediates of use in the preparation of examples were derived from intermediate I-6 according to scheme 2 below.



Scheme 2

STEP A. Intermediate I-29, ethyl 2-[7-(tert-butoxycarbonylamino)-1-oxo-isoindolin-2-yl]acetate. A mixture of ethyl 2-(7-bromo-1-oxoisoindolin-2-yl)acetate (4 g, 13.417 mol), tert-butyl carbamate (3.14 g , 26.8 mol), $Pd_2(dba)_3$ (1.3 g, 1.34 mol, 0.1 eq), Xantphos (775 mg, 1.34 mol) and Cs_2CO_3 (8.72 g, 26.8 mol) in 1,4-dioxane (30 mL) was stirred at 100°C under N_2 overnight. The mixture was concentrated under vacuum and purified by silica gel column chromatography (pet. ether/ EtOAc, 30/1 to pet. ether / EtOAc, 20/1, v/v) to give ethyl 2-[7-(tert-butoxycarbonylamino)-1-oxo-isoindolin-2-yl]acetate (I-29) (2.73 g, 60.8 % yield) as a colourless oil.

UPLC-MS (ES^+, Method 1): 4.38 min, m/z 334.4 $[M+H]^+$.

^1H NMR (400 MHz, DMSO-d_6) δ (ppm) 9.42 (s, 1H), 8.02-8.00 (m, 1H), 7.57-7.53 (m, 1H), 7.21-7.19 (m, 1H), 4.51 (s, 2H), 4.35, (s, 2H), 4.15 (q, *J* = 7.3 Hz, 2H), 1.49 (s, 9H), 1.21 (t, *J* = 7.3 Hz, 3H).

STEP B. Intermediate I-30, ethyl 2-(7-amino-1-oxo-isoindolin-2-yl)acetate. A mixture of ethyl 2-[7-(tert-butoxycarbonylamino)-1-oxo-isoindolin-2-yl]acetate (I-29) (500 mg, 1.5 mmol) in DCM (5 mL) and 4 M HCl in dioxane (3 mL) was stirred at room temperature for 2 h.The reaction was concentrated to give ethyl 2-(7-amino-1-oxo-isoindolin-2-yl)acetate (I-30) (530 mg, 90 % yield) as a crude solid used without further purification.

UPLC-MS (ES^+, Method 2): 1.00 min, m/z 235.1 $[M+H]^+$.

STEP C. Intermediate I-31, ethyl 2-[7-[[4-fluoro-3-methyl-1-(p-tolylsulfonyl)indazol-6-yl]amino]-1-oxo-isoindolin-2-yl]acetate. A solution of 6-bromo-4-fluoro-3-methyl-1-(p-tolylsulfonyl)indazole (410 mg,

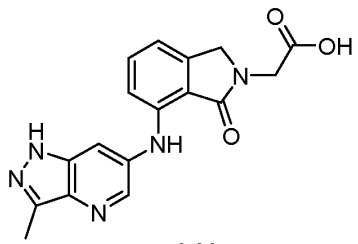
1.07 mmol), ethyl 2-(7-amino-1-oxo-isoindolin-2-yl)acetate (I-30) (276 mg, 1.181 mmol), Cs_2CO_3 (700 mg, 2.14 mmol), Xantphos(124. mg, 0.22 mmol), and $Pd_2(dba)_3$ (98 mg, 0.11 mmol), in 1,4-dioxane (5.0 mL) was stirred at 100 °C under N_2 overnight. The mixture was diluted with EtOAc (10 mL) and washed with H_2O (10 mL x 3). The organic layers were washed with EtOAc (20 mL × 3), combined, dried over anhydrous Na_2SO_4 and concentrated to give a yellow solid analysed as ethyl 2-[7-[[4-fluoro-3-methyl-1-(p-tolylsulfonyl)indazol-6-yl]amino]-1-oxo-isoindolin-2-yl]acetate (I-31) (400 mg, 69 % yield) which was used without further purification.

UPLC-MS (ES^+, Method 1): 4.62 min, m/z 537.0 $[M+H]^+$.

STEP D. Intermediate I-32, 2-[7-[(4-fluoro-3-methyl-1H-indazol-6-yl)amino]-1-oxo-isoindolin-2-yl]acetic acid. A mixture of ethyl 2-[7-[[4-fluoro-3-methyl-1-(p-tolylsulfonyl)indazol-6-yl]amino]-1-oxo-isoindolin-2-yl]acetate (I-31) (400 mg, 0.75 mmol), and $LiOH.H_2O$ (93.8 mg, 2.23 mmol) in THF (3 mL), MeOH (3 mL) and H_2O (2 mL) was stirred at 25°C overnight. The mixture was diluted with H_2O (10 mL) and 10% HCl in water (25 mL) was added to reach a pH of 2 - 3. The mixture was further diluted with water (20 mL x 3) and extracted with DCM (30 mL x 3). After drying over Na_2SO_4, the mixture was filtered and concentrated *in vacuo* to obtain 2-[7-[(4-fluoro-3-methyl-1H-indazol-6-yl)amino]-1-oxo-isoindolin-2-yl]acetic acid (I-32) (200 mg, 76 % yield) as a white solid.

UPLC-MS (ES^+, Method 1): 3.52 min, m/z 355.0 $[M+H]^+$.

Intermediate I-33, 2-[7-[(3-methyl-1H-pyrazolo[4,3-b]pyridin-6-yl)amino]-1-oxo-isoindolin-2-yl]acetic acid



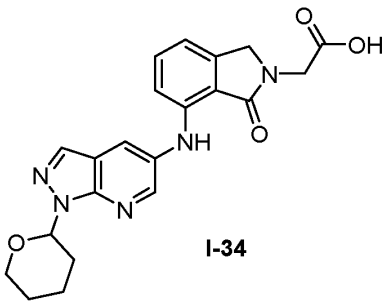
I-33

Intermediated I-33 was prepared following an analogous synthetic route to that used for I-32 (scheme 2). In step C, 6-bromo-4-fluoro-3-methyl-1-(p-tolylsulfonyl)indazole was replaced with 6-bromo-3-methyl-1-(p-tolylsulfonyl)pyrazolo[4,3-b]pyridine.

UPLC-MS (ES^+, Method 1): 2.88 min, m/z 338.1 $[M+H]^+$.

^1H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.49 (s, 1H), 7.81 – 7.78 (m, 2H), 7.48 – 7.09 (m, 6H), 4.51 (s, 2H), 4.23 (s, 2H), 2.30 (s, 3H).

Intermediate I-34, 2-[1-oxo-7-[(1-tetrahydropyran-2-ylpyrazolo[3,4-b]pyridin-5-yl)amino]isoindolin-2-yl]acetic acid.



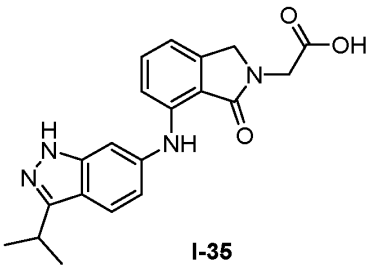
I-34

Intermediated I-34 was prepared following an analogous synthetic route to that used for I-32 (scheme 2). In step C, 6-bromo-4-fluoro-3-methyl-1-(p-tolylsulfonyl)indazole was replaced with 1-tetrahydropyran-2-ylpyrazolo[3,4-b]pyridin-5-amine.

UPLC-MS (ES^+, Method 2): 1.22 min, m/z 408.4 $[M+H]^+$.

^1H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.67 (s, 1H), 8.54 (s, 1H), 8.20 (s, 1H), 8.15 (s, 1H), 7.39 – 7.34 (m, 1H), 6.96 - 6.91 (m, 2H), 6.02 – 5.99 (m, 1H), 4.49 (s, 2H), 4.24 (s, 2H), 3.97 – 3.94 (m, 1H), 3.73 – 3.71 (m, 1H), 2.25 – 1.57 (m, 6H).

Intermediate I-35. 2-[7-[(3-isopropyl-1H-indazol-6-yl)amino]-1-oxo-isoindolin-2-yl]acetic acid.

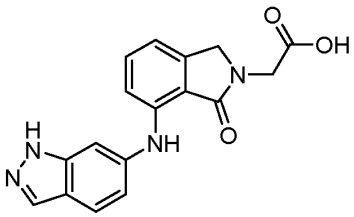


I-35

Intermediate I-35 was prepared by analogy with Intermediate I-32 (scheme 2). In step C, 6-bromo-4-fluoro-3-methyl-1-(p-tolylsulfonyl)indazole was replaced with 6-bromo-3-isopropyl-1-(p-tolylsulfonyl)indazole.

UPLC-MS (ES^+, Method 2): 1.27 min, m/z, 364.8 $[M+H]^+$.

Intermediate I-36. 2-[7-(1H-indazol-6-ylamino)-1-oxo-isoindolin-2-yl]acetic acid.

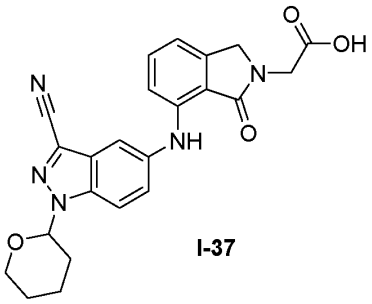


I-36

Intermediate I-36 was prepared by analogy with Intermediate I-32 (scheme 2). In step C, 6-bromo-4-fluoro-3-methyl-1-(p-tolylsulfonyl)indazole was replaced with 6-bromo-1-tetrahydropyran-2-yl-indazole.

UPLC-MS (ES^+, Method 1): 3.23 min, m/z, 323.1 $[M+H]^+$.

Intermediate I-37. 2-[7-[(3-cyano-1-tetrahydropyran-2-yl-indazol-5-yl)amino]-1-oxo-isoindolin-2-yl]acetic acid.

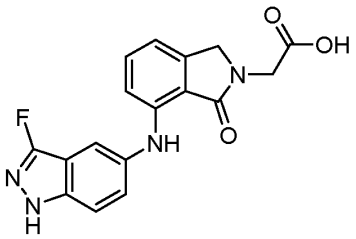


I-37

Intermediate I-37 was prepared by analogy with Intermediate I-32 (scheme 2). In step C, 6-bromo-4-fluoro-3-methyl-1-(p-tolylsulfonyl)indazole was replaced with 5-bromo-1-tetrahydropyran-2-yl-indazole-3-carbonitrile.

UPLC-MS (ES^+, Method 1): 4.11 min, m/z, 432.2 $[M+H]^+$.

Intermediate I-38. 2-[7-[(3-fluoro-1H-indazol-5-yl)amino]-1-oxo-isoindolin-2-yl]acetic acid.

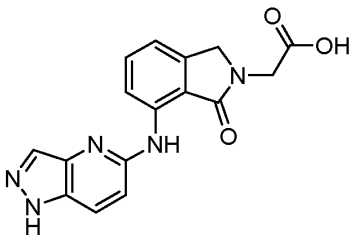


I-38

Intermediate I-38 was prepared by analogy with Intermediate I-32 (scheme 2). In step C, 6-bromo-4-fluoro-3-methyl-1-(p-tolylsulfonyl)indazole was replaced with 5-bromo-3-fluoro-1-(p-tolylsulfonyl)indazole.

UPLC-MS (ES^+, Method 1): 3.45 min, m/z, 351.1 $[M+H]^+$.

Intermediate I-39. 2-[1-oxo-7-(1H-pyrazolo[4,3-b]pyridin-5-ylamino)isoindolin-2-yl]acetic acid.

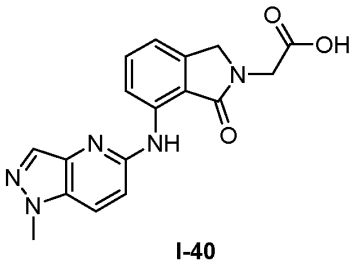


I-39

Intermediate I-39 was prepared by analogy with Intermediate I-32 (scheme 2). In step C, 6-bromo-4-fluoro-3-methyl-1-(p-tolylsulfonyl)indazole was replaced with 5-bromo-1-tetrahydropyran-2-yl-pyrazolo[4,3-b]pyridine.

UPLC-MS (ES^+, Method 2): 0.71 min, m/z, 323.6 $[M+H]^+$.

Intermediate I-40. 2-[7-[(1-methylpyrazolo[4,3-b]pyridin-5-yl)amino]-1-oxo-isoindolin-2-yl]acetic acid.



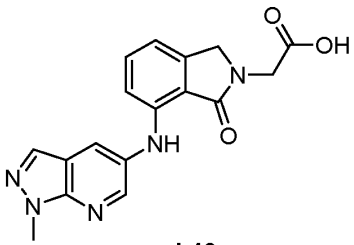
I-40

Intermediate I-40 was prepared by analogy with Intermediate I-32 (scheme 2). In step C, 6-bromo-4-fluoro-3-methyl-1-(p-tolylsulfonyl)indazole was replaced with 5-bromo-1-methyl-pyrazolo[4,3-b]pyridine.

UPLC-MS (ES^+, Method 1): 3.58 min, m/z 338.2 $[M+H]^+$.

^1H NMR (400 MHz, DMSO-d_6) δ (ppm) 9.82 (s, 1H), 8.78 (d, *J* = 8.3 Hz, 1H), 8.15 – 7.96 (m, 2H), 7.63 – 7.51 (m, 1H), 7.05 (dd, *J* = 26.4, 8.2 Hz, 2H), 4.52 (s, 2H), 4.41 (s, 2H), 4.04 (s, 3H), 3.70 (s, 3H).

Intermediate I-42. 2-[7-[(1-methylpyrazolo[3,4-b]pyridin-5-yl)amino]-1-oxo-isoindolin-2-yl]acetic acid

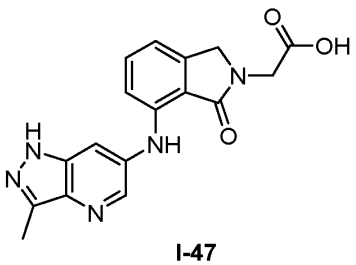


I-42

Intermediate I-42 was prepared by analogy with Intermediate I-32 (scheme 2). In step C, 6-bromo-4-fluoro-3-methyl-1-(p-tolylsulfonyl)indazole was replaced with 5-bromo-1N-methylpyrazolo[3,4-b]pyridine.

UPLC-MS (ES+, Method 1): 3.51 min, m/z 338.2 $[M+H]^+$.

Intermediate I-47. 2-[7-[(3-methyl-1H-pyrazolo[4,3-b]pyridin-6-yl)amino]-1-oxo-isoindolin-2-yl]acetic acid.

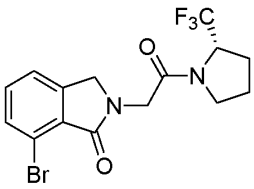


I-47

Intermediate I-47 was prepared by analogy with Intermediate I-32 (scheme 2). In step C, 6-bromo-4-fluoro-3-methyl-1-(p-tolylsulfonyl)indazole was replaced with 6-bromo-3-methyl-1-(p-tolylsulfonyl)pyrazolo[4,3-b]pyridine.

UPLC-MS (ES+, Method 1): 2.91 min, m/z 338.2 $[M+H]^+$.

Intermediate I-43. 7-bromo-2-[2-oxo-2-[(2S)-(trifluoromethyl)pyrrolidin-1-yl]ethyl]isoindolin-1-one.

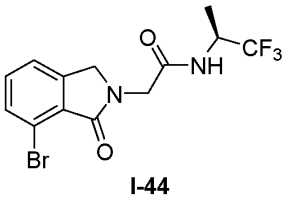


I-43

Intermediate I-43 was prepared by analogy with intermediate I-8 (scheme 1), replacing trifluoroethylamine in step H with (2S)–(trifluoromethyl)pyrrolidine.

UPLC-MS (ES+, Method 1): 3.72 min, m/z, 391.0/393.0 $[M+H]^+$.

Intermediate I-44. 2-(7-bromo-1-oxo-isoindolin-2-yl)-N-[(1S)-2,2,2-trifluoro-1-methyl-ethyl]acetamide

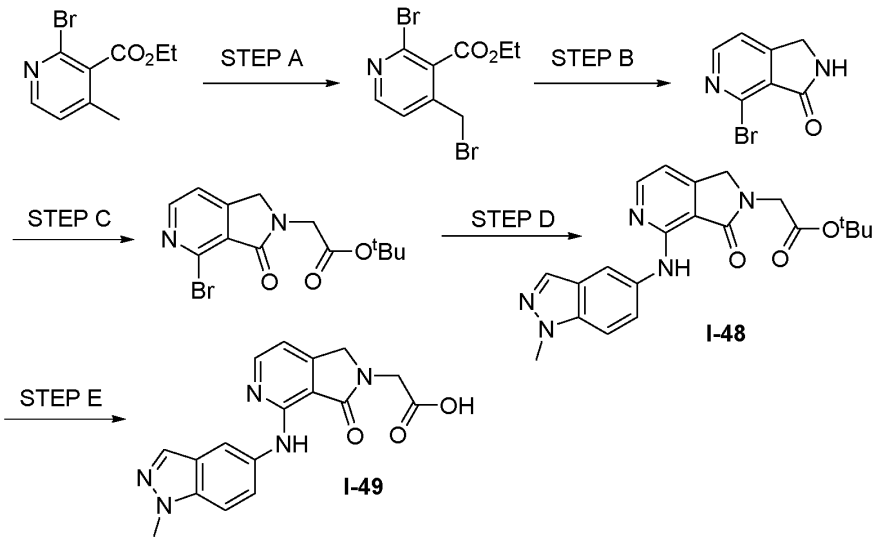


I-44

Intermediate I-44 was prepared by analogy with intermediate I-8 (scheme 1), replacing trifluoroethylamine in step H with (2S)-amino-1,1,1-trifluoropropane hydrochloride.

UPLC-MS (ES+, Method 1): 3.52 min, m/z, 365.1/367.1 $[M+H]^+$.

Further examples could be prepared from intermediates I-48 and I-49, the synthesis of which is described in scheme 3 and the methods below.



Scheme 3

STEP A. Ethyl 2-bromo-4-(bromomethyl)pyridine-3-carboxylate. A mixture of ethyl 2-bromo-4-methyl-pyridine-3-carboxylate (2 g, 8.19 mmol), NBS (2.92 g, 16.38 mmol) , benzoyl peroxide (396mg, 1.63 mmol) in CCl_4 (20 mL) was stirred at 90°C under N_2 overnight. The mixture was diluted with water (100 mL) and extracted with EtOAc (100 mL x 3) and was dried over Na_2CO_3. The mixture was purified by silica gel chromatography (pet. ether/EtOAc, 100/1 to pet. ether/EtOAc, 50/1) to afford ethyl 2-bromo-4-(bromomethyl)pyridine-3-carboxylate (1.14g, 21% yield).

UPLC-MS (ES^+, Method 1): 3.98 min, m/z 323.9 $[M+H]^+$.

STEP B. 4-Bromo-1,2-dihydropyrrolo[3,4-c]pyridin-3-one. A mixture of ethyl 2-bromo-4-(bromomethyl)pyridine-3-carboxylate (1.14g, 1.76 mmol and concentrated ammonium hydroxide (6 mL) in THF (10 mL) was stirred at 25°C under N_2. The mixture was partitioned between DCM and water and the combined organics dried over Na2SO4 and concentrated before purifying by silica gel chromatography (pet. ether/EtOAc, 5:1 to pet. ether/EtOAc, 1:2) to give 4-bromo-1,2-dihydropyrrolo[3,4-c]pyridin-3-one (320 mg, 43% yield) as a yellow solid.

UPLC-MS (ES^+, Method 1): 1.34 min, m/z 213.1 $[M+H]^+$.

STEP C. tert-Butyl 2-(4-bromo-3-oxo-1H-pyrrolo[3,4-c]pyridin-2-yl)acetate. A mixture of 4-bromo-1,2-dihydropyrrolo[3,4-c]pyridin-3-one (200 mg, 0.94 mmol) Cs_2CO_3 (610 mg, 1.88 mmol) tert-butyl bromoacetate (274 mg, 1.41 mmol) in THF (5mL) was stirred at 50°C for 2 hours. The mixture was diluted with water (20 mL) and extracted with EtOAc (15 mL x 3) and was dried by Na_2CO_3. The mixture was purified by silica gel chromatography (pet. ether/EtOAc, 1/2) to afford tert-butyl 2-(4-bromo-3-oxo-1H-pyrrolo[3,4-c]pyridin-2-yl)acetate (130 mg, 42% yield) as a brown solid.

UPLC-MS (ES^+, Method 1): 3.48 min, m/z 329.1 $[M+H]^+$.

STEP D. tert-Butyl 2-[4-[(1-methylindazol-5-yl)amino]-3-oxo-1H-pyrrolo[3,4-c]pyridin-2-yl]acetate (Intermediate I-48). A mixture of tert-butyl 2-(4-bromo-3-oxo-1H-pyrrolo[3,4-c]pyridin-2-yl)acetate (200 mg, 0.61 mmol), 1-methyl-1H-indazol-5-amine (89.9 mg, 0.61 mmol), $Pd_2(dba)_3$ (55.9 mg, 0.061 mmol) , Xantphos (35.3 mg, 0.061 mmol) and Cs_2CO_3 (397mg, 1.22 mmol) in 1,4-dioxane (3 mL) was stirred at 100°C under N_2 overnight. The mixture was diluted with saturated NH_4Cl (20 mL) and extracted with EtOAc (30mL x 3). The mixture was concentrated under vacuum and purified by silica gel chromatography (DCM methanol, 20/1) to afford tert-butyl 2-[4-[(1-methylindazol-5-yl)amino]-3-oxo-1H-pyrrolo[3,4-c]pyridin-2-yl]acetate (I-48) (50 mg, 21%) as a white solid.

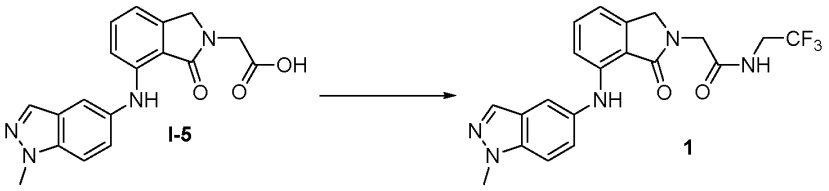
UPLC-MS (ES^+, Method 1): 3.82 min, m/z 394.2 $[M+H]^+$.

STEP E. 2-[4-[(1-Methylindazol-5-yl)amino]-3-oxo-1H-pyrrolo[3,4-c]pyridin-2-yl]acetic acid (Intermediate I-49). A mixture of tert-butyl 2-[4-[(1-methylindazol-5-yl)amino]-3-oxo-1H-pyrrolo[3,4-c]pyridin-2-yl]acetate (I-48) (40 mg, 0.1017 mmol, 1.0 eq) and TFA (1 mL) in DCM (2 mL) was stirred at 25°C for 4 hours. The mixture and was concentrated under vacuum to afford 2-[4-[(1-Methylindazol-5-yl)amino]-3-oxo-1H-pyrrolo[3,4-c]pyridin-2-yl]acetic acid (Intermediate I-49) (40 mg) as a brown solid containing residual TFA and used without further purification.

UPLC-MS (ES^+, Method 1): 2.55 min, m/z 338.2 $[M+H]^+$.

Synthesis of Examples

Example 1, 2-[7-[(1-Methylindazol-5-yl)amino]-1-oxo-isoindolin-2-yl]-N-(2,2,2-trifluoroethyl) acetamide

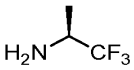
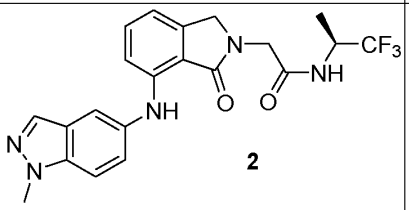
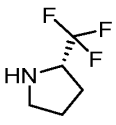
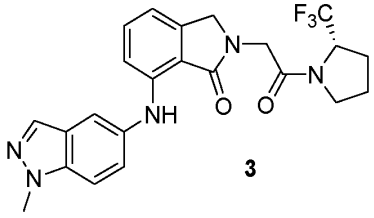


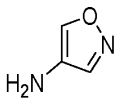
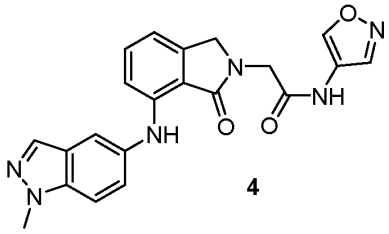
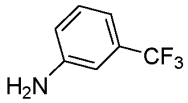
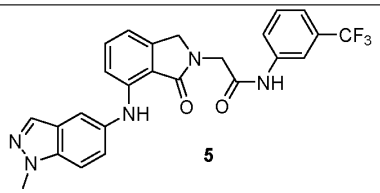
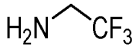
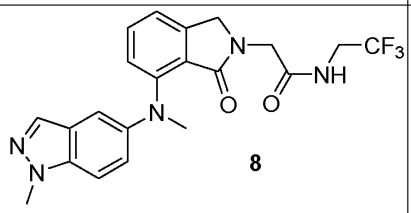
A mixture of 2-[7-[(1-methylindazol-5-yl)amino]-1-oxo-isoindolin-2-yl]acetic acid (Intermediate I-5, 60 mg, 0.18 mmol), trifluoroethylamine (27 mg, 0.27 mmol), T3P (170 mg, 0.3 mmol) and DIPEA (69 mg, 0.53 mmol) in dichloromethane (2 mL) was stirred at room temperature for 16 h. The mixture was concentrated under reduced pressure and purified by prep LCMS to give 2-[7-[(1-methylindazol-5-yl)amino]-1-oxo-isoindolin-2-yl]-N-(2,2,2-trifluoroethyl)acetamide (Example 1, 12 mg, 16% yield) as a yellow solid.

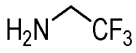
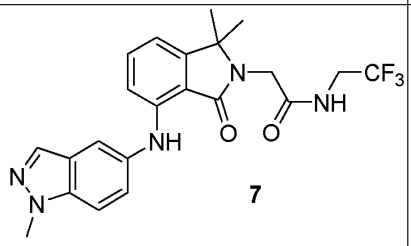
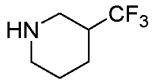
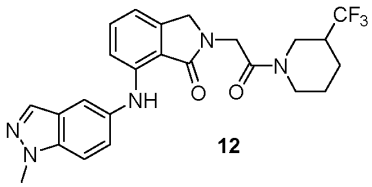
UPLC-MS (ES^+, Method 1): 3.74 min, m/z 418.2 $[M+H]^+$.

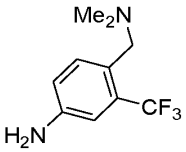
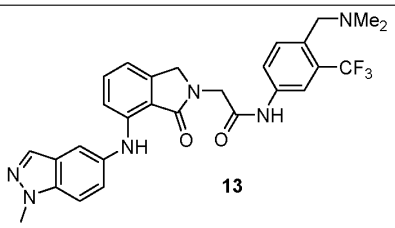
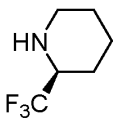
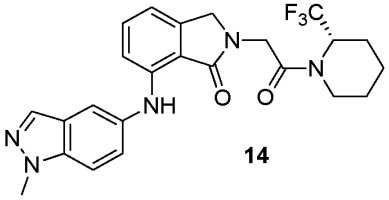
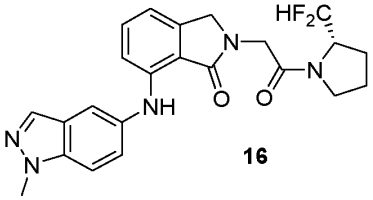
^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.88 (t, J=6.4 Hz, 1H), 8.68 (s, 1H), 8.05 (s, 1H), 7.75 - 7.71 (m, 2H), 7.46 - 7.37 (m, 2H), 7.07 (d, J=8.3 Hz, 1H), 6.94 (d, J=7.3 Hz, 1H), 4.54 (s, 2H), 4.32 (s, 2H), 4.12 (s, 3H), 4.02 (dq, J=6.6, 9.7 Hz, 2H).

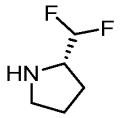
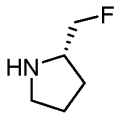
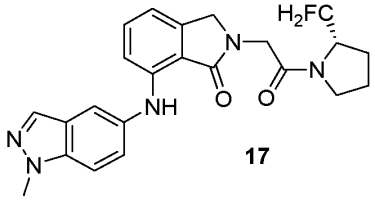
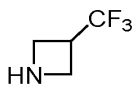
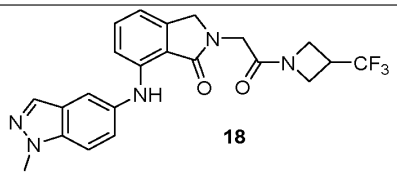
Examples synthesised following the same procedure as Example 1 replacing 2-[7-[(1-methylindazol-5-yl)amino]-1-oxo-isoindolin-2-yl]acetic acid (Intermediate I-5) and/or trifluoroethylamine with the appropriate building block are described in table 8.

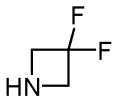
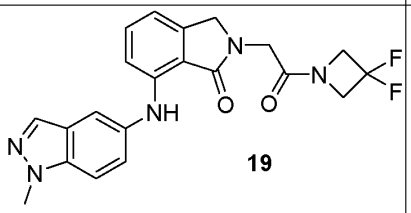
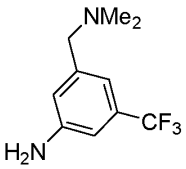
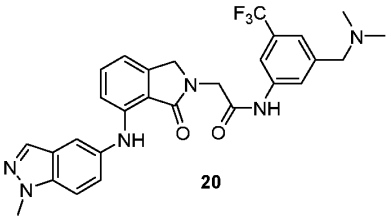
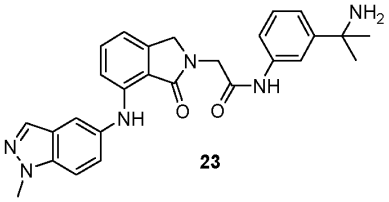
Building Block	Structure/Name	LCMS	^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm)
Intermediate I-5 and (2S)-Amino-1,1,1-trifluoropropane hydrochloride 	 **2** 2-[7-[(1-Methylindazol-5-yl)amino]-1-oxo-isoindolin-2-yl]-N-[(1S)-2,2,2-trifluoro-1-methyl-ethyl]acetamide **Example 2**	3.82 min, m/z 432.2 $[M+H]^+$ (Method 1)	8.75 (d, J=8.9 Hz, 1H), 8.62 (s, 1H), 7.99 (s, 1H), 7.69 - 7.65 (m, 2H), 7.41 - 7.31 (m, 2H), 7.02 (d, J=8.4 Hz, 1H), 6.89 (d, J=7.3 Hz, 1H), 4.69 - 4.58 (m, 1H), 4.49 (s, 2H), 4.28 (d, J=16.8 Hz, 1H), 4.22 (d, J=16.9 Hz, 1H), 4.06 (s, 3H), 1.30 (d, J=6.8 Hz, 3H).
Intermediate I-5 and (2S) - Trifluoromethyl pyrrolidine 	 **3** 7-[(1-Methylindazol-5-yl)amino]-2-[2-oxo-2-[(2S)-2-(trifluoromethyl)pyrrolidin-1-yl]ethyl]isoindolin-1-one **Example 3**	4.02 min, m/z 458.3 $[M+H]^+$ (Method 1)	8.64 (s, 1H), 8.00 (s, 1H), 7.69 - 7.66 (m, 2H), 7.41 - 7.32 (m, 2H), 7.03 (d, J=8.2 Hz, 1H), 6.90 (d, J=7.2 Hz, 1H), 4.84 - 4.75 (m, 1H), 4.53 - 4.42 (m, 4H), 4.07 (s, 3H), 3.74 - 3.66 (m, 2H), 2.17 - 1.95 (m, 4H).

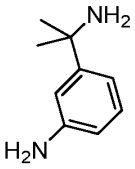
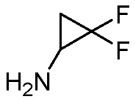
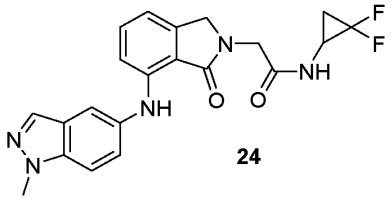
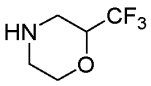
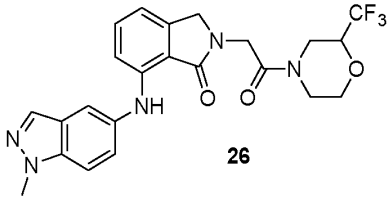
Intermediate I-5 and Isoxazol-4-amine 	 **4** N-isoxazol-4-yl-2-[7-[(1-methylindazol-5-yl)amino]-1-oxo-isoindolin-2-yl]acetamide **Example 4**	3.58 min, m/z 403.2 $[M+H]^+$ (Method 1)	10.47 (s, 1H), 9.12 (s, 1H), 8.65 (s, 1H), 8.61 (s, 1H), 8.00 – 7.95 (m, 1H), 7.68 – 7.62 (m, 2H), 7.37 (t, *J* = 7.8 Hz, 1H), 7.31 (dd, *J* = 8.9, 2.0 Hz, 1H), 7.01 (d, *J* = 8.3 Hz, 1H), 6.88 (d, *J* = 7.4 Hz, 1H), 4.52 (s, 2H), 4.37 (s, 2H), 4.04 (s, 3H).
Intermediate I-5 and 3-(Trifluoro methyl)aniline 	 **5** 2-{7-[(1-methyl-1H-indazol-5-yl)amino]-1-oxo-2,3-dihydro-1H-isoindol-2-yl}-N-[3-(trifluoromethyl)phenyl]acetamide **Example 5**	4.25 min, m/z 480.2 $[M+H]^+$ (Method 1)	10.56 (s, 1H), 8.62 (s, 1H), 8.11 (s, 1H), 7.97 (s, 1H), 7.79 (d, *J* = 8.2 Hz, 1H), 7.68 – 7.63 (m, 2H), 7.57 (t, *J* = 8.0 Hz, 1H), 7.42 (d, *J* = 7.8 Hz, 1H), 7.37 (t, *J* = 7.8 Hz, 1H), 7.32 (dd, *J* = 8.9, 2.0 Hz, 1H), 7.01 (d, *J* = 8.3 Hz, 1H), 6.88 (d, *J* = 7.4 Hz, 1H), 4.55 (s, 2H), 4.41 (s, 2H), 4.04 (s, 3H).
Intermediate I-12 and trifluoroethylamine 	 **8** 2-[7-[methyl-(1-methylindazol-5-yl)amino]-1-oxo-isoindolin-2-yl]-N-(2,2,2-trifluoroethyl)acetamide	3.61 min, m/z 432.2 $[M+H]^+$ (Method 1)	8.75 (d, *J* = 5.7 Hz, 1H), 7.86 (s, 1H), 7.47 (t, *J* = 7.7 Hz, 1H), 7.41 (d, *J* = 9.1 Hz, 1H), 7.27 (d, *J* = 7.4 Hz, 1H), 7.15 (d, *J* = 2.2 Hz, 1H), 7.00 (d, *J* = 8.0 Hz, 1H), 6.93

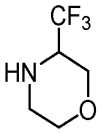
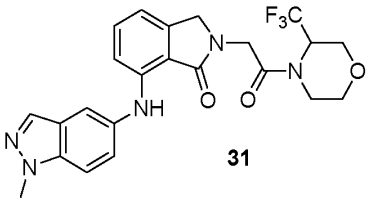
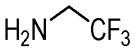
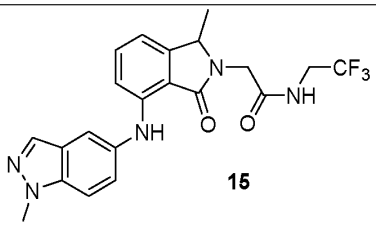
	Example 8		(dd, *J* = 9.1, 2.2 Hz, 1H), 4.48 (s, 2H), 4.19 (s, 2H), 3.98 (s, 3H), 3.92 (dd, *J* = 10.1, 5.0 Hz, 2H), 3.34 (s, 3H).
Intermediate I-17 and trifluoroethylamine 	 **7** 2-[1,1-dimethyl-4-[(1-methylindazol-5-yl)amino]-3-oxo-isoindolin-2-yl]-N-(2,2,2-trifluoroethyl)acetamide **Example 7**	3.93 min, m/z 446.3 $[M+H]^+$ (Method 1)	8.69 - 8.63 (m, 2H), 7.99 (s, 1H), 7.69 - 7.66 (m, 2H), 7.39 (t, J=7.8 Hz, 1H), 7.33 (d, J=10.6 Hz, 1H), 7.01 (d, J=8.2 Hz, 1H), 6.92 (d, J=7.4 Hz, 1H), 4.14 (s, 2H), 4.07 (s, 3H), 3.96 (dq, J=6.5, 9.7 Hz, 2H), 1.44 (s, 6H).
Intermediate I-5 and 3-(trifluoromethyl) piperidine 	 **12** 7-[(1-methylindazol-5-yl)amino]-2-[2-oxo-2-[3-(trifluoromethyl)-1-piperidyl]ethyl]isoquinolin-1-one **Example 12**	4.06 min, m/z 472.3 $[M+H]^+$ (Method 1)	8.63 (s, 1H), 7.98 (s, 1H), 7.68 - 7.64 (m, 2H), 7.39 - 7.29 (m, 2H), 7.01 (d, J=8.3 Hz, 1H), 6.87 (d, J=7.3 Hz, 1H), 4.50 - 4.37 (m, 5H), 4.20 - 4.16 (m, 1H), 4.05 (s, 3H), 4.01 - 3.97 (m, 1H), 3.91 - 3.86 (m, 1H), 3.20 - 3.11 (m, 1H), 2.85 - 2.76 (m, 1H), 2.00 - 1.97 (m, 1H), 1.81 - 1.71 (m, 1H), 1.59 - 1.53 (m, 1H).

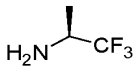
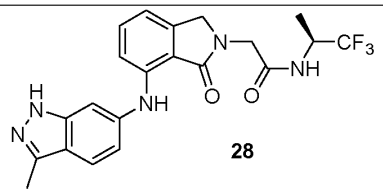
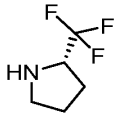
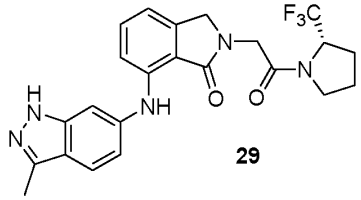
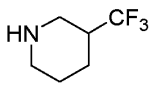
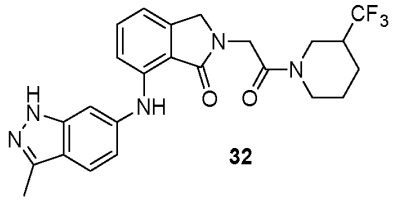
Intermediate I-5 and 4-((dimethylamino)methyl)-3-(trifluoromethyl) aniline 	 **13** N-[4-[(dimethylamino)methyl]-3-(trifluoromethyl)phenyl]-2-[7-[(1-methylindazol-5-yl)amino]-1-oxo-isoindolin-2-yl]acetamide **Example 13**	1.20 min, m/z 537.3 $[M+H]^+$ (Method 2)	10.52 (s, 1H), 8.64 (s, 1H), 8.07 (s, 1H), 8.00 (s, 1H), 7.81 (d, J=8.4 Hz, 1H), 7.72 - 7.65 (m, 3H), 7.39 (t, J=7.8 Hz, 1H), 7.34 (d, J=10.6 Hz, 1H), 7.03 (d, J=8.2 Hz, 1H), 6.90 (d, J=7.3 Hz, 1H), 4.56 (s, 2H), 4.42 (s, 2H), 4.06 (s, 3H), 2.18 (s, 6H). (One CH_2 signal under solvent peak)
Intermediate I-5 and (2S) -(trifluoromethyl)piperidine 	 **14** 7-[(1-methylindazol-5-yl)amino]-2-[2-oxo-2-[(2S)-(trifluoromethyl)-1-piperidyl]ethyl]isoindolin-1-one **Example 14**	2.07 min, m/z 472.1 $[M+H]^+$ (Method 2)	8.64 (s, 1H), 8.00 (s, 1H), 7.68 - 7.66 (m, 2H), 7.41 - 7.32 (m, 2H), 7.03 (d, J=8.3 Hz, 1H), 6.89 (d, J=6.7 Hz, 1H), 5.19 - 5.15 (m, 1H), 4.65 - 4.49 (m, 2H), 4.47 - 4.39 (m, 2H), 4.07 (s, 3H), 3.99 - 3.96 (m, 1H), 3.22 - 3.16 (m, 1H), 2.01 - 1.97 (m, 1H), 1.77 - 1.50 (m, 5H).
Intermediate I-5 and (2S)-(difluoromethyl) pyrrolidine hydrochloride	 **16**	3.88 min, m/z 440.3 $[M+H]^+$ (Method 1)	8.62 (d, *J* = 4.1 Hz, 1H), 7.97 (s, 1H), 7.70 – 7.61 (m, 2H), 7.35 (t, *J* = 7.8 Hz, 1H), 7.31 (dd, *J* = 8.9, 1.9

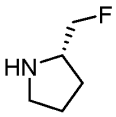
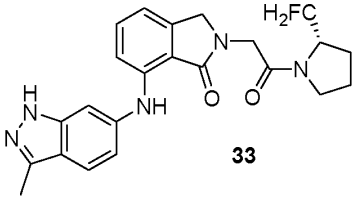
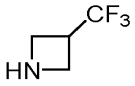
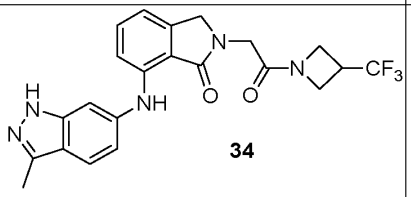
	2-[2-[(2S)-(difluoromethyl)pyrrolidin-1-yl]-2-oxo-ethyl]-7-[(1-methylindazol-5-yl)amino]isoindolin-1-one **Example 16**		Hz, 1H), 7.00 (d, *J* = 8.3 Hz, 1H), 6.86 (d, *J* = 7.3 Hz, 1H), 6.40 – 6.03 (m, 1H), 4.57 – 4.21 (m, 5H), 4.04 (s, 3H), 3.60 (t, *J* = 5.9 Hz, 2H), 2.10 – 1.81 (m, 4H).
Intermediate I-5 and (2S)-(fluoromethyl) pyrrolidine hydrochloride 	 **17** 2-[2-[(2S)-(fluoromethyl)pyrrolidin-1-yl]-2-oxo-ethyl]-7-[(1-methylindazol-5-yl)amino]isoindolin-1-one **Example 17**	3.75 min, m/z 422.3 $[M+H]^+$ (Method 1)	8.63 (d, *J* = 3.5 Hz, 1H), 7.97 (s, 1H), 7.68 – 7.62 (m, 2H), 7.35 (t, *J* = 7.8 Hz, 1H), 7.31 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.00 (d, *J* = 8.3 Hz, 1H), 6.86 (d, *J* = 7.3 Hz, 1H), 4.52 (t, *J* = 3.7 Hz, 1H), 4.45 (s, 2H), 4.42 – 4.39 (m, 1H), 4.36 (s, 1H), 4.14 (d, *J* = 22.6 Hz, 1H), 4.04 (s, 3H), 3.57 – 3.39 (m, 3H), 2.02 – 1.80 (m, 4H).
Intermediate I-5 and 3-(trifluoromethyl) azetidine 	 **18** 7-[(1-methylindazol-5-yl)amino]-2-[2-oxo-2-[3-(trifluoromethyl)73zetidine-1-yl]ethyl]isoindolin-1-one **Example 18**	3.78 min, m/z 444.3 $[M+H]^+$ (Method 1)	8.60 (s, 1H), 7.97 (s, 1H), 7.65 (dd, *J* = 5.6, 3.4 Hz, 2H), 7.38 – 7.29 (m, 2H), 6.99 (d, *J* = 8.3 Hz, 1H), 6.86 (d, *J* = 7.3 Hz, 1H), 4.50 (t, *J* = 9.1 Hz, 1H), 4.43 (s, 2H), 4.30 (dd, *J* = 9.5, 5.6 Hz, 1H), 4.23

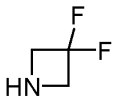
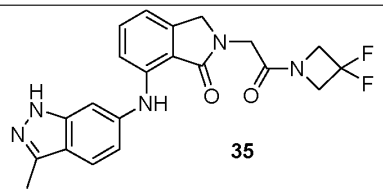
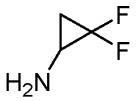
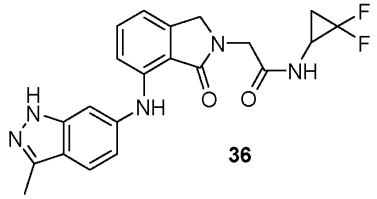
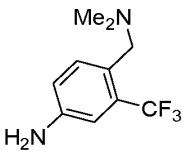
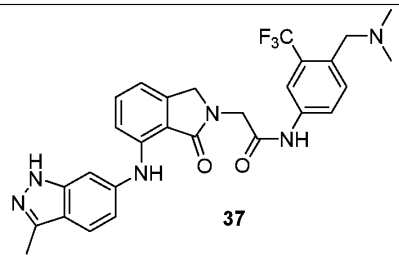
			(d, *J* = 2.7 Hz, 2H), 4.16 (t, *J* = 9.7 Hz, 1H), 4.04 (s, 3H), 3.90 (dd, *J* = 10.1, 5.4 Hz, 1H), 3.75 – 3.64 (m, 1H).
Intermediate I-5 and 3,3-difluoroazetidine 	 **19** 2-[2-(3,3-difluoroazetidin-1-yl)-2-oxo-ethyl]-7-[(1-methylindazol-5-yl)amino]isoindolin-1-one **Example 19**	3.65 min, m/z 412.3 $[M+H]^+$ (Method 1)	8.59 (s, 1H), 7.97 (s, 1H), 7.65 (d, *J* = 2.2 Hz, 2H), 7.39 – 7.29 (m, 2H), 6.99 (d, *J* = 8.3 Hz, 1H), 6.86 (d, *J* = 7.4 Hz, 1H), 4.75 (t, *J* = 12.5 Hz, 2H), 4.44 (s, 2H), 4.37 (t, *J* = 12.6 Hz, 2H), 4.29 (s, 2H), 4.04 (s, 3H).
Intermediate I-5 and 3-[(dimethylamino)methyl]-5-(trifluoromethyl) aniline 	 **20** N-[3-[(dimethylamino)methyl]-5-(trifluoromethyl)phenyl]-2-[7-[(1-methylindazol-5-yl)amino]-1-oxo-isoindolin-2-yl]acetamide **Example 20**	2.82 min, m/z 537.3 $[M+H]^+$ (Method 1)	10.56 (s, 1H), 8.61 (s, 1H), 7.98 (d, *J* = 8.0 Hz, 2H), 7.84 (s, 1H), 7.67 – 7.63 (m, 2H), 7.40 – 7.34 (m, 2H), 7.33 – 7.29 (m, 1H), 7.05 – 6.99 (m, 1H), 6.88 (d, *J* = 7.4 Hz, 1H), 4.54 (s, 2H), 4.40 (s, 2H), 4.04 (s, 3H), 3.65 (s, 2H), 2.29 (s, 6H).
Intermediate I-5 and 3-(1-amino-1-methyl-ethyl)aniline	 **23**	2.98 min, m/z 469.3 $[M+H]^+$ (Method 1)	8.64 (s, 1H), 8.37 (s, 1H), 7.98 (s, 1H), 7.69 - 7.64 (m, 2H), 7.38 - 7.29 (m, 2H), 7.17

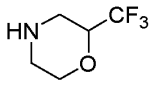
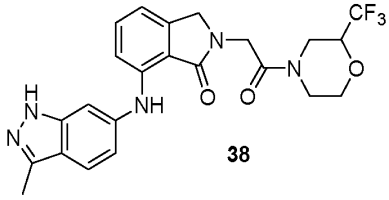
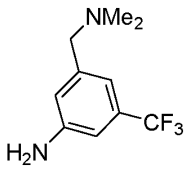
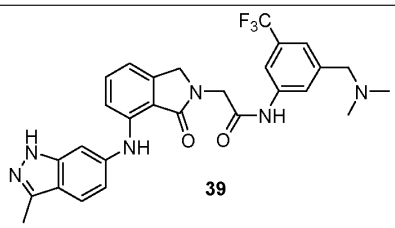
	N-[3-(1-amino-1-methyl-ethyl)phenyl]-2-[7-[(1-methylindazol-5-yl)amino]-1-oxo-isoindolin-2-yl]acetamide **Example 23**		(t, J=7.8 Hz, 1H), 7.00 (d, J=8.2 Hz, 1H), 6.97 - 6.91 (m, 2H), 6.85 (d, J=7.4 Hz, 1H), 6.75 (d, J=8.1 Hz, 1H), 4.44 (s, 2H), 4.20 (s, 2H), 4.06 (s, 3H), 1.57 (s, 6H). NH2 not observed.
Intermediate I-5 and 2,2-difluorocyclopropanamine 	 **24** N-(2,2-difluorocyclopropyl)-2-[7-[(1-methylindazol-5-yl)amino]-1-oxo-isoindolin-2-yl]acetamide **Example 24**	3.58 min, m/z 412.2 $[M+H]^+$ (Method 1)	8.61 (s, 2H), 7.97 (s, 1H), 7.65 (dd, *J* = 5.6, 3.4 Hz, 2H), 7.38 – 7.28 (m, 2H), 7.00 (d, *J* = 8.2 Hz, 1H), 6.86 (d, *J* = 7.3 Hz, 1H), 4.46 (s, 2H), 4.19 (s, 2H), 4.04 (s, 3H), 3.44 (s, 1H), 1.90 (s, 1H), 1.52 (dq, *J* = 12.4, 5.7 Hz, 1H).
Intermediate I-5 and 2-(trifluoromethyl)morpholine 	 **26** 7-[(1-methylindazol-5-yl)amino]-2-[2-oxo-2-[2-(trifluoromethyl)morpholin-4-yl]ethyl]isoindolin-1-one **Example 26**	3.88 min, m/z 474.3 $[M+H]^+$ (Method 1)	8.62 (s, 1H), 7.97 (s, 1H), 7.65 (dd, *J* = 5.5, 3.3 Hz, 2H), 7.38 – 7.29 (m, 2H), 7.00 (d, *J* = 8.3 Hz, 1H), 6.86 (d, *J* = 7.4 Hz, 1H), 4.63 – 4.53 (m, 1H), 4.43 (d, *J* = 7.2 Hz, 3H), 4.34 (t, *J* = 13.4 Hz, 1H), 4.20 (d, *J* = 31.4 Hz, 1H), 4.16 – 3.81 (m, 6H), 3.73 –

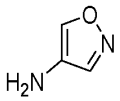
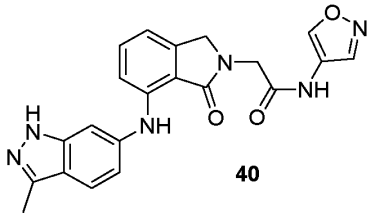
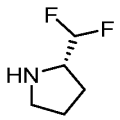
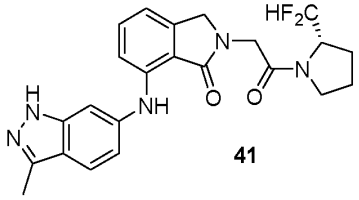
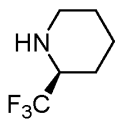
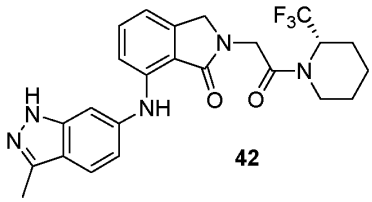
			3.52 (m, 1H), 2.90 (t, *J* = 11.9 Hz, 1H), 1.24 (s, 1H).
Intermediate I-5 and 3-(trifluoromethyl)morpholine hydrochloride 	 **31** 7-[(1-methylindazol-5-yl)amino]-2-[2-oxo-2-[3-(trifluoromethyl)morpholin-4-yl]ethyl]isoindolin-1-one **Example 31**	3.85 min, m/z 496.2 $[M+Na]^+$ (Method 1)	8.60 (s, 1H), 7.97 (s, 1H), 7.66 – 7.64 (m, 2H), 7.38 – 7.30 (m, 2H), 7.02 – 6.99 (m, 1H), 6.88 – 6.85 (m, 1H), 4.99 – 4.87 (m, 1H), 4.67 (t, *J* = 16.2 Hz, 1H), 4.51 – 4.34 (m, 3H), 4.19 – 4.10 (s, 1H), 4.04 (s, 3H), 3.93 – 3.80 (m, 2H), 3.69 – 3.41 (m, 3H).
Intermediate I-24 and trifluoroethyl amine 	 **15** 2-[1-methyl-4-[(1-methylindazol-5-yl)amino]-3-oxo-isoindolin-2-yl]-N-(2,2,2-trifluoroethyl)acetamide **Example 15**	3.82 min, m/z 432.2 $[M+H]^+$ (Method 1)	8.76 (t, *J* = 6.4 Hz, 1H), 8.61 (s, 1H), 7.97 (d, *J* = 0.9 Hz, 1H), 7.65 (dd, *J* = 5.6, 3.4 Hz, 2H), 7.37 (t, *J* = 7.8 Hz, 1H), 7.31 (dd, *J* = 9.0, 1.9 Hz, 1H), 6.99 (d, *J* = 8.3 Hz, 1H), 6.88 (d, *J* = 7.4 Hz, 1H), 4.62 (d, *J* = 6.7 Hz, 1H), 4.35 (d, *J* = 17.0 Hz, 1H), 4.06 (d, *J* = 9.8 Hz, 4H), 3.99 – 3.86 (m, 2H), 1.40 (d, *J* = 6.8 Hz, 3H).

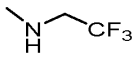
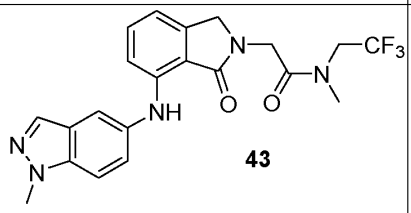
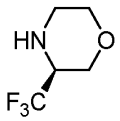
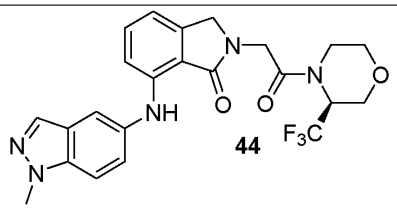
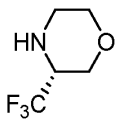
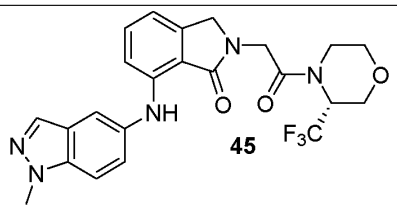
Intermediate I-26 and (2S)-Amino-1,1,1-trifluoropropane hydrochloride 	 **28** 2-[7-[(3-methyl-1H-indazol-6-yl)amino]-1-oxo-isoindolin-2-yl]-N-[(1S)-2,2,2-trifluoro-1-methyl-ethyl]acetamide **Example 28**	3.68 min, m/z 432.2 $[M+H]^+$ (Method 1)	12.37 (s, 1H), 8.83 (s, 1H), 8.73 (d, *J* = 8.8 Hz, 1H), 7.64 (d, *J* = 8.6 Hz, 1H), 7.43 (t, *J* = 7.8 Hz, 1H), 7.33 – 7.29 (m, 1H), 7.27 (d, *J* = 8.3 Hz, 1H), 6.98 – 6.93 (m, 2H), 4.68 – 4.56 (m, 1H), 4.48 (s, 2H), 4.31 – 4.17 (m, 2H), 2.45 (s, 3H), 1.27 (d, *J* = 7.1 Hz, 3H).
Intermediate I-26 and (2S)-trifluoromethyl pyrrolidine 	 **29** 7-[(3-methyl-1H-indazol-6-yl)amino]-2-[2-oxo-2-[(2S)-(trifluoromethyl)77yrrolidine-1-yl]ethyl]isoindolin-1-one **Example 29**	3.82 min, m/z 458.0 $[M+H]^+$ (Method 1)	12.37 (s, 1H), 8.84 (s, 1H), 7.64 (d, *J* = 8.5 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 1H), 7.31 – 7.26 (m, 2H), 6.96 – 6.94 (m, 2H), 5.07 – 4.73(m, 1H), 4.61 – 4.37 (m, 4H), 3.66 (p, *J* = 7.9, 7.3 Hz, 2H), 2.67 (s, 0.5H), 2.45 (s, 3H), 2.33 (s, 0.5H), 2.10 – 1.99 (m, 3H).
Intermediate I-26 and 3-(trifluoromethyl) piperidine 	 **32** 7-[(3-methyl-1H-indazol-6-yl)amino]-2-[2-oxo-2-[3-(trifluoromethyl)-1-piperidyl]ethyl]isoindolin-1-one	3.85 min, m/z 472.2 $[M+H]^+$ (Method 1)	12.37 (s, 1H), 8.86 (s, 1H), 7.64 (d, *J* = 8.5 Hz, 1H), 7.43 (t, *J* = 7.8 Hz, 1H), 7.31 (s, 1H), 7.27 (d, *J* = 8.3 Hz, 1H), 6.94 (d, *J* = 7.8 Hz, 2H), 4.51 – 3.83 (m, 6H), 3.28

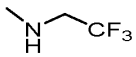
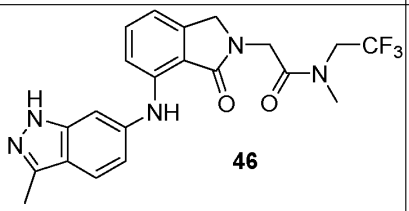
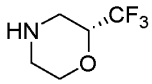
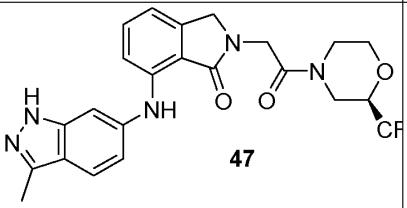
	Example 32		– 2.63 (m, 3H), 2.45 (s, 3H), 2.02 – 1.91 (m, 1H), 1.83 – 1.67 (m, 1H), 1.64 – 1.35 (m, 2H).
Intermediate I-26 and (2S)-(fluoromethyl) pyrrolidine hydrochloride 	 **33** 2-[2-[(2S)-(fluoromethyl)pyrrolidin-1-yl]-2-oxo-ethyl]-7-[(3-methyl-1H-indazol-6-yl)amino]isoindolin-1-one **Example 33**	3.58 min, m/z 422.3 $[M+H]^+$ (Method 1)	12.45 (s, 1H), 8.93 (s, 1H), 7.72 (d, *J* = 8.5 Hz, 1H), 7.51 (t, *J* = 7.8 Hz, 1H), 7.39 (s, 1H), 7.34 (d, *J* = 8.3 Hz, 1H), 7.02 (d, *J* = 7.9 Hz, 2H), 4.64 – 4.17 (m, 7H), 3.62 (d, *J* = 5.5 Hz, 2H), 2.52 (s, 3H), 2.12 – 1.87 (m, 4H).
Intermediate I-26 and 3-(trifluoromethyl) azetidine 	 **34** 7-[(3-methyl-1H-indazol-6-yl)amino]-2-[2-oxo-2-[3-(trifluoromethyl)azetidin-1-yl]ethyl]isoindolin-1-one **Example 34**	3.60 min, m/z 444.1 $[M+H]^+$ (Method 1)	12.37 (s, 1H), 8.82 (s, 1H), 7.64 (d, *J* = 8.5 Hz, 1H), 7.43 (t, *J* = 7.8 Hz, 1H), 7.31 (s, 1H), 7.26 (d, *J* = 8.3 Hz, 1H), 6.94 (d, *J* = 6.7 Hz, 2H), 4.50 (t, *J* = 9.1 Hz, 1H), 4.45 (s, 2H), 4.32 – 4.28 (m, 1H), 4.23 (s, 2H), 4.16 (t, *J* = 9.8 Hz, 1H), 3.9 – 3.88 (m, 1H), 3.72 – 3.67 (m, 1H), 2.45 (s, 3H).

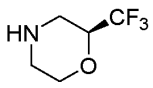
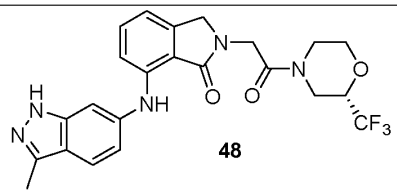
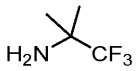
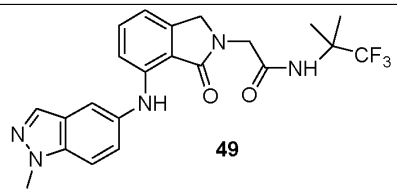
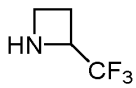
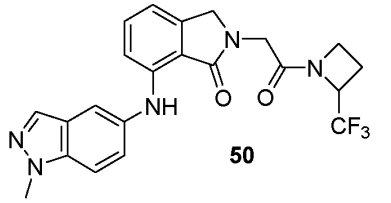
Intermediate I-26 and 3,3-difluoroazetidine 	 **35** 2-[2-(3,3-difluoroazetidin-1-yl)-2-oxo-ethyl]-7-[(3-methyl-1H-indazol-6-yl)amino]isoindolin-1-one **Example 35**	3.48 min, m/z 412.1 $[M+H]^+$ (Method 1)	12.38 (s, 1H), 8.82 (s, 1H), 7.64 (d, *J* = 8.5 Hz, 1H), 7.43 (t, *J* = 7.8 Hz, 1H), 7.31 (s, 1H), 7.26 (d, *J* = 8.2 Hz, 1H), 6.95 (d, *J* = 6.5 Hz, 2H), 4.74 (t, *J* = 12.5 Hz, 2H), 4.45 (s, 2H), 4.36 (t, *J* = 12.6 Hz, 2H), 4.30 (s, 2H), 2.45 (s, 3H).
Intermediate I-26 and 2,2-difluoro cyclo propanamine 	 **36** N-(2,2-difluorocyclopropyl)-2-[7-[(3-methyl-1H-indazol-6-yl)amino]-1-oxo-isoindolin-2-yl]acetamide **Example 36**	3.45 min, m/z 412.1 $[M+H]^+$ (Method 1)	12.37 (s, 1H), 8.83 (s, 1H), 8.60 (s, 1H), 7.64 (d, *J* = 8.5 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 1H), 7.31 – 7.26F (m, 2H), 6.95 (d, *J* = 7.9 Hz, 2H), 4.47 (s, 2H), 4.20 (s, 2H), 2.45 (s, 3H), 2.03 – 1.85 (m, 1.5H), 1.62 – 1.47 (m, 1.5H).
Intermediate I-26 and 4-[(dimethylamino)methyl]-3-(trifluoromethyl) aniline 	 **37** N-[4-[(dimethylamino)methyl]-3-(trifluoromethyl)phenyl]-2-[7-[(3-methyl-1H-indazol-6-yl)amino]-1-oxo-isoindolin-2-yl]acetamide **Example 37**	2.74 min, m/z 537.2 $[M+H]^+$ (Method 1)	10.76 (s, 1H), 9.71 (s, 1H), 8.83 (s, 1H), 8.16 (d, *J* = 2.2 Hz, 1H), 7.96 (d, *J* = 8.4 Hz, 1H), 7.79 (d, *J* = 8.6 Hz, 1H), 7.64 (d, *J* = 8.5 Hz, 1H), 7.46 (t, *J* = 7.8 Hz, 1H), 7.32 (s, 1H), 7.29 (d, *J* = 8.2 Hz, 1H), 6.96 (t, *J* = 7.8 Hz, 2H), 4.56 (s, 2H),

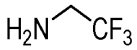
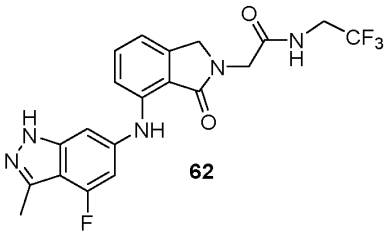
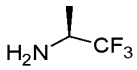
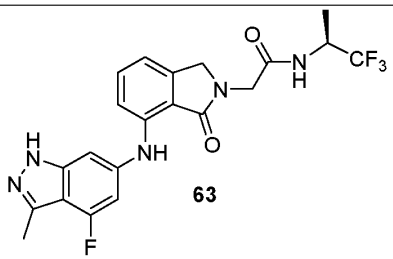
			4.44 (s, 2H), 4.41 (s, 2H), 2.80 (s, 6H), 2.45 (s, 3H).
Intermediate I-26 and 2-(trifluoromethyl)morpholine 	 **38** 7-[(3-methyl-1H-indazol-6-yl)amino]-2-[2-oxo-2-[2-(trifluoromethyl)morpholin-4-yl]ethyl]isoindolin-1-one **Example 38**	3.68 min, m/z 474.2 $[M+H]^+$ (Method 1)	12.37 (s, 1H), 8.85 (s, 1H), 7.64 (d, *J* = 8.5 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 1H), 7.31 (d, *J* = 1.8 Hz, 1H), 7.27 (d, *J* = 8.3 Hz, 1H), 6.95 (d, *J* = 7.9 Hz, 2H), 4.64 – 4.54 (m, 1H), 4.45 – 4.30 (m, 4H), 4.24 – 3.86 (m, 3H), 3.70 – 3.54 (m, 1H), 3.32 (s, 1H), 2.89 (t, *J* = 11.6 Hz, 1H), 2.45 (s, 3H).
Intermediate I-26 and 3-[(dimethylamino)methyl]-5-(trifluoromethyl) aniline 	 **39** N-[3-[(dimethylamino)methyl]-5-(trifluoromethyl)phenyl]-2-[7-[(3-methyl-1H-indazol-6-yl)amino]-1-oxo-isoindolin-2-yl]acetamide **Example 39**	2.80 min, m/z 537.3 $[M+H]^+$ (Method 1)	10.62 (s, 1H), 8.90 (s, 1H), 8.24 (s, 1H), 8.04 (s, 1H), 7.84 (s, 1H), 7.70 (d, *J* = 8.5 Hz, 1H), 7.51 (t, *J* = 7.8 Hz, 1H), 7.38 (s, 2H), 7.34 (d, *J* = 8.2 Hz, 1H), 7.05 – 6.99 (m, 2H), 4.62 (s, 2H), 4.46 (s, 2H), 3.52 (s, 2H), 2.51 (s, 3H), 2.22 (s, 6H).

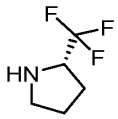
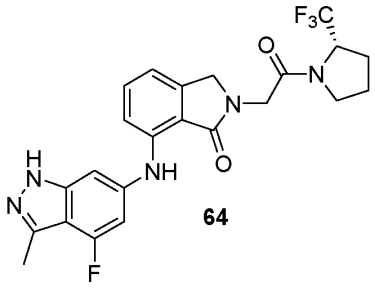
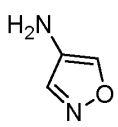
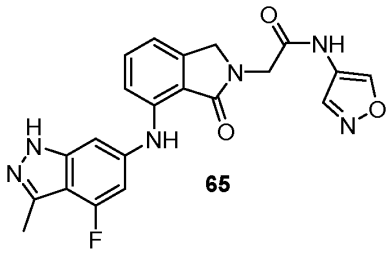
Intermediate I-26 and isoxazol-4-amine 	 **40** N-isoxazol-4-yl-2-[7-[(3-methyl-1H-indazol-6-yl)amino]-1-oxo-isoindolin-2-yl]acetamide **Example 40**	3.42 min, m/z 402.4 $[M+H]^+$ (Method 1)	12.37 (s, 1H), 10.50 (s, 1H), 9.11 (s, 1H), 8.82 (s, 1H), 8.64 (s, 1H), 7.64 (d, *J* = 8.6 Hz, 1H), 7.45 (t, *J* = 7.9 Hz, 1H), 7.31 – 7.27 (m, 2H), 6.97 – 6.94 (m, 2H), 4.53 (s, 2H), 4.37 (s, 2H), 2.45 (s, 3H).
Intermediate I-26 and (2S)-(difluoromethyl) pyrrolidine hydrochloride 	 **41** 7-[(3-methyl-1H-indazol-6-yl)amino]-2-[2-oxo-2-[(2S)-(difluoromethyl)pyrrolidin-1-yl]ethyl]isoindolin-1-one **Example 41**	3.70 min, m/z 440.2 $[M+H]^+$ (Method 1)	12.37 (s, 1H), 8.84 (s, 1H), 7.64 (d, J = 8.5 Hz, 1H), 7.44 (t, J = 7.8 Hz, 1H), 7.31 (s, 1H), 7.27 (d, J = 8.3 Hz, 1H), 6.97 – 6.92 (m, 2H), 6.20 (t, J = 56.7 Hz, 1H), 4.57 – 4.20 (m, 5H), 3.67 – 3.48 (m, 2H), 2.45 (s, 3H), 2.03 – 1.86 (m, 4H).
Intermediate I-26 and (2S)-(trifluoromethyl) piperidine 	 **42** 7-[(3-methyl-1H-indazol-6-yl)amino]-2-[2-oxo-2-[(2S)-(trifluoromethyl)-1-piperidyl]ethyl]isoindolin-1-one **Example 42**	1.90 min, m/z 472.1 $[M+H]^+$ (Method 2)	12.37 (s, 1H), 8.83 (s, 1H), 7.64 (d, J = 8.6 Hz, 1H), 7.44 (t, J = 7.8 Hz, 1H), 7.31 (s, 1H), 7.27 (d, J = 8.3 Hz, 1H), 6.95 (d, J = 7.9 Hz, 2H), 5.18 – 4.88 (m, 1H), 4.66 – 4.33 (m, 5H), 3.94 (d, J = 14.1 Hz, 1H), 3.19 – 3.12 (m, 1H), 2.45 (s,

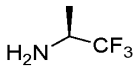
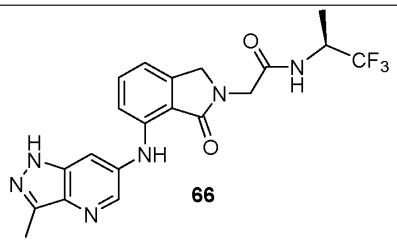
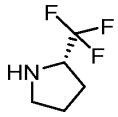
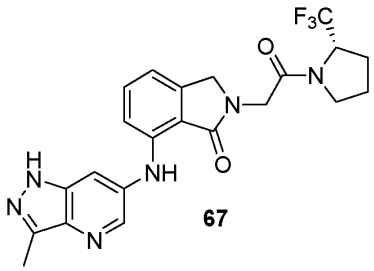
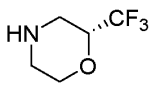
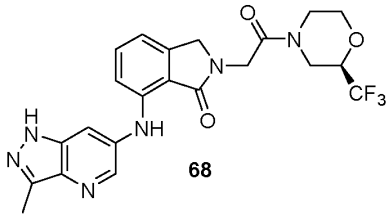
			3H), 2.02 – 1.94 (m, 1H), 1.75 – 1.52 (m, 4H).
Intermediate I-5 and 2,2,2-trifluoro-N-methyl-ethanamine hydrochloride 	 **43** N-methyl-2-[7-[(1-methylindazol-5-yl)amino]-1-oxo-isoindolin-2-yl]-N-(2,2,2-trifluoroethyl)acetamide **Example 43**	3.50 min, m/z 432.2 $[M+H]^+$ (Method 1)	8.61 (s, 1H), 7.97 (s, 1H), 7.64 (d, J = 6.6 Hz, 2H), 7.33 (m, 2H), 6.99 (d, J = 8.2 Hz, 1H), 6.86 (d, J = 7.3 Hz, 1H), 4.51 (d, J = 18.0 Hz, 2H), 4.43 (s, 2H), 4.20 (m, 2H), 4.04 (s, 3H), 3.07 (d, J = 90.2 Hz, 3H).
Intermediate I-5 and (3S)-(trifluoromethyl)morpholine 	 **44** 7-[(1-methylindazol-5-yl)amino]-2-[2-oxo-2-[(3S)-(trifluoromethyl)morpholin-4-yl]ethyl]isoindolin-1-one **Example 44**	3.85 min, m/z 474.2 $[M+H]^+$ (Method 1)	8.60 (s, 1H), 7.97 (s, 1H), 7.65 (d, 2H), 7.42 – 7.26 (m, 2H), 7.00 (d, J = 8.3 Hz, 1H), 6.87 (d, J = 6.9 Hz, 1H), 5.01 – 4.87 (m, 1H), 4.72 – 4.64 (t, J = 16.0 Hz, 1H), 4.51 – 4.34 (m, 3H), 4.21 – 4.10 (m, 1H), 4.04 (s, 3H), 3.93 – 3.65 (m, 3H), 3.58 – 3.41 (m, 2H).
Intermediate I-5 and (3R)-(trifluoromethyl)morpholine 	 **45** 7-[(1-methylindazol-5-yl)amino]-2-[2-oxo-2-[(3R)-	3.88 min, m/z 474.2 $[M+H]^+$ (Method 1)	8.60 (s, 1H), 7.97 (s, 1H), 7.65 (s, 2H), 7.37 – 7.30 (m, 2H), 7.00 (d, J = 8.3 Hz, 1H), 6.87 (d, J = 7.1 Hz, 1H), 4.98 – 4.88 (m, 1H), 4.68 (t, J =

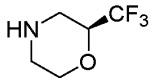
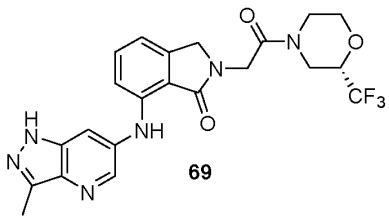
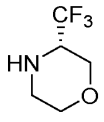
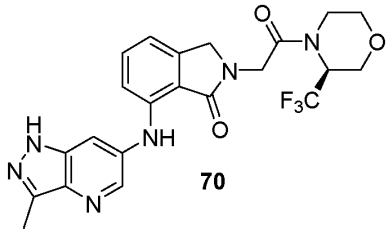
	(trifluoromethyl)morpholin-4-yl]ethyl]isoindolin-1-one **Example 45**		15.8 Hz, 1H), 4.48 – 4.34 (m, 3H), 4.20 – 4.10 (m, 1H), 4.04 (s, 3H), 3.93 – 3.66 (m, 3H), 3.58 – 3.44 (m, 2H).
Intermediate I-26 and 2,2,2-trifluoro-N-methyl-ethanamine hydrochloride 	 **46** N-methyl-2-[7-[(3-methyl-1H-indazol-6-yl)amino]-1-oxo-isoindolin-2-yl]-N-(2,2,2-trifluoroethyl)acetamide **Example 46**	3.73 min, m/z 454.1 $[M+Na]^+$ (Method 1)	12.37 (s, 1H), 8.83 (s, 1H), 7.64 (d, J = 8.5 Hz, 1H), 7.44 (t, J = 7.8 Hz, 1H), 7.31 (s, 1H), 7.27 (d, J = 8.2 Hz, 1H), 6.95 (d, J = 7.8 Hz, 2H), 4.53 – 4.39 (m, 5H), 4.19 (q, J = 9.7 Hz, 1H), 3.18 (s, 2H), 2.95 (s, 1H), 2.45 (s, 3H).
Intermediate I-26 and (2R)-(trifluoromethyl)morpholine hydrochloride 	 **47** 7-[(3-methyl-1H-indazol-6-yl)amino]-2-[2-oxo-2-[(2R)-(trifluoromethyl)morpholin-4-yl]ethyl]isoindolin-1-one **Example 47**	3.68 min, m/z 474.2 $[M+H]^+$ (Method 1)	12.37 (s, 1H), 8.85 (s, 1H), 7.64 (d, J = 8.6 Hz, 1H), 7.44 (t, J = 7.8 Hz, 1H), 7.31 (d, J = 1.7 Hz, 1H), 7.27 (d, J = 8.2 Hz, 1H), 6.99 – 6.91 (m, 2H), 4.67 – 4.53 (m, 1H), 4.51 – 4.29 (m, 4H), 4.27 – 3.84 (m, 3H), 3.74 – 3.52 (m, 1H), 3.39 – 3.33 (m, 1H), 2.89 (t, J = 11.8 Hz, 1H), 2.45 (s, 3H).

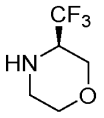
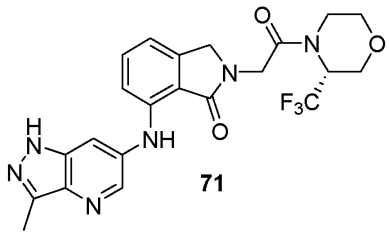
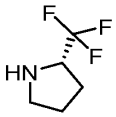
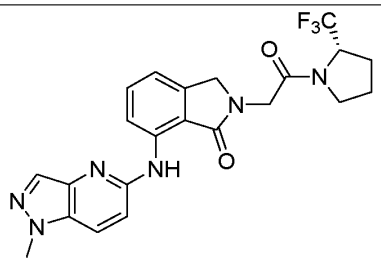
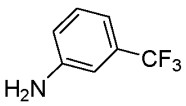
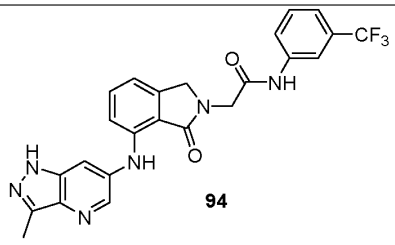
Intermediate I-26 and (2S)-(trifluoromethyl)morpholine hydrochloride 	 **48** 7-[(3-methyl-1H-indazol-6-yl)amino]-2-[2-oxo-2-[(2S)-(trifluoromethyl)morpholin-4-yl]ethyl]isoindolin-1-one **Example 48**	3.75 min, m/z 474.1 $[M+H]^+$ (Method 1)	12.37 (s, 1H), 8.85 (s, 1H), 7.64 (d, J = 8.5 Hz, 1H), 7.44 (t, J = 7.8 Hz, 1H), 7.31 (d, J = 1.7 Hz, 1H), 7.27 (d, J = 8.2 Hz, 1H), 6.97 – 6.92 (m, 2H), 4.67 – 4.52 (m, 1H), 4.50 – 4.29 (m, 4H), 4.27 – 3.84 (m, 3H), 3.72 – 3.53 (m, 1H), 2.94 – 2.84 (m, 1H), 2.45 (s, 3H).
Intermediate 1-5 and 1,1,1-trifluoro-2-methyl-propan-2-amine hydrochloride 	 **49** 2-[7-[(1-methylindazol-5-yl)amino]-1-oxo-isoindolin-2-yl]-N-(2,2,2-trifluoro-1,1-dimethyl-ethyl)acetamide **Example 49**	1.75 min, m/z 446.1 $[M+H]^+$ (Method 2)	8.61 (s, 1H), 8.21 (s, 1H), 7.97 (s, 1H), 7.65 (dd, J = 5.5, 3.4 Hz, 2H), 7.35 (t, J = 7.8 Hz, 1H), 7.31 (dd, J = 8.9, 2.0 Hz, 1H), 6.99 (d, J = 8.3 Hz, 1H), 6.85 (d, J = 7.4 Hz, 1H), 4.46 (s, 2H), 4.19 (s, 2H), 4.04 (s, 3H), 1.51 (s, 6H).
Intermediate 1-5 and 2-(trifluoromethyl)azetidine 	 **50** 7-[(1-methylindazol-5-yl)amino]-2-[2-oxo-2-[2-(trifluoromethyl)azetidin-1-yl]ethyl]isoindolin-1-one **Example 50**	1.80 min, m/z 444.0 $[M+H]^+$ (Method 2)	8.59 (s, 1H), 7.97 (d, J = 0.9 Hz, 1H), 7.65 (m, 2H), 7.35 (t, 1H), 7.29 – 7.32 (dd, J = 8.9, 2.0 Hz, 1H), 6.99 (d, J = 8.2 Hz, 1H), 6.86 (d, J = 7.4 Hz, 1H), 5.38 – 4.88 (m, 1H), 4.44 (s, 2H), 4.35 – 4.17 (m,

			4H), 4.04 (s, 3H), 2.66 – 2.59 (m, 1H), 2.32 – 2.24 (m, 1H).
Intermediate I-32 and trifluoroethylamine 	 **62** 2-[7-[(4-fluoro-3-methyl-1H-indazol-6-yl)amino]-1-oxo-isoindolin-2-yl]-N-(2,2,2-trifluoroethyl)acetamide **Example 62**	3.71 min, m/z 436.1 $[M+H]^+$ (Method 1)	12.60 (s, 1H), 8.84 – 8.79 (m, 2H), 7.47 (t, *J* = 7.8 Hz, 1H), 7.32 (d, *J* = 8.2 Hz, 1H), 7.12 (d, *J* = 1.5 Hz, 1H), 7.01 (d, *J* = 7.4 Hz, 1H), 6.76 (d, *J* = 12.2, 1.5 Hz, 1H), 4.49 (s, 2H), 4.25 (s, 2H), 3.96 – 3.92 (m, 2H), 3.30 (s, 3H).
Intermediate I-32 and (2S)-Amino-1,1,1-trifluoropropane hydrochloride 	 **63** 2-[7-[(4-fluoro-3-methyl-1H-indazol-6-yl)amino]-1-oxo-isoindolin-2-yl]-N-[(1S)-2,2,2-trifluoro-1-methyl-ethyl]acetamide **Example 63**	3.85 min, m/z 450.1 $[M+H]^+$ (Method 1)	12.60 (s, 1H), 8.84 (s, 1H), 8.73 (d, J = 8.8 Hz, 1H), 7.46 (t, J = 7.8 Hz, 1H), 7.32 (d, J = 8.2 Hz, 1H), 7.12 (d, J = 1.5 Hz, 1H), 7.00 (d, J = 7.4 Hz, 1H), 6.76 (dd, J = 12.2, 1.5 Hz, 1H), 4.67 – 4.56 (m, 1H), 4.48 (s, 2H), 4.29 – 4.18 (m, 2H), 2.52 (s, 3H), 1.27 (d, J = 7.1 Hz, 3H).

Intermediate I-32 and (2S)-trifluoromethylpyrrolidine 	 **64** 7-[(4-fluoro-3-methyl-1H-indazol-6-yl)amino]-2-[2-oxo-2-[(2S)-(trifluoromethyl)pyrrolidin-1-yl]ethyl]isoindolin-1-one **Example 64**	4.01 min, m/z 476.2 $[M+H]^+$ (Method 1)	12.60 (s, 1H), 8.85 (s, 1H), 7.48 – 7.44 (t, *J* = 7.8 Hz, 1H), 7.34 – 7.31(d, *J* = 8.3 Hz, 1H), 7.12 (d, *J* = 1.5 Hz, 1H), 7.01 (d, *J* = 7.3 Hz, 1H), 6.77 – 6.74 (d, *J* = 12.1 Hz, 1H), 4.79 – 4.73 (m, 1H), 4.60 – 4.46 (m, 2H), 4.45 – 4.37(m, 2H), 3.69 – 3.62 (m, 2H), 2.51 (s, 3H), 2.10 – 2.03 (m, 2H), 2.03 – 1.99 (m, 2H).
Intermediate I-32 and isoxazol-4-amine 	 **65** 2-[7-[(4-fluoro-3-methyl-1H-indazol-6-yl)amino]-1-oxo-isoindolin-2-yl]-N-isoxazol-4-yl-acetamide **Example 65**	1.43 min, m/z 421.1 $[M+H]^+$ (Method 2)	10.92 (s, 1H), 8.90 (t, *J* = 6.3 Hz, 1H), 8.18 (s, 1H), 7.58 (d, *J* = 8.5 Hz, 1H), 7.53 (d, *J* = 1.9 Hz, 1H), 7.39 – 7.33 (m, 2H), 7.19 (dd, *J* = 8.5, 1.9 Hz, 1H), 6.87 (d, *J* = 8.3 Hz, 1H), 6.80 (d, *J* = 7.6 Hz, 1H), 6.51 (d, *J* = 7.3 Hz, 1H), 4.66 (s, 2H), 4.03 – 3.92 (m, 2H), 3.85 (s, 3H).

Intermediate I-33 and (2S)-Amino-1,1,1-trifluoropropane hydrochloride 	 **66** 2-[7-[(3-methyl-1H-pyrazolo[4,3-b]pyridin-6-yl)amino]-1-oxo-isoindolin-2-yl]-N-[(1S)-2,2,2-trifluoro-1-methyl-ethyl]acetamide **Example 66**	3.28 min, m/z 433.2 $[M+H]^+$ (Method 1)	12.60 (s, 1H), 8.91 (s, 1H), 8.74 (d, *J* = 8.8 Hz, 1H), 8.39 (d, *J* = 2.3 Hz, 1H), 7.75 (d, *J* = 2.3 Hz, 1H), 7.45 (t, *J* = 7.8 Hz, 1H), 7.25 (d, *J* = 8.2 Hz, 1H), 7.01 (d, *J* = 7.4 Hz, 1H), 4.65 – 4.59F (m, 1H), 4.50 (s, 2H), 4.24 (d, *J* = 3.9 Hz, 2H), 2.50 (s, 3H), 1.27 (d, *J* = 7.0 Hz, 3H).
Intermediate I-33 and (2S)-trifluoromethylpyrrolidine 	 **67** 7-[(3-methyl-1H-pyrazolo[4,3-b]pyridin-6-yl)amino]-2-[2-oxo-2-[(2S)-(trifluoromethyl)pyrrolidin-1-yl]ethyl]isoindolin-1-one **Example 67**	3.42 min, m/z 459.2 $[M+H]^+$ (Method 1)	12.60 (s, 1H), 8.92 (s, 1H), 8.39 (d, *J* = 2.3 Hz, 1H), 7.75 (d, *J* = 2.3 Hz, 1H), 7.46 (t, *J* = 7.8 Hz, 1H), 7.25 (d, *J* = 8.2 Hz, 1H), 7.02 (d, *J* = 7.2 Hz, 1H), 5.08 – 4.72 (m, 0H), 4.61 – 4.38 (m, 5H), 3.70 – 3.63 (m, 3H), 2.50 (s, 3H), 2.10 – 2.00 (m, 3H).
Intermediate I-33 and (2R)-(trifluoromethyl)morpholine hydrochloride 	 **68** 7-[(3-methyl-1H-pyrazolo[4,3-b]pyridin-6-yl)amino]-2-[2-oxo-2-	3.18 min, m/z 475.3 $[M+H]^+$ (Method 1)	12.61 (s, 1H), 8.92 (s, 1H), 8.38 (d, *J* = 2.3 Hz, 1H), 7.75 (d, *J* = 2.2 Hz, 1H), 7.46 (t, *J* = 7.8 Hz, 1H), 7.25 (d, *J* = 8.2 Hz, 1H), 7.01 (d, *J* = 7.4 Hz, 1H), 4.64 – 4.55 (m, 1H), 4.47 –

	[(2R)-(trifluoromethyl)morpholin-4-yl]ethyl]isoindolin-1-one **Example 68**		4.43 (m, 3H), 4.33– 4.24 (m, 1H), 4.15 – 4.01 (m, 2H), 3.90 – 3.54 (m, 2H), 2.93 – 2.87 (m, 1H), 2.50 – 2.49 (m, 3H), 2.03 – 1.97 (m, 1H).
Intermediate I-33 and (2S)-(trifluoromethyl)morpholine hydrochloride 	 **69** 7-[(3-methyl-1H-pyrazolo[4,3-b]pyridin-6-yl)amino]-2-[2-oxo-2-[(2S)-(trifluoromethyl)morpholin-4-yl]ethyl]isoindolin-1-one **Example 69**	3.18 min, m/z 475.3 $[M+H]^+$ (Method 1)	11.71 (s, 1H), 8.02 (s, 1H), 7.47 (d, *J* = 2.3 Hz, 1H), 6.84 (d, 1H), 6.57-6.53 (t, *J* = 7.8 Hz, 1H), 6.35-6.33 (d, *J* = 8.2 Hz, 1H), 6.11-6.09 (d, *J* = 7.4 Hz, 1H), 3.69 – 3.33 (m, 7H), 3.21 – 2.98 (m, 3H), 2.80 – 2.63 (m, 2H), 2.02-1.96 (t, 1H), 1.12 – 1.06 (m, 1H).
Intermediate I-33 and (3S)-(trifluoromethyl)morpholine hydrochloride 	 **70** 7-[(3-methyl-1H-pyrazolo[4,3-b]pyridin-6-yl)amino]-2-[2-oxo-2-[(3S)-(trifluoromethyl)morpholin-4-yl]ethyl]isoindolin-1-one **Example 70**	3.30 min, m/z 475.3 $[M+H]^+$ (Method 1)	(CD_3CN): 10.74 (s, 1H), 8.94 (s, 1H), 8.40 (s, 1H), 7.77 (s, 1H), 7.46-7.42 (m, 1H), 7.30-7.28 (m, 1H), 6.98-6.96 (m, 1H), 5.00-4.91 (m, 1H), 4.61-4.41 (m, 4H), 4.20-4.16 (m, 1H), 3.94-3.90 (m, 1H), 3.73-3.58 (m, 3H), 2.53 (s, 3H), 2.03-2.00 (m, 1H).

Intermediate I-33 and (3R)-(trifluoromethyl)morpholine hydrochloride 	 **71** 7-[(3-methyl-1H-pyrazolo[4,3-b]pyridin-6-yl)amino]-2-[2-oxo-2-[(3R)-(trifluoromethyl)morpholin-4-yl]ethyl]isoindolin-1-one **Example 71**	3.28 min, m/z 475.3 $[M+H]^+$ (Method 1)	(CD_3CN): 10.74 (s, 1H), 8.94 (s, 1H), 8.40 (s, 1H), 7.77 (s, 1H), 7.46-7.42 (m, 1H), 7.30-7.28 (m, 1H), 6.98-6.96 (m, 1H), 5.00-4.91 (m, 1H), 4.61-4.41 (m, 4H), 4.20-4.16 (m, 1H), 3.94-3.90 (m, 1H), 3.73-3.58 (m, 3H), 2.53 (s, 3H), 2.03-2.00 (m, 1H).
Intermediate I-40 and (2S)-(trifluoromethyl)pyrrolidine 	 **85** 7-[(1-methylpyrazolo[4,3-b]pyridin-5-yl)amino]-2-[2-oxo-2-[(2S)-(trifluoromethyl)pyrrolidin-1-yl]ethyl]isoindolin-1-one **Example 85**	3.87 min, m/z 459.1 $[M+H]^+$ (Method 1)	9.88 (s, 1H), 8.77 (d, *J* = 8.3 Hz, 1H), 8.10 – 7.99 (m, 2H), 7.57 (t, *J* = 7.9 Hz, 1H), 7.08 (d, *J* = 7.4 Hz, 1H), 7.05 – 6.98 (m, 1H), 5.35 – 4.69 (m, 1H), 4.65 – 4.38 (m, 4H), 4.04 (s, 3H), 3.73 – 3.62 (m, 2H), 2.15 – 1.91 (m, 4H).
Intermediate I-47 and 3-(trifluoromethyl)aniline 	 **94** 2-[7-[(3-methyl-1H-pyrazolo[4,3-b]pyridin-6-yl)amino]-1-oxo-isoindolin-2-yl]-N-[3-(trifluoromethyl)phenyl]acetamide **Example 94**	1.73 min, m/z 481.2 $[M+H]^+$ (Method 2)	12.61 (s, 1H), 10.60 (s, 1H), 8.92 (s, 1H), 8.39 (d, *J* = 2.3 Hz, 1H), 8.10 (d, *J* = 2.0 Hz, 1H), 7.81 – 7.74 (m, 2H), 7.58 (t, *J* = 8.0 Hz, 1H), 7.49 – 7.41 (m, 2H), 7.27 (d, *J* = 8.2 Hz, 1H), 7.03 (d, *J* = 7.5 Hz, 1H),

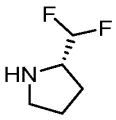
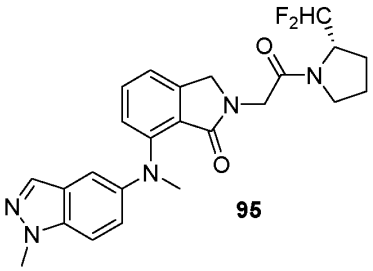
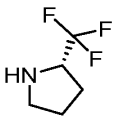
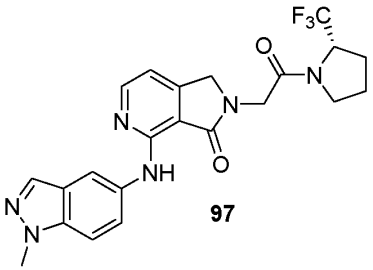
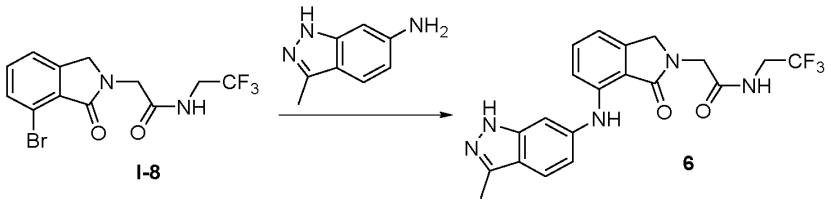
			4.58 (s, 2H), 4.43 (s, 2H), 1.23 (s, 3H).
Intermediate I-12 and (2S)-(difluoromethyl)pyrrolidine 	 **95** 7-[methyl-(1-methylindazol-5-yl)amino]-2-[2-oxo-2-[(2S)-(difluoromethyl)pyrrolidin-1-yl]ethyl]isoindolin-1-one **Example 95**	3.78 min, m/z 454.3 $[M+H]^+$ (Method 1)	7.85 (s, 1H), 7.48 (t, *J* = 7.6 Hz, 1H), 7.41 (d, *J* = 9.1 Hz, 1H), 7.27 (d, *J* = 7.4 Hz, 1H), 7.13 (s, 1H), 7.02 (d, *J* = 8.0 Hz, 1H), 6.93 (dd, *J* = 9.1, 2.3 Hz, 1H), 6.18 (t, *J* = 57.1 Hz, 1H), 4.46 – 4.45 (m, 2H), 4.34 (s, 2H), 4.27 – 4.21 (m, 1H), 3.97 (s, 3H), 3.55 – 3.52 (m, 2H), 3.35 (s, 3H), 2.01 – 1.89 (m, 4H).
Intermediate I-49 and (2S)-(trifluoromethyl) pyrrolidine hydrochloride 	 **97** 4-[(1-methylindazol-5-yl)amino]-2-[2-oxo-2-[(2S)-(trifluoromethyl)pyrrolidin-1-yl]ethyl]-1H-pyrrolo[3,4-c]pyridin-3-one **Example 97**	3.45 min, m/z 459.3 $[M+H]^+$ (Method 1)	9.00 (s, 1H), 8.40 (s, 1H), 8.33 (d, *J* = 5.2 Hz, 1H), 8.00 (s, 1H), 7.61 (d, *J* = 8.9 Hz, 1H), 7.50 (d, *J* = 10.4 Hz, 1H), 7.03 (d, *J* = 5.2 Hz, 1H), 4.77 – 4.73 (m, 1H), 4.52 – 4.40 (m, 4H), 4.03 (s, 3H), 3.70 – 3.66 (m, 2H), 2.05 – 2.00 (m, 4H).

Table 8

Example 6, 2-[7-[(3-Methyl-1H-indazol-6-yl)amino]-1-oxo-isoindolin-2-yl]-N-(2,2,2-trifluoroethyl) acetamide

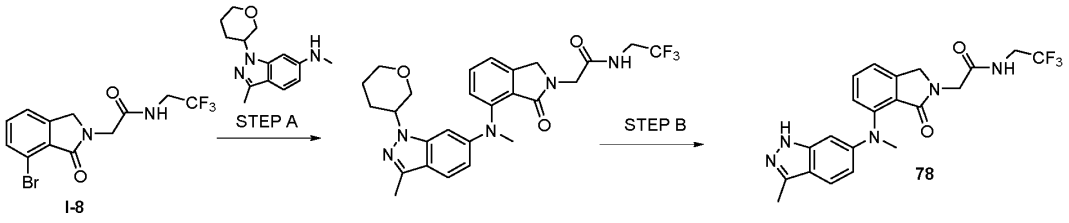


A mixture of 2-(7-bromo-1-oxo-isoindolin-2-yl)-N-(2,2,2-trifluoroethyl) acetamide (Intermediate I-8, 50 mg, 0.14 mmol), 3-methyl-1H-indazol-6-amine (25 mg, 0.17 mmol), $Pd_2(dba)_3$ (13 mg, 0.014 mmol), t-BuBrettphos (14 mg, 0.028 mmol), K_2CO_3 (40 mg, 0.28 mmol) and AcOH (4.2 mg, 0.07 mmol) in t-BuOH (2 mL) was heated to 110 °C and stirred for 16 h. The mixture was concentrated under reduced pressure and the crude product was purified by prep-HPLC to give 2-[7-[(3-methyl-1H-indazol-6-yl)amino]-1-oxo-isoindolin-2-yl]-N-(2,2,2-trifluoroethyl) acetamide (Example 6, 6.5 mg, 11% yield) as a white solid.

UPLC-MS (ES^+, Method 2): 1.58 min, m/z 418.0 $[M+H]^+$.

^1H NMR (400 MHz, DMSO-d_6) δ (ppm) 12.36 (s, 1H), 8.83-8.79 (m, 2H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.44 (t, *J* = 8.0 Hz, 1H), 7.31 (s, 1H), 7.27 (d, *J* = 8.0 Hz, 1H), 6.95 (d, *J* = 8.0 Hz, 2H), 4.48 (s, 2H), 4.25 (s, 2H), 3.99-3.90 (m, 2H), 2.45 (s, 3H).

Example 78, 2-[7-[methyl-(3-methyl-1H-indazol-6-yl)amino]-1-oxo-isoindolin-2-yl]-N-(2,2,2-trifluoroethyl)acetamide



Scheme 3

STEP A. 2-(7-bromo-1-oxo-isoindolin-2-yl)-N-(2,2,2-trifluoroethyl)acetamide (intermediate I-8) was reacted with N,3-dimethyl-1-tetrahydropyran-2-yl-indazol-6-amine in an analogous fashion to Scheme 6 to afford 2-[7-[methyl-(3-methyl-1-tetrahydropyran-2-yl-indazol-6-yl)amino]-1-oxo-isoindolin-2-yl]-N-(2,2,2-trifluoroethyl)acetamide.

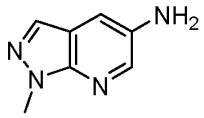
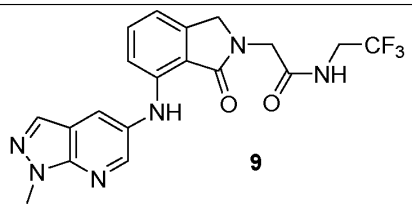
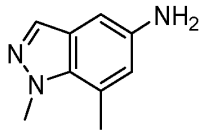
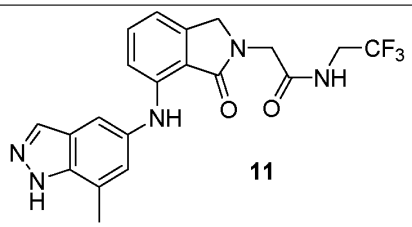
UPLC-MS (ES^+, Method 1): 3.81 min, m/z 516.3 $[M+H]^+$.

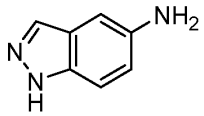
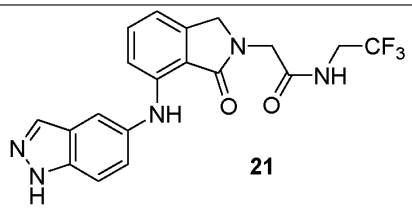
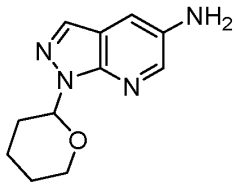
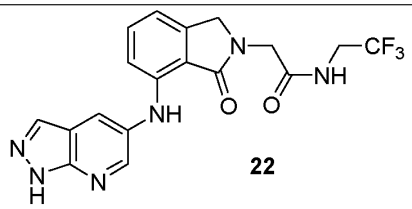
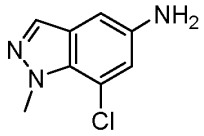
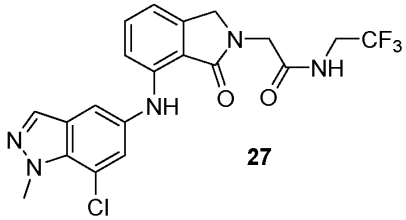
STEP B. 2-[7-[methyl-(3-methyl-1-tetrahydropyran-2-yl-indazol-6-yl)amino]-1-oxo-isoindolin-2-yl]-N-(2,2,2-trifluoroethyl)acetamide (200 mg, 0.39 mmol) was dissolved in DCM (6 mL) and TFA (2 mL) and stirred at room temperature for 30 mins. The solvents were removed *in vacuo* to leave a residue that was purified by preparative-HPLC to afford 2-[7-[methyl-(3-methyl-1H-indazol-6-yl)amino]-1-oxo-isoindolin-2-yl]-N-(2,2,2-trifluoroethyl)acetamide (21 mg, 13% yield) as a yellow solid.

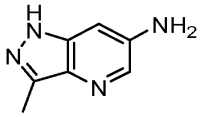
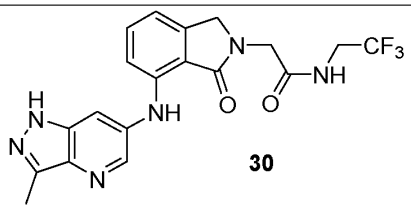
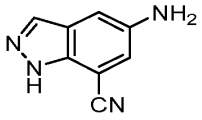
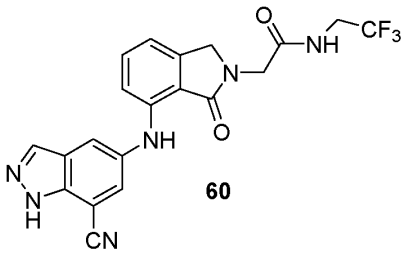
UPLC-MS (ES^+, Method 1): 3.35 min, m/z 432.2 $[M+H]^+$.

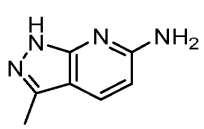
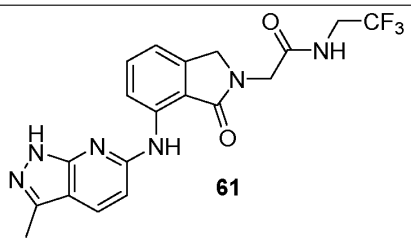
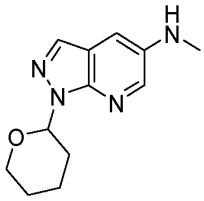
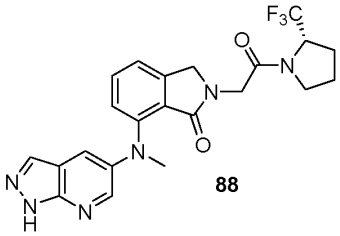
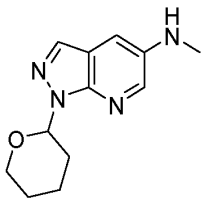
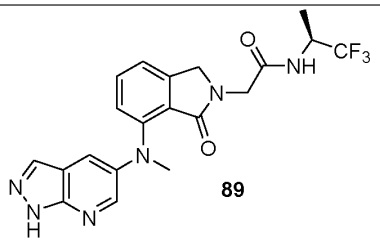
^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 12.12 (s, 1H), 8.79 (t, *J* = 6.4 Hz, 1H), 7.58 (t, *J* = 7.7 Hz, 1H), 7.43 (d, *J* = 7.4 Hz, 1H), 7.38 (d, *J* = 8.8 Hz, 1H), 7.21 (d, *J* = 7.9 Hz, 1H), 6.65 (d, *J* = 2.0 Hz, 1H), 6.50 (dd, *J* = 8.8, 2.0 Hz, 1H), 4.53 (s, 2H), 4.22 (s, 2H), 3.99 – 3.89 (m, 2H), 3.33 (s, 3H), 2.40 (s, 3H).

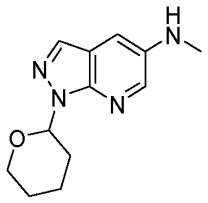
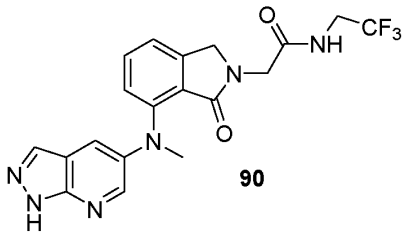
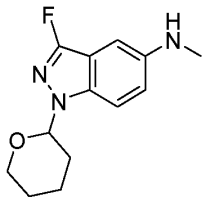
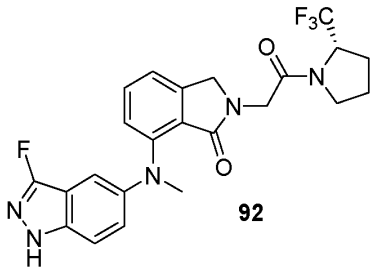
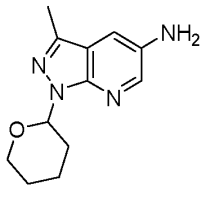
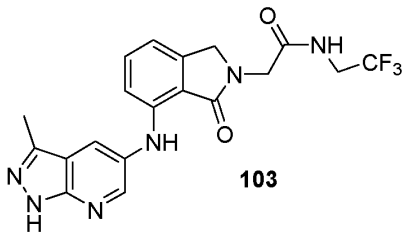
Examples synthesised following the same procedure as example 6 replacing 3-methyl-1H-indazol-6-amine and I-8 with the appropriate building blocks are described in table 9. In cases where a THP-protected building block was coupled with intermediate I-8 or analogues (as indicated in the table), a final THP deprotection step was required to afford the corresponding example. THP deprotection was carried out under standard conditions as described for example 78 in Scheme

Building Block	Structure/Name	LCMS	^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm)
Intermediate I-8 and 1-methylpyrazolo[3,4-b]pyridine-5-amine 	 **9** 2-[7-[(1-methylpyrazolo[3,4-b]pyridin-5-yl)amino]-1-oxo-isoindolin-2-yl]-N-(2,2,2-trifluoroethyl)acetamide **Example 9**	1.50 min, m/z 419.1 $[M+H]^+$. (Method 2)	8.80 (t, *J* = 6.3 Hz, 1H), 8.62 (s, 1H), 8.52 (d, *J* = 2.4 Hz, 1H), 8.16 (d, *J* = 2.4 Hz, 1H), 8.08 (s, 1H), 7.36 (t, *J* = 7.9 Hz, 1H), 6.91 (d, *J* = 7.8 Hz, 2H), 4.48 (s, 2H), 4.25 (s, 2H), 4.06 (s, 3H), 3.99-3.90 (m, 2H).
Intermediate I-8 and 7-methyl-1H-indazol-5-amine 	 **11** 2-[7-[(7-methyl-1H-indazol-5-yl)amino]-1-oxo-isoindolin-2-yl]-N-(2,2,2-trifluoroethyl)acetamide **Example 11**	3.56 min, m/z 418.2 $[M+H]^+$ (Method 1)	13.14 (s, 1H), 8.82 (t, J=6.1 Hz, 1H), 8.57 (s, 1H), 8.01 (s, 1H), 7.49 (s, 1H), 7.37 (t, J=7.8 Hz, 1H), 7.06 (s, 1H), 7.02 (d, J=8.4 Hz, 1H), 6.87 (d, J=7.2 Hz, 1H), 4.48 (s, 2H), 4.26 (s, 2H), 3.97 (dq, J=6.6, 9.6 Hz, 2H) (CH_3

			signal under solvent peak)
Intermediate I-8 and 1H-indazol-5-amine 	 **21** 2-[7-(1H-indazol-5-ylamino)-1-oxo-isoindolin-2-yl]-N-(2,2,2-trifluoroethyl)acetamide **Example 21**	1.32 min, m/z 404.1 $[M+H]^+$ (Method 2)	13.04 (s, 1H), 8.81 (t, *J* = 6.4 Hz, 1H), 8.58 (s, 1H), 8.01 (s, 1H), 7.65 (s, 1H), 7.56 (d, *J* = 8.8 Hz, 1H), 7.35 (t, *J* = 7.8 Hz, 1H), 7.26 (dd, *J* = 8.8, 2.0 Hz, 1H), 6.99 (d, *J* = 8.3 Hz, 1H), 6.86 (d, *J* = 7.4 Hz, 1H), 4.46 (s, 2H), 4.24 (s, 2H), 3.98-3.90 (m, 2H).
Intermediate I-8 and 1-tetrahydropyran-2-ylpyrazolo[3,4-b]pyridin-5-amine 	 **22** 2-[1-oxo-7-(1H-pyrazolo[3,4-b]pyridin-5-ylamino)isoindolin-2-yl]-N-(2,2,2-trifluoroethyl)acetamide **Example 22**	3.21 min, m/z 405.2 $[M+H]^+$ (Method 1)	13.63 (s, 1H), 8.82 (t, *J* = 6.4 Hz, 1H), 8.60 (s, 1H), 8.47 (d, *J* = 2.4 Hz, 1H), 8.15 (d, *J* = 2.4 Hz, 1H), 8.09 (s, 1H), 7.35 (t, *J* = 7.8 Hz, 1H), 6.91 (s, 1H), 6.89 (s, 1H), 4.48 (s, 2H), 4.25 (s, 2H), 4.00 – 3.89 (m, 2H).
Intermediate I-8 and 7-chloro-1-methyl-indazol-5-amine 	 **27**	4.06 min, m/z 452.1 $[M+H]^+$ (Method 1)	8.84 (t, J=6.4 Hz, 1H), 8.65 (s, 1H), 8.07 (s, 1H), 7.68 (s, 1H), 7.44 - 7.38 (m, 2H), 7.08 (d, J=8.2 Hz, 1H), 6.94 (d,

	2-[7-[(7-chloro-1-methyl-indazol-5-yl)amino]-1-oxo-isoindolin-2-yl]-N-(2,2,2-trifluoroethyl)acetamide **Example 27**		J=7.4 Hz, 1H), 4.49 (s, 2H), 4.32 (s, 3H), 4.27 (s, 2H), 3.96 (dq, J=6.4, 9.6 Hz, 2H).
Intermediate I-8 and 3-methyl-1H-pyrazolo[4,3-b]pyridin-6-amine 	 **30** 2-[7-[(3-methyl-1H-pyrazolo[4,3-b]pyridin-6-yl)amino]-1-oxo-isoindolin-2-yl]-N-(2,2,2-trifluoroethyl)acetamide **Example 30**	3.15 min, m/z 419.1 $[M+H]^+$ (Method 1)	12.62 (s, 1H), 8.90 (s, 1H), 8.83 (t, *J* = 6.4 Hz, 1H), 8.39 (d, *J* = 2.2 Hz, 1H), 7.75 (d, *J* = 2.2 Hz, 1H), 7.45 (t, *J* = 7.8 Hz, 1H), 7.25 (d, *J* = 8.2 Hz, 1H), 7.01 (d, *J* = 7.4 Hz, 1H), 4.50 (s, 2H), 4.26 (s, 2H), 3.99– 3.90 (m, 2H), 2.52 (s, 3H).
Intermediate I-8 and  5-amino-1H-indazole-7-carbonitrile	 **60** 2-[7-[(7-cyano-1H-indazol-5-yl)amino]-1-oxo-isoindolin-2-yl]-N-(2,2,2-trifluoroethyl)acetamide **Example 60**	1.45 min, m/z 429.1 $[M+H]^+$ (Method 1)	13.94 (s, 1H), 8.81 (t, *J* = 6.3 Hz, 1H), 8.65 (s, 1H), 8.23 (s, 1H), 8.07 (s, 1H), 7.89 (s, 1H), 7.38 (t, *J* = 7.8 Hz, 1H), 7.02 (d, *J* = 8.3 Hz, 1H), 6.93 (d, *J* = 7.4 Hz, 1H), 4.48 (s, 2H), 4.25 (s, 2H), 3.97-3.92 (m, 2H).

Intermediate I-8 and  3-methyl-1H-pyrazolo[3,4-b]pyridin-6-amine	 **61** **2**-[7-[(3-methyl-1H-pyrazolo[3,4-b]pyridin-6-yl)amino]-1-oxo-isoindolin-2-yl]-N-(2,2,2-trifluoroethyl)acetamide **Example 61**	3.45 min, m/z 419.2 $[M+H]^+$ (Method 1)	12.79 (s, 1H), 9.97 (s, 1H), 8.84 – 8.76 (m, 2H), 7.99 (d, *J* = 8.5 Hz, 1H), 7.57 (t, *J* = 7.9 Hz, 1H), 7.12 (d, *J* = 7.4 Hz, 1H), 6.66 (d, *J* = 8.6 Hz, 1H), 4.51 (s, 2H), 4.28 (s, 2H), 3.99 – 3.90 (m, 2H), 2.41 (s, 3H).
Intermediate I-43 and  N-methyl-1-tetrahydropyran-2-yl-pyrazolo[3,4-b]pyridin-5-amine	 **88** 7-[methyl(1H-pyrazolo[3,4-b]pyridin-5-yl)amino]-2-[2-oxo-2-[(2S)-(trifluoromethyl)pyrrolidin-1-yl]ethyl]isoindolin-1-one **Example 88**	3.38 min, m/z 459.3 $[M+H]^+$ (Method 1)	13.36 (s, 1H), 8.15 – 8.10 (m, 1H), 7.94 (s, 1H), 7.59 – 7.53 (m, 2H), 7.32 (d, J = 7.5 Hz, 1H), 7.15 (d, J = 8.0 Hz, 1H), 5.02 – 4.65 (m, 1H), 4.55 – 4.19 (m, 4H), 3.72 – 3.48 (m, 2H), 3.36 (s, 3H), 2.17 – 1.85 (m, 4H).
Intermediate I-44 and  N-methyl-1-tetrahydropyran-2-yl-pyrazolo[3,4-b]pyridin-5-amine	 **89** 2-[7-[methyl(1H-pyrazolo[3,4-b]pyridin-5-yl)amino]-1-oxo-isoindolin-2-yl]-N-[(1S)-2,2,2-trifluoro-1-methyl-ethyl]acetamide	1.23 min, m/z 433.1 $[M+H]^+$ (Method 2)	13.36 (s, 1H), 8.64 (d, *J* = 8.8 Hz, 1H), 8.12 (d, *J* = 2.6 Hz, 1H), 7.95 (s, 1H), 7.58 – 7.51 (m, 2H), 7.32 (d, *J* = 7.5 Hz, 1H), 7.12 (d, *J* = 8.0 Hz, 1H), 4.64 – 4.51 (m, 1H), 4.47 (s, 2H), 4.20 – 4.05

	Example 89		(m, 2H), 3.36 (s, 3H), 1.23 (d, *J* = 6.9 Hz, 3H).
Intermediate I-8 and  N-methyl-1-tetrahydropyran-2-yl-pyrazolo[3,4-b]pyridin-5-amine	 **90** 2-[7-[methyl(1H-pyrazolo[3,4-b]pyridin-5-yl)amino]-1-oxo-isoindolin-2-yl]-N-(2,2,2-trifluoroethyl)acetamide **Example 90**	3.15 min, m/z 419.2 $[M+H]^+$ (Method 1)	3.37 (s, 1H), 8.73 (t, *J* = 6.3 Hz, 1H), 8.12 (d, *J* = 2.6 Hz, 1H), 7.95 (s, 1H), 7.60 – 7.51 (m, 2H), 7.32 (d, *J* = 7.4 Hz, 1H), 7.12 (d, *J* = 8.0 Hz, 1H), 4.47 (s, 2H), 4.14 (s, 2H), 3.96 – 3.84 (m, 2H), 3.36 (s, 3H).
Intermediate I-43 and  3-fluoro-N-methyl-1-tetrahydropyran-2-yl-pyrazolo[3,4-b]pyridin-5-amine	 **92** 7-[(3-fluoro-1H-indazol-5-yl)-methyl-amino]-2-[2-oxo-2-[(2S)-(trifluoromethyl)pyrrolidin-1-yl]ethyl]isoindolin-1-one **Example 92**	3.88 min, m/z 476.2 $[M+H]^+$ (Method 1)	12.25 (s, 1H), 7.52 (t, *J* = 7.7 Hz, 1H), 7.29 (d, *J* = 32.2, 8.3 Hz, 2H), 7.08 (d, *J* = 8.0 Hz, 1H), 7.01 – 6.88 (m, 2H), 5.04 – 4.67 (m, 1H), 4.57 – 4.27 (m, 4H), 3.71 – 3.54 (m, 2H), 3.32 (s, 3H), 2.10 – 1.88 (m, 4H).
Intermediate I-8 and  3-methyl-1-tetrahydropyran-2-yl-	 **103**	3.31 min, m/z 419.3 $[M+H]^+$ (Method 1)	13.19 (s, 1H), 8.85 (t, *J* = 6.4 Hz, 1H), 8.56 (s, 1H), 8.43 (d, *J* = 2.4 Hz, 1H), 8.11 (d, *J* = 2.4 Hz, 1H), 7.35 (t, *J* = 7.8 Hz, 1H), 6.88

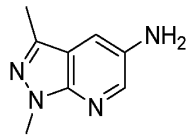
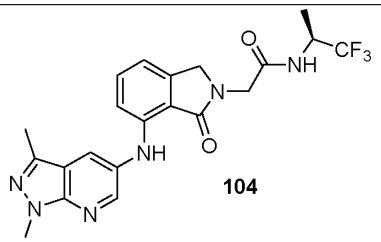
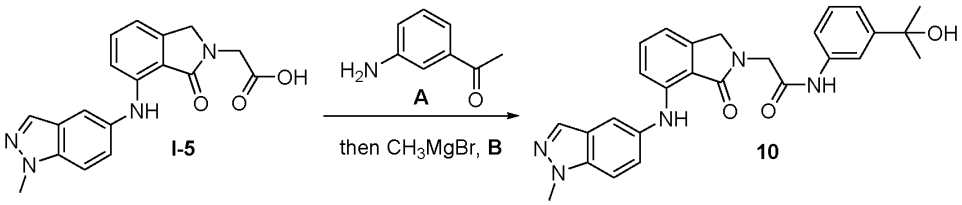
pyrazolo[3,4-b]pyridin-5-amine	2-[7-[(3-methyl-1H-pyrazolo[3,4-b]pyridin-5-yl)amino]-1-oxo-isoindolin-2-yl]-N-(2,2,2-trifluoroethyl)acetamide **Example 103**		(t, *J* = 8.2 Hz, 2H), 4.48 (s, 2H), 4.26 (s, 2H), 4.00 – 3.89 (m, 2H) – *Methyl (3H) under solvent signal (2.5ppm)*
Intermediate I-44 and  3-methyl-1-methyl-pyrazolo[3,4-b]pyridin-5-amine	 **104** 2-[7-[(1,3-dimethylpyrazolo[3,4-b]pyridin-5-yl)amino]-1-oxo-isoindolin-2-yl]-N-[(1S)-2,2,2-trifluoro-1-methyl-ethyl]acetamide **Example 104**	1.59 min, m/z 447.2 $[M+H]^+$ (Method 2)	8.80 (s, 1H), 8.58 (s, 1H), 8.48 (s, 1H), 8.14 (s, 1H), 7.37 – 7.33 (m, 1H), 6.90 – 6.86 (m, 2H), 4.65 – 4.58 (m, 1H), 4.56 (s, 2H), 4.25 (s, 2H), 3.98 (s, 3H), 2.48 (s, 3H), 1.27 (s, 3H).

Table 9

Example 10, N-[3-(1-hydroxy-1-methyl-ethyl)phenyl]-2-[7-[(1-methylindazol-5-yl)amino]-1-oxo-isoindolin-2-yl]acetamide



Scheme 4

STEP A. Intermediate N-(3-acetylphenyl)-2-[7-[(1-methylindazol-5-yl)amino]-1-oxo-isoindolin-2-yl]acetamide was synthesised following the same procedure as for Example 1, using 3-aminoacetophenone as the coupling partner with Intermediate I-5. The compound was obtained as a white solid (40 mg, 0.09 mmol, 37% yield from 80 mg of Intermediate I-5)

UPLC-MS (ES^+, Method 1): 3.82 min, m/z 454.2 $[M+H]^+$.

^1H NMR (400 MHz, DMSO-d_6) δ (ppm) 10.45 (s, 1H), 8.64 (s, 1H), 8.21 (s, 1H), 7.99 (s, 1H), 7.87 (d, J=8.0 Hz, 1H), 7.73 - 7.65 (m, 3H), 7.51 (t, J=7.9 Hz, 1H), 7.39 (t, J=7.8 Hz, 1H), 7.34 (dd, J=1.8, 8.9

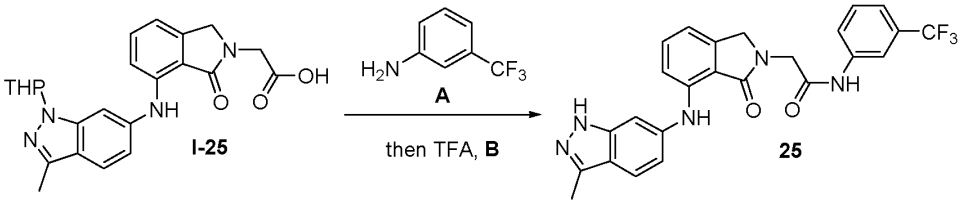
Hz, 1H), 7.03 (d, J=8.3 Hz, 1H), 6.91 (d, J=7.4 Hz, 1H), 4.57 (s, 2H), 4.42 (s, 2H), 4.06 (s, 3H), 2.58 (s, 3H).

STEP B. N-[3-(1-Hydroxy-1-methyl-ethyl)phenyl]-2-[7-[(1-methylindazol-5-yl)amino]-1-oxo-isoindolin-2-yl]acetamide (example 10). A solution of N-(3-acetylphenyl)-2-[7-[(1-methylindazol-5-yl)amino]-1-oxo-isoindolin-2-yl]acetamide (40 mg, 0.09 mmol) in THF (1 mL) was cooled to 0 °C and methylmagnesium bromide (1 M in THF, 3.5 mmol, 3.5 mL) was added dropwise. The mixture was stirred at 0 °C for 2 h. Saturated NH_4Cl (5 mL) and EtOAc (5 mL) were added, the layers were separated and the aqueous layer was extracted with EtOAc (3 x 5mL). The organic layers were combined, dried over Na_2SO_4 and concentrated in vacuo. Purification by prep HPLC afforded N-[3-(1-hydroxy-1-methyl-ethyl)phenyl]-2-[7-[(1-methylindazol-5-yl)amino]-1-oxo-isoindolin-2-yl]acetamide (5 mg, 0.1 mmol, 13% yield) as an off-white solid.

UPLC-MS (ES^+, Method 1): 3.69 min, m/z 452.3 $[M-H_2O+H]^+$.

^1H NMR (400 MHz, DMSO-d_6) δ (ppm) 10.18 (s, 1H), 8.65 (s, 1H), 8.00 (s, 1H), 7.72 - 7.65 (m, 3H), 7.50 (d, J=8.2 Hz, 1H), 7.39 (t, J=7.6 Hz, 1H), 7.34 (d, J=10.2 Hz, 1H), 7.25 (t, J=7.9 Hz, 1H), 7.17 (d, J=7.8 Hz, 1H), 7.03 (d, J=8.3 Hz, 1H), 6.90 (d, J=7.4 Hz, 1H), 5.01 (s, 1H), 4.56 (s, 2H), 4.38 (s, 2H), 4.07 (s, 3H), 1.43 (s, 6H).

Example 25, 2-[7-[(3-methyl-1H-indazol-6-yl)amino]-1-oxo-isoindolin-2-yl]-N-[3-(trifluoromethyl) phenyl]acetamide



Scheme 5

STEP A. Intermediate 2-[7-[(3-methyl-1-tetrahydropyran-2-yl-indazol-6-yl)amino]-1-oxo-isoindolin-2-yl]-N-[3-(trifluoromethyl)phenyl]acetamide was synthesised following the same procedure as for Example 1, using 3-(trifluoromethyl)aniline as the coupling partner with Intermediate I-25. The compound was obtained as an off-white solid (60 mg, 0.1 mmol, 24% yield from 150 mg of Intermediate I-25).

UPLC-MS (ES^+, Method 1): 4.52 min, m/z 564.2 $[M+H]^+$.

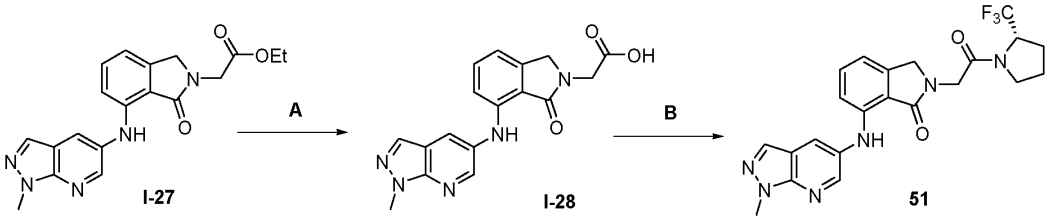
^1H NMR (400 MHz, DMSO-d_6) δ (ppm) 10.58 (s, 1H), 8.95 (s, 1H), 8.13 (s, 1H), 7.81 (d, J=8.3 Hz, 1H), 7.68 (d, J=8.7 Hz, 1H), 7.60 (t, J=7.9 Hz, 1H), 7.51 - 7.48 (m, 2H), 7.45 (d, J=7.6 Hz, 1H), 7.33 (d, J=7.9 Hz, 1H), 7.10 (d, J=7.2 Hz, 1H), 7.01 (d, J=7.1 Hz, 1H), 5.75 - 5.72 (m, 1H), 4.59 (s, 2H), 4.44 (s, 2H), 3.90 - 3.87 (m, 1H), 3.76 - 3.69 (m, 1H), 2.47 (s, 3H), 2.45 - 2.34 (m, 2H), 1.96 - 1.92 (m, 1H), 1.80 - 1.70 (m, 1H), 1.59 - 1.53 (m, 2H).

STEP B. 2-[7-[(3-methyl-1H-indazol-6-yl)amino]-1-oxo-isoindolin-2-yl]-N-[3-(trifluoromethyl)phenyl]acetamide (Example 25). To a solution of 2-[7-[(3-methyl-1-tetrahydropyran-2-yl-indazol-6-yl)amino]-1-oxo-isoindolin-2-yl]-N-[3-(trifluoromethyl)phenyl]acetamide (60 mg, 0.1 mmol) in DCM (3 mL) was added TFA (2.5 mL) dropwise. The mixture was stirred at room temperature for 2 h, then it was concentrated *in vacuo* and purified by prep-HPLC to give 2-[7-[(3-methyl-1H-indazol-6-yl)amino]-1-oxo-isoindolin-2-yl]-N-[3-(trifluoromethyl)phenyl]acetamide (Example 25, 13 mg, 0.03 mmol, 25% yield) as a yellow solid.

UPLC-MS (ES^+, Method 1): 4.05 min, m/z 480.2 $[M+H]^+$.

^1H NMR (400 MHz, DMSO-d_6) δ (ppm) 12.37 (s, 1H), 10.55 (s, 1H), 8.84 (s, 1H), 8.10 (s, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.64 (d, *J* = 8.4 Hz, 1H), 7.57 (t, 1H), 7.46 (d, *J* = 8.6 Hz, 1H), 7.43 (s, 1H), 7.32 (s, 1H), 7.29 (s, 1H), 6.97 (s, 1H), 4.56 (s, 2H), 4.41 (s, 2H), 2.45 (s, 3H).

Example 51, 7-[(1-methylpyrazolo[3,4-b]pyridin-5-yl)amino]-2-[2-oxo-2-[(2S)-2-(trifluoromethyl)pyrrolidin-1-yl]ethyl]isoindolin-1-one



Scheme 6

STEP A. Intermediate I-28, 2-[7-[(1-methylpyrazolo[3,4-b]pyridin-5-yl)amino]-1-oxo-isoindolin-2-yl]acetic acid. A mixture of ethyl 2-(7-((1-methyl-1H-pyrazolo[3,4-b]pyridin-5-yl)amino)-1-oxoisoindolin-2-yl)acetate (I-27) (1.12 g, 3.067 mmol, 1.0 eq) and $LiOH.H_2O$ (386 mg, 9.2 mmol) in H2O/THF/MeOH (1:1:1, 18 mL) was stirred at room temperature for 2 h. The reaction was diluted with water (200 mL) and was washed with DCM (100 mL x 3). The water layer was adjusted to pH~3 by slow addition of 1M HCl. The mixture was washed with DCM (200 mL x 3) and was concentrated to give I-28, 2-[7-[(1-methylpyrazolo[3,4-b]pyridin-5-yl)amino]-1-oxo-isoindolin-2-yl]acetic acid as a yellow solid (960 mg, 93% yield).

UPLC-MS (ES^+, Method 2): 0.82 min, m/z 338.2 $[M+H]^+$.

^1H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.62 (s, 1H), 8.52 (d, *J* = 5.9Hz, 1H), 8.17 (d, *J* = 5.9Hz, 1H), 8.08 (s, 1H), 7.38 – 7.34 (m, 1H), 6.91 (d, *J* = 6.9Hz, 2H), 4.27 (s, 2H), 4.06 (s, 3H).

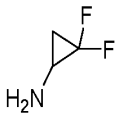
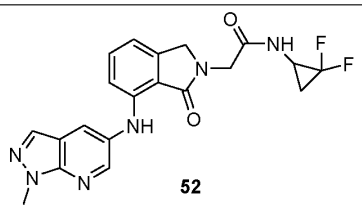
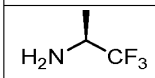
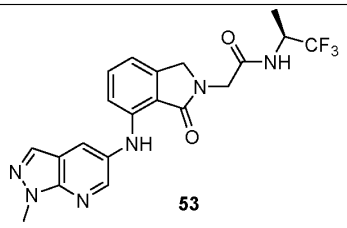
STEP B. 7-[(1-methylpyrazolo[3,4-b]pyridin-5-yl)amino]-2-[2-oxo-2-[(2S)-2-(trifluoromethyl)pyrrolidin-1-yl]ethyl]isoindolin-1-one (Example 51). A mixture of 2-(7-((1-methyl-1H-pyrazolo[3,4-b]pyridin-5-yl)amino)-1-oxoisoindolin-2-yl)acetic acid (I-28) (237 mg, 0.70 mmol), (S)-2-(trifluoromethyl)pyrrolidine (195.48 mg, 1.40 mmol), HATU (400.7 mg, 1.05 mmol) and DIEA (272.39 mg, 2.10 mmol) in DMF (8 mL) was stirred at room temperature overnight. The mixture was diluted with 40 mL of water and was

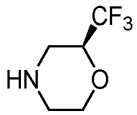
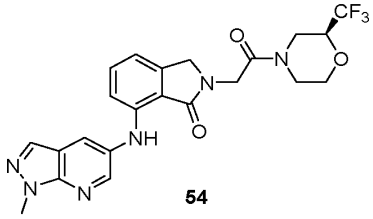
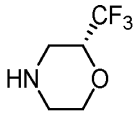
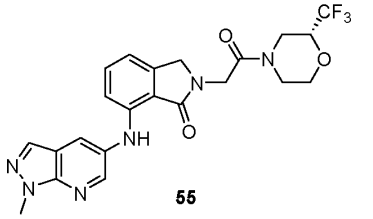
extracted with ethyl acetate (10 mL x 5). The organic solution was washed with brine (25 mL x 3), dried over Na_2SO_4 and concentrated under vacuum. The crude was purified by prep-TLC (DCM/MeOH=20/1, v/v). Methanol (2 mL) was added to the product and filtered, and the solid was concentrated and dried to give 7-[(1-methylpyrazolo[3,4-b]pyridin-5-yl)amino]-2-[2-oxo-2-[(2S)-2-(trifluoromethyl)pyrrolidin-1-yl]ethyl]isoindolin-1-one (Example 51) (140 mg, 43.4%.yield) as a yellow solid.

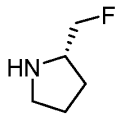
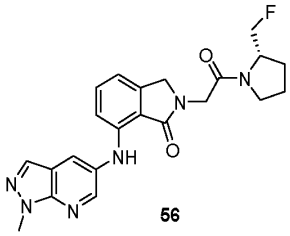
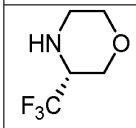
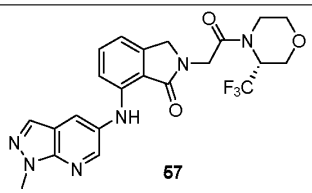
UPLC-MS (ES^+, Method 2): 1.70 min, m/z, 459.15 [M+H].

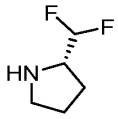
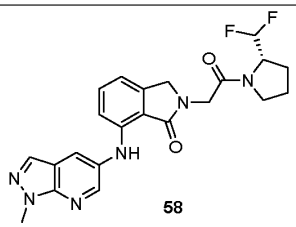
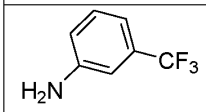
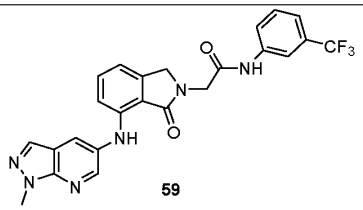
1H NMR (400 MHz, DMSO-d6) δ (ppm) 8.63 (s, 1H), 8.53 (d, J = 2.4 Hz, 1H), 8.17 (d, J = 2.4 Hz, 1H), 8.08 (s, 1H), 7.36 (t, J = 7.8 Hz, 1H), 6.91 (d, J = 7.8 Hz, 2H), 5.08 – 4.40 (m, 5H), 4.07 (s, 3H), 3.71 – 3.63 (m, 2H), 2.16 – 1.90 (m, 4H).

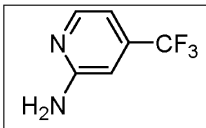
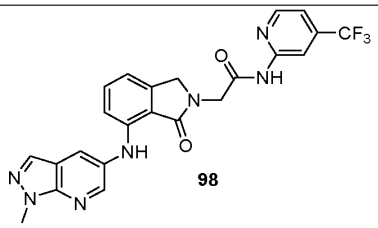
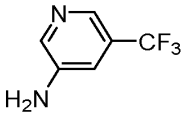
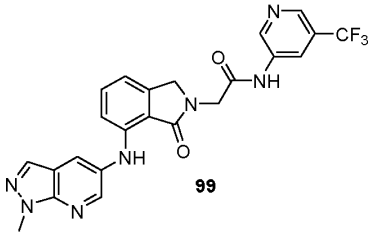
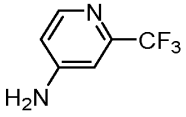
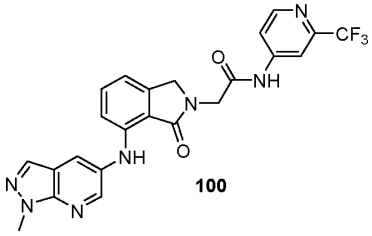
Examples synthesised from I-28 following the same procedure as in step B for example 51 (Scheme 6) replacing (S)-2-(trifluoromethyl)pyrrolidine with the appropriate building block are described in table 10.

Building Block	Structure/Name	LCMS	^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm)
 2,2-difluorocyclopropanamine	 **52** N-(2,2-difluorocyclopropyl)-2-[7-[(1-methylpyrazolo[3,4-b]pyridin-5-yl)amino]-1-oxo-isoindolin-2-yl]acetamide **Example 52**	3.38 min, m/z 413.1 $[M+H]^+$ (Method 1)	δ 8.63 (s, 1H), 8.59 (t, *J* = 3.3 Hz, 1H), 8.52 (d, *J* = 2.4 Hz, 1H), 8.16 (d, *J* = 2.4 Hz, 1H), 8.08 (s, 1H), 7.36 (t, *J* = 7.8 Hz, 1H), 6.91 (d, 2H), 4.48 (s, 2H), 4.20 (s, 2H), 4.07 (s, 3H), 3.33 (d, *J* = 6.3 Hz, 1H), 1.97 – 1.85 (m, 1H), 1.55 – 1.49 (m, 1H).
 (2S)-Amino-1,1,1-trifluoropropane hydrochloride	 **53**	3.61 min, m/z 433.2 $[M+H]^+$ (Method 1)	δ 8.73 (d, J = 8.9 Hz, 1H), 8.63 (s, 1H), 8.52 (d, J = 2.4 Hz, 1H), 8.17 (d, J = 2.4 Hz, 1H), 8.08 (s, 1H),

	2-[7-[(1-methylpyrazolo[3,4-b]pyridin-5-yl)amino]-1-oxo-isoindolin-2-yl]-N-[(1S)-2,2,2-trifluoro-1-methyl-ethyl]acetamide **Example 53**		7.35 (t, J = 7.8 Hz, 1H), 6.91 (d, J = 7.7 Hz, 2H), 4.67 – 4.58 (m, 1H), 4.48 (s, 2H), 4.29 – 4.19 (m, 2H), 4.07 (s, 3H), 1.27 (d, J = 7.0 Hz, 3H).
 (2S)-(trifluoromethyl)morpholine	 **54** 7-[(1-methylpyrazolo[3,4-b]pyridin-5-yl)amino]-2-[2-oxo-2-[(2S)-(trifluoromethyl)morpholin-4-yl]ethyl]isoindolin-1-one **Example 54**	3.72 min, m/z 475.2 $[M+H]^+$ (Method 1)	δ 8.63 (s, 1H), 8.52 (d, J = 2.4 Hz, 1H), 8.17 (d, J = 2.4 Hz, 1H), 8.08 (s, 1H), 7.36 (t, J = 7.8 Hz, 1H), 6.92 – 6.90 (m, 2H), 4.63 – 4.54 (m, 1H), 4.46 – 4.44 (m, 3H) , 4.38 – 4.31 (m, 1H), 4.24 – 4.13 (m, 1H), 4.07 – 3.88 (m, 1H), 3.71 – 3.54 (m, 1H), 3.38 – 3.37 (m, 1H), 2.90 (t, J = 11.8 Hz, 1H).
 (2R)-(trifluoromethyl)morpholine	 **55** 7-[(1-methylpyrazolo[3,4-b]pyridin-5-yl)amino]-2-[2-oxo-2-[(2R)-(trifluoromethyl)morpholin-4-yl]ethyl]isoindolin-1-one	3.68 min, m/z 475.1 $[M+H]^+$ (Method 1)	δ 8.63 (s, 1H), 8.52 (d, J = 2.4 Hz, 1H), 8.17 (d, J = 2.4 Hz, 1H), 8.08 (s, 1H), 7.36 (t, J = 7.8 Hz, 1H), 6.92 – 6.90 (m, 2H), 4.63 – 4.54 (m, 1H), 4.47 – 4.43 (m, 3H), 4.38 – 4.31

	Example 55		(m, 1H), 4.24 – 4.13 (m, 1H), 4.06 – 3.87 (m, 5H), 3.71 – 3.54 (m, 1H), 3.38 – 3.32 (m, 1H), 2.90 (t, J = 11.8 Hz, 1H).
 (2S)-(fluoromethyl)pyrrolidine	 **56** 7-[(1-methylpyrazolo[3,4-b]pyridin-5-yl)amino]-2-[2-oxo-2-[(2S)-(fluoromethyl)pyrrolidin-1-yl]ethyl]isoindolin-1-one **Example 56**	3.55 min, m/z 423.3 $[M+H]^+$ (Method 1)	δ 8.65 (d, J = 4.6 Hz, 1H), 8.52 (d, J = 2.4 Hz, 1H), 8.17 (d, J = 2.4 Hz, 1H), 8.08 (s, 1H), 7.35 (t, J = 7.8 Hz, 1H), 6.92-6.90 (m, 2H), 4.56 – 4.32 (m, 6H), 4.15 (d, J = 23.3 Hz, 1H), 4.06 (s, 3H), 3.57 – 3.45 (m, 2H), 2.0 – 1.81 (m, 4H).
 (3R)-(trifluoromethyl)morpholine	 **57** 7-[(1-methylpyrazolo[3,4-b]pyridin-5-yl)amino]-2-[2-oxo-2-[(3R)-(trifluoromethyl)morpholin-4-yl]ethyl]isoindolin-1-one **Example 57**	3.65 min, m/z 475.2 $[M+H]^+$ (Method 1)	δ 8.62 (s, 1H), 8.53 (d, J = 2.4 Hz, 1H), 8.17 (d, J = 2.4 Hz, 1H), 8.08 (s, 1H), 7.36 (t, J = 7.8 Hz, 1H), 6.93 – 6.90 (m, 2H), 4.99 – 4.88 (m, 1H), 4.68 (t, J = 17.0 Hz, 1H), 4.52 – 4.49 (m, 1H), 4.45 – 4.39 (m, 2H), 4.16 – 4.10 (m, 1H), 4.07 (s, 3H), 3.94 – 3.84

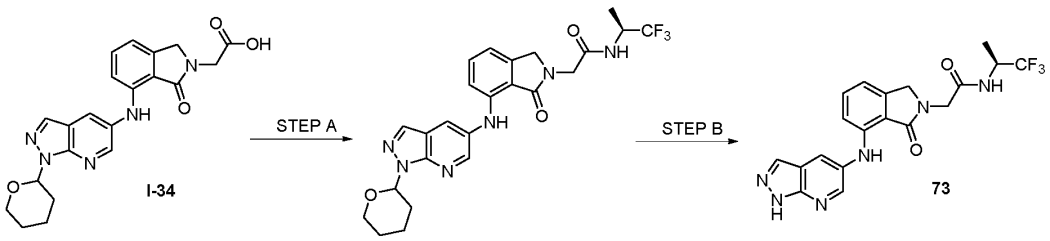
			(m, 2H), 3.77 – 3.66 (m, 1H), 3.58 – 3.44 (m, 2H).
 (2S)-(difluoromethyl)pyrrolidine	 58 7-[(1-methylpyrazolo[3,4-b]pyridin-5-yl)amino]-2-[2-oxo-2-[(2S)-(difluoromethyl)pyrrolidin-1-yl]ethyl]isoindolin-1-one **Example 58**	3.70 min, m/z 441.3 $[M+H]^+$ (Method 1)	δ 8.64 (d, J = 5.9 Hz, 1H), 8.52 (d, J = 2.4 Hz, 1H), 8.17 (d, J = 2.4 Hz, 1H), 8.08 (s, 1H), 7.35 (t, J = 7.9 Hz, 1H), 6.91 (d, J = 7.9 Hz, 2H), 6.20 (ddd, J = 57.7, 55.2, 1.9 Hz, 1H), 4.56 – 4.39 (m, 4H), 4.26 (d, J = 24.8 Hz, 1H), 4.06 (s, 3H), 3.65-3.52 (m, 2H), 2.06-1.92 (m, 4H).
 3-trifluoromethylanaline	 59 2-[7-[(1-methylpyrazolo[3,4-b]pyridin-5-yl)amino]-1-oxo-isoindolin-2-yl]-N-[3-(trifluoromethyl)phenyl]acetamide **Example 59**	2.01 min, m/z 481.2 $[M+H]^+$ (Method 1)	δ 10.54 (s, 1H), 8.64 (s, 1H), 8.53 (d, J = 2.4 Hz, 1H), 8.17 (d, J = 2.4 Hz, 1H), 8.10 (s, 1H), 8.09 (s, 1H), 7.83 – 7.73 (m, 1H), 7.58 (t, J = 8.0 Hz, 1H), 7.48 – 7.33 (m, 2H), 6.93 (d, J = 7.9 Hz, 2H), 4.56 (s, 2H), 4.42 (s, 2H), 4.07 (s, 3H).

 2-amino-4-(trifluoromethyl)pyridine	 **98** 2-[7-[(1-methylpyrazolo[3,4-b]pyridin-5-yl)amino]-1-oxo-isoindolin-2-yl]-N-[4-(trifluoromethyl)-2-pyridyl]acetamide **Example 98**	3.87 min, m/z 482.2 $[M+H]^+$ (Method 1)	11.30 (s, 1H), 8.63 (d, J = 5.9 Hz, 2H), 8.53 (d, J = 2.4 Hz, 1H), 8.36 (s, 1H), 8.17 (d, J = 2.4 Hz, 1H), 8.08 (s, 1H), 7.50 (d, J = 5.2 Hz, 1H), 7.37 (t, J = 7.8 Hz, 1H), 6.92 (d, J = 7.9 Hz, 2H), 4.55 (s, 2H), 4.50 (s, 2H), 4.06 (s, 3H).
 5-(trifluoromethyl)-3-aminopyridine	 **99** 2-[7-[(1-methylpyrazolo[3,4-b]pyridin-5-yl)amino]-1-oxo-isoindolin-2-yl]-N-[5-(trifluoromethyl)-3-pyridyl]acetamide **Example 99**	3.75 min, m/z 482.0 $[M+H]^+$ (Method 1)	0.87 (s, 1H), 8.97 (s, 1H), 8.66 (d, J = 21.0 Hz, 2H), 8.53 – 8.49 (m, 2H), 8.17 (d, J = 2.4 Hz, 1H), 8.08 (s, 1H), 7.38 (t, J = 7.8 Hz, 1H), 6.93 (d, J = 7.8 Hz, 2H), 4.57 (s, 2H), 4.46 (s, 2H), 4.07 (s, 3H).
 4-amino-2-trifluoromethylpyridine	 **100** 2-[7-[(1-methylpyrazolo[3,4-b]pyridin-5-yl)amino]-1-oxo-isoindolin-2-yl]-N-[2-(trifluoromethyl)-4-pyridyl]acetamide	3.78 min, m/z 482.2 $[M+H]^+$ (Method 1)	10.98 (s, 1H), 8.65 – 8.62 (m, 2H), 8.53 (d, J = 2.4 Hz, 1H), 8.17 (d, J = 2.4 Hz, 1H), 8.13 (d, J = 1.9 Hz, 1H), 8.08 (s, 1H), 7.77 (dd, J = 5.6, 1.9 Hz, 1H), 7.38 (t, J = 7.8 Hz, 1H), 6.94 – 6.91 (m, 2H),

	Example 100		4.56 (s, 2H), 4.46 (s, 2H), 4.06 (s, 3H).

Table 10

Exmaple 73, 2-[1-oxo-7-(1H-pyrazolo[3,4-b]pyridin-5-ylamino)isoindolin-2-yl]-N-[(1S)-2,2,2-trifluoro-1-methyl-ethyl]acetamide.



Scheme 7

STEP A. 2-[1-oxo-7-[(1-tetrahydropyran-2-ylpyrazolo[3,4-b]pyridin-5-yl)amino]isoindolin-2-yl]-N-[(1S)-2,2,2-trifluoro-1-methyl-ethyl]acetamide. A mixture of 2-(1-oxo-7-((1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridin-5-yl)amino)isoindolin-2-yl)acetic acid (80 mg, 0.19 mmol), (1S)-1,1,1-trifluoropropan-2-amine hydrochloride (44 mg, 0.29 mmol), HATU (110 mg, 0.29 mmol) and DIPEA (101 mg, 0.78 mmol) in DMF (2 mL) was stirred at room temperature overnight. The reaction was diluted with EtOAc (100 mL), washed with water (50 mL x3) and brine before drying with sodium sulfate. The crude was purified by silica gel flash column chromatography (DCM to DCM:MeOH, 50:1) and desired fractions were concentrated affording 2-[1-oxo-7-[(1-tetrahydropyran-2-ylpyrazolo[3,4-b]pyridin-5-yl)amino]isoindolin-2-yl]-N-[(1S)-2,2,2-trifluoro-1-methyl-ethyl]acetamide as a yellow solid (35 mg, 35% yield).

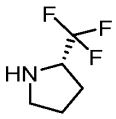
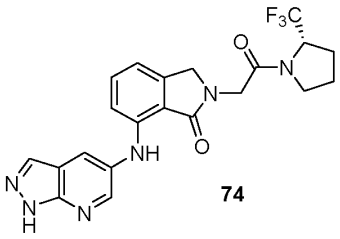
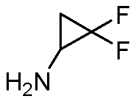
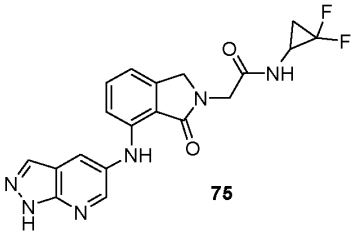
UPLC-MS (ES^+, Method 2): 2.04 min, m/z 503 $[M+H]^+$.

STEP B. 2-[1-oxo-7-(1H-pyrazolo[3,4-b]pyridin-5-ylamino)isoindolin-2-yl]-N-[(1S)-2,2,2-trifluoro-1-methyl-ethyl]acetamide (example 73). A mixture of 2-[1-oxo-7-[(1-tetrahydropyran-2-ylpyrazolo[3,4-b]pyridin-5-yl)amino]isoindolin-2-yl]-N-[(1S)-2,2,2-trifluoro-1-methyl-ethyl]acetamide (35 mg, 0.07 mmol) in HCl 1,4-dioxane solution (4M, 1 mL) and DCM (1 mL) and MeOH (1 mL) was stirred at room temperature for 1 h.. The mixture was concentrated to give 2-[1-oxo-7-(1H-pyrazolo[3,4-b]pyridin-5-ylamino)isoindolin-2-yl]-N-[(1S)-2,2,2-trifluoro-1-methyl-ethyl]acetamide (example 73) (29 mg, 92% yield) as a yellow solid

UPLC-MS (ES^+, Method 2): 1.29 min, m/z, 419.05 $[M+H]^+$.

^1H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.74 (d, J = 8.9 Hz, 1H), 8.47 (d, J = 2.4 Hz, 1H), 8.16 (d, J = 2.4 Hz, 1H), 8.09 (s, 1H), 7.35 (t, J = 7.8 Hz, 1H), 6.90 (d, J = 7.9 Hz, 2H), 4.62 (h, J = 7.7 Hz, 1H), 4.48 (s, 2H), 4.29 – 4.18 (m, 2H), 1.27 (d, J = 6.9 Hz, 3H).

The examples in table 11 were prepared from intermediate I-34 using analogous procedures to example 73 (scheme 7) replacing (1S)-1,1,1-trifluoropropan-2-amine hydrochloride in step A with the appropriate building block.

Building Block	Structure/Name	LCMS	^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm)
 (2S)-(trifluoromethyl)pyrrolidine	 **74** 2-[2-oxo-2-[(2S)-(trifluoromethyl)pyrrolidin-1-yl]ethyl]-7-(1H-pyrazolo[3,4-b]pyridin-5-ylamino)isoindolin-1-one **Example 74**	3.53 min, m/z 445.1 $[M+H]^+$ (Method 1)	(CD_3OD): 8.72 (d, *J* = 2.3 Hz, 1H), 8.57 (d, *J* = 2.3 Hz, 1H), 8.37 (s, 1H), 7.42 (t, *J* = 7.8 Hz, 1H), 7.06 (d, *J* = 8.2 Hz, 1H), 6.98 (d, *J* = 7.4 Hz, 1H), 4.81 – 4.75 (m, 1H), 4.59-4.44 (m, 4H), 3.82 – 3.68 (m, 2H), 2.27 – 2.11 (m, 4H).
 2,2-difluorocyclopropylamine	 **75** N-(2,2-difluorocyclopropyl)-2-[1-oxo-7-(1H-pyrazolo[3,4-b]pyridin-5-ylamino)isoindolin-2-yl]acetamide **Example 75**	2.98 min, m/z 399.1 $[M+H]^+$ (Method 1)	13.63 (s, 1H), 8.60 (d, *J* = 4.0 Hz, 2H), 8.47 (d, *J* = 2.4 Hz, 1H), 8.15 (d, *J* = 2.4 Hz, 1H), 8.09 (s, 1H), 7.35 (t, *J* = 7.8 Hz, 1H), 6.90 (d, *J* = 7.4 Hz, 2H), 4.47 (s, 2H), 4.20 (s, 2H), 3.42 – 3.38 (m, 1H), 1.95-1.85 (m, 1H), 1.57-1.48 (m, 1H).

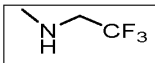
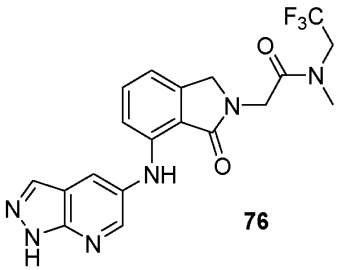
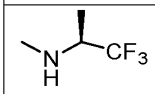
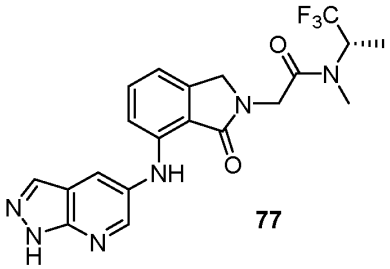
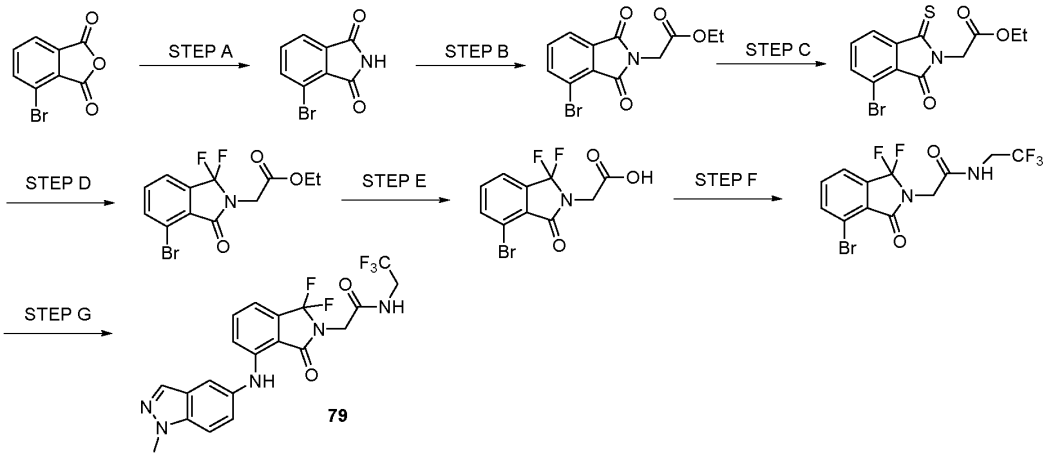
 N-methyl-(2,2,2)-trifluoromethylamine	 **76** N-methyl-2-[1-oxo-7-(1H-pyrazolo[3,4-b]pyridin-5-ylamino)isoindolin-2-yl]-N-(2,2,2-trifluoroethyl)acetamide **Example 76**	3.38 min, m/z 419.1 $[M+H]^+$ (Method 1)	13.62 (s, 1H), 8.60 (s, 1H), 8.47 (d, *J* = 2.4 Hz, 1H), 8.16 (d, *J* = 2.4 Hz, 1H), 8.08 (s, 1H), 7.36 (t, *J* = 7.8 Hz, 1H), 6.92 – 6.88 (m, 2H), 4.53 (s, 2H), 4.44 – 4.16 (m, 4H), 3.18 – 2.96 (d, *J* = 91.5 Hz, 3H).
 N-methyl-(1S)-1,1,1-trifluoropropan-2-amine	 **77** N-methyl-2-[1-oxo-7-(1H-pyrazolo[3,4-b]pyridin-5-ylamino)isoindolin-2-yl]-N-[(1S)-2,2,2-trifluoro-1-methyl-ethyl]acetamide **Example 77**	3.55 min, m/z 433.2 $[M+H]^+$ (Method 1)	13.62 (s, 1H), 8.60 (s, 1H), 8.47 (d, *J* = 2.4 Hz, 1H), 8.16 (d, *J* = 2.4 Hz, 1H), 8.13 –8.09 (s, 1H), 7.36 (t, *J* = 7.8 Hz, 1H), 6.93 – 6.89 (m, 2H), 5.29 – 4.92 (m, 1H), 4.61 – 4.44 (m, 4H), 3.03 –2.82 (d, *J* = 84.7 Hz, 3H), 1.47 –1.34 (dd, *J* = 42.3, 6.9 Hz, 3H).

Table 11

Example 79, 2-[1,1-difluoro-4-[(1-methylindazol-5-yl)amino]-3-oxo-isoindolin-2-yl]-N-(2,2,2-trifluoroethyl)acetamide.



Scheme 8

STEP A. 4-Bromoisoindoline-1,3-dione. A solution of 3-bromophthalic anhydride (1.1 g , 4.84 mmol), in formamide (4 mL) was stirred at 200 °C for 2 hrs. The resulting suspension was slurried with water and filtered to afford 4-bromoisoindoline-1,3-dione (1.0g, 91% yield) as a white solid after drying under suction.

UPLC-MS (ES^+, Method 1): 3.25 min, m/z, 224.00 $[M-H]^+$.

STEP B. Ethyl 2-(4-bromo-1,3-dioxo-isoindolin-2-yl)acetate. A solution of 4-bromoisoindoline-1,3-dione (1.0 g , 4.42 mmol), ethyl bromoacetate (886 mg, 5.3 mmol) and cesium carbonate (2.16 g, 6.6 mmol) in MeCN (10 mL) was stirred at 50 °C for 2 h. The mixture was filtered and the filter cake washed with MeCN, the combined organics were concentrated in vacuum and slurried with cold ether to give ethyl 2-(4-bromo-1,3-dioxo-isoindolin-2-yl)acetate (1.0 g, 72% yield) as an off-white semi-solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.07 – 8.05 (d, J = 8 Hz, 1H), 7.95 - 7.93 (d, J = 8 Hz, 1H), 7.80 – 7.76 (t, J = 8 Hz, 1H), 4.42 (s, 2H), 4.19 – 4.14 (q, J = 7 Hz 2H), 1.23 – 1.19 (t, J = 7 Hz 3H).

STEP C. Ethyl 2-(4-bromo-3-oxo-1-thioxo-isoindolin-2-yl)acetate. A mixture of ethyl 2-(4-bromo-1,3-dioxo-isoindolin-2-yl)acetate (360 mg, 1.15 mmol) and Lawessons's reagent (513 mg, 1.28 mmol) was added to toluene (10 mL) and heated to reflux for 14 hrs. Toluene was removed in vacuo after cooling to room temperature and the resulting residue purified by silica gel flash column chromatography (loading in DCM and eluting with 10:1 hexane/EtOAc affording ethyl 2-(4-bromo-3-oxo-1-thioxo-isoindolin-2-yl)acetate (250 mg, 66% yield) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.98 – 7.96 (d, J = 8 Hz, 1H), 7.86 - 7.84 (d, J = 8 Hz, 1H), 7.58 – 7.54 (t, J = 8 Hz, 1H), 4.79 (s, 2H), 4.25 – 4.20 (q, J = 7 Hz 2H), 1.30 – 1.26 (t, J = 7 Hz 3H).

STEP D. Ethyl 2-(4-bromo-1,1-difluoro-3-oxo-isoindolin-2-yl)acetate. A mixture of ethyl 2-(4-bromo-3-oxo-1-thioxo-isoindolin-2-yl)acetate (190 mg, 0.58 mmol), NBS (515 mg, 2.89 mmol) and n-$Bu_4NH_2F_3$ (3.5 g, 5.8 mmol) in DCM (10 mL) was stirred at room temperature for 14 hrs. The mixture was filtered and concentrated to an oily residue and purified by preparative TLC with 10:1 hexane/EtOAc)

affording ethyl 2-(4-bromo-1,1-difluoro-3-oxo-isoindolin-2-yl)acetate (80 mg, 39% yield) as a white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 7.86 – 7.84 (d, *J* = 8 Hz, 1H), 7.71 - 7.69 (d, *J* = 8 Hz, 1H), 7.60 – 7.66 (t, *J* = 8 Hz, 1H), 4.3 (s, 2H), 4.26 – 4.21 (q, *J* = 7 Hz 2H), 1.23 – 1.19 (t, *J* = 7 Hz 3H).

STEP E. 2-(4-Bromo-1,1-difluoro-3-oxo-isoindolin-2-yl)acetic acid. A solution of LiOH.H_2O (57.8 mg, 1.37 mmol) in water (2 mL) was added to a mixture of ethyl 2-(4-bromo-1,1-difluoro-3-oxo-isoindolin-2-yl)acetate (230 mg, 0.69 mmol) in 1:1 MeOH/THF (6mL), and the resulting mixture was stirred at 25 °C for 2 hrs. The mixture was concentrated and the residue was diluted with water (2 mL) and adjusted pH to 2 with 2N HCl, then filtered, the solid was dried to afford 2-(4-bromo-1,1-difluoro-3-oxo-isoindolin-2-yl)acetic acid (100 mg, 46% yield) as a white solid.

UPLC-MS (ES$^+$, Method 1): 3.50 min, m/z, 303.9/305.9 $[M-H]^+$.

STEP F. 2-(4-Bromo-1,1-difluoro-3-oxo-isoindolin-2-yl)-N-(2,2,2-trifluoroethyl)acetamide. A solution of 2-(4-bromo-1,1-difluoro-3-oxo-isoindolin-2-yl)acetic acid (80 mg , 0.29 mmol), 2,2,2-trifluoroethan-1-amine(38.8 mg, 0.39 mmol) DIEA (168 mg, 1.30 mmol) and T3P (297 mg, 0.39 mmol) in DCM (1 mL) was stirred at room temperature for 16 h. The mixture was concentrated to an oily residue and purified by preparative-TLC to give 2-(4-bromo-1,1-difluoro-3-oxo-isoindolin-2-yl)-N-(2,2,2-trifluoroethyl)acetamide (38.6 mg, 38% yield) as a white solid.

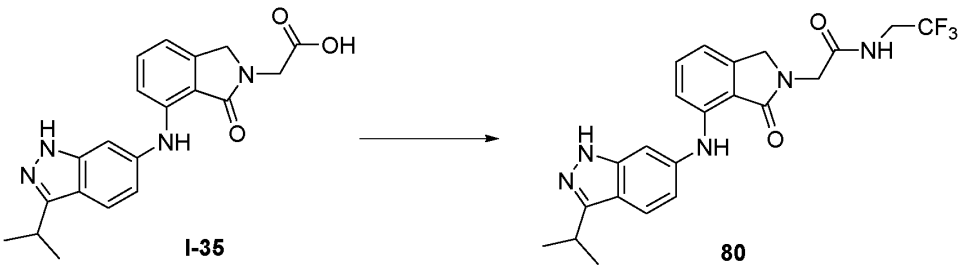
UPLC-MS (ES$^+$, Method 1): 3.51 min, m/z, 386.6/388.6 $[M+H]^+$.

STEP G. 2-[1,1-difluoro-4-[(1-methylindazol-5-yl)amino]-3-oxo-isoindolin-2-yl]-N-(2,2,2-trifluoroethyl)acetamide (Example 79). A solution 2-(4-bromo-1,1-difluoro-3-oxo-isoindolin-2-yl)-N-(2,2,2-trifluoroethyl)acetamide (80 mg , 0.2mmol), cesium carbonate (101 mg, 0.31 mmol) , Xantphos (11.9 mg, 0.02 mmol), bis(dibenzylideneacetone)palladium (0) (18.9g, 0.02 mmol) , 1-methyl-1H-indazol-5-amine (30.4 mg, 0.2 mmol) in 1,4-dioxane (2 mL) was stirred at 100 °C for 16 h. The mixture was concentrated in vacuo and purified by preparative-HPLC to give 2-[1,1-difluoro-4-[(1-methylindazol-5-yl)amino]-3-oxo-isoindolin-2-yl]-N-(2,2,2-trifluoroethyl)acetamide (example 79) (21 mg, 22% yield) as a yellow solid.

UPLC-MS (ES$^+$, Method 1): 3.75 min, m/z, 454.1 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.86 (t, *J* = 6.4 Hz, 1H), 8.32 (s, 1H), 8.01 (s, 1H), 7.68 (dd, *J* = 5.4, 3.4 Hz, 2H), 7.52 (t, *J* = 7.9 Hz, 1H), 7.36 (dd, *J* = 8.9, 1.9 Hz, 1H), 7.15 – 7.08 (m, 2H), 4.22 (s, 2H), 4.06 (s, 3H), 4.02 – 3.90 (m, 2H).

Example 80, 2-[7-[(3-isopropyl-1H-indazol-6-yl)amino]-1-oxo-isoindolin-2-yl]-N-(2,2,2-trifluoroethyl)acetamide.



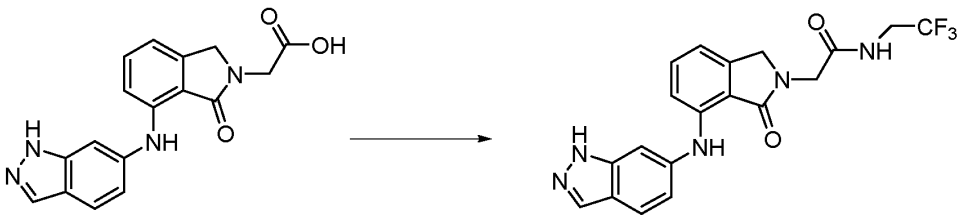
I-35 80

A mixture of 2-(7-((3-isopropyl-1H-indazol-6-yl)amino)-1-oxoisoindolin-2-yl)acetic acid (15 mg, 0.04 mmol), 2,2,2-trifluoroethan-1-amine (6.12 mg, 0.06 mmol), HATU (23.5 mg, 0.06 mmol,) and DIPEA (16 mg, 0.12 mmol) in DMF (1 mL) was stirred at room temperature overnight. The reaction mixture was concentrated in vacuo and was purified by preparative TLC (DCM:MeOH=20:1) to give 2-[7-[(3-isopropyl-1H-indazol-6-yl)amino]-1-oxo-isoindolin-2-yl]-N-(2,2,2-trifluoroethyl)acetamide (2.2 mg, 12% yield) as a white solid.

UPLC-MS (ES^+, Method 2): 1.66 min, m/z, 446.1 $[M+H]^+$.

^1H NMR (400 MHz, Acetonitrile-d_3) δ (ppm) 10.59 (s, 1H), 8.84 (s, 1H), 7.72 (d, J = 8.6 Hz, 1H), 7.45 – 7.41 (m, 1H), 7.40 (t, J = 1.7 Hz, 1H), 7.34-7.31 (m, 1H), 7.16 – 7.11 (m, 1H), 7.00 (dd, J = 8.7, 1.8 Hz, 1H), 6.92 (d, J = 8.0 Hz, 1H), 4.45 (s, 2H), 4.22 (s, 2H), 3.90 (qd, J = 9.5, 6.5 Hz, 2H), 3.36 (p, J = 7.0 Hz, 1H), 1.40 (d, J = 8.0 Hz, 6H).

Example 81, 2-[7-(1H-indazol-6-ylamino)-1-oxo-isoindolin-2-yl]-N-(2,2,2-trifluoroethyl)acetamide.



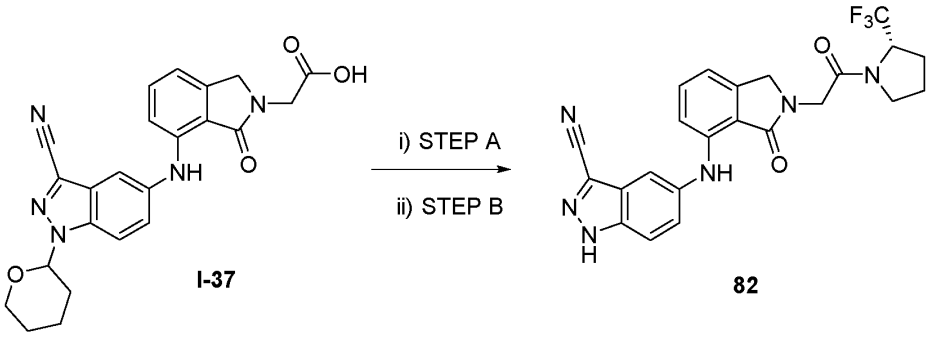
I-36 81

A solution of intermediate I-36 (90 mg, 0.27 mmol), trifluoroethylamine (33.19 mg, 0.33 mmol), T3P (133.27 mg, 0.41 mmol), and DIEA (180. mg, 1.39 mmol), in DCM (1.0 mL) was stirred at 25 °C for 2h.. The mixture was diluted with EtOAc (5 mL) and washed with H_2O (5 mL x 3). The organic layers were washed with EtOAc (10 mL×3), combined, dried over anhydrous Na_2SO_4 and concentrated to give a yellow solid which was purified by preparative-TLC (DCM:MeOH=20:1) to give 2-[7-(1H-indazol-6-ylamino)-1-oxo-isoindolin-2-yl]-N-(2,2,2-trifluoroethyl)acetamide (5.1 mg, 5% yield) as a white solid.

UPLC-MS (ES^+, Method 1): 3.35 min, m/z, 404.1 $[M+H]^+$.

^1H NMR (400 MHz, DMSO-d_6) δ (ppm) 12.81 (s, 1H), 8.84 (t, J = 5.2 Hz, 2H), 7.97 (s, 1H), 7.71 (d, J = 8.5 Hz, 1H), 7.46 – 7.40 (m, 2H), 7.29 (d, J = 8.3 Hz, 1H), 7.00 – 6.95 (m, 2H), 4.48 (s, 2H), 4.25 (s, 2H), 3.99 – 3.90 (m, 2H).

Example 82, 5-[[3-oxo-2-[2-oxo-2-[(2S)-(trifluoromethyl)pyrrolidin-1-yl]ethyl]isoindolin-4-yl]amino]-1H-indazole-3-carbonitrile.



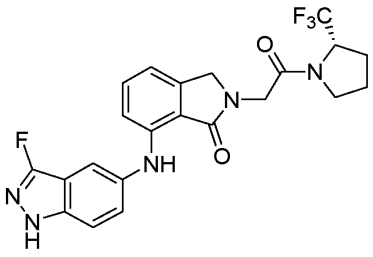
I-37 82

Example 82 was prepared from intermediate I-37 by analogy with the method used for example 25 (scheme 5) with I-37 in place of I-25 and replacing 3-(trifluoromethyl)aniline with (2S)-trifluoromethylpyrrolidine in step A.

UPLC-MS (ES^+, Method 1): 3.98 min, m/z, 469.2 $[M+H]^+$.

^1H NMR (400 MHz, DMSO-d_6) δ (ppm) 14.29 (s, 1H), 8.84 (s, 1H), 7.75 (d, *J* = 8.9 Hz, 1H), 7.68 (d, *J* = 1.9 Hz, 1H), 747 – 7.43 (m, 2H), 7.23 (d, *J* = 8.3 Hz, 1H), 6.97 (d, *J* = 7.4 Hz, 1H), 4.78 – 4.57 (m, 1H), 4.51 – 4.37 (m, 4H), 3.67 (d, *J* = 8.2 Hz, 2H), 2.14 – 1.99 (m, 3H).

Example 83, 7-[(3-fluoro-1H-indazol-5-yl)amino]-2-[2-oxo-2-[(2S)-(trifluoromethyl)pyrrolidin-1-yl]ethyl]isoindolin-1-one.



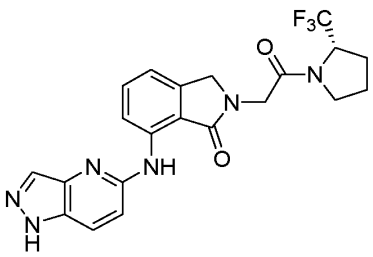
83

Example 83 was prepared by analogy with example 81 replacing I-36 with I-38 and replacing trifluoroethylamine with (2S)-(trifluoromethyl)pyrrolidine.

UPLC-MS (ES^+, Method 1): 4.02 min, m/z, 462.1 $[M+H]^+$.

^1H NMR (400 MHz, DMSO-d_6) δ (ppm) 12.50 (s, 1H), 8.64 (s, 1H), 7.55 (d, J = 1.9 Hz, 1H), 7.50 (dd, J = 8.9, 2.3 Hz, 1H), 7.41 – 7.33 (m, 2H), 7.04 (d, J = 8.2 Hz, 1H), 6.90 (d, J = 7.3 Hz, 1H), 4.81 – 4.70 (m, 1H), 4.51 – 4.35 (m, 4H), 3.67 (d, J = 8.6 Hz, 2H), 2.13 – 1.93 (m, 4H).

Example 84. 2-[2-oxo-2-[(2S)-(trifluoromethyl)pyrrolidin-1-yl]ethyl]-7-(1H-pyrazolo[4,3-b]pyridin-5-ylamino)isoindolin-1-one.



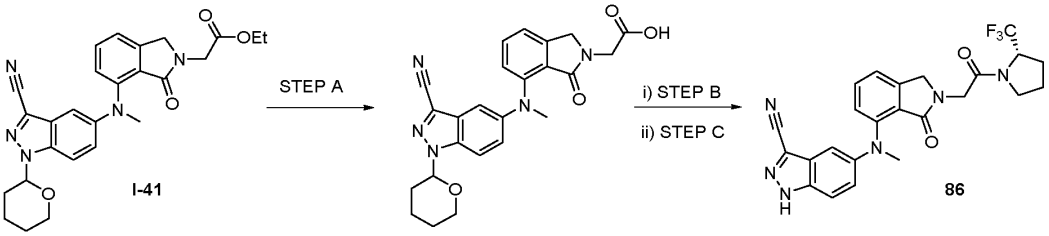
84

Example 83 was prepared by analogy with example 81 replacing I-38 with I-39.

UPLC-MS (ES$^+$, Method 1): 3.57 min, m/z, 445.2 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 13.2 (bs, 1H), 9.86 (s, 1H), 8.79 - 8.77 (m, 1H), 8.13 – 7.92 (m, 2H), 7.59 – 7.51 (m, 1H), 7.09 – 6.92 (m, 2H), 4.81 – 4.70 (m, 1H), 4.54 – 4.39 (m, 4H), 3.71 – 3.63 (m, 2H), 2.12 – 1.96 (m, 4H).

Example 86. 5-[methyl-[3-oxo-2-[2-oxo-2-[(2S)-(trifluoromethyl)pyrrolidin-1-yl]ethyl]isoindolin-4-yl]amino]-1H-indazole-3-carbonitrile.



I-41 86

Scheme 9

STEP A. 2-[7-[(3-cyano-1-tetrahydropyran-2-yl-indazol-5-yl)-methyl-amino]-1-oxo-isoindolin-2-yl]acetic acid. A mixture of ethyl 2-[7-[(3-cyano-1-tetrahydropyran-2-yl-indazol-5-yl)-methyl-amino]-1-oxo-isoindolin-2-yl]acetate (90 mg, 0.19 mol), LiOH (15.95 mg, 0.38 mmol), THF (2mL), MeOH (2 mL) and H_2O (0.5 mL) was stirred at 25°C for 2 hours. The mixture was diluted with H_2O and 10% HCl to achieve pH 1 - 2 and was concentrated in vacuum to afford 2-[7-[(3-cyano-1-tetrahydropyran-2-yl-indazol-5-yl)-methyl-amino]-1-oxo-isoindolin-2-yl]acetic acid (100 mg, quantitative yield) as a white solid.

UPLC-MS (ES$^+$, Method 1): 4.11 min, m/z 465.2 $[M+H]^+$.

STEP B. 5-[methyl-[3-oxo-2-[2-oxo-2-[(2S)-(trifluoromethyl)pyrrolidin-1-yl]ethyl]isoindolin-4-yl]amino]-1-tetrahydropyran-2-yl-indazole-3-carbonitrile. A mixture of 2-[7-[(3-cyano-1-tetrahydropyran-2-yl-indazol-5-yl)-methyl-amino]-1-oxo-isoindolin-2-yl]acetic acid (80 mg, 0.17 mmol), (2S)-trifluoromethylpyrrolidine (37.47 mg, 0.26 mmol), HATU (81.9 mg, 0.21 mmol) and DIEA (69.5 mg, 0.53 mmol) in DMF (1 mL) was stirred at 25°C overnight. The mixture was slurried with water (20 mL) and the solid was dried under vacuum to afford 5-[methyl-[3-oxo-2-[2-oxo-2-[(2S)-

(trifluoromethyl)pyrrolidin-1-yl]ethyl]isoindolin-4-yl]amino]-1-tetrahydropyran-2-yl-indazole-3-carbonitrile (100 mg, 97% yield) as a yellow solid.

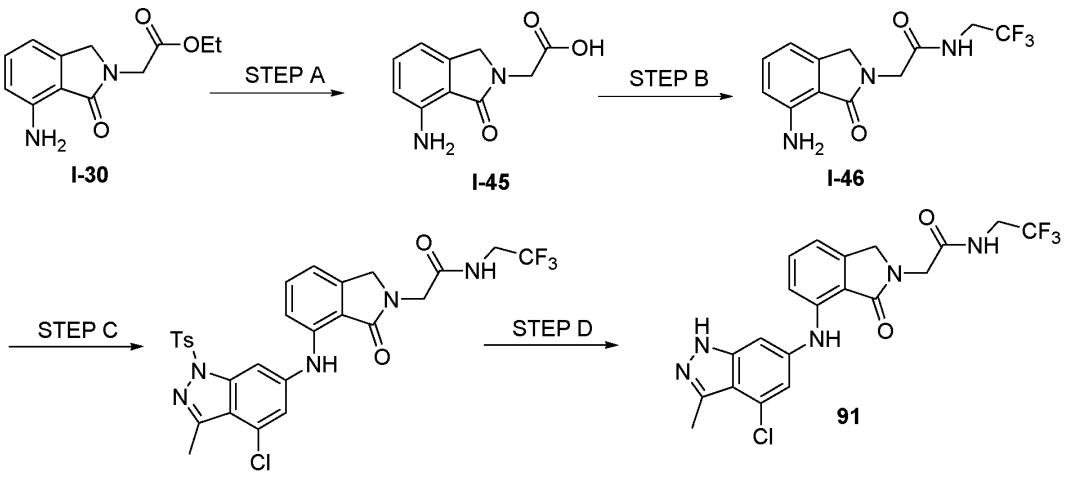
UPLC-MS (ES^+, Method 1): 4.35 min, m/z 567.2 $[M+H]^+$.

STEP C. 5-[methyl-[3-oxo-2-[2-oxo-2-[(2S)-(trifluoromethyl)pyrrolidin-1-yl]ethyl]isoindolin-4-yl]amino]-1H-indazole-3-carbonitrile (Example 86). A mixture of 5-[methyl-[3-oxo-2-[2-oxo-2-[(2S)-(trifluoromethyl)pyrrolidin-1-yl]ethyl]isoindolin-4-yl]amino]-1-tetrahydropyran-2-yl-indazole-3-carbonitrile (100 mg, 0.17 mmol,) and 4N HCl-dioxane (1.5 mL) in DCM (1 mL) was stirred at 25°C for 2 hours. The mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL x 3)and was dried over Na_2CO_3 .The mixture was purified by preparative TLC (Pet.ether/EtOAc=1/1) to give 5-[methyl-[3-oxo-2-[2-oxo-2-[(2S)-(trifluoromethyl)pyrrolidin-1-yl]ethyl]isoindolin-4-yl]amino]-1H-indazole-3-carbonitrile (example 86) (25 mg, 85% yield) as a yellow solid.

UPLC-MS (ES^+, Method 1): 3.85 min, m/z 483.1 $[M+H]^+$.

^1H NMR (400 MHz, DMSO-d_6) δ (ppm) 14.06 (s, 1H), 7.60 (t, J = 7.7 Hz, 1H), 7.48 – 7.43 (m, 2H), 7.20 (d, J = 7.9 Hz, 1H), 7.00 – 6.99 (m, 1H), 6.91 (dd, J = 9.2, 2.3 Hz, 1H), 5.02 – 4.68 (m, 1H), 4.49 – 4.31 (m, 4H), 3.66 – 3.56 (m, 2H), 3.35 (s, 3H), 2.07 – 1.97 (m, 4H).

Example 91. 2-[7-[(4-chloro-3-methyl-1H-indazol-6-yl)amino]-1-oxo-isoindolin-2-yl]-N-(2,2,2-trifluoroethyl)acetamide.



Scheme 10

STEP A. 2-(7-Amino-1-oxo-isoindolin-2-yl)acetic acid (Intermediate I-45). A solution of ethyl 2-(7-amino-1-oxoisoindolin-2-yl)acetate (200 mg, 0.85 mmol) and LiOH (93.14 mg, 2.27 mmol) in THF (3 mL) and H_2O (1 mL) was stirred at 25 °C for 2 h. The mixture was neutralised with dilute HCl, then extracted with EtOAc (15 mL x 3), dried over anhydrous Na_2SO_4 and concentrated under vacuum to afford 2-(7-amino-1-oxo-isoindolin-2-yl)acetic acid (150 mg, 85% yield) as a white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 12.83 (s, 1H), 7.21 (dd, *J* = 8.1, 7.3 Hz, 1H), 6.67 – 6.61 (m, 1H), 6.61 – 6.54 (m, 1H), 6.03 (s, 2H), 4.36 (s, 2H), 4.18 (s, 2H).

STEP B. 2-(7-Amino-1-oxo-isoindolin-2-yl)-N-(2,2,2-trifluoroethyl)acetamide (Intermediate I-46). A mixture of 2-(7-amino-1-oxoisoindolin-2-yl)acetic acid (150 mg, 0.72 mol), HATU (414mg, 1.09 mmol) and DIPEA (279 mg, 2.18 mmol) in DMF (2 mL) was stirred at 25 °C for 30 mins before adding 2,2,2-trifluoroethan-1-amine (79 mg, 0.80 mol), the mixture was stirred at room temperature for 2h. The mixture was diluted with water (15 mL) and extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 and concentrated under vacuum and purified by silica gel column chromatography (pet.ether/EtOAc, 5/1 to pet.ether/EtOAc, 1/1) to give 2-(7-amino-1-oxo-isoindolin-2-yl)-N-(2,2,2-trifluoroethyl)acetamide (110 mg, 53% yield) as a clear oil.

UPLC-MS (ES$^+$, Method 1): 3.12 min, m/z, 288.2 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.75 (t, *J* = 6.4 Hz, 1H), 7.21 (t, *J* = 7.7 Hz, 1H), 6.60 (dd, *J* = 24.5, 7.7 Hz, 2H), 6.03 (s, 2H), 4.35 (s, 2H), 4.16 (s, 2H), 3.91 (tt, *J* = 9.9, 4.9 Hz, 2H).

STEP C. 2-[7-[[4-Chloro-3-methyl-1-(p-tolylsulfonyl)indazol-6-yl]amino]-1-oxo-isoindolin-2-yl]-N-(2,2,2-trifluoroethyl)acetamide. A mixture of 6-bromo-4-chloro-3-methyl-1-tosyl-1H-indazole (130 mg, 0.32 mol), 2-(7-amino-1-oxoisoindolin-2-yl)-N-(2,2,2-trifluoroethyl)acetamide (93 mg, 0.32 mol) t-BuBrettphos (31.5 mg, 0.065 mmol) $Pd_2(dba)_3$ (29.7 mg, 0.032 mol, 0.1) K_2CO_3 (8 mg, 0.65 mmol) in t-BuOH (2 mL) and AcOH (0.5 mL) was irradiated in a microwave at 100 °C for 2h. The mixture was diluted with water (5 mL) and extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, concentrated in vacuum and purified by silica gel column chromatography (DCM/MeOH, 100/1 to DCM/MeOH, 50/1) to give 2-[7-[[4-chloro-3-methyl-1-(p-tolylsulfonyl)indazol-6-yl]amino]-1-oxo-isoindolin-2-yl]-N-(2,2,2-trifluoroethyl)acetamide (55 mg 28% yield) as a yellow solid.

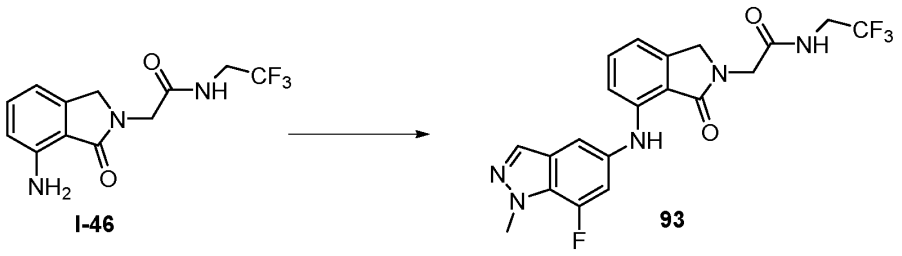
UPLC-MS (ES$^+$, Method 2): 2.15 min, m/z, 607.1 $[M+H]^+$

STEP D. 2-[7-[(4-chloro-3-methyl-1H-indazol-6-yl)amino]-1-oxo-isoindolin-2-yl]-N-(2,2,2-trifluoroethyl)acetamide (Example 91). A solution of ethyl 2-(7-amino-1-oxoisoindolin-2-yl)acetate (50 mg, 0.082 mmol) and LiOH (20 mg, 0.41 mmol) in THF (3 mL) and H_2O (1 mL) was stirred at 50 °C for 2 h. The mixture adjusted to pH 7.0 using dilute HCl, then concentrated to give crude material purified by preparative HPLC to give 2-[7-[(4-chloro-3-methyl-1H-indazol-6-yl)amino]-1-oxo-isoindolin-2-yl]-N-(2,2,2-trifluoroethyl)acetamide (3.3 mg, 37% yield) as a yellow solid.

UPLC-MS (ES$^+$, Method 1): 3.85 min, m/z, 452.20 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 12.63 (s, 1H), 8.89 – 8.71 (m, 2H), 7.47 (t, *J* = 7.8 Hz, 1H), 7.32 – 7.25 (m, 2H), 7.07 – 6.96 (m, 2H), 4.49 (s, 2H), 4.25 (s, 2H), 3.99 – 3.89 (m, 2H), 2.60 (s, 3H).

Example 93. 2-[7-[(7-fluoro-1-methyl-indazol-5-yl)amino]-1-oxo-isoindolin-2-yl]-N-(2,2,2-trifluoroethyl)acetamide.



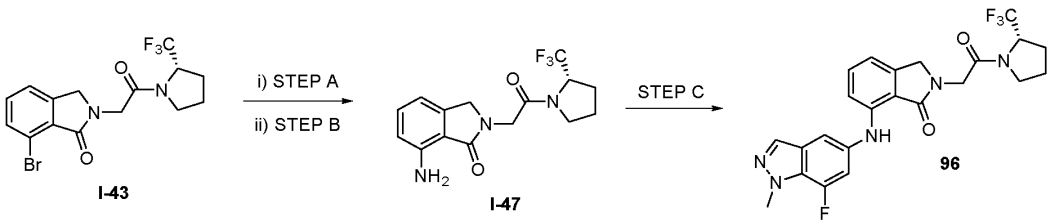
A solution of 5-bromo-7-fluoro-1-methyl-indazole (70 mg, 0.30 mmol), 2-(7-amino-1-oxo-isoindolin-2-yl)-N-(2,2,2-trifluoroethyl)acetamide (97 mg, 0.33 mmol), Cs_2CO_3 (199 mg, 0.61 mmol), Xantphos (35.3 mg, 0.061 mmol), and $Pd_2(dba)_3$ (28 mg, 0.031mmol), in 1,4-dioxane (2.0 mL) was stirred at 100 °C under N_2 overnight. The mixture was diluted with EtOAc (5 mL) and washed with H_2O (5 mL x3). The organic layers were washed with EtOAc (10 mL ×3), combined, dried over anhydrous Na_2SO_4 and concentrated to give a yellow solid. This was purified by preparative TLC to afford 2-[7-[(7-fluoro-1-methyl-indazol-5-yl)amino]-1-oxo-isoindolin-2-yl]-N-(2,2,2-trifluoroethyl)acetamide (21 mg, 16% yield) as a yellow solid.

UPLC-MS (ES^+, Method 1): 3.89 min, m/z, 436.2 $[M+H]^+$

^1H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.81 (t, *J* = 6.3 Hz, 1H), 8.63 (s, 1H), 8.03 (d, *J* = 2.4 Hz, 1H), 7.49 (d, *J* = 1.6 Hz, 1H), 7.39 (t, *J* = 7.9 Hz, 1H), 7.21 (dd, *J* = 13.2, 1.7 Hz, 1H), 7.09 (d, *J* = 8.2 Hz, 1H), 6.92 (d, *J* = 7.4 Hz, 1H), 4.47 (s, 2H), 4.24 (s, 2H), 4.16 (s, 3H), 3.99 – 3.90 (m, 2H).

UPLC-MS (ES^+, Method 1): 3.89 min, m/z, 436.2 $[M+H]^+$

Example 96. 7-[(7-fluoro-1-methyl-indazol-5-yl)amino]-2-[2-oxo-2-(2S)-(trifluoromethyl)pyrrolidin-1-yl]ethyl]isoindolin-1-one.



Scheme 11

STEPS A and B. Intermediate I-47, 7-amino-2-[2-oxo-2-[(2S)-(trifluoromethyl)pyrrolidin-1-yl]ethyl]isoindolin-1-one, was prepared using the same procedure as outlined in scheme 2 for intermediate I-30, starting from I-43 in place of I-6.

UPLC-MS (ES^+, Method 1): 3.45 min, m/z, 328.2 $[M+H]^+$

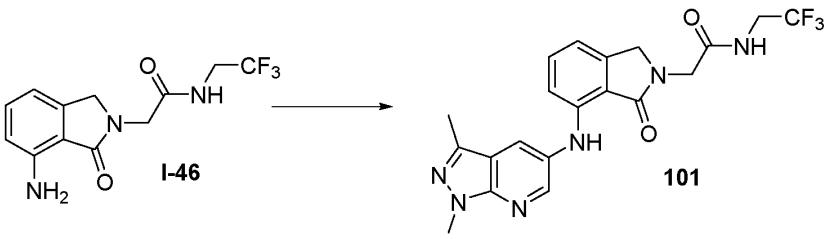
STEP C. 7-[(7-Fluoro-1-methyl-indazol-5-yl)amino]-2-[2-oxo-2-[(2S)-(trifluoromethyl)pyrrolidin-1-yl]ethyl]isoindolin-1-one (Example 96). A solution of 5-bromo-7-fluoro-1-methyl-indazole (60 mg, 0.26 mmol), -amino-2-[2-oxo-2-[(2S)-(trifluoromethyl)pyrrolidin-1-yl]ethyl]isoindolin-1-one (94.3 mg, 0.28

mmol), Cs_2CO_3 (172.22mg, 0.52 mmol), Xantphos (30.58 mg, 0.052 mmol), and $Pd_2(dba)_3$ (24.20 mg, 0.026 mmol), in 1,4-dioxane (1.0 mL) was stirred at 100 °C under N_2 overnight. The mixture was diluted with EtOAc (10 mL) and washed with H_2O (8 mL x 3). The organic layers were washed with EtOAc (10 mL × 3), combined, dried over anhydrous Na_2SO_4 and concentrated to give of yellow solid. The mixture were purified by preparative TLC to give 7-[(7-fluoro-1-methyl-indazol-5-yl)amino]-2-[2-oxo-2-[(2S)-(trifluoromethyl)pyrrolidin-1-yl]ethyl]isoindolin-1-one (16 mg, 21% yield) as a yellow solid.

UPLC-MS (ES^+, Method 1): 4.18 min, m/z 476.3 $[M+H]^+$

^1H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.64 (s, 1H), 8.03 (d, *J* = 2.4 Hz, 1H), 7.49 (d, *J* = 1.6 Hz, 1H), 7.39 (t, *J* = 7.8 Hz, 1H), 7.21 (dd, *J* = 13.3, 1.7 Hz, 1H), 7.09 (d, *J* = 8.2 Hz, 1H), 6.92 (d, *J* = 7.4 Hz, 1H), 5.08 – 4.72 (m, 1H), 4.60 – 4.36 (m, 4H), 4.16 (s, 3H), 3.70 – 3.63 (m, 2H), 2.07 – 2.00 (m, 4H).

Example 101. 2-[7-[(1,3-dimethylpyrazolo[3,4-b]pyridin-5-yl)amino]-1-oxo-isoindolin-2-yl]-N-(2,2,2-trifluoroethyl)acetamide.

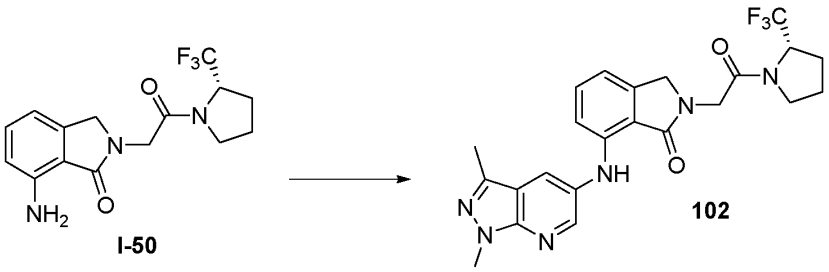


A mixture of 2-(7-amino-1-oxoisoindolin-2-yl)-N-(2,2,2-trifluoroethyl)acetamide (I-46) (80 mg, 0.28 mmol), 5-bromo-1,3-dimethyl-1H-pyrazolo[3,4-b]pyridine (75 mg, 0.33 mmol), Pd_2dba_3 (25.6 mg, 0.028 mmol), Xantphos (32.4 mg, 0.056mmol), Cs_2CO_3 (274 mg, 0.84 mmol) in 1,4-dioxane (3 mL) was stirred at 110 °C under an N_2 atmosphere overnight. The reaction was diluted with EtOAc (100 mL) and was washed with water (50 ml x 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 before concentrating and purifying by silica gel chromatography (EtOAc/pet. Ether, 1/1) affording 2-[7-[(1,3-dimethylpyrazolo[3,4-b]pyridin-5-yl)amino]-1-oxo-isoindolin-2-yl]-N-(2,2,2-trifluoroethyl)acetamide (20 mg, 16% yield) as a white solid.

UPLC-MS (ES^+, Method 1): 1.56 min, m/z 433.1 $[M+H]^+$

^1H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.81 (t, *J* = 6.3 Hz, 1H), 8.58 (s, 1H), 8.48 (d, *J* = 2.4 Hz, 1H), 8.13 (d, *J* = 2.4 Hz, 1H), 7.35 (t, *J* = 7.9 Hz, 1H), 6.92 – 6.86 (m, 2H), 4.48 (s, 2H), 4.25 (s, 2H), 3.98 – 3.90 (m, 5H), 2.48 (s, 3H).

Example 102. 7-[(1,3-dimethylpyrazolo[3,4-b]pyridin-5-yl)amino]-2-[2-oxo[(2S)-(trifluoromethyl)pyrrolidin-1-yl]ethyl]isoindolin-1-one.



Intermediate I-50, 7-amino-2-[2-oxo-2-[(2S)-(trifluoromethyl)pyrrolidin-1-yl]ethyl]isoindolin-1-one was prepared by analogy with I-46 (scheme 10) replacing 2,2,2-trifluoroethan-1-amine in step B with (2S)-(trifluoromethyl)pyrrolidine.

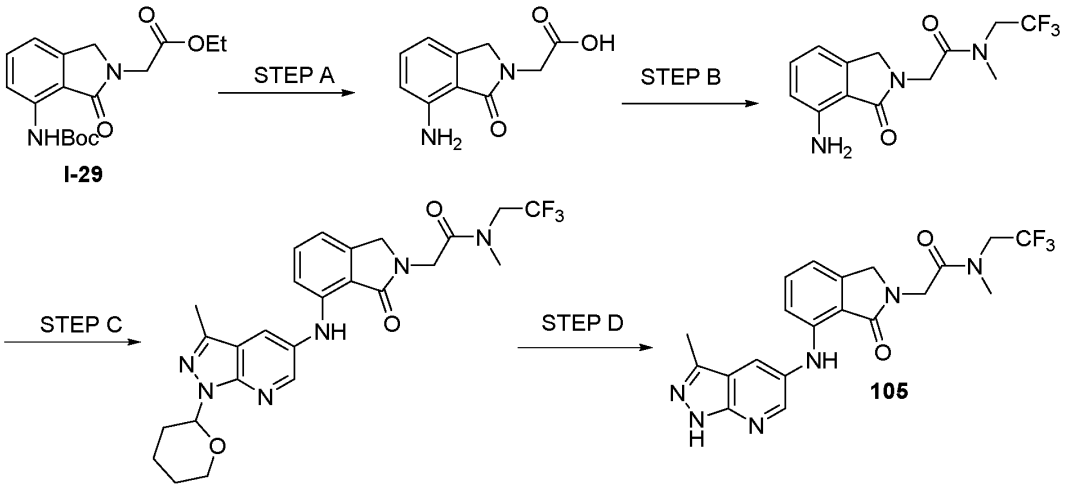
UPLC-MS (ES^+, Method 1): 3.45 min, m/z 328.2 $[M+H]^+$

7-[(1,3-dimethylpyrazolo[3,4-b]pyridin-5-yl)amino]-2-[2-oxo-2-[(2S)-(trifluoromethyl)pyrrolidin-1-yl]ethyl]isoindolin-1-one (example 102) was then prepared using the same method as for example 101, replacing I-46 with I-50.

UPLC-MS (ES^+, Method 1): 1.76 min, m/z 473.2 $[M+H]^+$

^1H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.55 (s, 1H), 8.46 (d, J = 2.4 Hz, 1H), 8.02 (d, J = 2.3 Hz, 1H), 7.33 (t, J = 7.8 Hz, 1H), 6.88 (dd, J = 11.9, 7.9 Hz, 2H), 5.36 – 4.31 (m, 5H), 4.00 (s, 3H), 3.70-3.60 (m, 2H), 2.49 (s, 3H), 2.12 – 2.09 (m, 4H).

Example 105. N-methyl-2-[7-[(3-methyl-1H-pyrazolo[3,4-b]pyridin-5-yl)amino]-1-oxo-isoindolin-2-yl]-N-(2,2,2-trifluoroethyl)acetamide.



Scheme 12

STEP A. 2-(7-amino-1-oxo-isoindolin-2-yl)acetic acid. A mixture of ethyl 2-[7-(tert-butoxycarbonylamino)-1-oxo-isoindolin-2-yl]acetate (6 g, 17.94 mmol) in DCM (10 mL) and HCl in dioxane (4M) (18 mL, 179.44 mmol was stirred at room temperature for 2 hours. The mixture was

concentrated in vacuo affording 2-(7-amino-1-oxo-isoindolin-2-yl)acetic acid hydrochloride salt as a yellow solid (4.5 g, quantitative yield).

UPLC-MS (ES^+, Method 2): 1.13 min, m/z 235.1 [M+H].

STEP B. 2-(7-amino-1-oxo-isoindolin-2-yl)-N-methyl-N-(2,2,2-trifluoroethyl)acetamide. A solution of 2-(7-amino-1-oxo-isoindolin-2-yl)acetic acid (400 mg, 1.94 mmol) HATU (1.1 g, 2.91 mmol DIEA (1.01 mL, 5.82 mmol) and 2,2,2-trifluoro-N-methyl-ethanamine hydrochloride (0.26 mL, 2.13 mmol) in DCM (5 mL) was stirred at 25 °C for 5 hours. The mixture was purified by reverse phase column chromatography on C-18 modified silca gel eluting with MeCN and water with 0.1% TFA as an additive affording 2-(7-amino-1-oxo-isoindolin-2-yl)-N-methyl-N-(2,2,2-trifluoroethyl)acetamide as a whith solid (340 mg, 58% yield).

UPLC-MS (ES^+, Method 1): 3.34 min, m/z 302.2 [M+H].

STEP C. N-methyl-2-[7-[(3-methyl-1-tetrahydropyran-2-yl-pyrazolo[3,4-b]pyridin-5-yl)amino]-1-oxo-isoindolin-2-yl]-N-(2,2,2-trifluoroethyl)acetamide. A solution of 2-(7-amino-1-oxo-isoindolin-2-yl)-N-methyl-N-(2,2,2-trifluoroethyl)acetamide (60 mg, 0.2 mmol), 5-bromo-3-methyl-1-tetrahydropyran-2-yl-pyrazolo[3,4-b]pyridine (71 mg, 0.24 mmol) K_2CO_3 (55 mg, 0.4 mmol), $Pd_2(dba)_3$ (18 mg, 0.0 2mmol) and t-BuBrettphos (19 mg, 0.04 mmol) in t-butanol (1m L) was strried at 110°C in a sealed tubefor 2 hours. The mixture was filtered through celite and the filter-cake washed with DCM. The combined orgaincs were dried over Na_2SO_4 and concentrated to an oily residue which was purified by preparative TLC, eluting with DCM in MeOH (20:1) to afford N-methyl-2-[7-[(3-methyl-1-tetrahydropyran-2-yl-pyrazolo[3,4-b]pyridin-5-yl)amino]-1-oxo-isoindolin-2-yl]-N-(2,2,2-trifluoroethyl)acetamide as a yellow solid (35 mg, 34% yield).

UPLC-MS (ES^+, Method 1): 4.08 min, m/z 517.4 [M+H].

STEP D. N-methyl-2-[7-[(3-methyl-1H-pyrazolo[3,4-b]pyridin-5-yl)amino]-1-oxo-isoindolin-2-yl]-N-(2,2,2-trifluoroethyl)acetamide (example 105).

To a solution of N-methyl-2-[7-[(3-methyl-1-tetrahydropyran-2-yl-pyrazolo[3,4-b]pyridin-5-yl)amino]-1-oxo-isoindolin-2-yl]-N-(2,2,2-trifluoroethyl)acetamide (35 mg, 0.07 mmol) in DCM (1 mL) was added 4M HCl in dioxane (0.5 mL). The mixture was strried at 25°C for 2 hrs,The mixture was concentrated and purified by preparative-TLC (DCM and MeOH 20:1) to give a yellow solid analysed as N-methyl-2-[7-[(3-methyl-1H-pyrazolo[3,4-b]pyridin-5-yl)amino]-1-oxo-isoindolin-2-yl]-N-(2,2,2-trifluoroethyl)acetamide (example 105) (23 mg, 80% yield).

UPLC-MS (ES^+, Method 1): 3.45 min, m/z 433.3 [M+H].

^1H NMR (400 MHz, DMSO-d_6) δ (ppm) 13.19 (s, 1H), 8.56 (d, J = 2.8 Hz, 1H), 8.43 (d, J = 2.4 Hz, 1H), 8.13 (d, J = 2.5 Hz, 1H), 7.35 (t, J = 7.8 Hz, 1H), 6.92 – 6.85 (m, 2H), 4.51 (d, J = 20.5 Hz, 2H), 4.44 (d, J = 2.7 Hz, 2H), 4.20 (q, J = 9.8 Hz, 2H), 3.19 (s, 3H), 2.48 (s, 3H).

DDR1 and DDR2 Biochemical assay method

The capacity of compounds to bind to DDR1 and DDR2 was quantified using a LanthaScreen Eu Kinase Binding Assay. Recombinant human DDR1 (2.5nM; aa440-876 containing a GST tag) and DDR2 (1.75nM; aa427-855 containing a GST tag) were diluted in assay buffer (50mM HEPES pH7.3, 10mM MgCl2, 1mM EGTA and 0.01% Tween) with various concentrations of compound in a 384-well plate and a volume of 5uL. After a 30-minute incubation at room temperature, 2.5uL of Eu-anti GST antibody (diluted to 1 nM in assay buffer) plus Kinase Tracer 178 (diluted in assay buffer to 5nM for DDR1 and 10nM for DDR2) were added to the plate. Following 60-minute incubation at room temperature, time-resolved fluorescence was measured on a BMG Labtech PHERAstar plate reader. DMSO (1%) and reference compound (1μM) were used to generate the Max and Min assay signals, respectively. Data was analysed using a four-parameter logistic model to calculate IC_{50} values, with at least two independent replicates were performed for each compound.

Biological activity values

The following table shows the pIC_{50} values for the above examples against the DDR1 and DDR2 kinases (A: $pIC_{50} > 8$; B: $8 \geq pIC_{50} > 7$; C: $7 \geq pIC_{50} > 6$; D: $pIC_{50} \leq 6$; ND: not determined).

Example	DDR1 pIC_{50}	DDR2 pIC_{50}
1	A	B
2	A	A
3	A	A
4	A	A
5	A	B
6	A	A
7	C	D
8	B	B
9	B	C
10	A	B
11	A	A
12	A	B
13	A	B
14	A	A

15	B	B
16	A	A
17	A	A
18	B	C
19	C	C
20	A	B
21	A	B
22	B	D
23	B	B
24	A	B
25	ND	ND
26	B	B
27	A	A
28	A	A
29	A	A
30	A	B
31	A	B
32	A	A
33	A	A
34	B	B
35	ND	ND
36	A	A
37	A	B
38	A	B
39	A	B
40	A	A
41	A	A

42	A	A
43	A	B
44	B	C
45	A	B
46	A	A
47	A	B
48	A	B
49	A	A
50	A	A
51	A	A
52	B	C
53	A	B
54	C	C
55	C	C
56	B	B
57	D	D
58	A	B
59	B	C
60	A	A
61	C	D
62	A	A
63	A	A
64	A	A
65	C	D
66	A	A
67	A	A
68	B	C

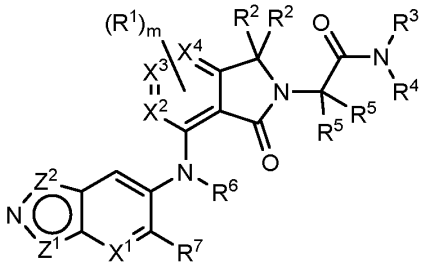
69	B	C
70	C	D
71	B	B
73	A	B
74	A	A
75	B	C
76	B	B
77	B	B
78	B	C
79	B	D
80	C	C
81	B	C
82	B	D
83	B	B
84	B	C
85	B	B
86	B	B
88	B	B
89	B	B
90	B	C
91	B	ND
92	B	C
93	A	B
94	ND	ND
95	B	B
96	A	A
97	B	C

98	ND	ND
99	B	B
100	ND	ND
101	D	D
102	B	C
103	ND	ND
104	ND	ND
105	ND	ND

Table 12

CLAIMS

1. A compound of formula (I) and pharmaceutically acceptable salts thereof:



(I); wherein

Z^1 and Z^2 are each selected from -CR^{8a}- and -NR^{8b}-, wherein one of Z^1 and Z^2 is -CR^{8a}- and the other is -NR^{8b}-; and wherein the ring comprising Z^1 and Z^2 is a pyrazole;

X^1 is independently selected from CR^{7a} and N;

X^2, X^3 and X^4 are each independently selected from carbon and nitrogen, wherein at least one of X^2, X^3 and X^4 is 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^2 is independently selected at each occurrence from H, fluoro, C_1-C_4-alkyl, C_1-C_4-haloalkyl and cyclopropyl, or the two R^2 groups and the carbon atom to which they are attached together form a C_3-C_6-cycloalkyl ring;

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 selected from H, C_1-C_4-alkyl, C_1-C_4-haloalkyl and cyclopropyl;

R^7 and R^{7a} are each independently selected from H, 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^{8a} is independently selected from H, 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 C_0-C_4-alkylene-R^{8c};

R^{8b} is independently selected from H, C_1-C_4-alkyl, C_2-C_4-alkyl substituted with NR^9R^{10}, C_2-C_4-alkyl substituted with OR^{11}, C_3-C_4-alkenyl, C_3-C_4-alkynyl, C_1-C_4-haloalkyl and C_0-C_4-alkylene-R^{8c};

R^{8c} is independently selected from C_3-C_6-cycloalkyl and 3- to 7-membered heterocycloalkyl; wherein said heterocycloalkyl group is attached to the C_0-C_4-alkylene via a carbon atom in the heterocycloalkyl ring; wherein said cycloalkyl or heterocycloalkyl group is optionally substituted with from 1 to 4 R^{13} groups;

R^9 is independently at each occurrence selected from H and C_1-C_4-alkyl; or two R^9 groups, together with the nitrogen atom to which they are attached together form a C_5-C_8-heterocycloalkyl group optionally substituted with from 0 to 4 R^{13} groups;

R^{10} 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; or R^9 and R^{10}, together with the nitrogen atom to which they are attached together form a C_5-C_8-heterocycloalkyl group optionally substituted with from 0 to 4 R^{13} groups;

R^{11} is independently at each occurrence selected from H, C_1-C_4-alkyl, C(O)-C_1-C_4-alkyl and C_1-C_4-haloalkyl;

R^{12} is independently selected from C_3-C_6-cycloalkyl, phenyl, 5- or 6- membered heteroaryl and 3- to 6-membered-heterocycloalkyl; wherein said cycloalkyl or heterocycloalkyl group is optionally substituted with from 1 to 4 R^{13} groups and wherein said phenyl or heteroaryl group is optionally substituted with from 1 to 3 R^{14} groups;

R^{13} is independently at each occurrence selected from =O, halo, nitro, cyano, NR^8R^9, OR^{14}, SR^8, $SO_2NR^8R^8$, CO_2R^8, $C(O)R^8$, $CONR^8R^8$, C_1-C_4-alkyl, C_1-C_4-alkyl substituted with OR^{11}, C_1-C_4-alkyl substituted with NR^9R^{10}, C_2-C_4-alkenyl, C_2-C_4-alkynyl, C_1-C_4-haloalkyl, C_6-C_{10}-aryl, and C_3-C_6-cycloalkyl;

R^{14} is independently at each occurrence selected from halo, nitro, cyano, NR^8R^9, OR^{10}, SR^8, SO_2R^8, $SO_2NR^8R^8$, CO_2R^8, $C(O)R^8$, $CONR^8R^8$, C_1-C_4-alkyl, C_2-C_4-alkenyl, C_2-C_4-alkynyl, C_1-C_4-haloalkyl, C_1-C_4--alkyl substituted with OR^{11}, C_1-C_4-alkyl substituted with NR^8R^9 and cyclopropyl;

m is an integer selected from 0, 1, 2 and 3;

wherein any of the aforementioned alkyl, alkylene or cyclopropyl groups is optionally substituted, where chemically possible, by 1 to 5 substituents which are each independently at each occurrence selected 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.

2. A compound of claim 1 wherein Z^1 is NR^{8b} and Z^2 is CH.

3. A compound of claim 1, wherein Z^1 is CR^{8a} and Z^2 is NH.

4. A compound of any one of claims 1 to 3, wherein m is 0.

5. A compound of any one of claims 1 to 4, wherein R^2 is at each occurrence independently selected from C_1-C_4-alkyl and H.

6. A compound of any one of claims 1 to 5, wherein R^5 is at each occurrence H.

7. A compound of any one of claims 1 to 6, wherein R^6 is H.

8. A compound of any one of claims 1 to 7, wherein R^7 is H.

9. A compound of any one of claims 1 to 8, wherein X^1 is N.

10. A compound of any one of claims 1 to 8, wherein X^1 is CR^{7a}.

11. A compound of claim 11, wherein R^{7a} is H.

12. A compound of claim 11, wherein R^{7a} is independently selected from halo, nitro, cyano, OR^{11}, CO_2R^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_1-C_4-haloalkyl and cyclopropyl.

13. A compound of any one of claims 1 to 12, wherein X^2, X^3 and X^4 are each carbon.

14. A compound of any one of claims 1 to 13, wherein R^3 is H and R^4 is selected from C_1-C_6-alkyl, C_1-C_6-haloalkyl and C_0-C_4-alkylene-R^{4a}.

15. A compound of claim 14, wherein R^4 is selected from C_1-C_6-alkyl and C_1-C_6-haloalkyl.

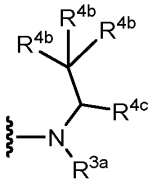
16. A compound of claim 14, wherein R^4 is C_0-C_4-alkylene-R^{4a}.

17. A compound of claim 16, wherein R^4 is R^{4a}.

18. A compound of claim 16 or claim 17, wherein R^{4a} is selected from C_3-C_8-cycloalkyl and 4- to 10-membered heterocycloalkyl, wherein said cycloalkyl or heterocycloalkyl group is optionally substituted with from 1 to 4 R^{13} groups.

19. A compound of claim 16 or claim 17, wherein R^{4a} is independently selected from: phenyl and 5- or 6- membered heteroaryl; wherein said phenyl or heteroaryl group is optionally substituted with a single R^{12} group and/or from 1 to 3 R^{14} groups.

20. A compound of any one of claims 1 to 13, wherein R^3 and R^4, together with the nitrogen atom to which they are attached together form a monocyclic 4- to 7- membered heterocycloalkyl group optionally substituted with from 1 to 4 R^{13} groups.

21. A compound of any one of claims 1 to 13, wherein NR^3R^4 has the formula ; wherein

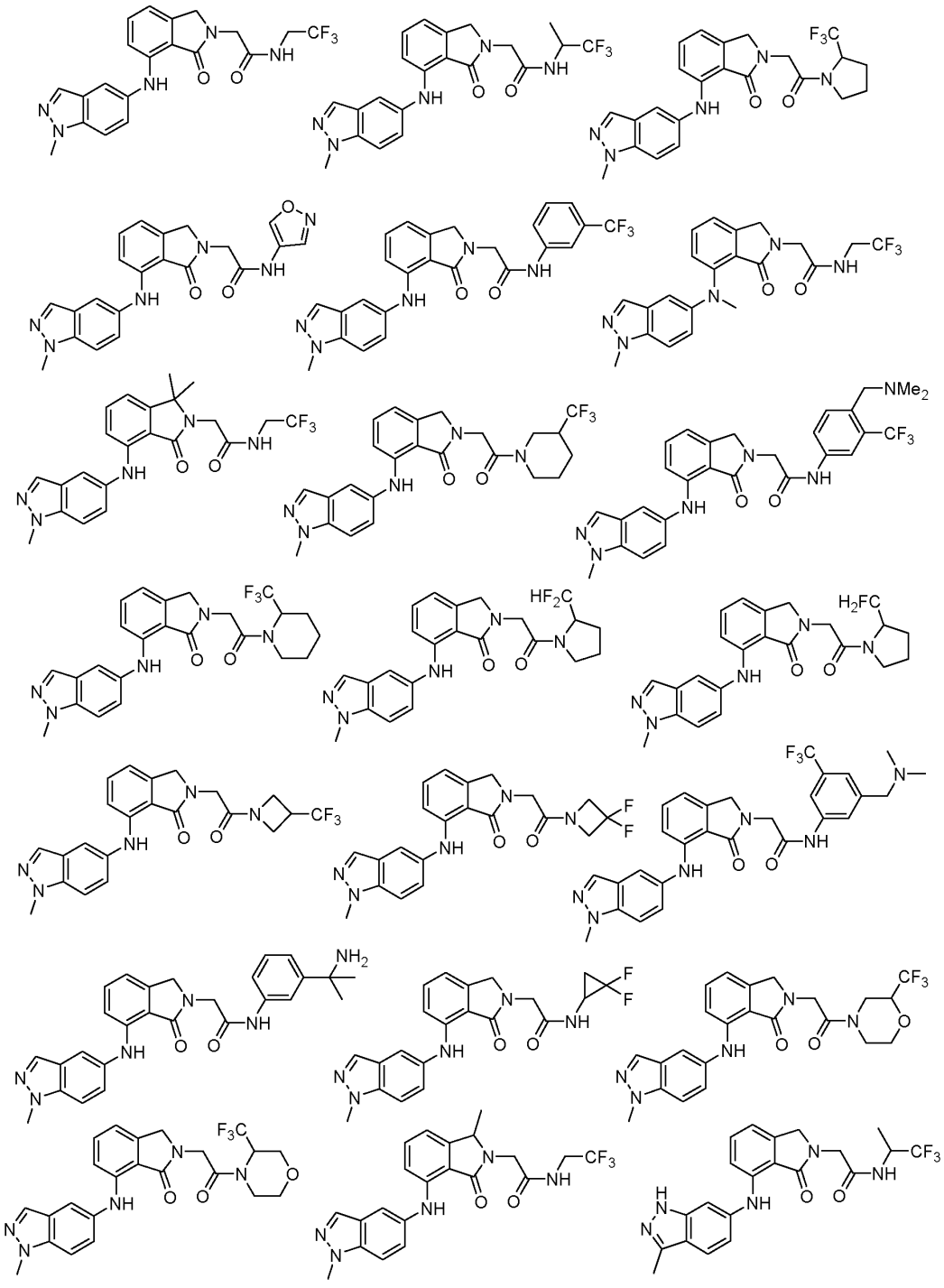
R^{4b} is at each occurence selected from H and F; wherein at least one R^{4b} group is F;

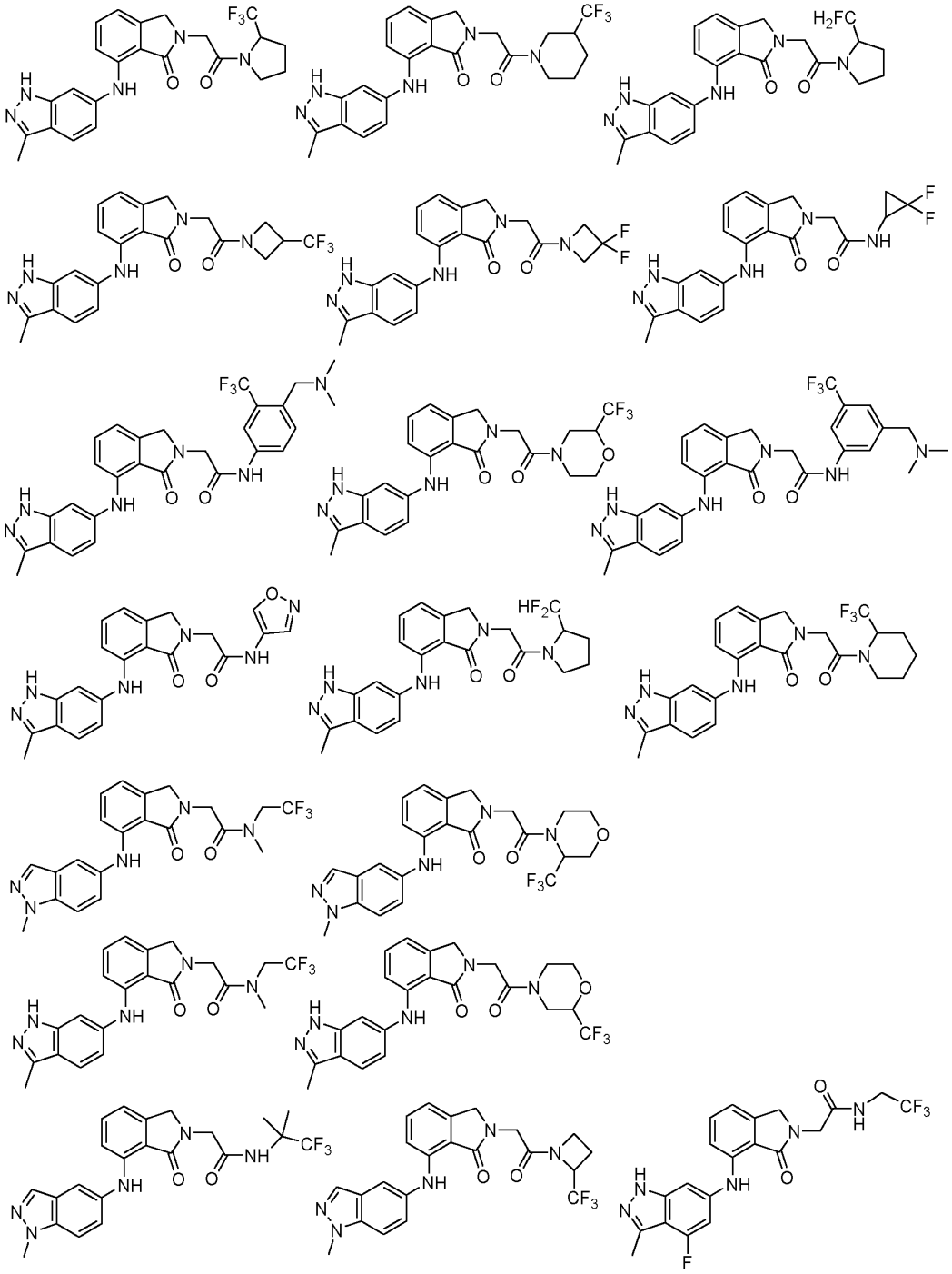
R^{3a} is independently selected from H and C_1-C_4-alkyl;

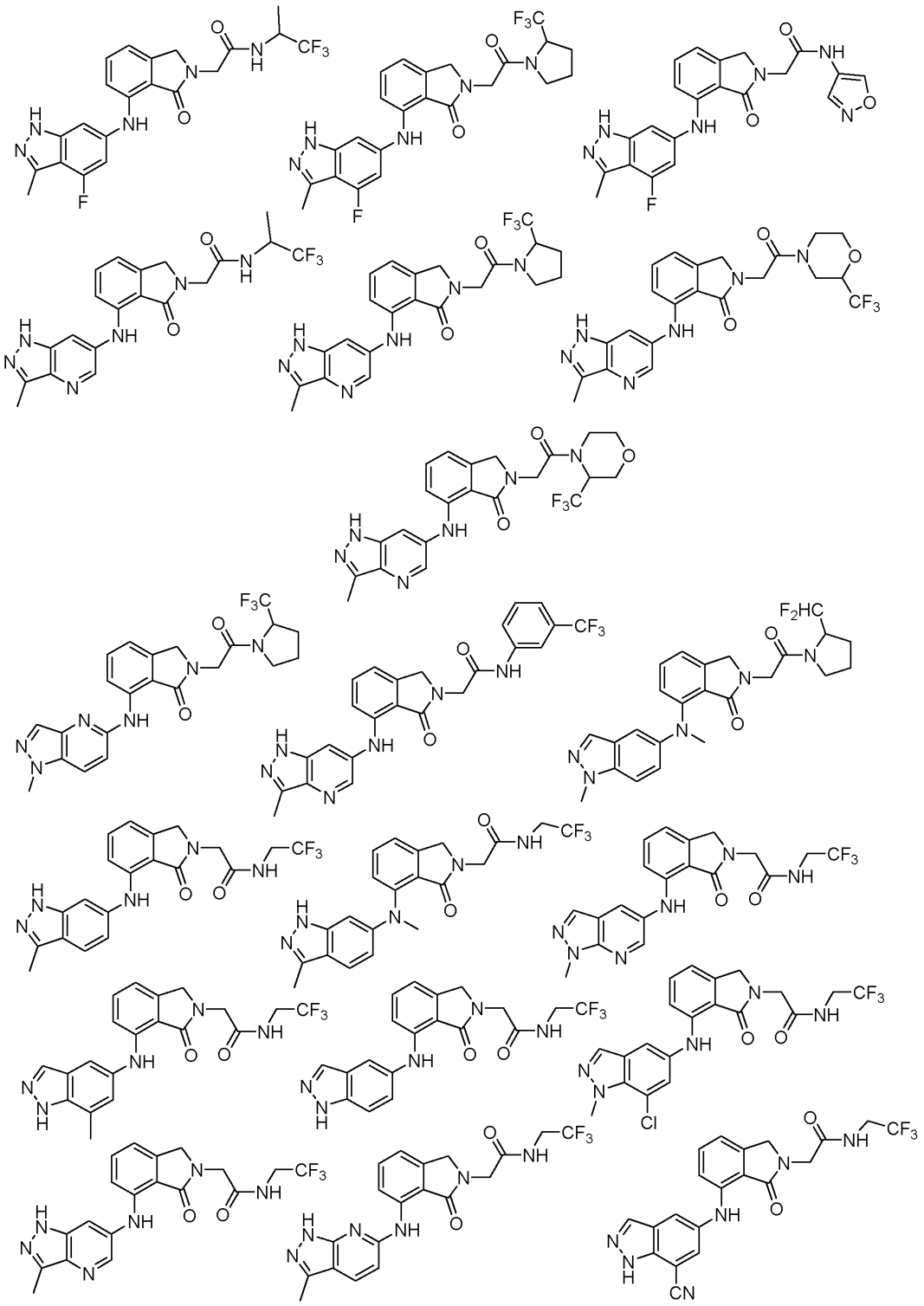
R^{4c} is independently selected from H, C_1-C_4-alkyl and C_4-C_6-cycloalkyl; or

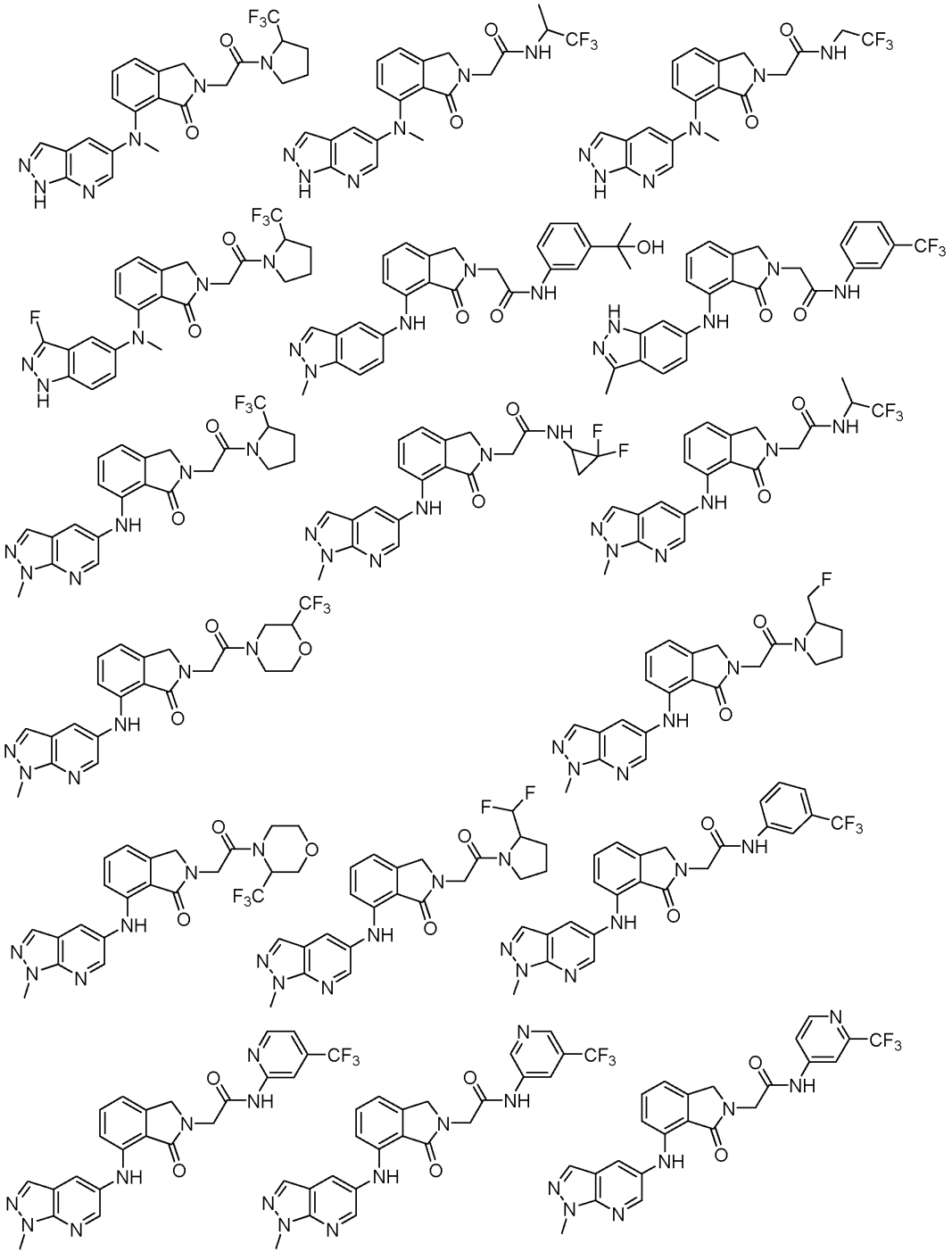
R^{3a} and R^{4c}, together with the carbon and nitrogen to which they are attached, form a 4- to 6-membered heterocycloalkyl group.

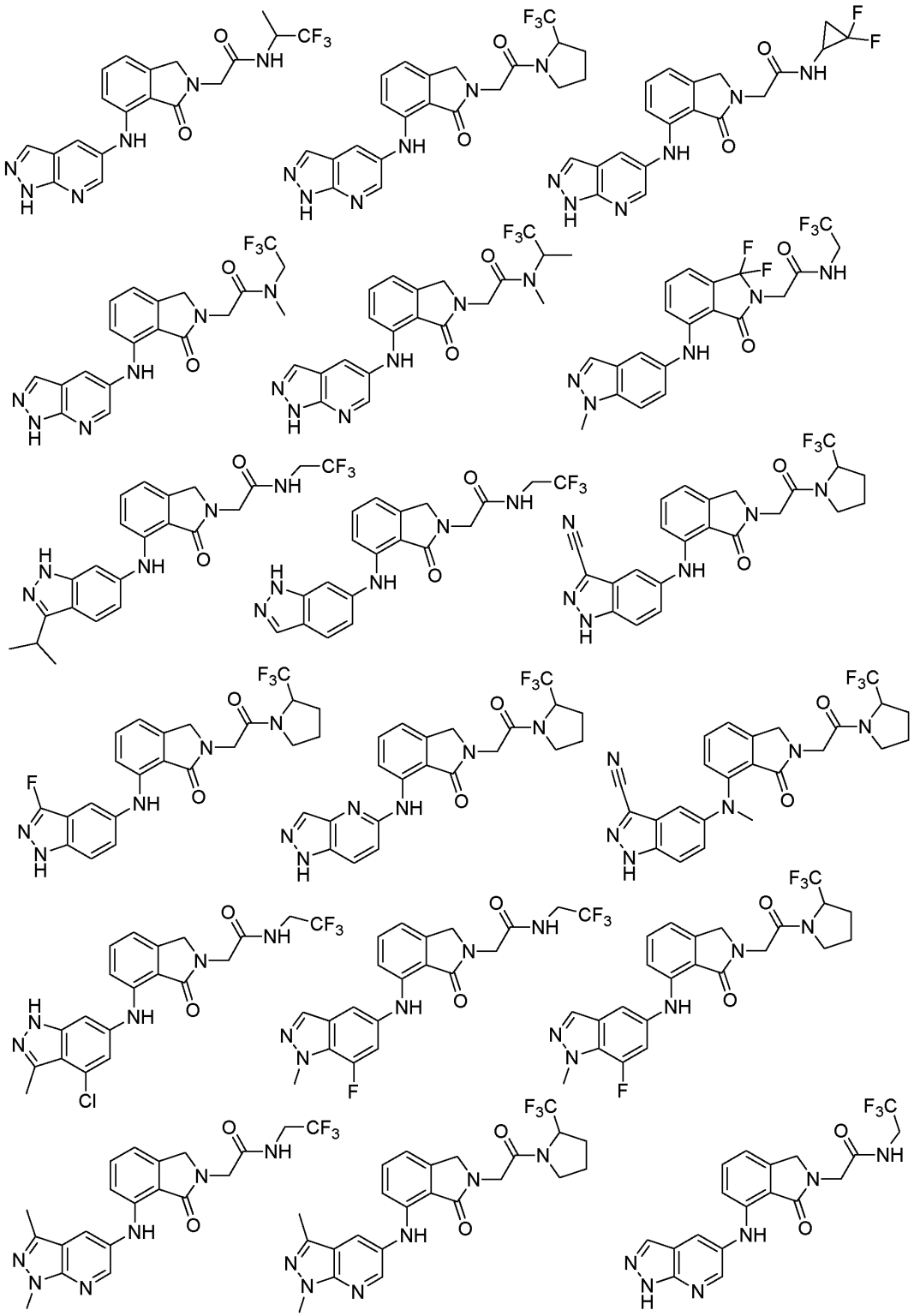
22. A compound of claim 1 wherein the compound of formula (**I**) is selected from:

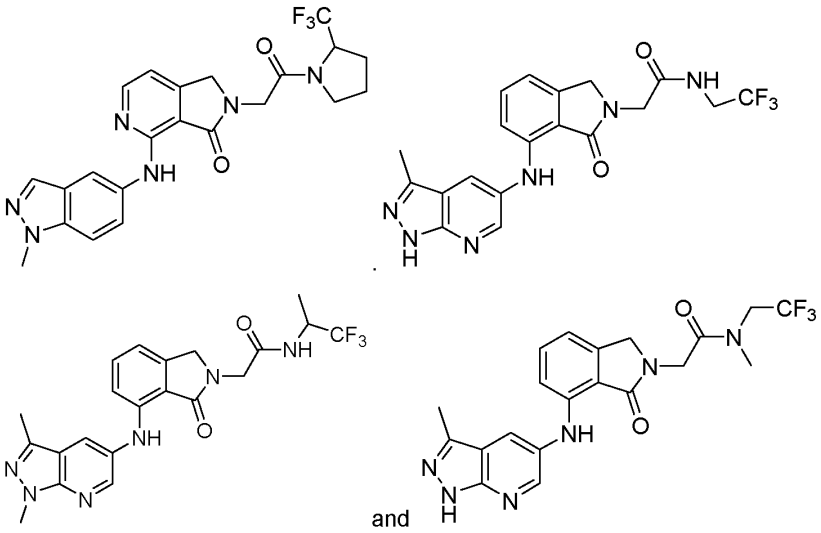












and

23. A pharmaceutical formulation comprising a compound of any one of claims 1 to 22 and a pharmaceutically acceptable excipient.

24. A compound of any one of claims 1 to 22 for use as a medicament.

25. A compound of any one of claims 1 to 22 for use in treating a a disease or disorder selected from renal conditions, liver conditions, inflammatory conditions, cardiovascular conditions, acute and chronic organ transplant rejection, fibrotic diseases and cancer.