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(54) Title: INDAZOLE DERIVATIVES FOR TREATING TRPM3-MEDIATED DISORDERS

(57) Abstract: The invention relates to compounds that are useful for the prevention or treatment of TRPM3 mediated disorders, more in particular disorders selected from pain and inflammatory hypersensitivity. The invention also relates to a method for the prevention or treatment of said TRPM3 mediated disorders.

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INDAZOLE DERIVATIVES FOR TREATING TRPM3-MEDIATED DISORDERS

TECHNICAL FIELD

[0001] The invention relates to compounds that are useful for the prevention or treatment of TRPM3 mediated disorders, more in particular disorders selected from pain, inflammatory hypersensitivity and epilepsy. The invention also relates to a method for the prevention or treatment of said TRPM3 mediated disorders.

BACKGROUND

[0002] The TRP superfamily consists of proteins with six transmembrane domains (6TM) that assemble as homo- or heterotetramers to form cation-permeable ion channels. The name TRP originates from the Drosophila trp (transient receptor potential) mutant, which is characterized by a transient receptor potential in the fly photoreceptors in the response to sustained light. In the last 15 years, trp-related channels have been identified in yeast, worms, insects, fish and mammals, including 27 TRPs in humans. Based on sequence homology, TRP channels can be divided into seven subfamilies: TRPC, TRPV, TRPM, TRPA, TRPP, TRPML and TRPN.

[0003] Members of the TRP superfamily are expressed in probably all mammalian organs and cell types, and in recent years great progress has been made in the understanding of their physiological role. The tailored selectivity of certain TRP channels enables them to play key roles in the cellular uptake and/or transepithelial transport of Ca^{2+}, Mg^{2+} and trace metal ions. Moreover, the sensitivity of TRP channels to a broad array of chemical and physical stimuli, allows them to function as dedicated biological sensors involved in processes ranging from vision to taste, and tactile sensation. In particular, several members of the TRP superfamily exhibit a very high sensitivity to temperature. These so-called thermoTRPs are highly expressed in sensory neurons and/or skin keratinocytes, where they act as primary thermosensors for the detection of innocuous and noxious (painful) temperatures.

[0004] It is becoming increasingly clear that TRP channel dysfunction is directly involved in the etiology of various inherited and acquired diseases. Indeed, both loss-of-function and gain-of-function mutations in the TRP channel genes have been identified as the direct cause of inherited diseases, including brachyolmia, hypomagnesemia with secondary hypocalcemia, polycystic kidney disease, mucolipidosis type IV and familial focal segmental glomerulosclerosis. Moreover, TRP channel function/dysfunction has been directly linked to a wide range of pathological conditions, including chronic pain, hypertension, cancer and neurodegenerative disorders.

[0005] TRPM3 (Transient receptor potential melastatin 3) represents a promising pharmacological target. TRPM3 is expressed in a large subset of small-diameter sensory neurons from dorsal root and trigeminal ganglia, and is involved in heat sensing. The

neurosteroid pregnenolone sulfate is a potent known activator of TRPM3 (Wagner et al., 2008). The neurosteroid pregnenolone sulfate evoked pain in wild type mice but not in knock-out TRPM3 mice. It was also recently shown that CFA induced inflammation and inflammatory pain are eliminated in TRPM3 knock-out mice. Therefore, TRPM3 antagonists could be used as analgesic drugs to counteract pain, such as inflammatory pain (Vriens J. et al. Neuron, May 2011). A relationship between TRPM3 and epilepsy has also been established (see e.g. Eur J Hum Genet. 2019 Oct; 27(10): 1611–1618; Elife 2020 May 19;9:e57190. doi: 10.7554/eLife.57190. DOI: 10.7554/eLife.57190; Channels (Austin). 2021; 15(1): 386–397. TRPM3 is therefore also a potential target for the treatment of epilepsy.

[0006] A few TRPM3 antagonists are known, but none of them points towards the compounds of the current invention (Straub I et al. Mol Pharmacol, November 2013). For instance, Liquiritigenin, a postulated TRPM3 blocker has been described to decrease mechanical and cold hyperalgesia in a rat pain model (Chen L et al. Scientific reports, July 2014). There is still a great medical need for novel, alternative and/or better therapeutics for the prevention or treatment of TRPM3 mediated disorders, more in particular for pain such as inflammatory pain and epilepsy. Therapeutics with good potency on a certain type of pain, low level or no side-effects (such as no possibilities for addiction as with opiates, no toxicity) and/or good or better pharmacokinetic or -dynamic properties are highly needed.

[0007] The invention provides a class of novel compounds which are antagonists of TRPM3 and can be used as modulators of TRPM3 mediated disorders.

SUMMARY

[0008] The invention provides indazole derivatives and pharmaceutical compositions comprising such indazole derivatives. The invention also provides indazole derivatives for use as a medicament, more in particular for use in the prevention and/or treatment of TRPM3 mediated disorders, especially for use in the prevention and/or treatment of pain and/or inflammatory hypersensitivity and/or epilepsy; and/or for counteracting pain and/or inflammatory hypersensitivity and/or epilepsy.

[0009] The invention also provides the use of indazole derivatives for the manufacture of pharmaceutical compositions or medicaments for the prevention and/or treatment of TRPM3 mediated disorders, especially for the prevention and/or treatment of pain and/or inflammatory hypersensitivity and/or epilepsy; and/or for counteracting pain and/or inflammatory hypersensitivity and/or epilepsy.

[0010] The invention also provides a method for the prevention or treatment of a TRPM3 mediated disorder by administering the indazole derivatives according to the invention to a subject in need thereof. More in particular, the invention relates to such method for the prevention and/or treatment of pain and/or inflammatory hypersensitivity and/or epilepsy;

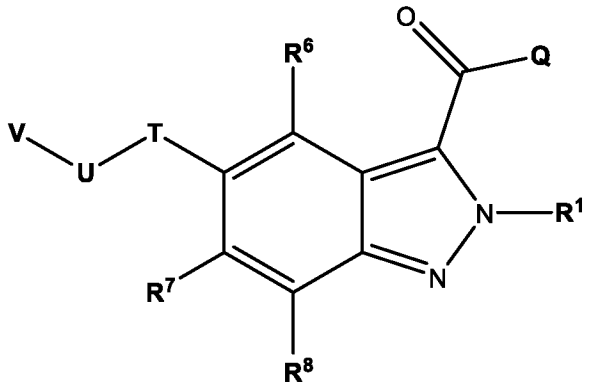
and/or for counteracting pain and/or inflammatory hypersensitivity and/or epilepsy.

[0011] The invention further provides a method for the preparation of the indazole derivatives of the invention.

DETAILED DESCRIPTION OF THE INVENTION

[0012] The invention will be further described and in some instances with respect to particular embodiments, but the invention is not limited thereto.

[0013] The first aspect of the invention is the provision of a compound of formula (I), a stereo-isomeric form, a physiologically acceptable salt, solvate and/or polymorph thereof



(I)

optionally for use in the treatment of pain or epilepsy or methods of treating pain or epilepsy;

wherein

R^1 represents -F, -Cl, -Br, -I, -CN, -**R**^{W}, -O**R**^{W}, -OC(=O)**R**^{W}, -N**R**^{W}**R**^{X}, -N**R**^{W}C(=O)**R**^{X}, -S**R**^{W}, -S(=O)**R**^{W}, -S(=O)$_2$**R**^{W}, -C(=O)**R**^{W}, -C(=O)O**R**^{W}, or -C(=O)N**R**^{W}**R**^{X};

Q represents -O**R**^{2} or -N**R**^{3}**R**^{4};

R^2 represents -**R**^{Y};

R^3 represents -OH or -**R**^{Y};

R^4 represents -**R**^{Y} or -S(=O)$_2$**R**^{Y};

or **R**^{3} and **R**^{4} together form a 4, 5, 6, 7 or 8 membered heterocycle containing 1 to 3 heteroatoms selected from N, O and S, saturated or unsaturated, unsubstituted or mono- or polysubstituted;

T represents -O- and **U** represents -C**R**^{5}**R**$^{5'}$-; or **T** represents -C**R**^{5}**R**$^{5'}$- and **U** represents -O-;

R^5 and **R**$^{5'}$ independently of one another represent -**R**^{Y};

R^6, **R**^{7} and **R**^{8} independently of one another represent -F, -Cl, -Br, -I, -CN, -NO$_2$, -SF$_5$, -**R**^{W}, -O**R**^{W}, -OC(=O)**R**^{W}, -N**R**^{W}**R**^{X}, -N**R**^{W}C(=O)**R**^{X}, -S**R**^{W}, -S(=O)**R**^{W}, -S(=O)$_2$**R**^{W}, -C(=O)**R**^{W}, -C(=O)O**R**^{W}, or -C(=O)N**R**^{W}**R**^{X};

V represents 3-14-membered heterocycloalkyl, saturated or unsaturated; 3-14-membered

cycloalkyl, saturated or unsaturated; 5-14-membered aryl; -C_1-C_6 alkyl, -C_1-C_6 heteroalkyl; or 5-14-membered heteroaryl; in each case unsubstituted, mono- or polysubstituted with substituents independently of one another selected from -F, -Cl, -Br, -I, -CF_3, -CF_2H, C_1-C_6 alkyl, -CN, -NO, -NO_2, =O, =S, -SF_5, -$\mathbf{R^Y}$, -O$\mathbf{R^Y}$, -OC(=O)$\mathbf{R^Y}$, -N$\mathbf{R^Y}\mathbf{R^Z}$, -N$\mathbf{R^Y}$C(=O)$\mathbf{R^Z}$, -S$\mathbf{R^Y}$, -S(=O)$\mathbf{R^Y}$, -S(=O)$_2\mathbf{R^Y}$, -C(=O)$\mathbf{R^Y}$, -C(=O)O$\mathbf{R^Y}$, or -C(=O)N$\mathbf{R^Y}\mathbf{R^Z}$;

wherein

$\mathbf{R^W}$ and $\mathbf{R^X}$ independently of one another and in each case independently represent

-H;

-C_1-C_6-alkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted;

-C_1-C_6-heteroalkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted;

3-14-membered cycloalkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted; wherein said 3-14-membered cycloalkyl is optionally connected through -C_1-C_6-alkylene- or -C_1-C_6-heteroalkylene-, in each case saturated or unsaturated, unsubstituted, mono- or polysubstituted; or

3-14-membered heterocycloalkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted; wherein said 3-14-membered heterocycloalkyl is optionally connected through -C_1-C_6-alkylene- or -C_1-C_6-heteroalkylene-, in each case saturated or unsaturated, unsubstituted, mono- or polysubstituted;

$\mathbf{R^Y}$ and $\mathbf{R^Z}$ independently of one another and in each case independently represent

-H;

-C_1-C_6-alkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted;

-C_1-C_6-heteroalkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted;

3-14-membered cycloalkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted; wherein said 3-14-membered cycloalkyl is optionally connected through -C_1-C_6-alkylene- or -C_1-C_6-heteroalkylene-, in each case saturated or unsaturated, unsubstituted, mono- or polysubstituted;

3-14-membered heterocycloalkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted; wherein said 3-14-membered heterocycloalkyl is optionally connected through -C_1-C_6-alkylene- or -C_1-C_6-heteroalkylene-, in each case saturated or unsaturated, unsubstituted, mono- or polysubstituted;

6-14-membered aryl, unsubstituted, mono- or poly-substituted; wherein said 6-14-membered aryl is optionally connected through -C_1-C_6-alkylene- or -C_1-C_6-heteroalkylene-, in each case saturated or unsaturated, unsubstituted, mono- or polysubstituted; or

5-14-membered heteroaryl, unsubstituted, mono- or polysubstituted; wherein said 5-14-membered heteroaryl is optionally connected through -C_1-C_6-alkylene- or -C_1-C_6-heteroalkylene-, in each case saturated or unsaturated, unsubstituted, mono- or polysubstituted;

or R^Y and R^Z together form a 4, 5, 6, 7 or 8 membered heterocycle containing 1 to 3 heteroatoms selected from N, O and S, saturated or unsaturated, unsubstituted or mono- or polysubstituted;

and wherein "mono- or polysubstituted" in each case independently means substituted with one or more, e.g. 1, 2, 3, 4, or more substituents independently of one another selected from -F, -Cl, -Br, -I, -CN, -C_{1-6}-alkyl, -CF_3, -CF_2H, -CFH_2, -CF_2Cl, -$CFCl_2$, -C_{1-6}-alkylene-CF_3, -C_{1-6}-alkylene-CF_2H, -C_{1-6}-alkylene-CFH_2, -C_{1-6}-alkylene-O-CF_3, -C_{1-6}-alkylene-O-CF_2H, -C_{1-6}-alkylene-O-CFH_2, -C_{1-6}-alkylene-NH-C_{1-6}-alkylene-CF_3, -C_{1-6}-alkylene-N(C_{1-6}-alkyl)-C_{1-6}-alkylene-CF_3, -C(=O)-C_{1-6}-alkyl, -C_{1-6}-alkylene-C(=O)-C_{1-6}-alkyl, -C(=O)OH, -C_{1-6}-alkylene-C(=O)-OH, -C(=O)-OC_{1-6}-alkyl, -C_{1-6}-alkylene-C(=O)-OC_{1-6}-alkyl, -C(=O)O-C_{1-6}-alkylene-CF_3, -C(=O)-NH_2, -C_{1-6}-alkylene-C(=O)-NH_2, -C(=O)-NH(C_{1-6}-alkyl), -C_{1-6}-alkylene-C(=O)-NH(C_{1-6}-alkyl), -C(=O)-N(C_{1-6}-alkyl)$_2$, -C_{1-6}-alkylene-C(=O)-N(C_{1-6}-alkyl)$_2$, -C(=O)-NH(OH), -C_{1-6}-alkylene-C(=O)-NH(OH), -OH, -C_{1-6}-alkylene-OH, =O, -OCF_3, -OCF_2H, -$OCFH_2$, -OCF_2Cl, -$OCFCl_2$, -O-C_{1-6}-alkyl, -C_{1-6}-alkylene-O-C_{1-6}-alkyl, -O-C_{1-6}-alkylene-O-C_{1-6}-alkyl, -O-C_{1-6}-alkylene-NH_2, -O-C_{1-6}-alkylene-NH-C_{1-6}-alkyl, -O-C_{1-6}-alkylene-N(C_{1-6}-alkyl)$_2$, -O-C(=O)-C_{1-6}-alkyl, -C_{1-6}-alkylene-O-C(=O)-C_{1-6}-alkyl, -O-C(=O)-O-C_{1-6}-alkyl, -C_{1-6}-alkylene-O-C(=O)-O-C_{1-6}-alkyl, -O-C(=O)-NH(C_{1-6}-alkyl), -C_{1-6}-alkylene-O-C(=O)-NH(C_{1-6}-alkyl), -O-C(=O)-N(C_{1-6}-alkyl)$_2$, -C_{1-6}-alkylene-O-C(=O)-N(C_{1-6}-alkyl)$_2$, -O-S(=O)$_2$-NH_2, -C_{1-6}-alkylene-O-S(=O)$_2$-NH_2, -O-S(=O)$_2$-NH(C_{1-6}-alkyl), -C_{1-6}-alkylene-O-S(=O)$_2$-NH(C_{1-6}-alkyl), -O-S(=O)$_2$-N(C_{1-6}-alkyl)$_2$, -C_{1-6}-alkylene-O-S(=O)$_2$-N(C_{1-6}-alkyl)$_2$, -NH_2, -NO, -NO_2, -C_{1-6}-alkylene-NH_2, -NH(C_{1-6}-alkyl), -N(3-14-membered cycloalkyl)(C_{1-6}-alkyl), -N(C_{1-6}-alkyl)-C_{1-6}-alkylene-OH, -N(H)-C_{1-6}-alkylene-OH, -C_{1-6}-alkylene-NH(C_{1-6}-alkyl), -N(C_{1-6}-alkyl)$_2$, -C_{1-6}-alkylene-N(C_{1-6}-alkyl)$_2$, -NH-C(=O)-C_{1-6}-alkyl, -C_{1-6}-alkylene-NH-C(=O)-C_{1-6}-alkyl, -NH-C(=O)-O-C_{1-6}-alkyl, -C_{1-6}-alkylene-NH-C(=O)-O-C_{1-6}-alkyl, -NH-C(=O)-NH_2, -C_{1-6}-alkylene-NH-C(=O)-NH_2, -NH-C(=O)-NH(C_{1-6}-alkyl), -C_{1-6}-alkylene-NH-C(=O)-NH(C_{1-6}-alkyl), -NH-C(=O)-N(C_{1-6}-alkyl)$_2$, -C_{1-6}-alkylene-NH-C(=O)-N(C_{1-6}-alkyl)$_2$, -N(C_{1-6}-alkyl)-C(=O)-C_{1-6}-alkyl, -C_{1-6}-alkylene-N(C_{1-6}-alkyl)-C(=O)-C_{1-6}-alkyl, -N(C_{1-6}-alkyl)-C(=O)-O-C_{1-6}-alkyl, -C_{1-6}-alkylene-N(C_{1-6}-alkyl)-C(=O)-O-C_{1-6}-alkyl, -N(C_{1-6}-alkyl)-C(=O)-NH_2, -C_{1-6}-alkylene-N(C_{1-6}-alkyl)-C(=O)-NH_2, -N(C_{1-6}-alkyl)-C(=O)-NH(C_{1-6}-alkyl), -C_{1-6}-alkylene-N(C_{1-6}-alkyl)-C(=O)-NH(C_{1-6}-alkyl), -N(C_{1-6}-alkyl)-C(=O)-N(C_{1-6}-alkyl)$_2$, -C_{1-6}-alkylene-N(C_{1-6}-alkyl)-C(=O)-N(C_{1-6}-alkyl)$_2$, -NH-S(=O)$_2$OH, -C_{1-6}-alkylene-NH-S(=O)$_2$OH, -NH-S(=O)$_2$-C_{1-6}-alkyl, -C_{1-6}-alkylene-NH-S(=O)$_2$-C_{1-6}-alkyl, -NH-S(=O)$_2$-O-C_{1-6}-alkyl, -C_{1-6}-alkylene-NH-S(=O)$_2$-O-C_{1-6}-alkyl, -NH-S(=O)$_2$-NH_2, -C_{1-6}-alkylene-NH-S(=O)$_2$-NH_2, -NH-S(=O)$_2$-NH(C_{1-6}-alkyl), -C_{1-6}-alkylene-NH-S(=O)$_2$-NH(C_{1-6}-alkyl), -NH-S(=O)$_2$N(C_{1-6}-alkyl)$_2$, -C_{1-6}-alkylene-NH-S(=O)$_2$N(C_{1-6}-alkyl)$_2$, -N(C_{1-6}-alkyl)-S(=O)$_2$-OH, -C_{1-6}-alkylene-N(C_{1-6}-alkyl)-S(=O)$_2$-OH, -N(C_{1-6}-alkyl)-S(=O)$_2$-C_{1-6}-alkyl, -C_{1-6}-alkylene-N(C_{1-6}-alkyl)-S(=O)$_2$-C_{1-6}-alkyl, -N(C_{1-6}-alkyl)-S(=O)$_2$-O-C_{1-6}-alkyl, -C_{1-6}-alkylene-N(C_{1-6}-alkyl)-S(=O)$_2$-O-C_{1-6}-alkyl, -N(C_{1-6}-alkyl)-S(=O)$_2$-NH_2, -C_{1-6}-alkylene-N(C_{1-6}-alkyl)-S(=O)$_2$-NH_2, -N(C_{1-6}-alkyl)-S(=O)$_2$-NH(C_{1-6}-alkyl), -C_{1-6}-alkylene-N(C_{1-6}-

alkyl)-S(=O)$_2$-NH(C_{1-6}-alkyl), -N(C_{1-6}-alkyl)-S(=O)$_2$-N(C_{1-6}-alkyl)$_2$, -C_{1-6}-alkylene-N(C_{1-6}-alkyl)-S(=O)$_2$-N(C_{1-6}-alkyl)$_2$, -SH, =S, -SF_5, -SCF_3, -SCF_2H, -$SCFH_2$, -S-C_{1-6}-alkyl, -C_{1-6}-alkylene-S-C_{1-6}-alkyl, -S(=O)-C_{1-6}-alkyl, -C_{1-6}-alkylene-S(=O)-C_{1-6}-alkyl, -S(=O)$_2$-C_{1-6}-alkyl, -C_{1-6}-alkylene-S(=O)$_2$-C_{1-6}-alkyl, -S(=O)$_2$-OH, -C_{1-6}-alkylene-S(=O)$_2$-OH, -S(=O)$_2$-O-C_{1-6}-alkyl, -C_{1-6}-alkylene-S(=O)$_2$-O-C_{1-6}-alkyl, -S(=O)$_2$-NH_2, -C_{1-6}-alkylene-S(=O)$_2$-NH_2, -S(=O)$_2$-NH(C_{1-6}-alkyl), -C_{1-6}-alkylene-S(=O)$_2$-NH(C_{1-6}-alkyl), -S(=O)$_2$-N(C_{1-6}-alkyl)$_2$, -C_{1-6}-alkylene-S(=O)$_2$-N(C_{1-6}-alkyl)$_2$, 3-14-membered cycloalkyl, -C_{1-6}-alkylene-(3-14-membered cycloalkyl), 3 to 14-membered heterocycloalkyl, -C_{1-6}-alkylene-(3 to 14-membered heterocycloalkyl), -phenyl, -C_{1-6}-alkylene-phenyl, 5 to 14-membered heteroaryl, -C_{1-6}-alkylene-(5 to 14-membered heteroaryl), -O-(3-14-membered cycloalkyl), -O-(3 to 14-membered heterocycloalkyl), -O-phenyl, -O-(5 to 14-membered heteroaryl), -C(=O)-(3-14-membered cycloalkyl), -C(=O)-(3 to 14-membered heterocycloalkyl), -C(=O)-phenyl, -C(=O)-(5 to 14-membered heteroaryl), -S(=O)$_2$-(3-14-membered cycloalkyl), -S(=O)$_2$-(3 to 14-membered heterocycloalkyl), -S(=O)$_2$-phenyl, -S(=O)$_2$-(5 to 14-membered heteroaryl).

[0014] In some embodiments of the indazole derivatives according to the invention

(a-1) **Q** represents -N**R^{3}R^4**; **R^1** represents **R^W** ; and **R^W** represents -C_1-C_6-alkyl - and/or

(a-2) **Q** represents -N**R^{3}R^4**; and at least one of **R^5** and **R$^{5'}$** represents -H; and/or

(a-3) **Q** represents -N**R^{3}R^4** ; and **R^6** represents -H; and/or

(a-4) **Q** represents -N**R^{3}R^4** ; and **R^8** represents -H;

or

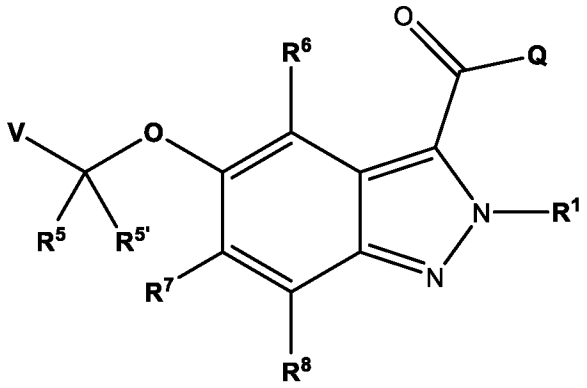
(b-1)

(b-1) Q represents -N**R^{3}R^4**; and **R^1** represents -CH_2F, -CHF_2, -CF_3, -CN, -methyl, -ethyl, -propyl or -cyclopropyl; and/or

(b-2) Q represents -N**R^{3}R^4**; and at least one of **R^5** and **R$^{5'}$** does not represent -H; and/or

(b-3) Q represents -N**R^{3}R^4**; and **R^3** represents -H.

[0015] In an embodiment of the indazole derivatives according to the invention **T** represents -O- and **U** represents -C**R^{5}R$^{5'}$**-. According to this embodiment, the indazole derivative according to the invention is a compound of formula (II), a stereo-isomeric form, a physiologically acceptable salt, solvate and/or polymorph thereof



(II).

[0016] In another embodiment of the indazole derivatives according to Formula I, **T** represents -C**R**^{5}**R**$^{5'}$- and **U** represents -O-.

[0017] In an embodiment of the indazole derivatives according to Formulas I or II, **R**^{1} is methyl, ethyl, or other C_1-C_6 alkyl. In another preferred embodiment, **R**^{1} is methyl.

[0018] In an embodiment of the indazole derivatives according to the invention **Q** represents -N**R**^{3}**R**^{4}.

[0019] In an embodiment of the indazole derivatives according to the invention **Q** represents -O**R**^{2}.

[0020] In some embodiments of the indazole derivatives according to the invention **V** represents 3-14-membered cycloalkyl, saturated or unsaturated; 3-14-membered heterocycloalkyl, saturated or unsaturated 5-14-membered aryl; C_1-C_6 alkyl; or 5-14-membered heteroaryl; in each case unsubstituted, mono- or polysubstituted with substituents independently of one another selected from -F, -Cl, -Br, -I, -CF_3, -CF_2H, C_1-C_6 alkyl, -CN, -NO, -NO_2, =O, =S, -SF_5, -**R**^{Y}, -O**R**^{Y}, -OC(=O)**R**^{Y}, -N**R**^{Y}**R**^{Z}, -N**R**^{Y}C(=O)**R**^{Z}, -S**R**^{Y}, -S(=O)**R**^{Y}, -$S(=O)_2$**R**^{Y}, -C(=O)**R**^{Y}, -C(=O)O**R**^{Y}, or -C(=O)N**R**^{Y}**R**^{Z}.

[0021] .

[0022] In some embodiments, the 5-14-membered heteroaryl within the definition of **V** is selected from benzimidazole, benzisoxazole, benzoazole, benzodioxole, benzofuran, benzothiadiazole, benzothiazole, benzothiophene, carbazole, cinnoline, dibenzofuran, furane, furazane, imidazole, imidazopyridine, indazole, indole, indolizine, isobenzofuran, isoindole, isoquinoline, isothiazole, isoxazole, naphthyridine, oxadiazole, oxazole, oxindole, phthalazine, purine, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, pyrrole, quinazoline, quinoline, quinoxaline, tetrazole, thiadiazole, thiazole, thiophene, triazine, triazole, and [1,2,4]triazolo[4,3-a]pyrimidine; in each case unsubstituted, mono- or polysubstituted with substituents independently of one another selected from -F, -Cl, -Br, -I, -CF_3, -CF_2H, C_1-C_6 alkyl, -CN, -NO, -NO_2, =O, =S, -SF_5, -**R**^{Y}, -O**R**^{Y}, -OC(=O)**R**^{Y}, -N**R**^{Y}**R**^{Z}, -N**R**^{Y}C(=O)**R**^{Z}, -S**R**^{Y}, -S(=O)**R**^{Y}, -$S(=O)_2$**R**^{Y}, -C(=O)**R**^{Y}, -C(=O)O**R**^{Y}, or -C(=O)N**R**^{Y}**R**^{Z}.

[0023] Preferably, the 5-14-membered heteroaryl within the definition of **V** is selected from the

group consisting of furane, thiophene, imidazole, pyrazole, oxazole, isoxazole, thiazole, triazole, pyridine, isoquinoline, benzothiazole, pyridazine, pyrimidine, imidazopyridine; in each case unsubstituted, mono- or polysubstituted with substituents independently of one another selected from -F, -Cl, -Br, -I, CF_3, $-CF_2H$, C_1-C_6 alkyl, -CN, -NO, $-NO_2$, =O, =S, $-SF_5$, $-\mathbf{R}^Y$, $-O\mathbf{R}^Y$, $-OC(=O)\mathbf{R}^Y$, $-N\mathbf{R}^Y\mathbf{R}^Z$, $-N\mathbf{R}^YC(=O)\mathbf{R}^Z$, $-S\mathbf{R}^Y$, $-S(=O)\mathbf{R}^Y$, $-S(=O)_2\mathbf{R}^Y$, $-C(=O)\mathbf{R}^Y$, $-C(=O)O\mathbf{R}^Y$, or $-C(=O)N\mathbf{R}^Y\mathbf{R}^Z$.

[0024] Preferably, the 5-14-membered heteroaryl within the definition of **V** is selected from the group consisting of furan-2-yl, furan-3-yl, thiophen-2-yl, thiophen-3-yl, pyrazol-3-yl, pyrazol-4-yl, pyrazol-5-yl, oxazol-5-yl, isoxazol-4-yl, thiazol-2-yl, thiazol-4-yl, thiazol-5-yl, 1,2,4-triazol-3-yl, 1,2,3-triazol-4-yl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, isoquinolin-1-yl, isoquinolin-5-yl, benzo[d]thiazol-2-yl, pyridazin-3-yl, pyrimidin-5-yl, and imidazo[1,2-a]pyridin-6-yl; in each case unsubstituted, mono- or polysubstituted with substituents independently of one another selected from -F, -Cl, -Br, -I, , CF_3, $-CF_2H$, C_1-C_6 alkyl, -CN, -NO, $-NO_2$, =O, =S, $-SF_5$, $-\mathbf{R}^Y$, $-O\mathbf{R}^Y$, $-OC(=O)\mathbf{R}^Y$, $-N\mathbf{R}^Y\mathbf{R}^Z$, $-N\mathbf{R}^YC(=O)\mathbf{R}^Z$, $-S\mathbf{R}^Y$, $-S(=O)\mathbf{R}^Y$, $-S(=O)_2\mathbf{R}^Y$, $-C(=O)\mathbf{R}^Y$, $-C(=O)O\mathbf{R}^Y$, or $-C(=O)N\mathbf{R}^Y\mathbf{R}^Z$.

[0025] In some embodiments, the 5-14-membered heteroaryl within the definition of **V** is selected form the group consisting of pyrazol-3-yl, pyrazol-4-yl, thiazol-4-yl, thiazol-5-yl, pyridin-2-yl, pyridin-3-yl, and pyridine-4-yl; in each case unsubstituted, mono- or polysubstituted with substituents independently of one another selected from -F, -Cl, -Br, -I, , CF_3, $-CF_2H$, C_1-C_6 alkyl, -CN, -NO, $-NO_2$, =O, =S, $-SF_5$, $-\mathbf{R}^Y$, $-O\mathbf{R}^Y$, $-OC(=O)\mathbf{R}^Y$, $-N\mathbf{R}^Y\mathbf{R}^Z$, $-N\mathbf{R}^YC(=O)\mathbf{R}^Z$, $-S\mathbf{R}^Y$, $-S(=O)\mathbf{R}^Y$, $-S(=O)_2\mathbf{R}^Y$, $-C(=O)\mathbf{R}^Y$, $-C(=O)O\mathbf{R}^Y$, or $-C(=O)N\mathbf{R}^Y\mathbf{R}^Z$.

[0026] In an embodiment, the 3-14-membered cycloalkyl, saturated or unsaturated within the definition of **V** is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, or cyclodecyl including unfused or unbridged, fused, or bridged cycloalkyls; in each case unsubstituted, mono- or polysubstituted with substituents independently of one another selected from -F, -Cl, -Br, -I, , CF_3, $-CF_2H$, C_1-C_6 alkyl, -CN, -NO, $-NO_2$, =O, =S, $-SF_5$, $-\mathbf{R}^Y$, $-O\mathbf{R}^Y$, $-OC(=O)\mathbf{R}^Y$, $-N\mathbf{R}^Y\mathbf{R}^Z$, $-N\mathbf{R}^YC(=O)\mathbf{R}^Z$, $-S\mathbf{R}^Y$, $-S(=O)\mathbf{R}^Y$, $-S(=O)_2\mathbf{R}^Y$, $-C(=O)\mathbf{R}^Y$, $-C(=O)O\mathbf{R}^Y$, or $-C(=O)N\mathbf{R}^Y\mathbf{R}^Z$.

[0027] In an embodiment, the 5-14-membered aryl within the definition of **V** is phenyl or another 5-14-membered aryl, unsubstituted, mono- or polysubstituted with substituents independently of one another selected from -F, -Cl, -Br, -I, CF_3, $-CF_2H$, C_1-C_6 alkyl, -CN, -NO, $-NO_2$, =O, =S, $-SF_5$, $-\mathbf{R}^Y$, $-O\mathbf{R}^Y$, $-OC(=O)\mathbf{R}^Y$, $-N\mathbf{R}^Y\mathbf{R}^Z$, $-N\mathbf{R}^YC(=O)\mathbf{R}^Z$, $-S\mathbf{R}^Y$, $-S(=O)\mathbf{R}^Y$, $-S(=O)_2\mathbf{R}^Y$, $-C(=O)\mathbf{R}^Y$, $-C(=O)O\mathbf{R}^Y$, or $-C(=O)N\mathbf{R}^Y\mathbf{R}^Z$.

[0028] In further embodiments of the indazole derivatives according to the invention **V** represents 3-14-membered heterocycloalkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted with substituents independently of one another selected from -F, -Cl, -Br, -I, CF_3, $-CF_2H$, C_1-C_6 alkyl, -CN, -NO, $-NO_2$, =O, =S, $-SF_5$, $-\mathbf{R}^Y$, $-O\mathbf{R}^Y$, $-OC(=O)\mathbf{R}^Y$, $-N\mathbf{R}^Y\mathbf{R}^Z$, -

$NR^YC(=O)R^Z$, $-SR^Y$, $-S(=O)R^Y$, $-S(=O)_2R^Y$, $-C(=O)R^Y$, $-C(=O)OR^Y$, or $-C(=O)NR^YR^Z$.

[0029] In some embodiments, the 3-14-membered heterocycloalkyl within the definition of **V** is selected from azepane, 1,4-oxazepane, azetane, azetidine, aziridine, azocane, diazepane, dioxane, dioxolane, dithiane, dithiolane, imidazolidine, isothiazolidine, isoxalidine, morpholine, oxazolidine, oxane, oxepane, oxetane, oxirane, piperazine, piperidine, pyrazolidine, pyrrolidine, quinuclidine, tetrahydrofurane, tetrahydropyrane, tetrahydrothiopyrane, thiazolidine, thietane, thiirane, thiolane, thiomorpholine, indoline, dihydrobenzofuran, dihydrobenzo-thiophene, 1,1-dioxothia-cyclohexane, 2-azaspiro[3.3]heptane, 2-oxaspiro[3.3]heptane, 7-azaspiro[3.5]nonane, 8-azabicyclo[3.2.1]octane, 9-azabicyclo[3.3.1]nonane, hexahydro-1H-pyrrolizine, hexa-hydro-cyclopenta[c]pyrrole, octahydro-cyclopenta[c]pyrrole, and octahydro-pyrrolo[1,2-a]pyrazine; in each case unsubstituted, mono- or polysubstituted with substituents independently of one another selected from -F, -Cl, -Br, -I, CF_3, $-CF_2H$, C_1-C_6 alkyl, -CN, -NO, $-NO_2$, =O, =S, $-SF_5$, $-R^Y$, $-OR^Y$, $-OC(=O)R^Y$, $-NR^YR^Z$, $-NR^YC(=O)R^Z$, $-SR^Y$, $-S(=O)R^Y$, $-S(=O)_2R^Y$, $-C(=O)R^Y$, $-C(=O)OR^Y$, or $-C(=O)NR^YR^Z$.

[0030] In some embodiments, the 3-14-membered heterocycloalkyl within the definition of **V** is oxane, oxan-4-yl, oxetane, or oxetan-3-yl; in each case unsubstituted, mono- or polysubstituted with substituents independently of one another selected from -F, -Cl, -Br, -I, CF_3, $-CF_2H$, C_1-C_6 alkyl, -CN, -NO, $-NO_2$, =O, =S, $-SF_5$, $-R^Y$, $-OR^Y$, $-OC(=O)R^Y$, $-NR^YR^Z$, $-NR^YC(=O)R^Z$, $-SR^Y$, $-S(=O)R^Y$, $-S(=O)_2R^Y$, $-C(=O)R^Y$, $-C(=O)OR^Y$, or $-C(=O)NR^YR^Z$.

[0031] In another preferred embodiment of the indazole derivatives according to the invention **V** represents C_1-C_6 alkyl or C_1-C_6 heteroalkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted with substituents independently of one another selected from -F, -Cl, -Br, -I, CF_3, $-CF_2H$, C_1-C_6 alkyl, -CN, -NO, $-NO_2$, =O, =S, $-SF_5$, $-R^Y$, $-OR^Y$, $-OC(=O)R^Y$, $-NR^YR^Z$, $-NR^YC(=O)R^Z$, $-SR^Y$, $-S(=O)R^Y$, $-S(=O)_2R^Y$, $-C(=O)R^Y$, $-C(=O)OR^Y$, or $-C(=O)NR^YR^Z$.

[0032] In some embodiments of the indazole derivative according to the invention **V** is unsubstituted, mono- or polysubstituted with substituents independently of one another selected from

-F, -Cl, -Br, -I, -CN, -C(=O)OH, $-NH_2$, $-NO_2$, -OH, =O, $-SF_5$;

$-C_{1-6}$-alkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted;

$-C(=O)O-C_{1-6}$-alkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted;

$-NHC_{1-6}$-alkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted;

$-N(C_{1-6}\text{-alkyl})_2$, saturated or unsaturated, unsubstituted, mono- or polysubstituted;

$-O-C_{1-6}$-alkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted;

$-S(=O)_2-C_{1-6}$-alkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted;

3-14-membered cycloalkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted;

wherein said 3-14-membered cycloalkyl is optionally connected through $-C_1$-C_6-alkylene- or -

C_1-C_6-heteroalkylene-, in each case saturated or unsaturated, unsubstituted, mono- or polysubstituted; or

3-14-membered heterocycloalkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted; wherein said 3-14-membered heterocycloalkyl is optionally connected through -C_1-C_6-alkylene- or -C_1-C_6-heteroalkylene-, in each case saturated or unsaturated, unsubstituted, mono- or polysubstituted.

[0033] In some embodiments, **V** is unsubstituted, mono- or polysubstituted with substituents independently of one another selected from

-OH, -F, -Cl, -Br, -I, -SH, $-CF_3$, $-CHF_2$, $-CH_2F$, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, SF_5, -CN, $-NO_2$, -C(=O)OH, $-NH_2$, or $-N(CH_3)_2$;

-C_{1-6}-alkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted with substituents independently of one another , selected from the group consisting of -F, -Cl, -Br, -I, -C_{1-6}-alkyl, C_{2-6}-alkenyl, -C_{2-6}-alkynyl, -OH, =O, -SH, =S, -CN, $-CF_3$, $-CHF_2$, $-CH_2F$, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, SF_5, $-NO_2$, -C(=O)OH, $-NH_2$, C(=O)CHF_2, and -C(=O)NH_2;

-C_{1-6}-heteroalkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted with substituents independently of one another , selected from the group consisting of -F, -Cl, -Br, -I, -C_{1-6}-alkyl, C_{2-6}-alkenyl, -C_{2-6}-alkynyl, -OH, =O, -SH, =S, -CN, $-CF_3$, $-CHF_2$, $-CH_2F$, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, SF_5, $-NO_2$, -C(=O)OH, $-NH_2$, C(=O)CHF_2, and -C(=O)NH_2;

-OC_{1-6}-alkyl, unsubstituted, mono- or polysubstituted with substituents independently of one another, selected from the group consisting of -F, -Cl, -Br, -I, -C_{1-6}-alkyl, C_{2-6}-alkenyl, -C_{2-6}-alkynyl, -OH, =O, -SH, =S, -CN, $-CF_3$, $-CHF_2$, $-CH_2F$, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, SF_5, $-NO_2$, -C(=O)OH, $-NH_2$, C(=O)CHF_2, and -C(=O)NH_2;

-O(C=O)C_{1-6}-alkyl, unsubstituted, mono- or polysubstituted with substituents independently of one another , selected from the group consisting of -F, -Cl, -Br, -I, -C_{1-6}-alkyl, C_{2-6}-alkenyl, -C_{2-6}-alkynyl, -OH, =O, -SH, =S, -CN, $-CF_3$, $-CHF_2$, $-CH_2F$, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, SF_5, $-NO_2$, -C(=O)OH, $-NH_2$, C(=O)CHF_2, and -C(=O)NH_2;

-C(=O)OC_{1-6}-alkyl, unsubstituted, mono- or polysubstituted with substituents independently of one another , selected from the group consisting of -F, -Cl, -Br, -I, -C_{1-6}-alkyl, C_{2-6}-alkenyl, -C_{2-6}-alkynyl, -OH, =O, -SH, =S, -CN, $-CF_3$, $-CHF_2$, $-CH_2F$, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, SF_5, $-NO_2$, -C(=O)OH, $-NH_2$, C(=O)CHF_2, and -C(=O)NH_2;

3-14-membered cycloalkyl selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl; in each case unsubstituted, mono- or polysubstituted with substituents independently of one another , selected from the group consisting of -F, -Cl, -Br, -I, -C_{1-6}-alkyl, C_{2-6}-alkenyl, -C_{2-6}-alkynyl, -OH, =O, -SH, =S, -CN, $-CF_3$, $-CHF_2$, $-CH_2F$, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, SF_5, $-NO_2$, -C(=O)OH, $-NH_2$, C(=O)CHF_2, and -C(=O)NH_2;

3-14-membered heterocycloalkyl selected from the group consisting of azepane, 1,4-oxazepane, azetane, azetidine, aziridine, azocane, diazepane, dioxane, dioxolane, dithiane,

dithiolane, imidazolidine, isothiazolidine, isoxalidine, morpholine, oxazolidine, oxepane, oxetane, oxirane, piperazine, piperidine, pyrazolidine, pyrrolidine, quinuclidine, tetrahydrofuran, tetrahydropyran, tetrahydrothiopyran, thiazolidine, thietane, thiirane, thiolane, thiomorpholine, indoline, dihydrobenzofuran, dihydrobenzothiophene, 1,1-dioxothiacyclohexane, 2-azaspiro[3.3]heptane, 2-oxaspiro[3.3]heptane, 7-azaspiro[3.5]nonane, 8-azabicyclo[3.2.1]octane, 9-azabicyclo[3.3.1]nonane, hexahydro-1H-pyrrolizine, hexahydrocyclopenta[c]pyrrole, octahydrocyclopenta[c]pyrrole, and octahydropyrrolo[1,2-a]pyrazine, in each case unsubstituted, mono- or polysubstituted with substituents independently of one another , selected from the group consisting of -F, -Cl, -Br, -I, -C_{1-6}-alkyl, C_{2-6}-alkenyl, -C_{2-6}-alkynyl, -OH, =O, -SH, =S, -CN, -CF_3, -CHF_2, -CH_2F, -OCF_3, -$OCHF_2$, -OCH_2F, SF_5, -NO_2, -C(=O)OH, -NH_2, C(=O)CHF_2, and -C(=O)NH_2.

[0034] In some embodiments, **V** is unsubstituted, mono- or polysubstituted with substituents independently of one another selected from -F, -Cl, -CN, -OH, =O, -C_{1-6}-alkyl, methyl, ethyl, -CHF_2, -CF_3, -C_{1-6}-alkylene-NH_2, -C_{1-6}-alkylene-NHC(=O)O-C_{1-6}-alkyl, -C_{1-6}-alkylene-OH, -C_{1-6}-alkylene-NHC(=O)-O-C_{1-6}-alkyl, -C(=O)O-C_{1-6}-alkyl, -N(C_{1-6}-alkyl)$_2$, -OC_{1-6}-alkyl, -OCF_3, -O-C_{1-6}-alkylene-N(C_{1-6}-alkyl)$_2$, -S(=O)$_2$-C_{1-6}-alkyl, -azetidine, -C_{1-6}-alkylene-O-tetrahydropyran, or -piperazine substituted with -C_{1-6}-alkyl.

[0035] In some embodiments of the indazole derivative according to the invention **V** is

(i) unsubstituted;

(ii) monosubstituted;

(iii) disubstituted;

(iv) trisubstituted; or

(v) tetrasubstituted.

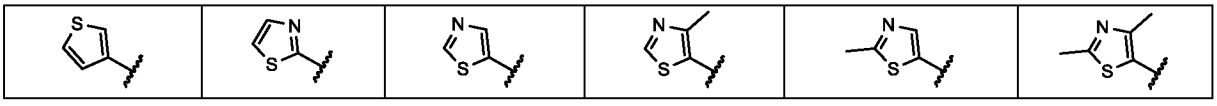
[0036] In some embodiments of the indazole derivatives according to the invention **V** is

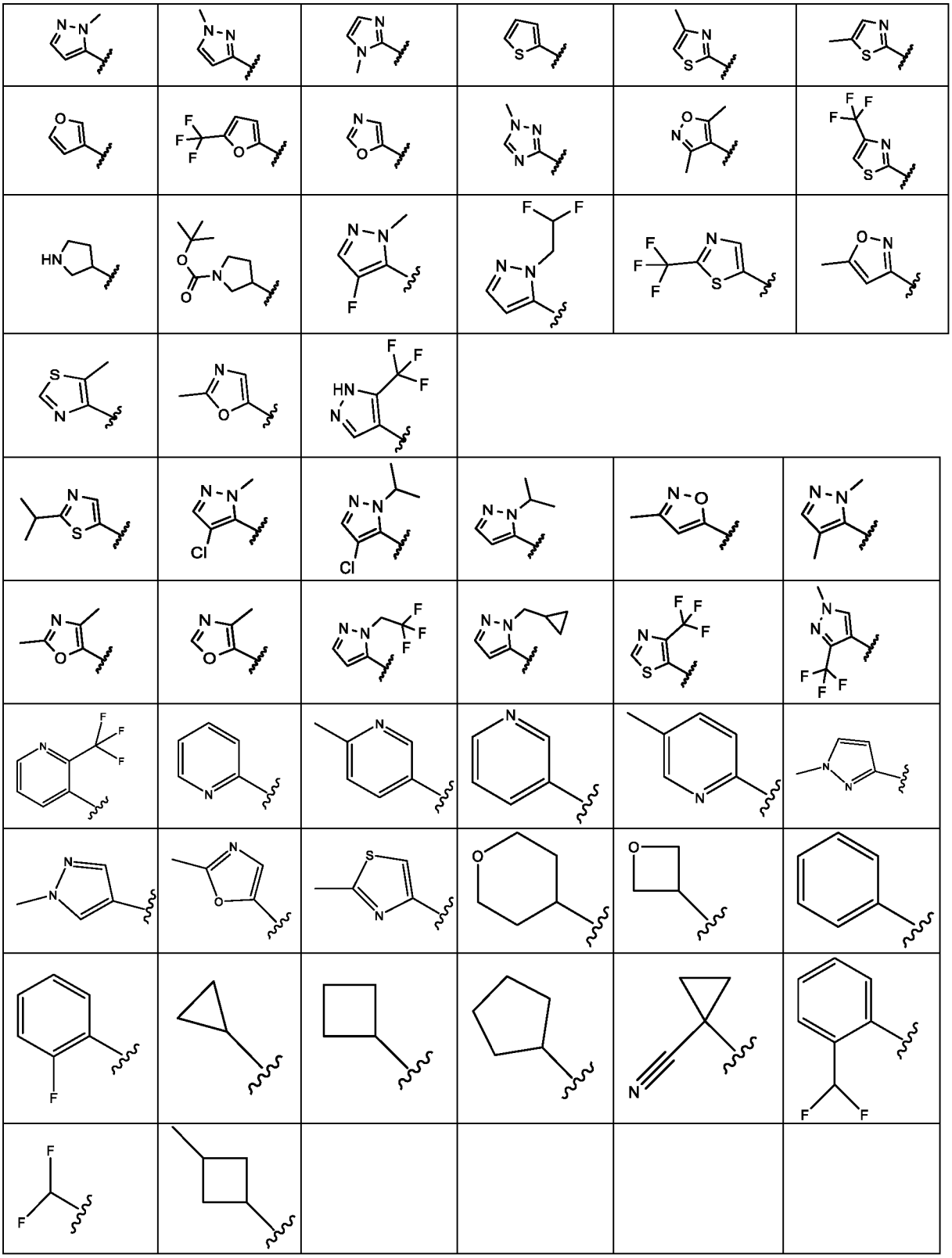
(i) unsubstituted;

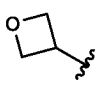
(ii) monosubstituted; or

(iii) disubstituted.

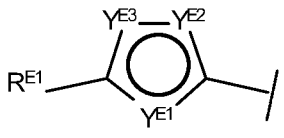
[0037] In some embodiments, **V** represents a 3-14-membered heterocycloalkyl (preferably 3-5-membered heterocycloalkyl), saturated or unsaturated; 5-14-membered heteroaryl (preferably 5-6-membered heteroaryl); 3-14-membered cycloalkyl, saturated or unsaturated; 5-14-membered aryl; or C_1-C_6 alkyl; in each case unsubstituted, mono- or polysubstituted; preferably a residue selected from the group consisting of:





[0038] In an embodiment, **V** represents -oxetanyl, unsubstituted, mono- or polysubstituted; preferably .

[0039] In some embodiments, **V** represents a residue according to general formula (E)



(E)

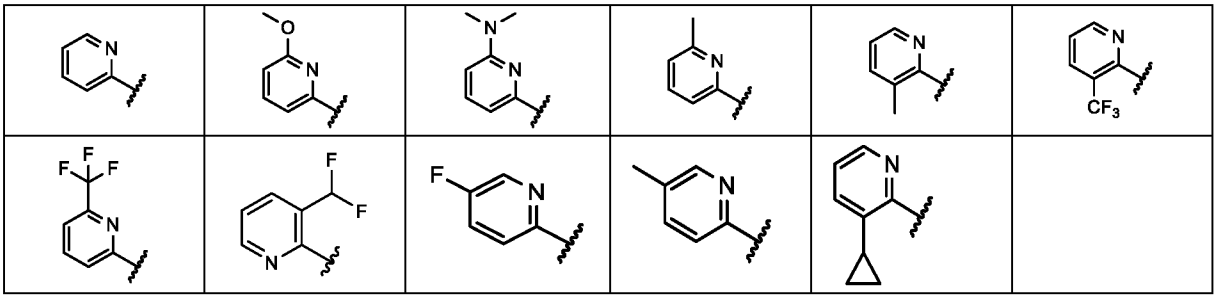
wherein

Y^{E1} represents -N=, -NR^{E2}-, S, O, or -CR^{E3}=; Y^{E2} represents -N=, -NR^{E3}-, S, O, or -CR^{E4}=; and Y^{E3} represent -N=, -NR^{E4}-, S, O, or -CR^{E5}=; with the proviso that at least one of Y^{E1}, Y^{E2}, and Y^{E3} is not -CR^{E3}=, -CR^{E4}=, and -CR^{E5}=, respectively. In another preferred embodiment, V represents a residue according to general formula (E)

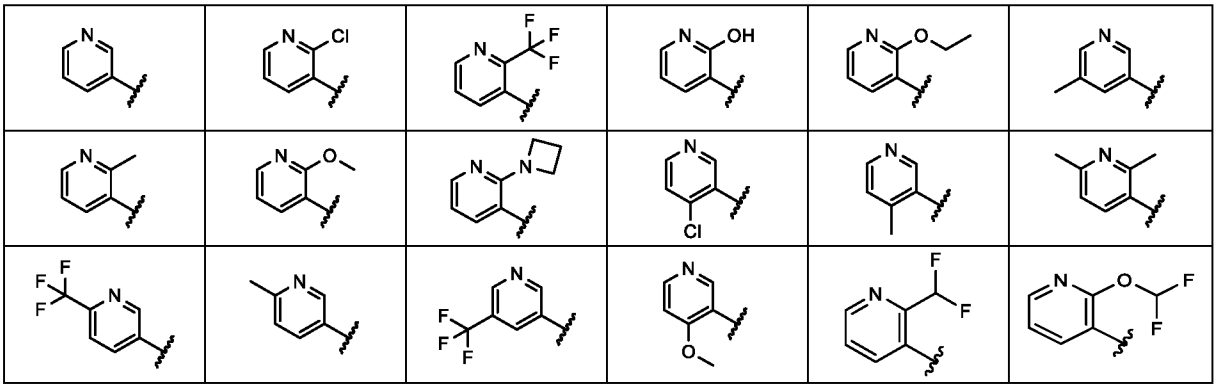
wherein YE1 represents -N=, -NRE2-, S, or -CRE3=; YE2 represents -N=, -NRE3-, S, or -CRE4=; and YE3 represent -N=, -NRE4-, S, or -CRE5=; with the proviso that at least one of YE1, YE2, and YE3 is not -CRE3=, -CRE4=, and -CRE5=, respectively.

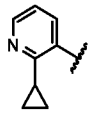
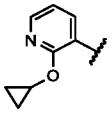
R^{E1}, R^{E2}, R^{E3}, and R^{E4} independently of one another represent -H, -CH_3,-CH_2-cyclopropyl, -CH_2CF_3, -CH_2CHF_2 or -CF_3; more in particular R^{E1}, R^{E2}, R^{E3}, and R^{E4} independently of one another represent -H, -CH_3, or -CF_3; preferably with the proviso that only one of R^{E1}, R^{E2}, R^{E3}, and R^{E4} represents a residue that is not -H.

[0040] In some embodiments, **V** represents 2-pyridine, unsubstituted, mono- or polysubstituted. In some embodiments, **V** represents a residue selected from the group consisting of:

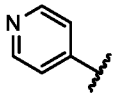


[0041] In some embodiments, **V** represents 3-pyridine, unsubstituted, mono- or polysubstituted. In preferred embodiments, **V** represents a residue selected from the group consisting of:



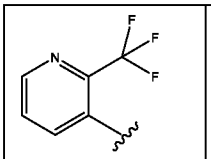
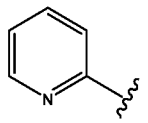
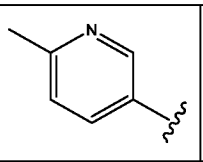
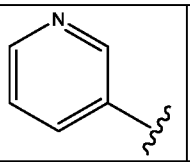
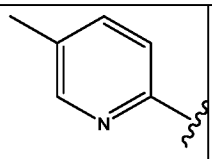
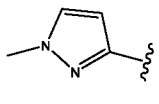
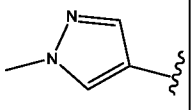
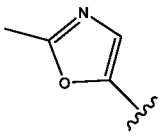
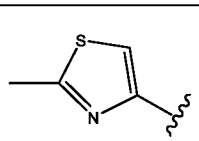
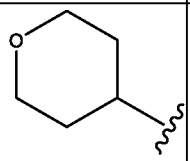
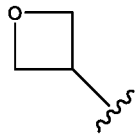
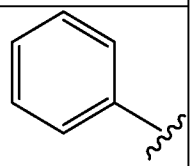
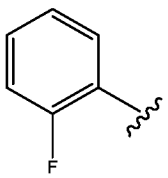
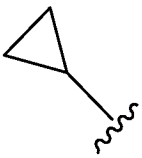
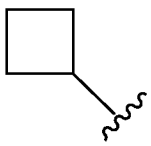
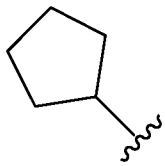
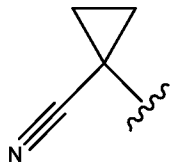
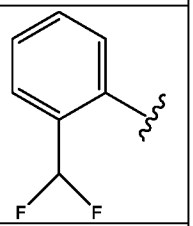
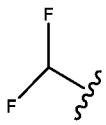
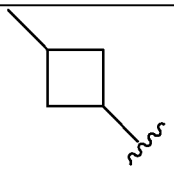
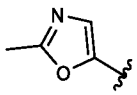
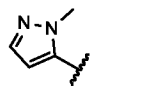
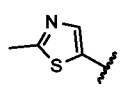
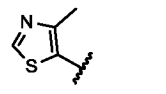
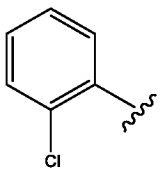
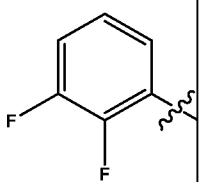
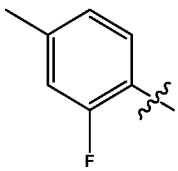
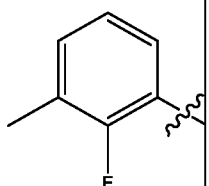
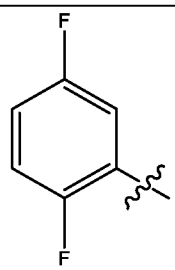
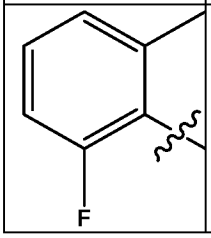
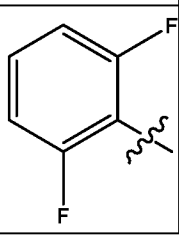
					

[0042] In some embodiments, **V** represents 4-pyridine, unsubstituted, mono- or polysubstituted. In preferred embodiments, **V** represents a residue selected from the group consisting of:

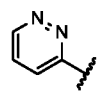
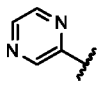
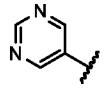
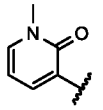
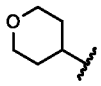
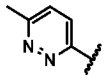
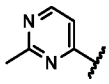


.

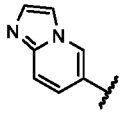
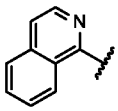
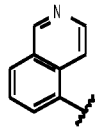
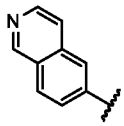
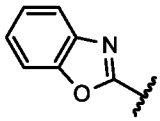
[0043] In some embodiments, optionally where **U** – CH_2, **V** represents a residue selected from the group consisting of:

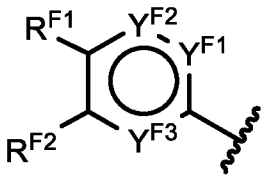
[0044] In alternative embodiments, **V** represents a residue selected from the group consisting of:

[0045] In some embodiments, **V** represents a bicyclic heteroaryl, unsubstituted, mono- or polysubstituted, preferably selected from the group consisting of:

[0046] In some embodiments, **V** represents a residue according to general formula (F')



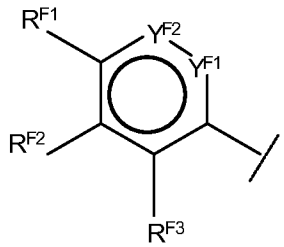
(F')

wherein

$\mathbf{Y^{F1}}$ represents -N= or -C$\mathbf{R^{F4}}$=; and $\mathbf{Y^{F2}}$ represents -N= or -C$\mathbf{R^{F5}}$=; and Y^{F3} represents -N= or -C$\mathbf{R^{F3}}$=; with the proviso that at least one of $\mathbf{Y^{F1}}$ and $\mathbf{Y^{F2}}$ is not -C$\mathbf{R^{F4}}$= and -C$\mathbf{R^{F5}}$=, respectively;

$\mathbf{R^{F1}}$, $\mathbf{R^{F2}}$, $\mathbf{R^{F3}}$, $\mathbf{R^{F4}}$, and $\mathbf{R^{F5}}$ independently of one another represent -H, -CH_3, -CF_3,-OH, -OCH_3, -OCH_2CH_3, -Cl, or -azetidinyl; preferably with the proviso that only one of $\mathbf{R^{F1}}$, $\mathbf{R^{F2}}$, $\mathbf{R^{F3}}$, $\mathbf{R^{F4}}$, and $\mathbf{R^{F5}}$ represents a residue that is not -H.

In another embodiment, **V** represents a residue according to general formula (F)



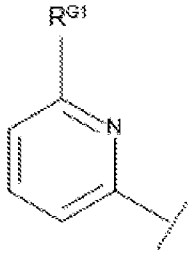
(F)

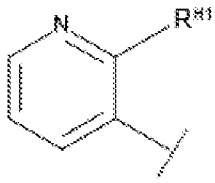
wherein

$\mathbf{Y^{F1}}$ represents -N= or -C$\mathbf{R^{F4}}$=; and $\mathbf{Y^{F2}}$ represents -N= or -C$\mathbf{R^{F5}}$=; with the proviso that at least one of $\mathbf{Y^{F1}}$ and $\mathbf{Y^{F2}}$ is not -C$\mathbf{R^{F4}}$= and -C$\mathbf{R^{F5}}$=, respectively;

$\mathbf{R^{F1}}$, $\mathbf{R^{F2}}$, $\mathbf{R^{F3}}$, $\mathbf{R^{F4}}$, and $\mathbf{R^{F5}}$ independently of one another represent -H, -CH_3, -CF_3,-OH, -OCH_3, -OCH_2CH_3, -Cl, or -azetidinyl; preferably with the proviso that only one of $\mathbf{R^{F1}}$, $\mathbf{R^{F2}}$, $\mathbf{R^{F3}}$, $\mathbf{R^{F4}}$, and $\mathbf{R^{F5}}$ represents a residue that is not -H.

[0047] In some embodiments, **V** represents a residue according to general formula (G) or (H)

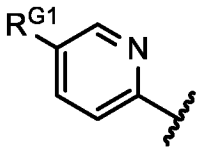


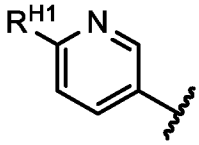


(G) (H)

wherein $\mathbf{R^{G1}}$ and $\mathbf{R^{H1}}$ are selected from the group consisting of -H, -CH_3, -CF_3, -OH, -OCH_3, -OCH_2CH_3, -Cl, azetidinyl, -cyclopropyl, -O-cyclopropyl, and -CHF_2; or wherein $\mathbf{R^{G1}}$ and $\mathbf{R^{H1}}$ are selected from the group consisting of -H, -CH_3, -CF_3, -OH, -OCH_3, -OCH_2CH_3, -Cl, and azetidinyl.

In other embodiments, **V** represents a residue according to general formula (G') or (H')





(G') (H')

wherein $\mathbf{R^{G1}}$ and $\mathbf{R^{H1}}$ are selected from the group consisting of -H, -CH_3, -CF_3, -OH, -OCH_3, -OCH_2CH_3, -Cl, azetidinyl, -cyclopropyl, -O-cyclopropyl, and -CHF_2; or wherein $\mathbf{R^{G1}}$ and $\mathbf{R^{H1}}$ are selected from the group consisting of -H, -CH_3, -CF_3, -OH, -OCH_3, -OCH_2CH_3, -Cl, and azetidinyl;

[0048] In an embodiment of the indazole derivatives according to the invention $\mathbf{R^1}$ represents -H, -F, -Cl, -Br, -I, -CN;

-C_{1-6}-alkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted; -O-C_{1-6}-alkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted;

-C(=O)C_{1-6}-alkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted;

-C(=O)OC_{1-6}-alkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted;

-C(=O)NHC_{1-6}-alkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted;

-C(=O)N(C_{1-6}-alkyl)$_2$, saturated or unsaturated, unsubstituted, mono- or polysubstituted;

-S(=O)C_{1-6}-alkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted;

-S(=O)$_2$-C_{1-6}-alkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted;

-C_1-C_6-heteroalkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted; or

3-14-membered cycloalkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted; wherein said 3-14-membered cycloalkyl is optionally connected through -C_1-C_6-alkylene- or -C_1-C_6-heteroalkylene-, in each case saturated or unsaturated, unsubstituted, mono- or polysubstituted.

[0049] In some embodiments, **R**^{1} represents -H, -F, -Cl, -Br, -I, -C_{1-6}-alkyl, -O-C_{1-6}-alkyl, -C_{1-6}-alkylene-O-C_{1-6}-alkyl, -C_{1-6}-alkylene-NH(C_{1-6}-alkyl), -C_{1-6}-alkylene-N(C_{1-6}-alkyl)$_2$, -CF_3, -CF_2H, -CFH_2, -CF_2Cl, -$CFCl_2$, -C_{1-6}-alkylene-CF_3, -C_{1-6}-alkylene-CF_2H, -C_{1-6}-alkylene-CFH_2, -C_{1-6}-alkylene-NH-C_{1-6}-alkylene-CF_3, -C_{1-6}-alkylene-N(C_{1-6}-alkyl)-C_{1-6}-alkylene-CF_3, -C(=O)C_{1-6}-alkyl, -C(=O)OC_{1-6}-alkyl, -C(=O)NH_2, -C(=O)NHC_{1-6}-alkyl, -C(=O)N(C_{1-6}-alkyl)$_2$, -S(=O)-C_{1-6}-alkyl, -S(=O)$_2$-C_{1-6}-alkyl, -O-C_{1-6}-alkyl, -cyclopropyl unsubstituted, cyclobutyl unsubstituted, cyclopentyl unsubstituted or cyclohexyl unsubstituted.

[0050] In some embodiments, **R**^{1} represents -H, -C_{1-6}-alkyl, -C_{1-6}-alkylene-O-C_{1-6}-alkyl, -CH_2F, -CHF_2, -CF_3, -cyclopentyl, unsubstituted, or -cyclopropyl. Preferably, **R**^{1} represents -H, -C_{1-6}-alkyl, -C_{1-6}-alkylene-O-C_{1-6}-alkyl, -CH_2F, -CHF_2, -CF_3, -cyclopentyl, or unsubstituted. In some embodiments, **R**^{1} represents -CH_3.

[0051] In some embodiments, **R**^{1} represents -CH_2F, -CHF_2, -CH_3, or -cyclopropyl. Preferably, **R**^{1} represents -CH_2F, -CHF_2, or -CH_3. In some embodiments, **R**^{1} represents -C(=O)NH_2, or -CHF_2.

[0052] In some embodiments, **R**^{1} represents -H, -C_{1-3}-alkyl, -CF_3, -CF_2H, -CFH_2, -CF_2Cl, -$CFCl_2$, -C_{1-3}-alkylene-CF_3, -C_{1-3}-alkylene-CF_2H, -C_{1-3}-alkylene-CFH_2, or -cyclopropyl; preferably, **R**^{1} represents -H, -C_{1-3}-alkyl, -CF_3, -CF_2H, -CFH_2, -CF_2Cl, -$CFCl_2$, -C_{1-3}-alkylene-CF_3, -C_{1-3}-alkylene-CF_2H, or -C_{1-3}-alkylene-CFH_2; for example -CH_3.

[0053] In some embodiments of the indazole derivative according to the invention **R**^{2} represents

-H;

-C_1-C_6-alkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted;

-C_1-C_6-heteroalkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted;

3-14-membered cycloalkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted; wherein said 3-14-membered cycloalkyl is optionally connected through -C_1-C_6-alkylene- or -C_1-C_6-heteroalkylene-, in each case saturated or unsaturated, unsubstituted, mono- or polysubstituted; or

3-14-membered heterocycloalkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted; wherein said 3-14-membered heterocycloalkyl is optionally connected through -C_1-C_6-alkylene- or -C_1-C_6-heteroalkylene-, in each case saturated or unsaturated, unsubstituted, mono- or polysubstituted.

[0054] In some embodiments, **R**^{2} represents -H, -C_{1-6}-alkyl, -C_{1-6}-alkylene-O-C_{1-6}-alkyl, -C_{1-6}-alkylene-NH(C_{1-6}-alkyl), -C_{1-6}-alkylene-N(C_{1-6}-alkyl)$_2$, -CF_3, -CF_2H, -CFH_2, -CF_2Cl, -$CFCl_2$, -C_{1-6}-alkylene-CF_3, -C_{1-6}-alkylene-CF_2H, -C_{1-6}-alkylene-CFH_2, -C_{1-6}-alkylene-NH-C_{1-6}-alkylene-CF_3, or -C_{1-6}-alkylene-N(C_{1-6}-alkyl)-C_{1-6}-alkylene-CF_3.

[0055] In some embodiments, **R**^{2} represents -H or -C_{1-6}-alkyl.

[0056] In an embodiment of the indazole derivative according to the invention **R**^{3} represents

-H;

-OH;

-C_1-C_6-alkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted; or

-C_1-C_6-heteroalkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted.

[0057] In some embodiments, $\mathbf{R^3}$ represents -H, -OH, -C_{1-6}-alkyl, -C_{1-6}-alkylene-OH, -C_{1-6}-alkylene-O-C_{1-6}-alkyl, -C_{1-6}-alkylene-NH_2, -C_{1-6}-alkylene-NH(C_{1-6}-alkyl), -C_{1-6}-alkylene-N(C_{1-6}-alkyl)$_2$, -CF_3, -CF_2H, -CFH_2, -CF_2Cl, -$CFCl_2$, -C_{1-6}-alkylene-CF_3, -C_{1-6}-alkylene-CF_2H, -C_{1-6}-alkylene-CFH_2, -C_{1-6}-alkylene-NH-C_{1-6}-alkylene-CF_3, or -C_{1-6}-alkylene-N(C_{1-6}-alkyl)-C_{1-6}-alkylene-CF_3.

[0058] In some embodiments, $\mathbf{R^3}$ represents -H, -OH, or -C_{1-6}-alkyl, saturated, unsubstituted or monosubstituted with -OH. Preferably, $\mathbf{R^3}$ represents -H.

[0059] In some embodiments, $\mathbf{R^3}$ represents -H and $\mathbf{R^4}$ represents a residue other than -H.

[0060] In an embodiment of the indazole derivatives according to the invention $\mathbf{R^4}$ represents

-H;

-S(=O)C_{1-6}-alkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted;

-S(=O)$_2$-C_{1-6}-alkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted;

-C_1-C_6-alkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted;

-C_1-C_6-heteroalkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted;

3-14-membered cycloalkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted; wherein said 3-14-membered cycloalkyl is optionally connected through -C_1-C_6-alkylene- or -C_1-C_6-heteroalkylene-, in each case saturated or unsaturated, unsubstituted, mono- or polysubstituted;

3-14-membered heterocycloalkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted; wherein said 3-14-membered heterocycloalkyl is optionally connected through -C_1-C_6-alkylene- or -C_1-C_6-heteroalkylene-, in each case saturated or unsaturated, unsubstituted, mono- or polysubstituted;

6-14-membered aryl, unsubstituted, mono- or polysubstituted; wherein said 6-14-membered aryl is optionally connected through -C_1-C_6-alkylene- or -C_1-C_6-heteroalkylene-, in each case saturated or unsaturated, unsubstituted, mono- or polysubstituted; or

5-14-membered heteroaryl, unsubstituted, mono- or polysubstituted; wherein said 5-14-membered heteroaryl is optionally connected through -C_1-C_6-alkylene- or -C_1-C_6-heteroalkylene-, in each case saturated or unsaturated, unsubstituted, mono- or polysubstituted.

[0061] In some embodiments, $\mathbf{R^4}$ represents

-S(=O)$_2$$C_{1-6}$-alkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted with substituents independently of one another selected from the group consisting of -F, -Cl, -C_{1-6}-alkyl, -C_{1-6}-alkylene-CF_3, -OH, =O, -OC_{1-6}-alkyl, -C_{1-6}-alkylene-OH, -C_{1-6}-alkylene-O-C_{1-6}-alkyl,

$-NH_2$, $-NHC_{1-6}$-alkyl, $-N(C_{1-6}\text{-alkyl})_2$, $-NHC(=O)O-C_{1-6}$-alkyl, $-N(C_{1-6}\text{-alkyl})C(=O)O-C_{1-6}$-alkyl, $-C_{1-6}$-alkylene-$NHC(=O)O-C_{1-6}$-alkyl, $-C_{1-6}$-alkylene-NH_2, $-C_{1-6}$-alkylene-$NH-C_{1-6}$-alkyl, $-C_{1-6}$-alkylene-$N(C_{1-6}\text{-alkyl})_2$, $-C_{1-6}$-alkylene-$NH-C_{1-6}$-alkylene-CF_3, $-C(=O)-C_{1-6}$-alkyl, $-C(=O)OH$, $-C(=O)O-C_{1-6}$-alkyl, $-C(=O)O-C_{1-6}$-alkylene-CF_3, $-C(=O)NH_2$, $-C(=O)NH(C_{1-6}\text{-alkyl})$, $-C(=O)N(C_{1-6}\text{-alkyl})_2$, $-S(=O)_2C_{1-6}$-alkyl, -phenyl, $-C_{1-6}$-alkylene-phenyl, 3-14-membered heterocycloalkyl, saturated or unsaturated, unsubstituted; and 5-14-membered heteroaryl, unsubstituted;

$-S(=O)_2$(3-14-membered cycloalkyl), wherein said 3-14-membered cycloalkyl is selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl, in each case saturated or unsaturated, unsubstituted, mono- or polysubstituted with substituents independently of one another selected from the group consisting of -F, -Cl, $-C_{1-6}$-alkyl, $-C_{1-6}$-alkylene-CF_3, -OH, =O, $-OC_{1-6}$-alkyl, $-C_{1-6}$-alkylene-OH, $-C_{1-6}$-alkylene-$O-C_{1-6}$-alkyl, $-NH_2$, $-NHC_{1-6}$-alkyl, $-N(C_{1-6}\text{-alkyl})_2$, $-NHC(=O)O-C_{1-6}$-alkyl, $-N(C_{1-6}\text{-alkyl})C(=O)O-C_{1-6}$-alkyl, $-C_{1-6}$-alkylene-$NHC(=O)O-C_{1-6}$-alkyl, $-C_{1-6}$-alkylene-NH_2, $-C_{1-6}$-alkylene-$NH-C_{1-6}$-alkyl, $-C_{1-6}$-alkylene-$N(C_{1-6}\text{-alkyl})_2$, $-C_{1-6}$-alkylene-$NH-C_{1-6}$-alkylene-CF_3, $-C(=O)-C_{1-6}$-alkyl, -C(=O)OH, $-C(=O)O-C_{1-6}$-alkyl, $-C(=O)O-C_{1-6}$-alkylene-CF_3, $-C(=O)NH_2$, $-C(=O)NH(C_{1-6}\text{-alkyl})$, $-C(=O)N(C_{1-6}\text{-alkyl})_2$, $-S(=O)_2C_{1-6}$-alkyl, -phenyl, $-C_{1-6}$-alkylene-phenyl, 3-14-membered heterocycloalkyl, saturated or unsaturated, unsubstituted; and 5-14-membered heteroaryl, unsubstituted;

$-C_{1-6}$-alkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted with substituents independently of one another selected from the group consisting of -F, -Cl, $-C_{1-6}$-alkyl, $-C_{1-6}$-alkylene-CF_3, -OH, =O, $-OC_{1-6}$-alkyl, $-C_{1-6}$-alkylene-OH, $-C_{1-6}$-alkylene-$O-C_{1-6}$-alkyl, $-NH_2$, $-NHC_{1-6}$-alkyl, $-N(C_{1-6}\text{-alkyl})_2$, $-NHC(=O)O-C_{1-6}$-alkyl, $-N(C_{1-6}\text{-alkyl})C(=O)O-C_{1-6}$-alkyl, $-C_{1-6}$-alkylene-$NHC(=O)O-C_{1-6}$-alkyl, $-C_{1-6}$-alkylene-NH_2, $-C_{1-6}$-alkylene-$NH-C_{1-6}$-alkyl, $-C_{1-6}$-alkylene-$N(C_{1-6}\text{-alkyl})_2$, $-C_{1-6}$-alkylene-$NH-C_{1-6}$-alkylene-CF_3, $-C(=O)-C_{1-6}$-alkyl, -C(=O)OH, $-C(=O)O-C_{1-6}$-alkyl, $-C(=O)O-C_{1-6}$-alkylene-CF_3, $-C(=O)NH_2$, $-C(=O)NH(C_{1-6}\text{-alkyl})$, $-C(=O)N(C_{1-6}\text{-alkyl})_2$, $-S(=O)_2C_{1-6}$-alkyl, -phenyl, $-C_{1-6}$-alkylene-phenyl, 3-14-membered heterocycloalkyl, saturated or unsaturated, unsubstituted; and 5-14-membered heteroaryl, unsubstituted;

3-14-membered cycloalkyl or $-C_{1-6}$-alkylene-(3-14-membered cycloalkyl), wherein $-C_{1-6}$-alkylene- is unsubstituted or monosubstituted with -OH, wherein said 3-14-membered cycloalkyl is selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl, in each case saturated or unsaturated, in each case unsubstituted, mono- or polysubstituted with substituents independently of one another selected from the group consisting of -F, -Cl, $-C_{1-6}$-alkyl, $-C_{1-6}$-alkylene-CF_3, -OH, =O, $-OC_{1-6}$-alkyl, $-C_{1-6}$-alkylene-OH, $-C_{1-6}$-alkylene-$O-C_{1-6}$-alkyl, $-NH_2$, $-NHC_{1-6}$-alkyl, $-N(C_{1-6}\text{-alkyl})_2$, $-NHC(=O)O-C_{1-6}$-alkyl, $-N(C_{1-6}\text{-alkyl})C(=O)O-C_{1-6}$-alkyl, $-C_{1-6}$-alkylene-$NHC(=O)O-C_{1-6}$-alkyl, $-C_{1-6}$-alkylene-NH_2, $-C_{1-6}$-alkylene-$NH-C_{1-6}$-alkyl, $-C_{1-6}$-alkylene-$N(C_{1-6}\text{-alkyl})_2$, $-C_{1-6}$-alkylene-$NH-C_{1-6}$-alkylene-CF_3, $-C(=O)-C_{1-6}$-alkyl, -C(=O)OH, $-C(=O)O-C_{1-6}$-alkyl, $-C(=O)O-C_{1-6}$-alkylene-CF_3, $-C(=O)NH_2$, $-C(=O)NH(C_{1-6}\text{-alkyl})$, $-C(=O)N(C_{1-6}\text{-alkyl})_2$, $-S(=O)_2C_{1-6}$-alkyl, -

phenyl, -C_{1-6}-alkylene-phenyl, 3-14-membered heterocycloalkyl, saturated or unsaturated, unsubstituted; and 5-14-membered heteroaryl, unsubstituted;

3-14-membered heterocycloalkyl or -C_{1-6}-alkylene-(3-14-membered heterocycloalkyl), wherein -C_{1-6}-alkylene- is unsubstituted or monosubstituted with -OH, wherein said 3-14-membered heterocycloalkyl in each case is selected from the group consisting of azepane, 1,4-oxazepane, azetane, azetidine, aziridine, azocane, diazepane, dioxane, dioxolane, dithiane, dithiolane, imidazolidine, isothiazolidine, isoxalidine, morpholine, oxazolidine, oxepane, oxetane, oxirane, piperazine, piperidine, pyrazolidine, pyrrolidine, quinuclidine, tetrahydrofuran, tetrahydropyran, tetrahydrothiopyran, thiazolidine, thietane, thiirane, thiolane, thiomorpholine, indoline, dihydrobenzofuran, dihydrobenzothiophene, 1,1-dioxothiacyclohexane, 2-azaspiro[3.3]heptane, 2-oxaspiro[3.3]heptane, 7-azaspiro[3.5]nonane, 8-azabicyclo[3.2.1]octane, 9-azabicyclo[3.3.1]nonane, hexahydro-1H-pyrrolizine, hexahydrocyclopenta[c]pyrrole, octahydrocyclopenta[c]pyrrole, and octahydropyrrolo[1,2-a]pyrazine; in each case unsubstituted, mono- or polysubstituted with substituents independently of one another selected from the group consisting of -F, -Cl, -C_{1-6}-alkyl, -C_{1-6}-alkylene-CF_3, -OH, =O, -OC_{1-6}-alkyl, -C_{1-6}-alkylene-OH, -C_{1-6}-alkylene-O-C_{1-6}-alkyl, -NH_2, -NHC_{1-6}-alkyl, -N(C_{1-6}-alkyl)$_2$, -NHC(=O)O-C_{1-6}-alkyl, -N(C_{1-6}-alkyl)C(=O)O-C_{1-6}-alkyl, -C_{1-6}-alkylene-NHC(=O)O-C_{1-6}-alkyl, -C_{1-6}-alkylene-NH_2, -C_{1-6}-alkylene-NH-C_{1-6}-alkyl, -C_{1-6}-alkylene-N(C_{1-6}-alkyl)$_2$, -C_{1-6}-alkylene-NH-C_{1-6}-alkylene-CF_3, -C(=O)-C_{1-6}-alkyl, -C(=O)OH, -C(=O)O-C_{1-6}-alkyl, -C(=O)O-C_{1-6}-alkylene-CF_3, -C(=O)NH_2, -C(=O)NH(C_{1-6}-alkyl), -C(=O)N(C_{1-6}-alkyl)$_2$, -S(=O)$_2$$C_{1-6}$-alkyl, -phenyl, -$C_{1-6}$-alkylene-phenyl, 3-14-membered heterocycloalkyl, saturated or unsaturated, unsubstituted; and 5-14-membered heteroaryl, unsubstituted;

-phenyl unsubstituted, mono- or polysubstituted with substituents independently of one another selected from the group consisting of -F, -Cl, -CN, -C_{1-6}-alkyl, -C_{1-6}-alkylene-CF_3, -OH, =O, -OC_{1-6}-alkyl, -C_{1-6}-alkylene-OH, -C_{1-6}-alkylene-O-C_{1-6}-alkyl, -NH_2, -NHC_{1-6}-alkyl, -N(C_{1-6}-alkyl)$_2$, -NHC(=O)O-C_{1-6}-alkyl, -N(C_{1-6}-alkyl)C(=O)O-C_{1-6}-alkyl, -C_{1-6}-alkylene-NHC(=O)O-C_{1-6}-alkyl, -C_{1-6}-alkylene-NH_2, -C_{1-6}-alkylene-NH-C_{1-6}-alkyl, -C_{1-6}-alkylene-N(C_{1-6}-alkyl)$_2$, -C_{1-6}-alkylene-NH-C_{1-6}-alkylene-CF_3, -C(=O)-C_{1-6}-alkyl, -C(=O)OH, -C(=O)O-C_{1-6}-alkyl, -C(=O)O-C_{1-6}-alkylene-CF_3, -C(=O)NH_2, -C(=O)NH(C_{1-6}-alkyl), -C(=O)N(C_{1-6}-alkyl)$_2$, -S(=O)$_2$$C_{1-6}$-alkyl, -phenyl, -$C_{1-6}$-alkylene-phenyl, 3-14-membered heterocycloalkyl, saturated or unsaturated, unsubstituted; and 5-14-membered heteroaryl, unsubstituted;

5-14-membered heteroaryl or -C_{1-6}-alkylene-(5-14-membered heteroaryl), wherein -C_{1-6}-alkylene- is unsubstituted or monosubstituted with -OH, wherein said 5-14-membered heteroaryl in each case is selected from the group consisting of benzimidazole, benzisoxazole, benzoazole, benzodioxole, benzofuran, benzothiadiazole, benzothiazole, benzothiophene, carbazole, cinnoline, dibenzofuran, furane, furazane, imidazole, imidazopyridine, indazole, indole, indolizine, isobenzofuran, isoindole, isoquinoline, isothiazole, isoxazole, naphthyridine,

oxadiazole, oxazole, oxindole, phthalazine, purine, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, pyrrole, quinazoline, quinoline, quinoxaline, tetrazole, thiadiazole, thiazole, thiophene, triazine, triazole, and [1,2,4]triazolo[4,3-a]pyrimidine; in each case unsubstituted, mono- or polysubstituted with substituents independently of one another selected from the group consisting of -F, -Cl, -CN, -C_{1-6}-alkyl, -C_{1-6}-alkylene-CF_3, -OH, =O, -OC_{1-6}-alkyl, -C_{1-6}-alkylene-OH, -C_{1-6}-alkylene-O-C_{1-6}-alkyl, -NH_2, -NHC_{1-6}-alkyl, -$N(C_{1-6}$-alkyl$)_2$, -NHC(=O)O-C_{1-6}-alkyl, -N(C_{1-6}-alkyl)C(=O)O-C_{1-6}-alkyl, -C_{1-6}-alkylene-NHC(=O)O-C_{1-6}-alkyl, -C_{1-6}-alkylene-NH_2, -C_{1-6}-alkylene-NH-C_{1-6}-alkyl, -C_{1-6}-alkylene-$N(C_{1-6}$-alkyl$)_2$, -C_{1-6}-alkylene-NH-C_{1-6}-alkylene-CF_3, -C(=O)-C_{1-6}-alkyl, -C(=O)OH, -C(=O)O-C_{1-6}-alkyl, -C(=O)O-C_{1-6}-alkylene-CF_3, -$C(=O)NH_2$, -C(=O)NH(C_{1-6}-alkyl), -$C(=O)N(C_{1-6}$-alkyl$)_2$, -$S(=O)_2C_{1-6}$-alkyl, -phenyl, -C_{1-6}-alkylene-phenyl, 3-14-membered heterocycloalkyl, saturated or unsaturated, unsubstituted; and 5-14-membered heteroaryl, unsubstituted.

[0062] In some embodiments, **R^4** represents

-H;

-$S(=O)_2C_{1-6}$-alkyl, saturated, unsubstituted, monosubstituted or polysubstituted with -F;

-$S(=O)_2$(3-14-membered cycloalkyl), saturated, unsubstituted;

-C_{1-6}-alkyl, saturated, unsubstituted, monosubstituted or disubstituted with substituents independently of one another selected from the group consisting of -OH, =O, -NH_2, -NHC_{1-6}-alkyl, -$N(C_{1-6}$-alkyl$)_2$, -OC_{1-6}-alkyl, -C_{1-6}-alkylene-NH_2, -C_{1-6}-alkylene-NH-C_{1-6}-alkyl, -$C(=O)NH_2$, -C(=O)-NH-C_{1-3}-alkyl, -C(=O)-$N(C_{1-3}$-alkyl$)_2$, -phenyl unsubstituted;

3-14-membered cycloalkyl or -C_{1-6}-alkylene-(3-14-membered cycloalkyl), wherein -C_{1-6}-alkylene- is unsubstituted or monosubstituted with -OH, wherein said 3-14-membered cycloalkyl is saturated, unsubstituted, monosubstituted or disubstituted with substituents independently of one another selected from the group consisting of -C_{1-6}-alkyl, -C_{1-6}-alkylene-NH_2, -C_{1-6}-alkylene-NH-C_{1-6}-alkylene-CF_3, -C_{1-6}-alkylene-OH, -C_{1-6}-alkylene-NHC(=O)O-C_{1-6}-alkyl, -OH, -OC_{1-6}-alkyl, -NH_2, -$N(C_{1-6}$-alkyl$)_2$, -NHC(=O)O-C_{1-6}-alkyl;

3-14-membered heterocycloalkyl or -C_{1-6}-alkylene-(3-14-membered heterocycloalkyl), wherein -C_{1-6}-alkylene- is unsubstituted or monosubstituted with -OH, wherein said 3-14-membered heterocycloalkyl in each case is selected from azetane, 1,4-oxazepane, pyrrolidine, piperidine, azepane, diazepane, tetrahydrofuran, tetrahydropyran, oxetane, morpholine, piperazine, hexahydrocyclopenta[c]pyrrole, octahydrocyclopenta[c]pyrrole, octahydropyrrolo[1,2-a]pyrazine, 8-azabicyclo[3.2.1]octane, 9-azabicyclo[3.3.1]nonane, quinuclidine, hexahydro-1H-pyrrolizine, 2-oxaspiro[3.3]heptane, 2-azaspiro[3.3]heptane, 7-azaspiro[3.5]nonane, 1,1-dioxothiacyclohexane, in each case unsubstituted, mono- or polysubstituted with substituents independently of one another selected from the group consisting of -F, -OH, =O, -C_{1-6}-alkyl, -C_{1-6}-alkylene-CF_3, -C_{1-6}-alkylene-OH, -C_{1-6}-alkylene-O-C_{1-6}-alkyl, -NH_2, -$N(C_{1-6}$-alkyl$)_2$, -C_{1-6}-alkylene-NH_2, -C_{1-6}-alkylene-$N(C_{1-6}$-alkyl$)_2$, -C(=O)-C_{1-6}-alkyl, -C(=O)OH, -C(=O)O-C_{1-6}-alkyl, -

$C(=O)O$-C_{1-6}-alkylene-CF_3, $-C(=O)NH_2$, $-C(=O)NH(C_{1-6}$-alkyl), $-S(=O)_2C_{1-6}$-alkyl, oxetanyl, pyrimidinyl, $-C_{1-6}$-alkylene-phenyl;

-phenyl unsubstituted;

5-14-membered heteroaryl or $-C_{1-6}$-alkylene-(5-14-membered heteroaryl), wherein $-C_{1-6}$-alkylene- is unsubstituted or monosubstituted with -OH, wherein said 5-14-membered heteroaryl in each case is selected from the group consisting of pyridine, pyridazine, pyrazine, pyrazole, isoxazole, triazole, and [1,2,4]triazolo[4,3-a]pyrimidine, in each case unsubstituted, monosubstituted or disubstituted with substituents independently of one another selected from the group consisting of $-C_{1-6}$-alkyl, -OH.

[0063] In an embodiment of the indazole derivative according to the invention **R^3** and **R^4** together form a 5- or 6-membered heterocycle containing 1 or 2 heteroatoms selected from N, O and S, saturated or unsaturated, unsubstituted or mono- or polysubstituted.

[0064] In some embodiments, **R^3** and **R^4** together form a heterocycle selected from the group consisting of pyrrolidine, piperidine, morpholine, and piperazine, in each case unsubstituted, mono- or polysubstituted with substituents independently of one another selected from the group consisting of -F, $-C_{1-6}$-alkyl, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-C(=O)NH-C_{1-6}$-alkyl, $-C(=O)N(C_{1-6}$-alkyl$)_2$, $-C(=O)O-C_{1-6}$-alkyl, $-NHC(=O)O-C_{1-6}$-alkyl, -pyridyl unsubstituted, and 1,2,4-oxadiazole unsubstituted or monosubstituted with $-C_{1-6}$-alkyl. In an embodiment, **R^3** and **R^4** together do not form morpholine unsubstituted, mono- or polysubstituted.

[0065] In some embodiments, **R^3** and **R^4** together form a

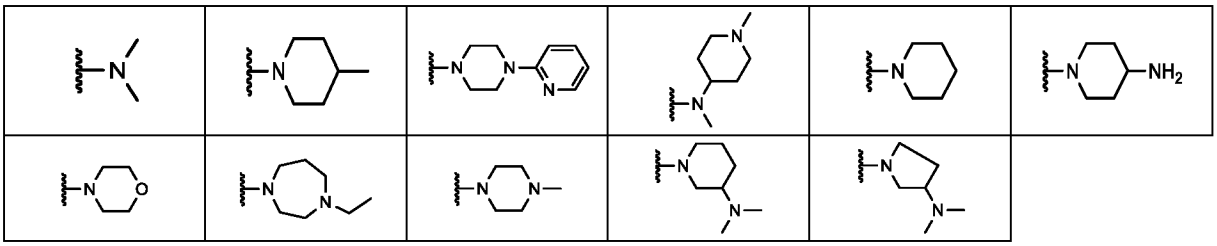
pyrrolidine ring, unsubstituted or monosubstituted with $-N(CH_3)_2$;

piperidine ring, unsubstituted or monosubstituted with a substituent selected from the group consisting of $-C_{1-6}$-alkyl, $-NH_2$, $-N(CH_3)_2$, $-C(=O)NH-C_{1-6}$-alkyl, $-C(=O)O-C_{1-6}$-alkyl, $-NHC(=O)O-C_{1-6}$-alkyl, and 1,2,4-oxadiazole unsubstituted or monosubstituted with $-C_{1-6}$-alkyl;

morpholine ring, unsubstituted; or

piperazine ring, unsubstituted or N-substituted with a substituent selected from the group consisting of $-C_{1-6}$-alkyl and -pyridyl unsubstituted.

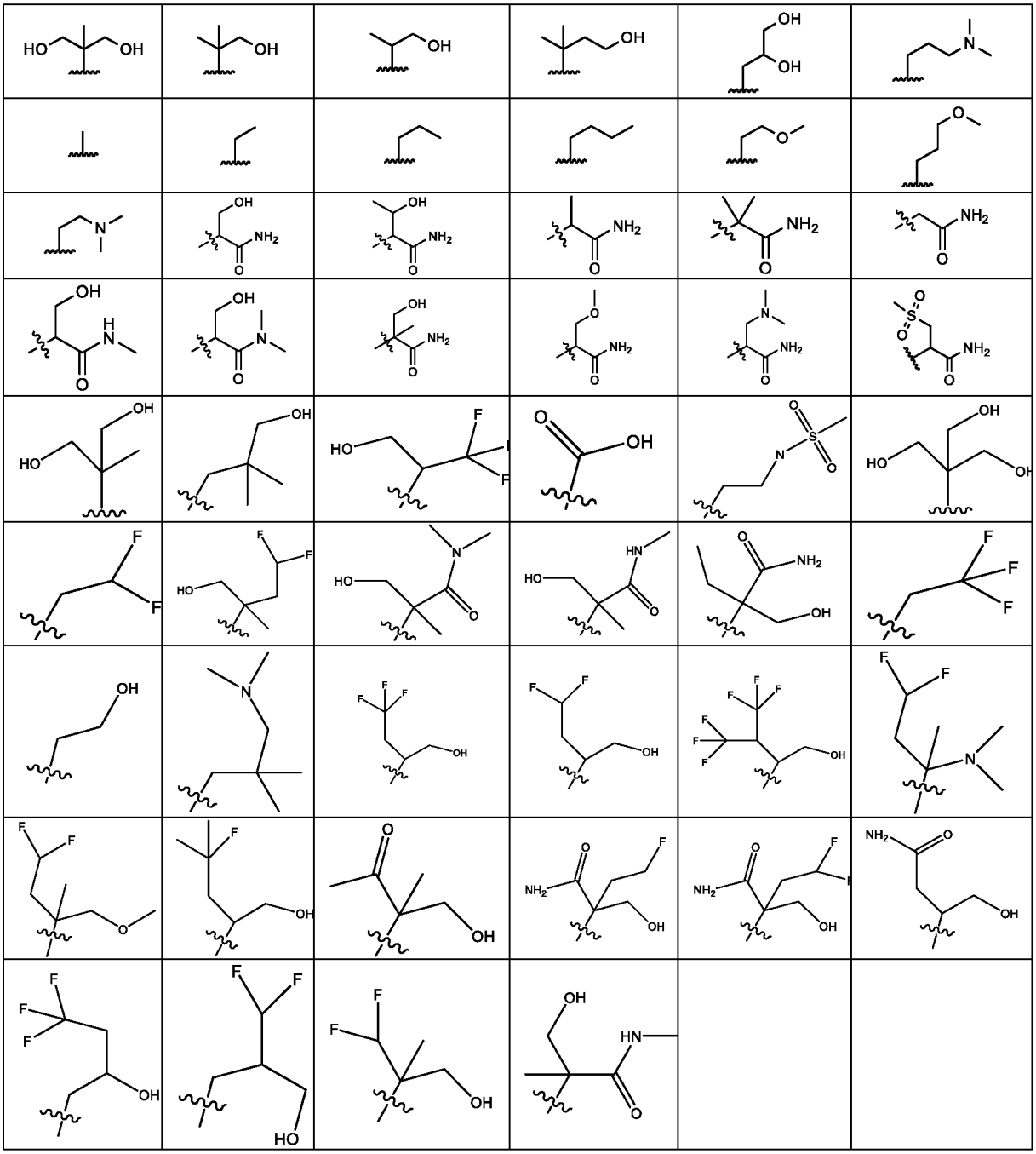
[0066] In some embodiments, **R^3** and **R^4** both do not represent -H. In some embodiments, **R^3** and **R^4** together with the nitrogen atom to which they are attached form a residue selected from the group consisting of:



[0067] In other embodiments, **R^3** represents -H and **R^4** does not represent -H.

[0068] In some embodiments, **R^3** represents -H and **R^4** represents $-C_1$-C_6-alkyl, saturated or

unsaturated, unsubstituted, mono- or polysubstituted. In some embodiments, **R**^{3} represents -H and **R**^{4} represents a residue selected from the group consisting of:

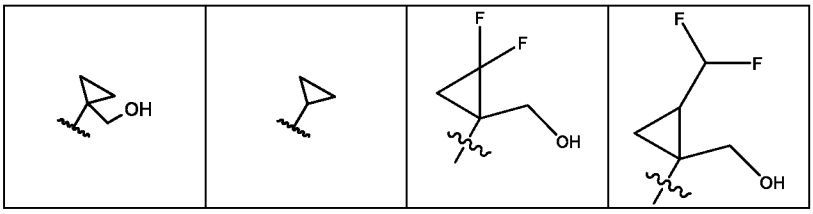


[0069] In further embodiments, **R**^{3} represents -H and **R**^{4} represents a residue -C**R'R"**-$(CH_2)_m$-OH, wherein **m** is an integer of from 1 to 6, preferably from 1 to 3; and wherein **R'** and **R"** independently of one another represent -H, -C_{1-3}-alkyl, -CF_3, -CF_2H, -CFH_2, -C_{1-3}-alkylene-CF_3, -C_{1-3}-alkylene-CF_2H, -C_{1-3}-alkylene-CFH_2, -C_{1-3}-alkylene-O-C_{1-3}-alkyl, -C_{1-3}-alkylene-OH, -C(=O)-NH_2, or C(=O)-NH-C_{1-3}-alkyl; preferably -H, -CH_3, -C_{1-3}-alkylene-OH, -C(=O)-NH_2, or C(=O)-NH-C_{1-3}-alkyl. In an embodiment, at least **R'** or **R"** does not represent -H. In alternative embodiments, neither **R'** nor **R"** represents -H.

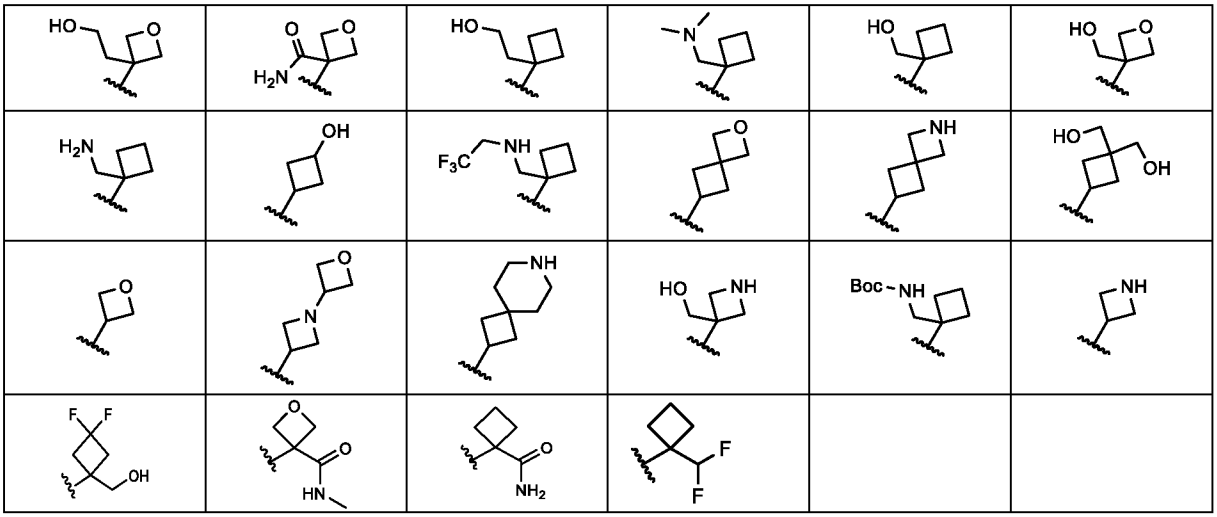
[0070] In further embodiments, **R**^{3} represents -H and **R**^{4} represents a 3-14-membered

cycloalkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted; or a 3-14-membered heterocycloalkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted.

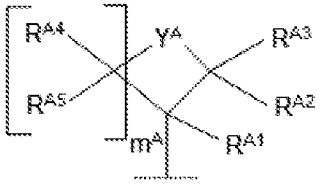
[0071] In further embodiments, $\mathbf{R^3}$ represents -H and $\mathbf{R^4}$ represents a 3-membered cycloalkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted; or a 3-membered heterocycloalkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted. In some embodiments, $\mathbf{R^3}$ represents -H and $\mathbf{R^4}$ represents a residue selected from the group consisting of:



[0072] In some embodiments, $\mathbf{R^3}$ represents -H and $\mathbf{R^4}$ represents a 4-membered cycloalkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted; or a 3-14-membered heterocycloalkyl (preferably a 4-membered heterocycloalkyl), saturated or unsaturated, unsubstituted, mono- or polysubstituted. In some embodiments, $\mathbf{R^3}$ represents -H and $\mathbf{R^4}$ represents a residue selected from the group consisting of:



[0073] In some embodiments, $\mathbf{R^3}$ represents -H and $\mathbf{R^4}$ represents a residue according to general formula (A),



(A)

wherein

m^A is 0 or 1;

Y^A is selected from -O-, -NR^{A6}- and -$CR^{A7}R^{A8}$-; and

R^{A1}, R^{A2}, R^{A3}, R^{A4}, R^{A5}, R^{A6}, R^{A7}, and R^{A8} independently of one another represent -H, F, -C_{1-3}-alkyl, -C_{1-3}-alkylene-OH, -C_{1-3}-alkylene-NH_2, -C_{1-3}-alkylene-NH(C_{1-3}-alkyl), -C_{1-3}-alkylene-N(C_{1-3}-alkyl)$_2$, -C_{1-3}-alkylene-NH(C_{1-3}-alkylene-CF_3), -C_{1-3}-alkylene-C(=O)NH_2, -C_{1-3}-alkylene-NH-C(=O)OC_{1-4}-alkyl, -C(=O)NH_2, -C(=O)-NH-C_{1-3}-alkyl, -C(=O)-N(C_{1-3}-alkyl)$_2$, -3-oxetanyl, or -CHF_2; preferably, R^{A1}, R^{A2}, R^{A3}, R^{A4}, R^{A5}, R^{A6}, R^{A7}, and R^{A8} independently of one another represent -H, F, -C_{1-3}-alkyl, -C_{1-3}-alkylene-OH, -C_{1-3}-alkylene-NH_2, -C_{1-3}-alkylene-NH(C_{1-3}-alkyl), -C_{1-3}-alkylene-N(C_{1-3}-alkyl)$_2$, -C_{1-3}-alkylene-NH(C_{1-3}-alkylene-CF_3), -C_{1-3}-alkylene-C(=O)NH_2, -C_{1-3}-alkylene-NH-C(=O)OC_{1-4}-alkyl, -C(=O)NH_2, -C(=O)-NH-C_{1-3}-alkyl, -C(=O)-N(C_{1-3}-alkyl)$_2$, or -3-oxetanyl; or R^{A7} and R^{A8} together with the carbon atom to which they are attached form a ring and represent -CH_2OCH_2-, -$CH_2OCH_2CH_2$- or -$CH_2CH_2OCH_2CH_2$-, -CH_2NHCH_2-, -$CH_2NHCH_2CH_2$- or -$CH_2CH_2NHCH_2CH_2$-.

[0074] In some embodiments, R^3 represents -H and R^4 represents a residue according to general formula (A) as defined above, wherein

m^A is 0 or 1;

Y^A is selected from -O- and -$CR^{A7}R^{A8}$-; and

R^{A1}, R^{A2}, R^{A3}, R^{A4}, R^{A5}, R^{A7}, and R^{A8} independently of one another represent -H, -C_{1-3}-alkylene-OH, -C_{1-3}-alkylene-N(C_{1-3}-alkyl)$_2$, -C(=O)NH_2, or -CHF_2; preferably R^{A1}, R^{A2}, R^{A3}, R^{A4}, R^{A5}, R^{A7}, and R^{A8} independently of one another represent -H, -C_{1-3}-alkylene-OH, -C_{1-3}-alkylene-N(C_{1-3}-alkyl)$_2$, or -C(=O)NH_2; preferably with the proviso that only one of R^{A1}, R^{A2}, R^{A3}, R^{A4}, R^{A5}, R^{A7}, and R^{A8} represents a residue that is not -H.

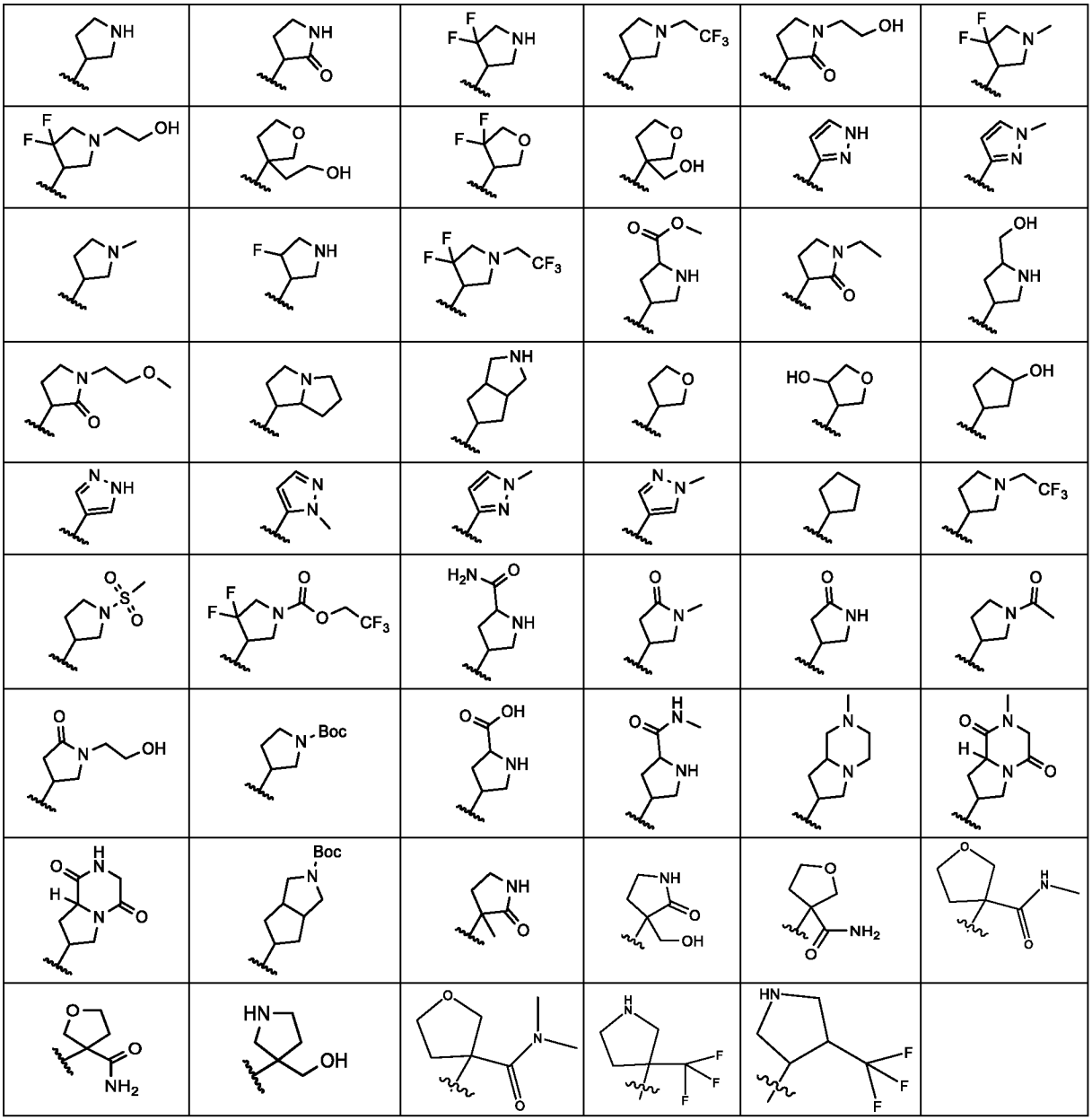
[0075] In some embodiments, R^3 represents -H and R^4 represents a residue according to general formula (A) as defined above, wherein

m^A is 0 or 1;

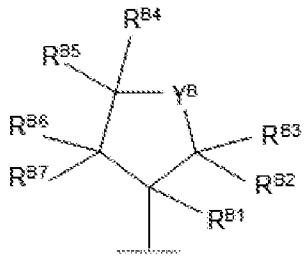
Y^A is selected from -O- and -$CR^{A7}R^{A8}$-; and

R^{A1} represents -C_{1-3}-alkylene-OH, -C_{1-3}-alkylene-N(C_{1-3}-alkyl)$_2$, -C(=O)NH_2, or -CHF_2; preferably R^{A1} represents -C_{1-3}-alkylene-OH, -C_{1-3}-alkylene-N(C_{1-3}-alkyl)$_2$, or -C(=O)NH_2; and R^{A2}, R^{A3}, R^{A4}, R^{A5}, R^{A7}, and R^{A8} represent -H.

[0076] In some embodiments, R^3 represents -H and R^4 represents a 3-14-membered cycloalkyl (preferably a 5-membered cycloalkyl), saturated or unsaturated, unsubstituted, mono- or polysubstituted; or a 3-14-membered heterocycloalkyl (preferably a 5-membered heterocycloalkyl), saturated or unsaturated, unsubstituted, mono- or polysubstituted; or a 5-14-membered heteroaryl (preferably a 5-membered heteroaryl), unsubstituted, mono- or polysubstituted. In preferred embodiments, R^3 represents -H and R^4 represents a residue selected from the group consisting of:



[0077] In some embodiments, $\mathbf{R^3}$ represents -H and $\mathbf{R^4}$ represents a residue according to general formula (B),



(B)

wherein

$\mathbf{Y^B}$ is selected from -O-, -N$\mathbf{R^{B8}}$- and -C$\mathbf{R^{B9}R^{B10}}$-; and

$\mathbf{R^{B1}}$, $\mathbf{R^{B2}}$, $\mathbf{R^{B3}}$, $\mathbf{R^{B4}}$, $\mathbf{R^{B5}}$, $\mathbf{R^{B6}}$, $\mathbf{R^{B7}}$, $\mathbf{R^{B8}}$, $\mathbf{R^{B9}}$ and $\mathbf{R^{B10}}$ independently of one another represent -

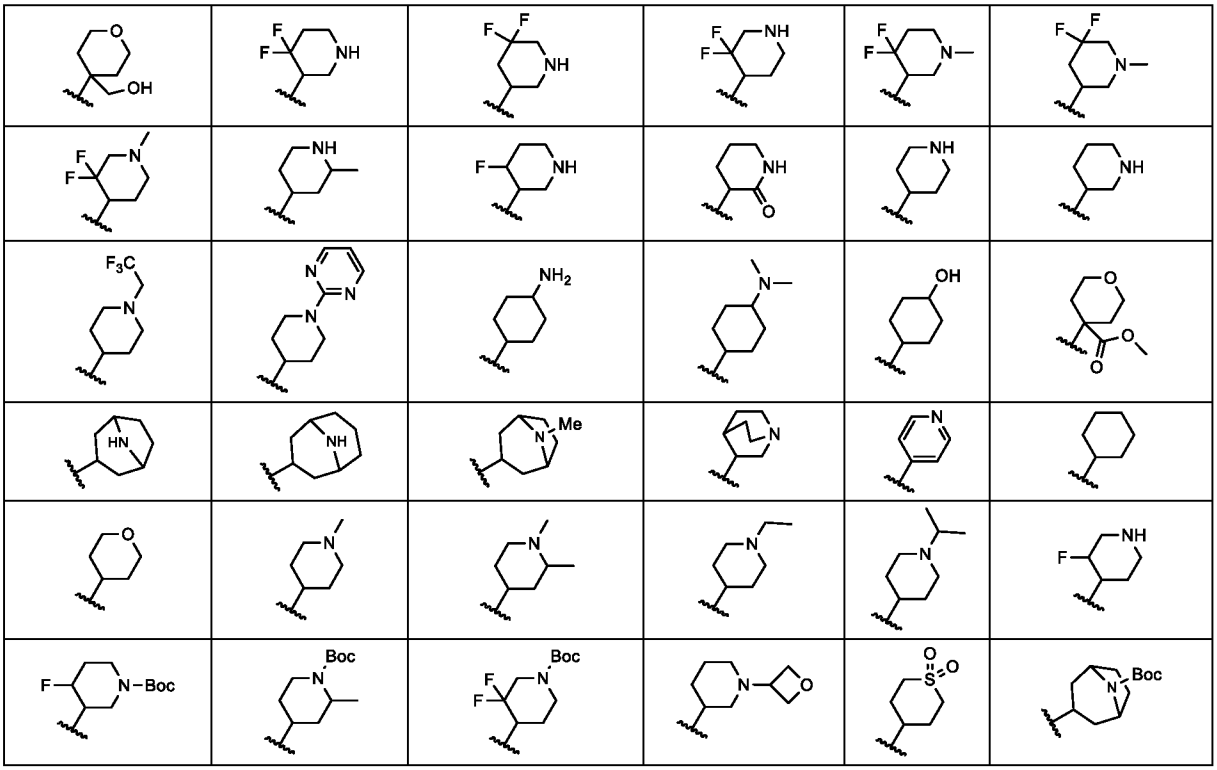
H, -F, -OH, -C_{1-3}-alkyl, -C_{1-3}-alkylene-OH, -C_{1-3}-alkylene-O-C_{1-3}-alkyl, -C_{1-3}-alkylene-CF_3, -C_{1-3}-alkylene-CO_2H, -C_{1-3}-alkylene-C(=O)O-C_{1-3}-alkyl, -C(=O)NH_2, -C(=O)NH-C_{1-3}-alkyl, or -C(=O)N(C_{1-3}-alkyl)$_2$; or $\mathbf{R^{B2}}$ and $\mathbf{R^{B3}}$ together represent =O; or $\mathbf{R^{B4}}$ and $\mathbf{R^{B5}}$ together represent =O.

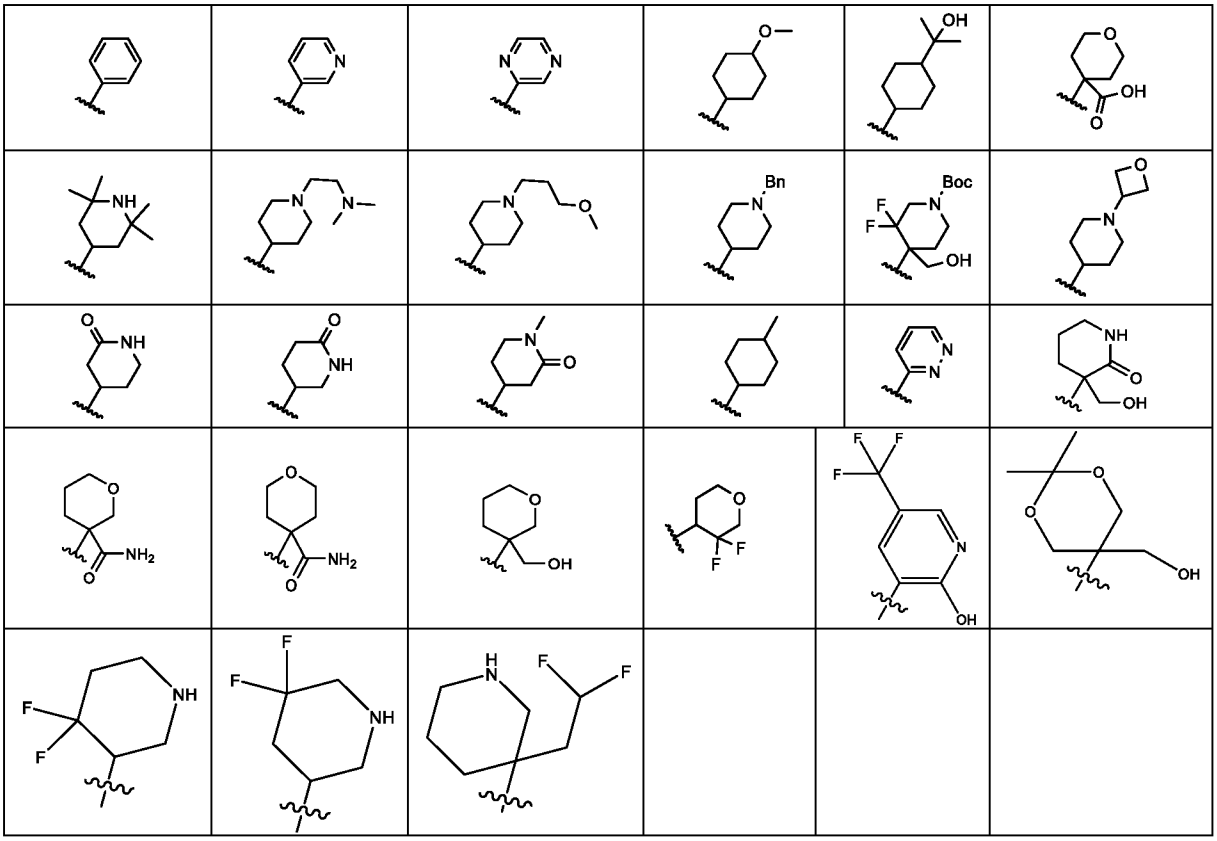
[0078] In some embodiments, $\mathbf{R^3}$ represents -H and $\mathbf{R^4}$ represents a residue according to general formula (B) as defined above, wherein

$\mathbf{Y^B}$ is selected from -O- and -N$\mathbf{R^{B8}}$-; and

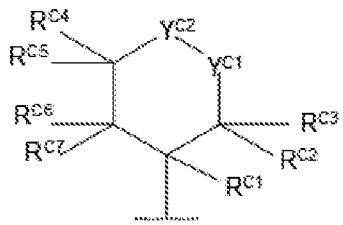
$\mathbf{R^{B1}}$, $\mathbf{R^{B2}}$, $\mathbf{R^{B3}}$, $\mathbf{R^{B4}}$, $\mathbf{R^{B5}}$, $\mathbf{R^{B6}}$, $\mathbf{R^{B7}}$, $\mathbf{R^{B8}}$ independently of one another represent -H, -F, -C_{1-3}-alkyl, -C_{1-3}-alkylene-OH, -C_{1-3}-alkylene-CF_3 or -C(=O)NH_2; or $\mathbf{R^{B2}}$ and $\mathbf{R^{B3}}$ together represent =O; or $\mathbf{R^{B4}}$ and $\mathbf{R^{B5}}$ together represent =O; preferably with the proviso that only 1, 2 or 3 of $\mathbf{R^{A1}}$, $\mathbf{R^{A2}}$, $\mathbf{R^{A3}}$, $\mathbf{R^{A4}}$, $\mathbf{R^{A5}}$, $\mathbf{R^{A7}}$, and $\mathbf{R^{A8}}$ represent a residue that is not -H; preferably with the proviso that at least one of $\mathbf{R^{A1}}$, $\mathbf{R^{A2}}$, $\mathbf{R^{A3}}$, $\mathbf{R^{A4}}$, $\mathbf{R^{A5}}$, $\mathbf{R^{A7}}$, and $\mathbf{R^{A8}}$ represent a residue that is not -H.

[0079] In some embodiments, $\mathbf{R^3}$ represents -H and $\mathbf{R^4}$ represents a 3-14-membered cycloalkyl (preferably a 6-membered cycloalkyl), saturated or unsaturated, unsubstituted, mono- or polysubstituted; or a 3-14-membered heterocycloalkyl (preferably a 6-membered heterocycloalkyl), saturated or unsaturated, unsubstituted, mono- or polysubstituted; or a 6-14-membered aryl (preferably a 6-membered aryl), unsubstituted, mono- or polysubstituted; or a 5-14-membered heteroaryl (preferably a 6-membered heteroaryl), unsubstituted, mono- or polysubstituted. In preferred embodiments, $\mathbf{R^3}$ represents -H and $\mathbf{R^4}$ represents a residue selected from the group consisting of:





[0080] In some embodiments, $\mathbf{R^3}$ represents -H and $\mathbf{R^4}$ represents a residue according to general formula (C),



(C)

wherein

$\mathbf{Y^{C1}}$ is selected from -O-, -S(=O)$_2$-, -N$\mathbf{R^{C8}}$- and -C$\mathbf{R^{C9}R^{C10}}$- and $\mathbf{Y^{C2}}$ represents -C$\mathbf{R^{C11}R^{C12}}$-; or $\mathbf{Y^{C1}}$ represents -C$\mathbf{R^{C9}R^{C10}}$- and $\mathbf{Y^{C2}}$ is selected from -O-, -S(=O)$_2$-, and -N$\mathbf{R^{C8}}$-;

$\mathbf{R^{C1}}$, $\mathbf{R^{C2}}$, $\mathbf{R^{C3}}$, $\mathbf{R^{C4}}$, $\mathbf{R^{C5}}$, $\mathbf{R^{C6}}$, $\mathbf{R^{C7}}$, $\mathbf{R^{C8}}$,$\mathbf{R^{C9}}$, $\mathbf{R^{C10}}$, $\mathbf{R^{C11}}$ and $\mathbf{R^{C12}}$ independently of one another represent

-H, -F, -OH, -C(=O)OC$_{1-3}$-alkyl, -NH$_2$, -NH(C$_{1-3}$-alkyl), -N(C$_{1-3}$-alkyl)$_2$, -C$_{1-3}$-alkyl, -C$_{1-3}$-alkylene-OH, -C$_{1-3}$-alkylene-, -C(=O)NH$_2$, -C(=O)NH-C$_{1-3}$-alkyl, or -C(=O)N(C$_{1-3}$-alkyl)$_2$: or $\mathbf{R^{C2}}$ and $\mathbf{R^{C3}}$ together represent =O; or $\mathbf{R^{C4}}$ and $\mathbf{R^{C5}}$ together represent =O; or $\mathbf{R^{C9}}$ and $\mathbf{R^{C10}}$ together represent =O; or $\mathbf{R^{C11}}$ and $\mathbf{R^{C12}}$ together represent =O.

[0081] In some embodiments, $\mathbf{R^3}$ represents -H and $\mathbf{R^4}$ represents a residue according to general formula (C) as defined above, wherein

$\mathbf{Y^{C1}}$ is selected from -O- or -N$\mathbf{R^{C8}}$- and $\mathbf{Y^{C2}}$ represents -C$\mathbf{R^{C11}R^{C12}}$-; or $\mathbf{Y^{C1}}$ represents -

$CR^{C9}R^{C10}$- and Y^{C2} is selected from -O-, and -NR^{C8}-;

R^{C1}, R^{C2}, R^{C3}, R^{C4}, R^{C5}, R^{C6}, R^{C7}, R^{C8} ,R^{C9}, R^{C10}, R^{C11} and R^{C12} independently of one another represent -H, -F , -C_{1-3}-alkyl, -C_{1-3}-alkylene-OH, or -C(=O)NH_2; preferably with the proviso that only 1, 2 or 3 of R^{C1}, R^{C2}, R^{C3}, R^{C4}, R^{C5}, R^{C6}, R^{C7}, R^{C8} ,R^{C9}, R^{C10}, R^{C11} and R^{C12} represent a residue that is not -H; preferably with the proviso that at least one of R^{C1}, R^{C2}, R^{C3}, R^{C4}, R^{C5}, R^{C6}, R^{C7}, R^{C8} ,R^{C9}, R^{C10}, R^{C11} and R^{C12} represent a residue that is not -H.

[0082] In some embodiments, R^3 represents -H and R^4 represents a 7-membered cycloalkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted; or a 7-membered heterocycloalkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted. In some embodiments, R^3 represents -H and R^4 represents a residue:



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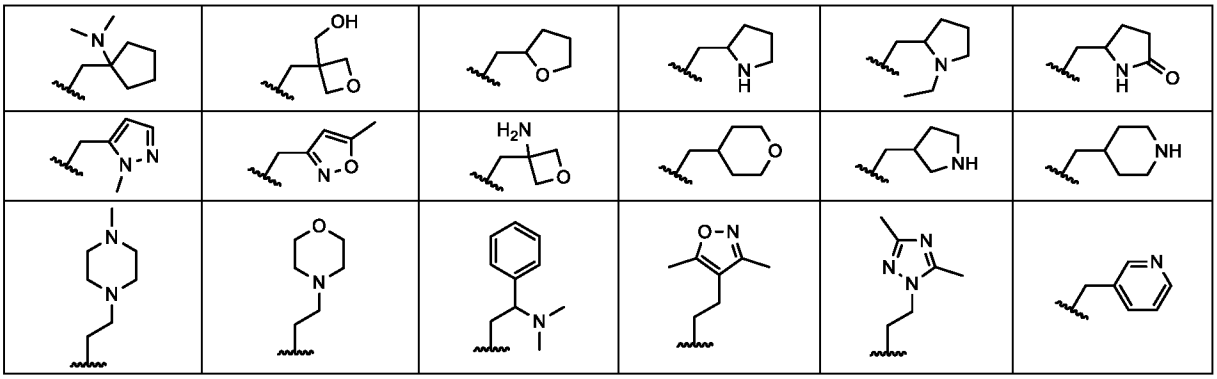
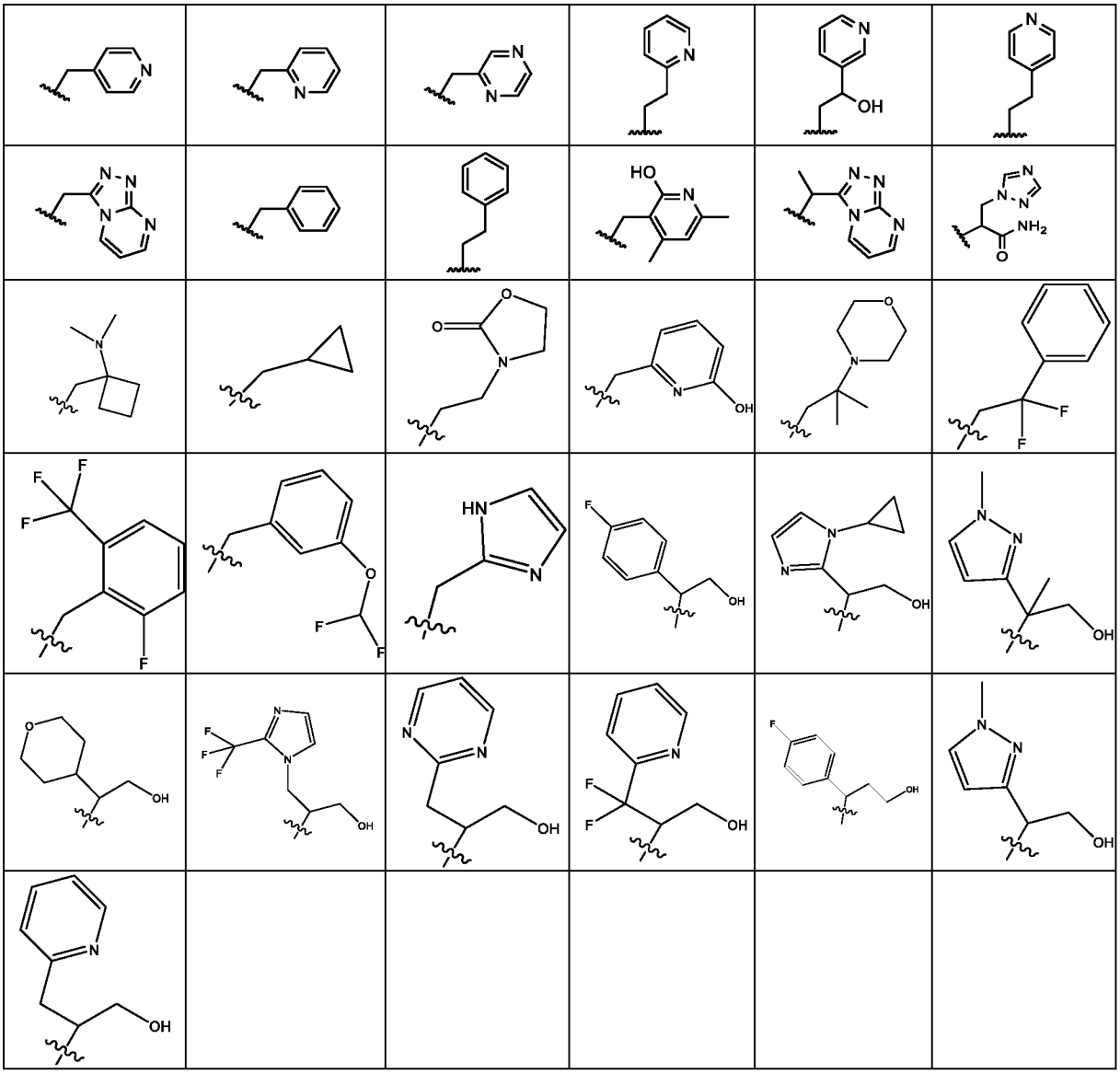
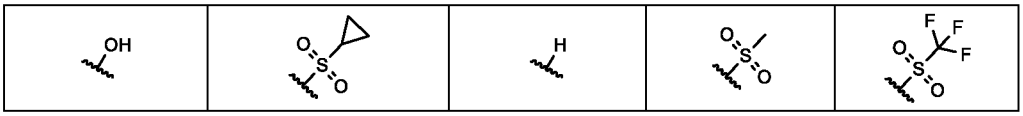
[0083] In some embodiments, R^3 represents -H and R^4 represents a 3-14-membered cycloalkyl (preferably a 3, 4, 5 or 6-membered cycloalkyl), saturated or unsaturated, unsubstituted, mono- or polysubstituted; wherein said 3-14-membered cycloalkyl is connected through -C_1-C_6-alkylene-, saturated or unsaturated, unsubstituted, mono- or polysubstituted; or a 3-14-membered heterocycloalkyl (preferably a 4, 5 or 6-membered heterocycloalkyl), saturated or unsaturated, unsubstituted, mono- or polysubstituted; wherein said 3-14-membered heterocycloalkyl is connected through -C_1-C_6-alkylene-, saturated or unsaturated, unsubstituted, mono- or polysubstituted; or a 6-14-membered aryl (preferably a 6-membered aryl), unsubstituted, mono- or polysubstituted; wherein said 6-14-membered aryl is connected through -C_1-C_6-alkylene-, saturated or unsaturated, unsubstituted, mono- or polysubstituted; or a 5-14-membered heteroaryl (preferably a 5 or 6-membered heteroaryl), unsubstituted, mono- or polysubstituted; wherein said 5-14-membered heteroaryl is connected through -C_1-C_6-alkylene-, saturated or unsaturated, unsubstituted, mono- or polysubstituted. In preferred embodiments, R^3 represents -H and R^4 represents a residue selected from the group consisting of:





[0084] In some embodiments, **R**^{3} represents -H and **R**^{4} represents a 5-membered heterocycloalkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted; wherein said 5-membered heterocycloalkyl is connected through -C_1-C_6-alkylene-, saturated or unsaturated, unsubstituted, mono- or polysubstituted; or a 5-membered heteroaryl, unsubstituted, mono- or polysubstituted; wherein said 5-membered heteroaryl is connected through -C_1-C_6-alkylene-, saturated or unsaturated, unsubstituted, mono- or polysubstituted.

[0085] In some embodiments, **R**^{3} represents -H and **R**^{4} represents a residue selected from the group consisting of:

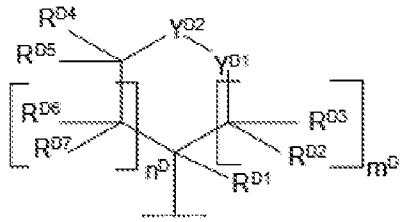


[0086] In some embodiments, **R**^{3} represents -H and **R**^{4} represents

(i) a residue -C**R'R"**-$(CH_2)_m$-OH, wherein **m** is an integer of from 1 to 6, preferably from 1 to 3; and wherein **R'** and **R"** independently of one another represent -H, -C_{1-3}-alkyl, -CF_3, -

CF_2H, $-CFH_2$, $-C_{1-3}$-alkylene-CF_3, $-C_{1-3}$-alkylene-CF_2H, $-C_{1-3}$-alkylene-CFH_2, $-C_{1-3}$-alkylene-O-C_{1-3}-alkyl, or $-C_{1-3}$-alkylene-OH; preferably -H, $-CH_3$, or $-C_{1-3}$-alkylene-OH. In an embodiment, at least **R'** or **R"** does not represent -H. In an embodiment, neither **R'** nor **R"** represents -H; or

(ii) a residue according to general formula (D),



(D)

wherein

$\mathbf{m^D}$ and $\mathbf{n^D}$ independently of one another are 0, 1, 2, or 3; preferably with the proviso that $\mathbf{m^D} + \mathbf{n^D} \leq 3$;

$\mathbf{Y^{D1}}$ is selected from -O-, $-S(=O)_2-$, -S(=O)(=NH)-, $-NR^{D8}-$ and $-CR^{D9}R^{D10}-$ and $\mathbf{Y^{D2}}$ represents $-CR^{D11}R^{D12}-$; **or** $\mathbf{Y^{D1}}$ is selected from -O-, $-S(=O)_2-$, $-NR^{D8}-$ and $-CR^{D9}R^{D10}-$ and $\mathbf{Y^{D2}}$ represents $-CR^{D11}R^{D12}-$; or $\mathbf{Y^{D1}}$ represents $-CR^{D9}R^{D10}-$ and $\mathbf{Y^{D2}}$ is selected from -O-, $-S(=O)_2-$, and $-NR^{D8}-$;

$\mathbf{R^{D1}}$, $\mathbf{R^{D2}}$, $\mathbf{R^{D3}}$, $\mathbf{R^{D4}}$, $\mathbf{R^{D5}}$, $\mathbf{R^{D6}}$, $\mathbf{R^{D7}}$, $\mathbf{R^{D8}}$,$\mathbf{R^{D9}}$, $\mathbf{R^{D10}}$, $\mathbf{R^{D11}}$ and $\mathbf{R^{D12}}$ independently of one another represent -H, -F , -OH, $-C_{1-3}$-alkylene-OH, $-C(=O)NH_2$, $-C_{1-3}$-alkylene-$C(O)NH_2$, $-C(=O)O-C_{1-3}$-alkyl, $-NH_2$, $-C_{1-3}$-alkylene-NH_2, $-NH(C_{1-3}$-alkyl), $-N(C_{1-3}$-alkyl$)_2$, $-NH(C_{1-3}$-alkylene-$CF_3)$, $-C_{1-3}$-alkylene-OCH_3, $-C_{1-3}$-alkyl, $-C_{1-3}$-alkylene-CF_3: or $\mathbf{R^{D2}}$ and $\mathbf{R^{D3}}$ together represent =O; or $\mathbf{R^{D4}}$ and $\mathbf{R^{D5}}$ together represent =O; or $\mathbf{R^{D9}}$ and $\mathbf{R^{D10}}$ together represent =O; or $\mathbf{R^{D11}}$ and $\mathbf{R^{D12}}$ together represent =O;

preferably wherein

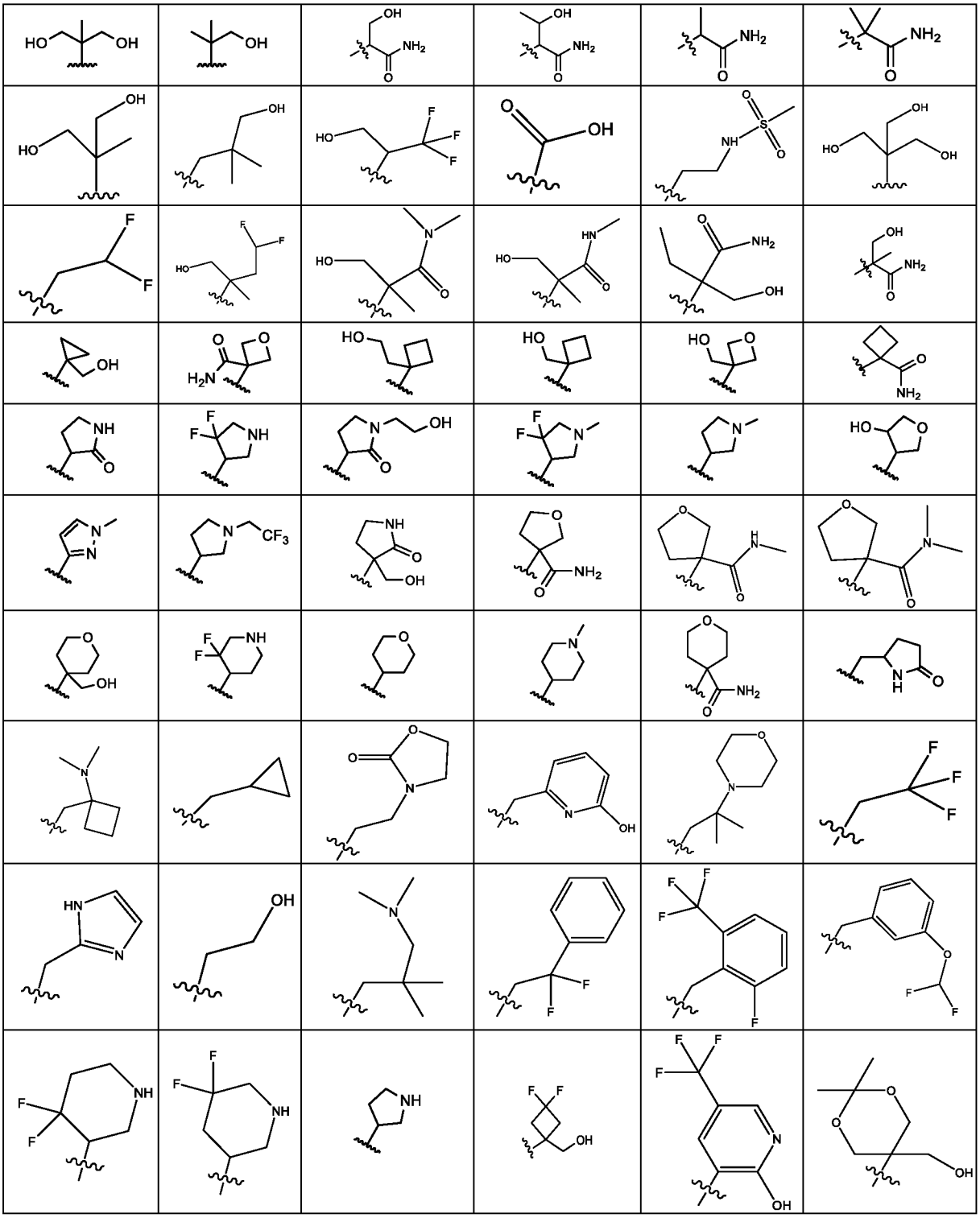
$\mathbf{m^D}$ and $\mathbf{n^D}$ independently of one another are 0, 1, 2 or 3; preferably with the proviso that $\mathbf{m^D} + \mathbf{n^D} \leq 3$;

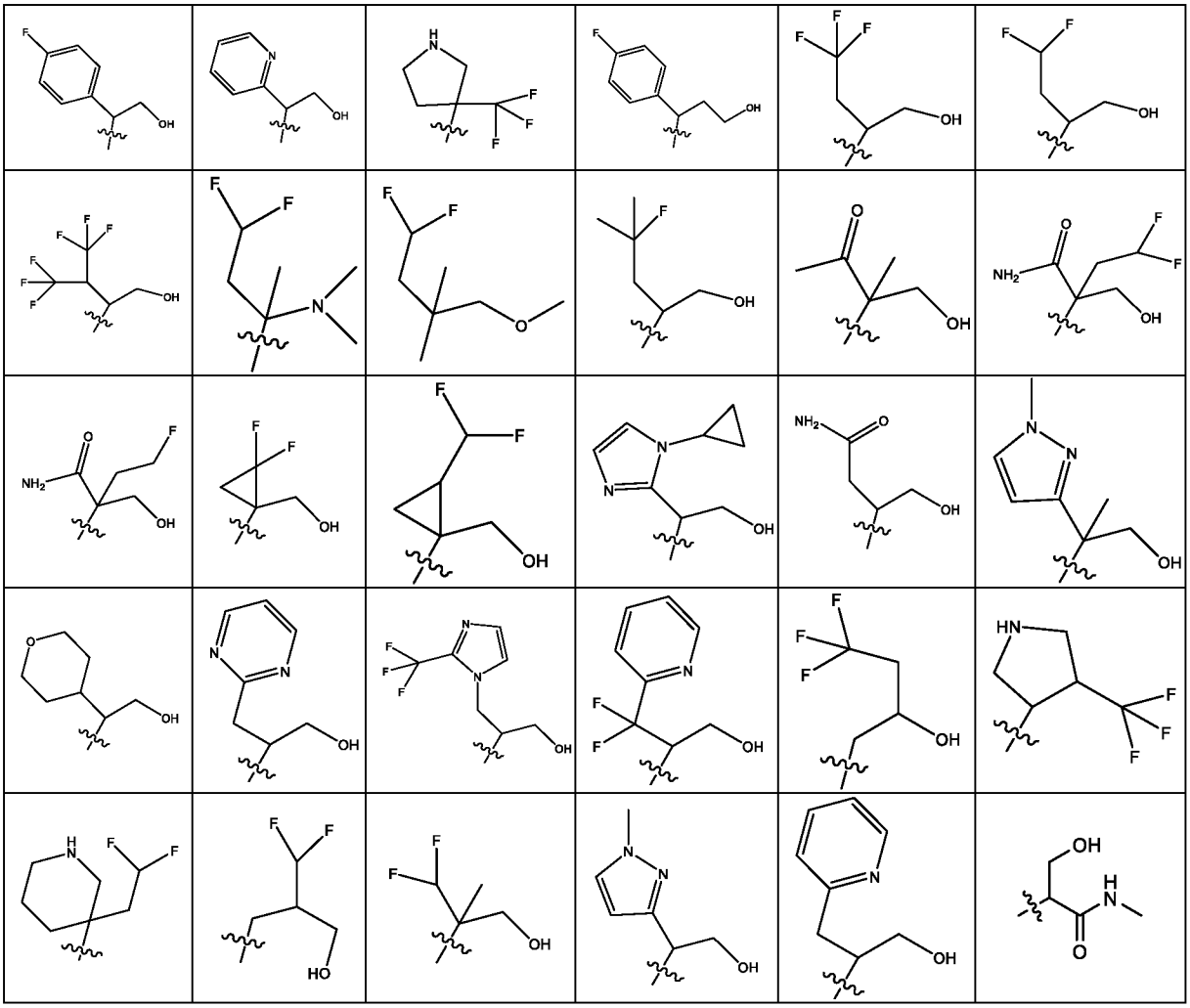
$\mathbf{Y^{D1}}$ is selected from -O-, $-NR^{D8}-$ and $-CR^{D9}R^{D10}-$ and $\mathbf{Y^{D2}}$ represents $-CR^{D11}R^{D12}-$; or $\mathbf{Y^{D1}}$ represents $-CR^{D9}R^{D10}-$ and $\mathbf{Y^{D2}}$ is selected from -O- and $-NR^{D8}-$;

$\mathbf{R^{D1}}$, $\mathbf{R^{D2}}$, $\mathbf{R^{D3}}$, $\mathbf{R^{D4}}$, $\mathbf{R^{D5}}$, $\mathbf{R^{D6}}$, $\mathbf{R^{D7}}$, $\mathbf{R^{D8}}$,$\mathbf{R^{D9}}$, $\mathbf{R^{D10}}$, $\mathbf{R^{D11}}$ and $\mathbf{R^{D12}}$ independently of one another represent -H, -F , -OH, $-C_{1-3}$-alkylene-OH, $-C(=O)NH_2$, $-CH_2NH_2$, $-CH_2N(CH_3)_2$, $-NHCH_2CF_3$, $-CH_3$, or $-CH_2CF_3$: or $\mathbf{R^{D2}}$ and $\mathbf{R^{D3}}$ together represent =O; or $\mathbf{R^{D4}}$ and $\mathbf{R^{D5}}$ together represent =O; or $\mathbf{R^{D9}}$ and $\mathbf{R^{D10}}$ together represent =O; or $\mathbf{R^{D11}}$ and $\mathbf{R^{D12}}$ together represent =O; preferably with the proviso that only 1, 2 or 3 of $\mathbf{R^{D1}}$, $\mathbf{R^{D2}}$, $\mathbf{R^{D3}}$, $\mathbf{R^{D4}}$, $\mathbf{R^{D5}}$, $\mathbf{R^{D6}}$, $\mathbf{R^{D7}}$, $\mathbf{R^{D8}}$,$\mathbf{R^{D9}}$, $\mathbf{R^{D10}}$, $\mathbf{R^{D11}}$ and $\mathbf{R^{D12}}$ represent a residue that is not -H; preferably with the proviso that at least one of $\mathbf{R^{D1}}$, $\mathbf{R^{D2}}$, $\mathbf{R^{D3}}$, $\mathbf{R^{D4}}$, $\mathbf{R^{D5}}$, $\mathbf{R^{D6}}$, $\mathbf{R^{D7}}$, $\mathbf{R^{D8}}$,$\mathbf{R^{D9}}$, $\mathbf{R^{D10}}$, $\mathbf{R^{D11}}$ and $\mathbf{R^{D12}}$

represent a residue that is not -H.

[0087] In some embodiments, R^3 represents -H and R^4 represents a residue selected from the group consisting of:





[0088] In some embodiments of the indazole derivative according to the invention $\mathbf{R^5}$ and $\mathbf{R^{5'}}$ independently of one another represent

-H;

-C_1-C_6-alkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted;

-C_1-C_6-heteroalkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted;

3-14-membered cycloalkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted;

wherein said 3-14-membered cycloalkyl is optionally connected through -C_1-C_6-alkylene- or -C_1-C_6-heteroalkylene-, in each case saturated or unsaturated, unsubstituted, mono- or polysubstituted.

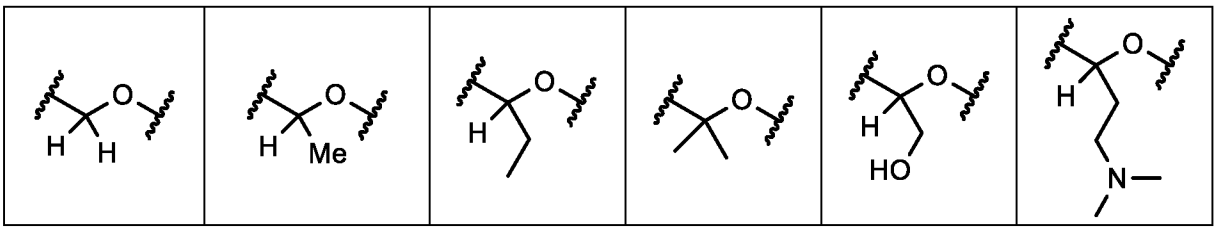
[0089] In some embodiments, $\mathbf{R^5}$ and $\mathbf{R^{5'}}$ independently of one another represent -H, -C_1-C_6-alkyl, or -C_1-C_6-alkylene-N(C_1-C_6-alkyl)$_2$.

[0090] In some embodiments of the indazole derivatives according to the invention, at least one of $\mathbf{R^5}$ and $\mathbf{R^{5'}}$ is not -H.

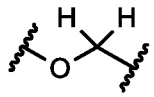
[0091] In some embodiments of the indazole derivatives according to the invention, $\mathbf{R^5}$ and $\mathbf{R^{5'}}$

are both -H.

[0092] In some embodiments, **T** represents -O- and **U** represents -C**R**^{5}**R**$^{5'}$- and the resultant moiety -O-C**R**^{5}**R**$^{5'}$- represents a residue selected from the group consisting of:



[0093] In some embodiments, **T** represents -C**R**^{5}**R**$^{5'}$- and **U** represents -O- and the resultant moiety -C**R**^{5}**R**$^{5'}$-O- represents a residue:



[0094] In some embodiments, **R**^{5} represents -H and **R**$^{5'}$ represents a residue selected from the group consisting of -H, -C_{1-3}-alkyl, -CF_3, -CF_2H, -CFH_2, -C_{1-3}-alkylene-CF_3, -C_{1-3}-alkylene-CF_2H, -C_{1-3}-alkylene-CFH_2, and -C_{1-3}-alkylene-OH; preferably -H or C_{1-3}-alkyl.

[0095] In some embodiments of the indazole derivatives according to the invention **R**^{6}, **R**^{7} and **R**^{8} independently of one another represent

-H;

-F, -Cl, -Br, -I, -OH, -SH, -SF_5, -CN, -NO_2, -C(=O)OH, -NH_2;

-C_{1-6}-alkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted;

-O-C_{1-6}-alkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted;

-NHC_{1-6}-alkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted;

-N(C_{1-6}-alkyl)$_2$, saturated or unsaturated, unsubstituted, mono- or polysubstituted;

-C(=O)OC_{1-6}-alkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted;

-OC(=O)C_{1-6}-alkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted;

-C_{1-6}-heteroalkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted.

[0096] In some embodiments, **R**^{6}, **R**^{7} and **R**^{8} independently of one another represent

-H, -F, -Cl, -Br, -I, -OH, -SH, -SF_5, -CN, -NO_2, -C(=O)OH, -NH_2,

-C_{1-6}-alkyl, -CF_3, -CHF_2, -CH_2F,

-O-C_{1-6}-alkyl, -OCF_3, -$OCHF_2$, -OCH_2F,

-NHC_{1-6}-alkyl unsubstituted or substituted with one or more substituents independently of one another selected from -OH, =O, -F, -Cl, -Br, -I, -SH, =S, -CN, -CF_3, -CHF_2, -CH_2F, -OCF_3, -$OCHF_2$, -OCH_2F, SF_5, -NO_2, -C(=O)OH, -NH_2, and -C(=O)NH_2;

-N(C_{1-6}-alkyl)$_2$ unsubstituted or substituted with one or more substituents independently of one another selected from -OH, =O, -F, -Cl, -Br, -I, -SH, =S, -CN, -CF_3, -CHF_2, -CH_2F, -OCF_3, -$OCHF_2$, -OCH_2F, SF_5, -NO_2, -C(=O)OH, -NH_2, and -C(=O)NH_2;

-C(=O)OC$_{1-6}$-alkyl unsubstituted or substituted with one or more substituents independently of one another selected from -OH, =O, -F, -Cl, -Br, -I, -SH, =S, -CN, -CF_3, -CHF_2, -CH_2F, -OCF_3, -$OCHF_2$, -OCH_2F, SF_5, -NO_2, -C(=O)OH, -NH_2, and -C(=O)NH_2;

-OC(=O)C$_{1-6}$-alkyl unsubstituted or substituted with one or more substituents independently of one another selected from -OH, =O, -F, -Cl, -Br, -I, -SH, =S, -CN, -CF_3, -CHF_2, -CH_2F, -OCF_3, -$OCHF_2$, -OCH_2F, SF_5, -NO_2, -C(=O)OH, -NH_2, and -C(=O)NH_2; or

-C$_{1-6}$-heteroalkyl unsubstituted or substituted with one or more substituents independently of one another selected from -OH, =O, -F, -Cl, -Br, -I, -SH, =S, -CN, -CF_3, -CHF_2, -CH_2F, -OCF_3, -$OCHF_2$, -OCH_2F, SF_5, -NO_2, -C(=O)OH, -NH_2, and -C(=O)NH_2.

[0097] In some embodiments, **R^6**, **R^7** and **R^8** independently of one another represents a residue selected from the group consisting of -H, -F, -Cl, -Br, -I, -CN, C$_{1-3}$-alkyl, -CF_3, -CF_2H, and -CFH_2; preferably -H or -F.

[0098] In some embodiments of the indazole derivatives according to the invention **R^6** represents -H, -F, -Cl, -CN, or -C$_1$-C$_6$-alkyl.

[0099] In some embodiments of the indazole derivatives according to the invention, **R^6** does not represent -H.

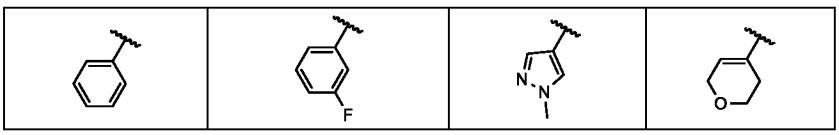
[0100] In some embodiments, **R^6** represents a residue selected from the group consisting of -H, -F, -Cl, -CN or -CH_3; preferably -H, -F, -CN or -CH_3.

[0101] In some embodiments of the indazole derivatives according to the invention **R^7** represents -H, -F, -Cl, -CN, or -C$_1$-C$_6$-alkyl.

[0102] In some embodiments of the indazole derivatives according to the invention **R^7** does not represent -H.

[0103] In some embodiments, especially when Q represents -N**R^{3}R^4**, **R^7** represents a residue selected from the group consisting of -H, -F, -Cl, -CN or CH_3.

[0104] In some embodiments, especially when Q represents -O**R^2**, **R^7** represents a residue selected from the group consisting of -H or



[0105] In some embodiments of the indazole derivatives according to the invention **R^8** represents -H, -F, -Cl, -CN, or -C$_1$-C$_6$-alkyl.

[0106] In some embodiments of the indazole derivatives according to the invention **R^8** does not represent -H.

[0107] In some embodiments, **R^8** represents a residue selected from the group consisting of -H, -F, -Cl, -CN or CH_3; preferably -F.

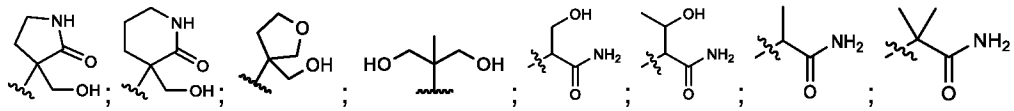
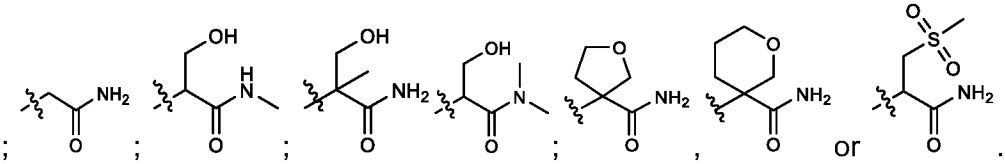
[0108] In some embodiments of the indazole derivatives according to the invention

(i) **R^6**, **R^7** and **R^8** each represent -H; or

(ii) two of **R**^{6}, **R**^{7} and **R**^{8} represent -H and the other of **R**^{6}, **R**^{7} and **R**^{8} represents -F, -Cl, -CN, or -CH_3; or

(iii) one of **R**^{6}, **R**^{7} and **R**^{8} represents -H and the other of **R**^{6}, **R**^{7} and **R**^{8} independently of one another represent -F, -Cl, -CN, or -CH_3.

[0109] In some embodiments, the compound is according to general formula (I), wherein

- **R**^{1} represents -CH_3; and/or
- **R**^{6}, **R**^{7} and **R**^{8} each represent -H; and/or
- **T** represents -O-; and/or
- **U** represents -CH_2-; and/or
- **V** represents thiazolyl, pyridyl, or pyrazolyl; wherein said thiazolyl, pyridyl, and pyrazolyl each independently from one another can be unsubstituted, monosubstituted or disubstituted with a substituent selected from the group consisting of -CH_3; -F; -CH_2CHF_2; and -CF_3; and/or
- **Q** represents N**R**^{3}**R**^{4}; and/or
- **R**^{3} represents H; and/or
- **R**^{4} represents ; .

[0110] In exemplary embodiments of the invention, the indazole derivative is selected from the group consisting of:

Cpd 001 - N-[4-(hydroxymethyl)oxan-4-yl]-2-methyl-5-[(4-methyl-1,3-thiazol-5-yl)methoxy]-2H-indazole-3-carboxamide;

Cpd 002 - 5-(benzyloxy)-N-(4,4-difluoropyrrolidin-3-yl)-2-methyl-2H-indazole-3-carboxamide;

Cpd 003 - N-(3,3-difluoropiperidin-4-yl)-2-methyl-5-{[2-(trifluoromethyl)pyridin-3-yl]methoxy}-2H-indazole-3-carboxamide;

Cpd 004 - 5-(benzyloxy)-N-[1-(hydroxymethyl)cyclopropyl]-2-methyl-2H-indazole-3-carboxamide;

Cpd 005 - N-(1-hydroxy-2-methylpropan-2-yl)-2-methyl-5-[(4-methyl-1,3-thiazol-5-yl)methoxy]-2H-indazole-3-carboxamide;

Cpd 006 - 2-methyl-N-(1-methyl-1H-pyrazol-3-yl)-5-[(1-methyl-1H-pyrazol-5-yl)methoxy]-2H-indazole-3-carboxamide;

Cpd 007 - 2-methyl-N-(2-oxopyrrolidin-3-yl)-5-{[2-(trifluoromethyl)pyridin-3-yl]methoxy}-2H-

indazole-3-carboxamide;
Cpd 008 - 5-(benzyloxy)-2-methyl-N-(2-oxopyrrolidin-3-yl)-2H-indazole-3-carboxamide;
Cpd 009 - N-(1,3-dihydroxy-2-methylpropan-2-yl)-2-methyl-5-[(1-methyl-1H-pyrazol-5-yl)methoxy]-2H-indazole-3-carboxamide;
Cpd 010 - N-[4-hydroxyoxolan-3-yl]-2-methyl-5-{[2-(trifluoromethyl)pyridin-3-yl]methoxy}-2H-indazole-3-carboxamide;
Cpd 011 - 5-(benzyloxy)-N-[4-hydroxyoxolan-3-yl]-2-methyl-2H-indazole-3-carboxamide;
Cpd 012 - N-(3-hydroxy-2,2-dimethylpropyl)-2-methyl-5-[(1-methyl-1H-pyrazol-5-yl)methoxy]-2H-indazole-3-carboxamide;
Cpd 013 - 2-methyl-N-(1-methyl-1H-pyrazol-3-yl)-5-{[2-(trifluoromethyl)pyridin-3-yl]methoxy}-2H-indazole-3-carboxamide;
Cpd 014 - 5-(benzyloxy)-2-methyl-N-(1-methyl-1H-pyrazol-3-yl)-2H-indazole-3-carboxamide;
Cpd 015 - N-(1-hydroxy-2-methylpropan-2-yl)-2-methyl-5-[(1-methyl-1H-pyrazol-5-yl)methoxy]-2H-indazole-3-carboxamide;
Cpd 016 - N-(1,3-dihydroxy-2-methylpropan-2-yl)-2-methyl-5-{[2-(trifluoromethyl)pyridin-3-yl]methoxy}-2H-indazole-3-carboxamide;
Cpd 017 - 5-(benzyloxy)-N-(1,3-dihydroxy-2-methylpropan-2-yl)-2-methyl-2H-indazole-3-carboxamide;
Cpd 018 - 2-methyl-5-[(4-methyl-1,3-thiazol-5-yl)methoxy]-N-(1-methyl-1H-pyrazol-3-yl)-2H-indazole-3-carboxamide;
Cpd 019 - N-(3-hydroxy-2,2-dimethylpropyl)-2-methyl-5-{[2-(trifluoromethyl)pyridin-3-yl]methoxy}-2H-indazole-3-carboxamide;
Cpd 020 - 5-(benzyloxy)-N-(3-hydroxy-2,2-dimethylpropyl)-2-methyl-2H-indazole-3-carboxamide;
Cpd 021 - N-(1,3-dihydroxy-2-methylpropan-2-yl)-2-methyl-5-[(4-methyl-1,3-thiazol-5-yl)methoxy]-2H-indazole-3-carboxamide;
Cpd 022 - N-[1-(hydroxymethyl)cyclopropyl]-2-methyl-5-{[2-(trifluoromethyl)pyridin-3-yl]methoxy}-2H-indazole-3-carboxamide;
Cpd 023 - 5-(benzyloxy)-N-(1-hydroxy-2-methylpropan-2-yl)-2-methyl-2H-indazole-3-carboxamide;
Cpd 024 - N-(3-hydroxy-2,2-dimethylpropyl)-2-methyl-5-[(4-methyl-1,3-thiazol-5-yl)methoxy]-2H-indazole-3-carboxamide;
Cpd 025 - 5-(benzyloxy)-N-[(6-hydroxypyridin-2-yl)methyl]-2-methyl-2H-indazole-3-carboxamide;
Cpd 026 - 3-hydroxy-2-[(2-methyl-5-{[2-(trifluoromethyl)pyridin-3-yl]methoxy}-2H-indazol-3-yl)formamido]propanamide;

Cpd 027 - 3-hydroxy-2-({2-methyl-5-[(1-methyl-1H-pyrazol-5-yl)methoxy]-2H-indazol-3-yl}formamido)propanamide;

Cpd 028 - N-[1-(hydroxymethyl)cyclobutyl]-2-methyl-5-{[2-(trifluoromethyl)pyridin-3-yl]methoxy}-2H-indazole-3-carboxamide;

Cpd 029 - N-[4-(hydroxymethyl)oxan-4-yl]-2-methyl-5-{[2-(trifluoromethyl)pyridin-3-yl]methoxy}-2H-indazole-3-carboxamide;

Cpd 030 - N-(3-carbamoyloxetan-3-yl)-2-methyl-5-[(1-methyl-1H-pyrazol-5-yl)methoxy]-2H-indazole-3-carboxamide;

Cpd 031 - N-(3-carbamoyloxetan-3-yl)-2-methyl-5-[(4-methyl-1,3-thiazol-5-yl)methoxy]-2H-indazole-3-carboxamide;

Cpd 032 - N-(4,4-difluoro-1-methylpyrrolidin-3-yl)-2-methyl-5-[(4-methyl-1,3-thiazol-5-yl)methoxy]-2H-indazole-3-carboxamide;

Cpd 033 - 5-(benzyloxy)-N-(1-carbamoylcyclobutyl)-2-methyl-2H-indazole-3-carboxamide;

Cpd 034 - 5-(benzyloxy)-N-(4,4-difluoro-1-methylpyrrolidin-3-yl)-2-methyl-2H-indazole-3-carboxamide;

Cpd 035 - N-[(6-hydroxypyridin-2-yl)methyl]-2-methyl-5-[(1-methyl-1H-pyrazol-5-yl)methoxy]-2H-indazole-3-carboxamide;

Cpd 036 - N-[(6-hydroxypyridin-2-yl)methyl]-2-methyl-5-{[2-(trifluoromethyl)pyridin-3-yl]methoxy}-2H-indazole-3-carboxamide;

Cpd 037 - N-[1-(2-hydroxyethyl)-2-oxopyrrolidin-3-yl]-2-methyl-5-[(4-methyl-1,3-thiazol-5-yl)methoxy]-2H-indazole-3-carboxamide;

Cpd 038 - 5-(benzyloxy)-N-[1-(2-hydroxyethyl)-2-oxopyrrolidin-3-yl]-2-methyl-2H-indazole-3-carboxamide;

Cpd 039 - N-[1-(2-hydroxyethyl)-2-oxopyrrolidin-3-yl]-2-methyl-5-[(1-methyl-1H-pyrazol-5-yl)methoxy]-2H-indazole-3-carboxamide;

Cpd 040 - 2-methyl-N-(1-methylpyrrolidin-3-yl)-5-{[2-(trifluoromethyl)pyridin-3-yl]methoxy}-2H-indazole-3-carboxamide;

Cpd 041 - 5-(benzyloxy)-N-(3-carbamoyloxetan-3-yl)-2-methyl-2H-indazole-3-carboxamide;

Cpd 042 - N-{[1-(dimethylamino)cyclobutyl]methyl}-2-methyl-5-{[2-(trifluoromethyl)pyridin-3-yl]methoxy}-2H-indazole-3-carboxamide;

Cpd 043 - N-[1-(hydroxymethyl)cyclobutyl]-2-methyl-5-[(4-methyl-1,3-thiazol-5-yl)methoxy]-2H-indazole-3-carboxamide;

Cpd 044 - N-[1-(hydroxymethyl)cyclobutyl]-2-methyl-5-[(1-methyl-1H-pyrazol-5-yl)methoxy]-2H-indazole-3-carboxamide;

Cpd 045 - 5-(benzyloxy)-2-methyl-N-[2-(2-oxo-1,3-oxazolidin-3-yl)ethyl]-2H-indazole-3-carboxamide;

Cpd 046 - N-{[1-(dimethylamino)cyclobutyl]methyl}-2-methyl-5-[(1-methyl-1H-pyrazol-5-yl)methoxy]-2H-indazole-3-carboxamide;

Cpd 047 - N-[1-(hydroxymethyl)cyclopropyl]-2-methyl-5-[(4-methyl-1,3-thiazol-5-yl)methoxy]-2H-indazole-3-carboxamide;

Cpd 048 - N-[1-(2-hydroxyethyl)cyclobutyl]-2-methyl-5-[(4-methyl-1,3-thiazol-5-yl)methoxy]-2H-indazole-3-carboxamide;

Cpd 049 - 2-methyl-5-[(1-methyl-1H-pyrazol-5-yl)methoxy]-N-[2-methyl-2-(morpholin-4-yl)propyl]-2H-indazole-3-carboxamide;

Cpd 050 - 2-methyl-5-[(1-methyl-1H-pyrazol-5-yl)methoxy]-N-[1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl]-2H-indazole-3-carboxamide;

Cpd 051 - 5-(benzyloxy)-N-[1-(2-hydroxyethyl)cyclobutyl]-2-methyl-2H-indazole-3-carboxamide;

Cpd 052 - 2-methyl-5-[(4-methyl-1,3-thiazol-5-yl)methoxy]-N-[2-methyl-2-(morpholin-4-yl)propyl]-2H-indazole-3-carboxamide;

Cpd 053 - 2-methyl-5-[(4-methyl-1,3-thiazol-5-yl)methoxy]-N-[2-(2-oxo-1,3-oxazolidin-3-yl)ethyl]-2H-indazole-3-carboxamide;

Cpd 054 - 2-methyl-N-[(5-oxopyrrolidin-2-yl)methyl]-5-{[2-(trifluoromethyl)pyridin-3-yl]methoxy}-2H-indazole-3-carboxamide;

Cpd 055 - 2-methyl-5-[(1-methyl-1H-pyrazol-5-yl)methoxy]-N-[2-(2-oxo-1,3-oxazolidin-3-yl)ethyl]-2H-indazole-3-carboxamide;

Cpd 056 - N-[4-hydroxyoxolan-3-yl]-2-methyl-5-[(1-methyl-1H-pyrazol-5-yl)methoxy]-2H-indazole-3-carboxamide;

Cpd 057 - 2-methyl-5-[(4-methyl-1,3-thiazol-5-yl)methoxy]-N-[1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl]-2H-indazole-3-carboxamide;

Cpd 058 - N-[4-(hydroxymethyl)oxan-4-yl]-2-methyl-5-[(1-methyl-1H-pyrazol-5-yl)methoxy]-2H-indazole-3-carboxamide;

Cpd 059 - 5-(benzyloxy)-2-methyl-N-[2-methyl-2-(morpholin-4-yl)propyl]-2H-indazole-3-carboxamide;

Cpd 060 - 5-(benzyloxy)-2-methyl-N-[1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl]-2H-indazole-3-carboxamide;

Cpd 061 - N-(1-carbamoylcyclobutyl)-2-methyl-5-[(1-methyl-1H-pyrazol-5-yl)methoxy]-2H-indazole-3-carboxamide;

Cpd 062 - 2-methyl-5-[(1-methyl-1H-pyrazol-5-yl)methoxy]-N-(2-oxopyrrolidin-3-yl)-2H-indazole-3-carboxamide;

Cpd 063 - 2-methyl-5-[(4-methyl-1,3-thiazol-5-yl)methoxy]-N-[(5-oxopyrrolidin-2-yl)methyl]-2H-indazole-3-carboxamide;

Cpd 064 - 2-methyl-5-[(4-methyl-1,3-thiazol-5-yl)methoxy]-N-(2-oxopyrrolidin-3-yl)-2H-

indazole-3-carboxamide;
Cpd 065 - N-[1-(2-hydroxyethyl)cyclobutyl]-2-methyl-5-{[2-(trifluoromethyl)pyridin-3-yl]methoxy}-2H-indazole-3-carboxamide;
Cpd 066 - 5-(benzyloxy)-2-methyl-N-[(5-oxopyrrolidin-2-yl)methyl]-2H-indazole-3-carboxamide;
Cpd 067 - N-[1-(hydroxymethyl)cyclopropyl]-2-methyl-5-[(1-methyl-1H-pyrazol-5-yl)methoxy]-2H-indazole-3-carboxamide;
Cpd 068 - 2-methyl-N-[2-methyl-2-(morpholin-4-yl)propyl]-5-{[2-(trifluoromethyl)pyridin-3-yl]methoxy}-2H-indazole-3-carboxamide;
Cpd 069 - 2-methyl-5-[(1-methyl-1H-pyrazol-5-yl)methoxy]-N-[(5-oxopyrrolidin-2-yl)methyl]-2H-indazole-3-carboxamide;
Cpd 070 - N-(1-carbamoylcyclobutyl)-2-methyl-5-[(4-methyl-1,3-thiazol-5-yl)methoxy]-2H-indazole-3-carboxamide;
Cpd 071 - 2-methyl-5-[(1-methyl-1H-pyrazol-5-yl)methoxy]-N-(1-methylpyrrolidin-3-yl)-2H-indazole-3-carboxamide;
Cpd 072 - N-{[1-(dimethylamino)cyclobutyl]methyl}-2-methyl-5-[(4-methyl-1,3-thiazol-5-yl)methoxy]-2H-indazole-3-carboxamide;
Cpd 073 - 2-methyl-N-[2-(2-oxo-1,3-oxazolidin-3-yl)ethyl]-5-{[2-(trifluoromethyl)pyridin-3-yl]methoxy}-2H-indazole-3-carboxamide;
Cpd 074 - 5-(benzyloxy)-N-[4-(hydroxymethyl)oxan-4-yl]-2-methyl-2H-indazole-3-carboxamide;
Cpd 075 - 2-methyl-5-[(4-methyl-1,3-thiazol-5-yl)methoxy]-N-(1-methylpyrrolidin-3-yl)-2H-indazole-3-carboxamide;
Cpd 076 - N-(1-hydroxy-2-methylpropan-2-yl)-2-methyl-5-{[2-(trifluoromethyl)pyridin-3-yl]methoxy}-2H-indazole-3-carboxamide;
Cpd 077 - 2-methyl-N-[1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl]-5-{[2-(trifluoromethyl)pyridin-3-yl]methoxy}-2H-indazole-3-carboxamide;
Cpd 078 - 5-(benzyloxy)-N-{[1-(dimethylamino)cyclobutyl]methyl}-2-methyl-2H-indazole-3-carboxamide;
Cpd 079 - N-[1-(2-hydroxyethyl)cyclobutyl]-2-methyl-5-[(1-methyl-1H-pyrazol-5-yl)methoxy]-2H-indazole-3-carboxamide;
Cpd 080 - N-[(3S,4S)-4-hydroxyoxolan-3-yl]-2-methyl-5-[(4-methyl-1,3-thiazol-5-yl)methoxy]-2H-indazole-3-carboxamide;
Cpd 081 - N-(4,4-difluoro-1-methylpyrrolidin-3-yl)-2-methyl-5-{[2-(trifluoromethyl)pyridin-3-yl]methoxy}-2H-indazole-3-carboxamide;
Cpd 082 - (2S)-2-({2-methyl-5-[(pyridin-2-yl)methoxy]-2H-indazol-3-yl}formamido)propanamide;

Cpd 083 - (2R)-2-({2-methyl-5-[(pyridin-2-yl)methoxy]-2H-indazol-3-yl}formamido)propanamide;

Cpd 084 - 2-methyl-N-(1-methylpiperidin-4-yl)-5-[(pyridin-2-yl)methoxy]-2H-indazole-3-carboxamide;

Cpd 085 - N-(4-carbamoyloxan-4-yl)-2-methyl-5-[(pyridin-2-yl)methoxy]-2H-indazole-3-carboxamide;

Cpd 086 - N-[1-(hydroxymethyl)cyclobutyl]-2-methyl-5-[(pyridin-2-yl)methoxy]-2H-indazole-3-carboxamide;

Cpd 087 - N-(3-carbamoyloxetan-3-yl)-2-methyl-5-{[2-(trifluoromethyl)pyridin-3-yl]methoxy}-2H-indazole-3-carboxamide;

Cpd 088 - N-(4,4-difluoro-1-methylpyrrolidin-3-yl)-2-methyl-5-[(1-methyl-1H-pyrazol-5-yl)methoxy]-2H-indazole-3-carboxamide;

Cpd 089 - N-[(6-hydroxypyridin-2-yl)methyl]-2-methyl-5-[(4-methyl-1,3-thiazol-5-yl)methoxy]-2H-indazole-3-carboxamide;

Cpd 090 - N-[1-(2-hydroxyethyl)-2-oxopyrrolidin-3-yl]-2-methyl-5-{[2-(trifluoromethyl)pyridin-3-yl]methoxy}-2H-indazole-3-carboxamide;

Cpd 091 - 5-(benzyloxy)-2-methyl-N-(1,1,1-trifluoro-3-hydroxypropan-2-yl)-2H-indazole-3-carboxamide;

Cpd 092 - 5-(benzyloxy)-2-methyl-N-(1-methylpyrrolidin-3-yl)-2H-indazole-3-carboxamide;

Cpd 093 - 5-[(2-fluorophenyl)methoxy]-2-methyl-N-(1-methylpiperidin-4-yl)-2H-indazole-3-carboxamide;

Cpd 094 - 5-[(2-fluorophenyl)methoxy]-N-[1-(hydroxymethyl)cyclobutyl]-2-methyl-2H-indazole-3-carboxamide;

Cpd 095 - 5-[(2-fluorophenyl)methoxy]-N-[1-(hydroxymethyl)cyclopropyl]-2-methyl-2H-indazole-3-carboxamide;

Cpd 096 - 5-[(2-fluorophenyl)methoxy]-N-[4-(hydroxymethyl)oxan-4-yl]-2-methyl-2H-indazole-3-carboxamide;

Cpd 097 - N-(4-carbamoyloxan-4-yl)-5-[(2-fluorophenyl)methoxy]-2-methyl-2H-indazole-3-carboxamide;

Cpd 098 - (2R)-2-({5-[(2-fluorophenyl)methoxy]-2-methyl-2H-indazol-3-yl}formamido)propanamide;

Cpd 099 - (2S)-2-({5-[(2-fluorophenyl)methoxy]-2-methyl-2H-indazol-3-yl}formamido)propanamide;

Cpd 100 - N-[3-(hydroxymethyl)oxetan-3-yl]-2-methyl-5-[(pyridin-2-yl)methoxy]-2H-indazole-3-carboxamide;

Cpd 101 - (2S)-2-({2-methyl-5-[(4-methyl-1,3-thiazol-5-yl)methoxy]-2H-indazol-3-yl}formamido)propanamide;

Cpd 102 - 2-methyl-N-(oxan-4-yl)-5-[(pyridin-2-yl)methoxy]-2H-indazole-3-carboxamide;
Cpd 103 - 2-methyl-2-({2-methyl-5-[(2-methyl-1,3-thiazol-5-yl)methoxy]-2H-indazol-3-yl}formamido)propanamide;
Cpd 104 - N-[1-(hydroxymethyl)cyclopropyl]-2-methyl-5-[(pyridin-2-yl)methoxy]-2H-indazole-3-carboxamide;
Cpd 105 - N-[3-(hydroxymethyl)oxetan-3-yl]-2-methyl-5-[(2-methyl-1,3-thiazol-5-yl)methoxy]-2H-indazole-3-carboxamide;
Cpd 106 - N-[4-(hydroxymethyl)oxan-4-yl]-2-methyl-5-[(pyridin-2-yl)methoxy]-2H-indazole-3-carboxamide;
Cpd 107 - N-(4-carbamoyloxan-4-yl)-2-methyl-5-[(4-methyl-1,3-thiazol-5-yl)methoxy]-2H-indazole-3-carboxamide;
Cpd 108 - N-[1-(hydroxymethyl)cyclobutyl]-2-methyl-5-[(2-methyl-1,3-thiazol-5-yl)methoxy]-2H-indazole-3-carboxamide;
Cpd 109 - N-[3-(hydroxymethyl)oxetan-3-yl]-2-methyl-5-[(4-methyl-1,3-thiazol-5-yl)methoxy]-2H-indazole-3-carboxamide;
Cpd 110 - 2-methyl-2-({2-methyl-5-[(4-methyl-1,3-thiazol-5-yl)methoxy]-2H-indazol-3-yl}formamido)propanamide;
Cpd 111 - 2-methyl-5-[(2-methyl-1,3-thiazol-5-yl)methoxy]-N-(1-methylpiperidin-4-yl)-2H-indazole-3-carboxamide;
Cpd 112 - 2-methyl-5-[(4-methyl-1,3-thiazol-5-yl)methoxy]-N-(1-methylpiperidin-4-yl)-2H-indazole-3-carboxamide;
Cpd 113 - (2R)-3-hydroxy-2-({2-methyl-5-[(4-methyl-1,3-thiazol-5-yl)methoxy]-2H-indazol-3-yl}formamido)propanamide;
Cpd 114 - N-[1-(hydroxymethyl)cyclopropyl]-2-methyl-5-[(2-methyl-1,3-thiazol-5-yl)methoxy]-2H-indazole-3-carboxamide;
Cpd 115 - 2-methyl-5-[(4-methyl-1,3-thiazol-5-yl)methoxy]-N-(oxan-4-yl)-2H-indazole-3-carboxamide;
Cpd 116 - (2S)-3-hydroxy-2-({2-methyl-5-[(4-methyl-1,3-thiazol-5-yl)methoxy]-2H-indazol-3-yl}formamido)propanamide;
Cpd 117 - (2R)-2-({2-methyl-5-[(2-methyl-1,3-thiazol-5-yl)methoxy]-2H-indazol-3-yl}formamido)propanamide;
Cpd 118 - (2R)-2-({2-methyl-5-[(4-methyl-1,3-thiazol-5-yl)methoxy]-2H-indazol-3-yl}formamido)propanamide;
Cpd 119 - (2S)-2-({2-methyl-5-[(2-methyl-1,3-thiazol-5-yl)methoxy]-2H-indazol-3-yl}formamido)propanamide;
Cpd 120 - 2-methyl-5-[(2-methyl-1,3-thiazol-5-yl)methoxy]-N-(oxan-4-yl)-2H-indazole-3-carboxamide;

Cpd 121 - (2R)-2-{[5-(cyclopropylmethoxy)-2-methyl-2H-indazol-3-yl]formamido}propanamide;

Cpd 122 - 2-methyl-5-{[2-(trifluoromethyl)pyridin-3-yl]methoxy}-2H-indazole-3-carboxylic acid;

Cpd 123 - 2-methyl-5-[(1-methyl-1H-pyrazol-5-yl)methoxy]-2H-indazole-3-carboxylic acid;

Cpd 124 - N-[4-(hydroxymethyl)oxan-4-yl]-2-methyl-5-[(2-methyl-1,3-thiazol-5-yl)methoxy]-2H-indazole-3-carboxamide;

Cpd 125 - (2R)-3-hydroxy-2-({2-methyl-5-[(pyridin-2-yl)methoxy]-2H-indazol-3-yl}formamido)propanamide;

Cpd 126 - (2S)-3-hydroxy-2-({2-methyl-5-[(2-methyl-1,3-thiazol-5-yl)methoxy]-2H-indazol-3-yl}formamido)propanamide;

Cpd 127 - N-(1,3-dihydroxy-2-methylpropan-2-yl)-2-methyl-5-[(pyridin-2-yl)methoxy]-2H-indazole-3-carboxamide;

Cpd 128 - N-(3,3-difluoropiperidin-4-yl)-2-methyl-5-[(pyridin-2-yl)methoxy]-2H-indazole-3-carboxamide;

Cpd 129 - 5-(cyclobutylmethoxy)-N-(1,3-dihydroxy-2-methylpropan-2-yl)-2-methyl-2H-indazole-3-carboxamide;

Cpd 130 - (2S)-2-{[5-(cyclobutylmethoxy)-2-methyl-2H-indazol-3-yl]formamido}-3-hydroxypropanamide;

Cpd 131 - N-(1,3-dihydroxy-2-methylpropan-2-yl)-2-methyl-5-[(2-methyl-1,3-oxazol-5-yl)methoxy]-2H-indazole-3-carboxamide;

Cpd 132 - N-(3,3-difluoropiperidin-4-yl)-2-methyl-5-[(4-methyl-1,3-thiazol-5-yl)methoxy]-2H-indazole-3-carboxamide;

Cpd 133 - 5-(cyclopropylmethoxy)-N-(cyclopropylmethyl)-2-methyl-2H-indazole-3-carboxamide;

Cpd 134 - 2-{[5-(cyclopropylmethoxy)-2-methyl-2H-indazol-3-yl]formamido}-2-methylpropanamide;

Cpd 135 - 5-(cyclopropylmethoxy)-N-(1,3-dihydroxy-2-methylpropan-2-yl)-2-methyl-2H-indazole-3-carboxamide;

Cpd 136 - (2R)-2-{[5-(cyclopropylmethoxy)-2-methyl-2H-indazol-3-yl]formamido}-3-hydroxypropanamide;

Cpd 137 - (2S)-2-{[5-(cyclopropylmethoxy)-2-methyl-2H-indazol-3-yl]formamido}-3-hydroxypropanamide;

Cpd 138 - (2S,3R)-2-{[5-(cyclopropylmethoxy)-2-methyl-2H-indazol-3-yl]formamido}-3-hydroxybutanamide;

Cpd 139 - (2S)-2-{[5-(cyclopropylmethoxy)-2-methyl-2H-indazol-3-yl]formamido}propanamide;

Cpd 140 - 5-(cyclopropylmethoxy)-N-(2-methanesulfonamidoethyl)-2-methyl-2H-indazole-3-carboxamide;

Cpd 141 - (2S)-3-hydroxy-2-({2-methyl-5-[(2-methyl-1,3-oxazol-5-yl)methoxy]-2H-indazol-3-yl}formamido)propanamide;

Cpd 142 - (2S,3R)-3-hydroxy-2-({2-methyl-5-[(2-methyl-1,3-oxazol-5-yl)methoxy]-2H-indazol-3-yl}formamido)butanamide;

Cpd 143 - (2S)-2-{[5-(cyclopentylmethoxy)-2-methyl-2H-indazol-3-yl]formamido}-3-hydroxypropanamide;

Cpd 144 - 5-(cyclopentylmethoxy)-N-(1,3-dihydroxy-2-methylpropan-2-yl)-2-methyl-2H-indazole-3-carboxamide;

Cpd 145 - 2-{[5-(cyclopentylmethoxy)-2-methyl-2H-indazol-3-yl]formamido}-2-methylpropanamide;

Cpd 146 - 5-[(1-cyanocyclopropyl)methoxy]-N-(1,3-dihydroxy-2-methylpropan-2-yl)-2-methyl-2H-indazole-3-carboxamide;

Cpd 147 - N-[1,3-dihydroxy-2-(hydroxymethyl)propan-2-yl]-2-methyl-5-[(2-methyl-1,3-thiazol-5-yl)methoxy]-2H-indazole-3-carboxamide;

Cpd 148 - (2S)-2-({5-[(1-cyanocyclopropyl)methoxy]-2-methyl-2H-indazol-3-yl}formamido)-3-hydroxypropanamide;

Cpd 149 - (2S,3R)-3-hydroxy-2-({2-methyl-5-[(2-methyl-1,3-thiazol-5-yl)methoxy]-2H-indazol-3-yl}formamido)butanamide;

Cpd 150 - N-(2,2-difluoroethyl)-2-methyl-5-[(2-methyl-1,3-thiazol-5-yl)methoxy]-2H-indazole-3-carboxamide;

Cpd 151 - 3-hydroxy-2-methyl-2-({2-methyl-5-[(4-methyl-1,3-thiazol-5-yl)methoxy]-2H-indazol-3-yl}formamido)propanamide;

Cpd 152 - N-[(3R)-1-(2-hydroxyethyl)-2-oxopyrrolidin-3-yl]-2-methyl-5-[(pyridin-2-yl)methoxy]-2H-indazole-3-carboxamide;

Cpd 153 - N-[(3S)-1-(2-hydroxyethyl)-2-oxopyrrolidin-3-yl]-2-methyl-5-[(pyridin-2-yl)methoxy]-2H-indazole-3-carboxamide;

Cpd 154 - 3-hydroxy-2-methyl-2-({2-methyl-5-[(1-methyl-1H-pyrazol-5-yl)methoxy]-2H-indazol-3-yl}formamido)propanamide;

Cpd 155 - 3-hydroxy-2-methyl-2-({2-methyl-5-[(1-methyl-1H-pyrazol-3-yl)methoxy]-2H-indazol-3-yl}formamido)propanamide;

Cpd 156 - 3-hydroxy-2-methyl-2-({2-methyl-5-[(1-methyl-1H-pyrazol-4-yl)methoxy]-2H-indazol-3-yl}formamido)propanamide;

Cpd 157 - 3-hydroxy-2-methyl-2-({2-methyl-5-[(2-methyl-1,3-thiazol-5-yl)methoxy]-2H-indazol-3-yl}formamido)propanamide;

Cpd 158 - 3-hydroxy-2-methyl-2-({2-methyl-5-[(oxan-4-yl)methoxy]-2H-indazol-3-

yl}formamido)propanamide;

Cpd 159 - 5-(cyclobutylmethoxy)-N-[3-(hydroxymethyl)-2-oxopyrrolidin-3-yl]-2-methyl-2H-indazole-3-carboxamide;

Cpd 160 - 3-hydroxy-2-methyl-2-({2-methyl-5-[(2-methyl-1,3-thiazol-4-yl)methoxy]-2H-indazol-3-yl}formamido)propanamide;

Cpd 161 - 5-(cyclopropylmethoxy)-N-[3-(hydroxymethyl)-2-oxopyrrolidin-3-yl]-2-methyl-2H-indazole-3-carboxamide;

Cpd 162 - 3-hydroxy-2-methyl-2-({2-methyl-5-[(pyridin-2-yl)methoxy]-2H-indazol-3-yl}formamido)propanamide;

Cpd 163 - N-[3-(hydroxymethyl)-2-oxopyrrolidin-3-yl]-2-methyl-5-[(4-methyl-1,3-thiazol-5-yl)methoxy]-2H-indazole-3-carboxamide;

Cpd 164 - N-(3-carbamoyloxolan-3-yl)-2-methyl-5-[(6-methylpyridin-3-yl)methoxy]-2H-indazole-3-carboxamide;

Cpd 165 - N-(3-carbamoyloxolan-3-yl)-5-(cyclopropylmethoxy)-2-methyl-2H-indazole-3-carboxamide;

Cpd 166 - N-(3-carbamoyloxolan-3-yl)-5-[(2-fluorophenyl)methoxy]-2-methyl-2H-indazole-3-carboxamide;

Cpd 167 - 3-hydroxy-2-methyl-2-({2-methyl-5-[(oxetan-3-yl)methoxy]-2H-indazol-3-yl}formamido)propanamide;

Cpd 168 - N-(3-carbamoyloxolan-3-yl)-2-methyl-5-[(pyridin-3-yl)methoxy]-2H-indazole-3-carboxamide;

Cpd 169 - N-[3-(hydroxymethyl)-2-oxopyrrolidin-3-yl]-2-methyl-5-[(6-methylpyridin-3-yl)methoxy]-2H-indazole-3-carboxamide;

Cpd 170 - N-(3-carbamoyloxolan-3-yl)-2-methyl-5-[(4-methyl-1,3-thiazol-5-yl)methoxy]-2H-indazole-3-carboxamide;

Cpd 171 - 5-[(2-fluorophenyl)methoxy]-N-[3-(hydroxymethyl)-2-oxopyrrolidin-3-yl]-2-methyl-2H-indazole-3-carboxamide;

Cpd 172 - 3-hydroxy-2-[(5-methoxy-2-methyl-2H-indazol-3-yl)formamido]-2-methylpropanamide;

Cpd 173 - 2-{[5-(cyclobutylmethoxy)-2-methyl-2H-indazol-3-yl]formamido}-3-hydroxy-2-methylpropanamide;

Cpd 174 - 3-hydroxy-2-methyl-2-({2-methyl-5-[(6-methylpyridin-3-yl)methoxy]-2H-indazol-3-yl}formamido)propanamide;

Cpd 175 - N-(3-carbamoyloxolan-3-yl)-5-{[2-(difluoromethyl)phenyl]methoxy}-2-methyl-2H-indazole-3-carboxamide;

Cpd 176 - 5-{[2-(difluoromethyl)phenyl]methoxy}-N-[3-(hydroxymethyl)-2-oxopyrrolidin-3-yl]-2-methyl-2H-indazole-3-carboxamide;

Cpd 177 - N-[3-(hydroxymethyl)-2-oxopyrrolidin-3-yl]-2-methyl-5-{[2-(trifluoromethyl)pyridin-3-yl]methoxy}-2H-indazole-3-carboxamide;

Cpd 178 - N-(3-carbamoyloxolan-3-yl)-2-methyl-5-{[2-(trifluoromethyl)pyridin-3-yl]methoxy}-2H-indazole-3-carboxamide;

Cpd 179 - 3-hydroxy-2-methyl-2-({2-methyl-5-[(2-methyl-1,3-oxazol-5-yl)methoxy]-2H-indazol-3-yl}formamido)propanamide;

Cpd 180 - N-[3-(hydroxymethyl)-2-oxopyrrolidin-3-yl]-2-methyl-5-[(pyridin-3-yl)methoxy]-2H-indazole-3-carboxamide;

Cpd 181 - 3-hydroxy-2-methyl-2-({2-methyl-5-[(5-methylpyridin-2-yl)methoxy]-2H-indazol-3-yl}formamido)propanamide;

Cpd 182 - N-(4,4-difluoro-1-hydroxy-2-methylbutan-2-yl)-2-methyl-5-[(4-methyl-1,3-thiazol-5-yl)methoxy]-2H-indazole-3-carboxamide;

Cpd 183 - 2-methyl-N-[3-(methylcarbamoyl)oxolan-3-yl]-5-{[2-(trifluoromethyl)pyridin-3-yl]methoxy}-2H-indazole-3-carboxamide;

Cpd 184 - 3-hydroxy-N,N,2-trimethyl-2-({2-methyl-5-[(4-methyl-1,3-thiazol-5-yl)methoxy]-2H-indazol-3-yl}formamido)propanamide;

Cpd 185 - 3-hydroxy-N,2-dimethyl-2-({2-methyl-5-[(4-methyl-1,3-thiazol-5-yl)methoxy]-2H-indazol-3-yl}formamido)propanamide;

Cpd 186 - N-[3-(dimethylcarbamoyl)oxolan-3-yl]-2-methyl-5-{[2-(trifluoromethyl)pyridin-3-yl]methoxy}-2H-indazole-3-carboxamide;

Cpd 187 - 2-{[5-(2,2-difluoroethoxy)-2-methyl-2H-indazol-3-yl]formamido}-3-hydroxy-2-methylpropanamide;

Cpd 188 - 2-({2-ethyl-5-[(pyridin-2-yl)methoxy]-2H-indazol-3-yl}formamido)-3-hydroxy-2-methylpropanamide;

Cpd 189 - 2-(hydroxymethyl)-2-({2-methyl-5-[(pyridin-2-yl)methoxy]-2H-indazol-3-yl}formamido)butanamide;

Cpd 190 - 3-hydroxy-2-methyl-2-({2-methyl-5-[(pyridin-3-yl)methoxy]-2H-indazol-3-yl}formamido)propanamide;

Cpd 191 - 2-[(5-{[2-(difluoromethyl)phenyl]methoxy}-2-methyl-2H-indazol-3-yl)formamido]-3-hydroxy-2-methylpropanamide;

Cpd 192 - 3-hydroxy-2-methyl-2-[(2-methyl-5-{[2-(trifluoromethyl)pyridin-3-yl]methoxy}-2H-indazol-3-yl)formamido]propanamide;

Cpd 193 - 3-hydroxy-N,N,2-trimethyl-2-[(2-methyl-5-{[2-(trifluoromethyl)pyridin-3-yl]methoxy}-2H-indazol-3-yl)formamido]propanamide;

Cpd 194 - 2-({5-[(2-fluorophenyl)methoxy]-2-methyl-2H-indazol-3-yl}formamido)-3-hydroxy-2-methylpropanamide;

Cpd 195 - 3-hydroxy-2-methyl-2-({5-[(2-methyl-1,3-thiazol-5-yl)methoxy]-2-(propan-2-yl)-

2H-indazol-3-yl}formamido)propanamide;

Cpd 196 - 3-hydroxy-2-methyl-2-({2-methyl-5-[(3-methylcyclobutyl)methoxy]-2H-indazol-3-yl}formamido)propenamide;

Cpd 197 - 5-(benzyloxy)-2-methyl-2H-indazole-3-carboxylic acid;

Cpd 198 - 5-[(2-fluorophenyl)methoxy]-2-methyl-2H-indazole-3-carboxylic acid;

Cpd 199 - 2-methyl-5-[(4-methyl-1,3-thiazol-5-yl)methoxy]-2H-indazole-3-carboxylic acid ;

Cpd 200 - N-(4,4-difluoro-1-hydroxy-2-methylbutan-2-yl)-5-{[2-(difluoromethyl)phenyl]methoxy}-2-methyl-2H-indazole-3-carboxamide;

Cpd 201 - N-(4,4-difluoro-1-hydroxy-2-methylbutan-2-yl)-2-methyl-5-[(pyridin-2-yl)methoxy]-2H-indazole-3-carboxamide,

Cpd 202 - N-(4,4-difluoro-1-hydroxy-2-methylbutan-2-yl)-2-methyl-5-{[2-(trifluoromethyl)pyridin-3-yl]methoxy}-2H-indazole-3-carboxamide,

Cpd 203 - N-(4,4-difluoro-1-hydroxy-2-methylbutan-2-yl)-5-[(2-fluorophenyl)methoxy]-2-methyl-2H-indazole-3-carboxamide,

Cpd 204 - 2-methyl-5-[(pyridin-2-yl)methoxy]-N-(2,2,2-trifluoroethyl)-2H-indazole-3-carboxamide,

Cpd 205 - N-(2-hydroxyethyl)-2-methyl-5-[(pyridin-2-yl)methoxy]-2H-indazole-3-carboxamide,

Cpd 206 - N-[(1H-imidazol-2-yl)methyl]-2-methyl-5-[(pyridin-2-yl)methoxy]-2H-indazole-3-carboxamide,

Cpd 207 - N-[3-(dimethylamino)-2,2-dimethylpropyl]-2-methyl-5-[(pyridin-2-yl)methoxy]-2H-indazole-3-carboxamide,

Cpd 208 - N-(2,2-difluoro-2-phenylethyl)-2-methyl-5-[(pyridin-2-yl)methoxy]-2H-indazole-3-carboxamide,

Cpd 209 - N-{[2-fluoro-6-(trifluoromethyl)phenyl]methyl}-2-methyl-5-[(pyridin-2-yl)methoxy]-2H-indazole-3-carboxamide,

Cpd 210 - N-{[3-(difluoromethoxy)phenyl]methyl}-2-methyl-5-[(pyridin-2-yl)methoxy]-2H-indazole-3-carboxamide,

Cpd 211 - N-(4,4-difluoropiperidin-3-yl)-2-methyl-5-[(4-methyl-1,3-thiazol-5-yl)methoxy]-2H-indazole-3-carboxamide,

Cpd 212 - N-(4,4-difluoropiperidin-3-yl)-2-methyl-5-[(pyridin-2-yl)methoxy]-2H-indazole-3-carboxamide,

Cpd 213 - N-(5,5-difluoropiperidin-3-yl)-2-methyl-5-[(4-methyl-1,3-thiazol-5-yl)methoxy]-2H-indazole-3-carboxamide,

Cpd 214 - N-(5,5-difluoropiperidin-3-yl)-2-methyl-5-[(pyridin-2-yl)methoxy]-2H-indazole-3-carboxamide,

Cpd 215 - 2-methyl-5-[(4-methyl-1,3-thiazol-5-yl)methoxy]-N-(pyrrolidin-3-yl)-2H-indazole-3-carboxamide,

Cpd 216 - 2-methyl-5-[(pyridin-2-yl)methoxy]-N-(pyrrolidin-3-yl)-2H-indazole-3-carboxamide,

Cpd 217 - N-[3,3-difluoro-1-(hydroxymethyl)cyclobutyl]-2-methyl-5-[(pyridin-2-yl)methoxy]-2H-indazole-3-carboxamide,

Cpd 218 - 3-[(1-{2-methyl-5-[(pyridin-2-yl)methoxy]-2H-indazol-3-yl}ethenyl)amino]-5-(trifluoromethyl)pyridin-2-ol,

Cpd 219 - N-[5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxan-5-yl]-2-methyl-5-[(pyridin-2-yl)methoxy]-2H-indazole-3-carboxamide,

Cpd 220 - N-[1-(4-fluorophenyl)-2-hydroxyethyl]-2-methyl-5-[(pyridin-2-yl)methoxy]-2H-indazole-3-carboxamide,

Cpd 221 - N-[2-hydroxy-1-(pyridin-2-yl)ethyl]-2-methyl-5-[(pyridin-2-yl)methoxy]-2H-indazole-3-carboxamide,

Cpd 222 - N-[3-(trifluoromethyl)pyrrolidin-3-yl]-2-methyl-5-[(pyridin-2-yl)methoxy]-2H-indazole-3-carboxamide;

Cpd 223 - N-[1-(4-fluorophenyl)-3-hydroxypropyl]-2-methyl-5-[(pyridin-2-yl)methoxy]-2H-indazole-3-carboxamide,

Cpd 224 - 2-(9-[(2-fluorophenyl)methoxy]-1H,3H,4H,5H-[1,4]diazepino[1,2-b]indazol-1-one-2-yl)-3-hydroxypropanamide;

Cpd 225 - 2-(9-[(2-fluorophenyl)methoxy]-1H,2H,3H,4H-pyrazino[1,2-b]indazol-1-one-2-yl)-3-hydroxypropanamide;

Cpd 226 - 2-methyl-5-[(pyridin-2-yl)methoxy]-N-(4,4,4-trifluoro-1-hydroxybutan-2-yl)-2H-indazole-3-carboxamide,

Cpd 227 - 2-methyl-5-[(pyridin-2-yl)methoxy]-N-[4,4,4-trifluoro-1-hydroxy-3-(trifluoromethyl)butan-2-yl]-2H-indazole-3-carboxamide,

Cpd 228 - N-(4,4-difluoro-1-hydroxybutan-2-yl)-2-methyl-5-[(pyridin-2-yl)methoxy]-2H-indazole-3-carboxamide,

Cpd 229 - N-[1-(dimethylamino)-4,4-difluoro-2-methylbutan-2-yl]-2-methyl-5-[(pyridin-2-yl)methoxy]-2H-indazole-3-carboxamide,

Cpd 230 - N-(4,4-difluoro-1-methoxy-2-methylbutan-2-yl)-2-methyl-5-[(pyridin-2-yl)methoxy]-2H-indazole-3-carboxamide,

Cpd 231 - N-(4-fluoro-1-hydroxy-4-methylpentan-2-yl)-2-methyl-5-[(pyridin-2-yl)methoxy]-2H-indazole-3-carboxamide;

Cpd 232 - N-(1-hydroxy-2-methyl-3-oxobutan-2-yl)-2-methyl-5-[(pyridin-2-yl)methoxy]-2H-indazole-3-carboxamide,

Cpd 233 - 4,4-difluoro-2-(hydroxymethyl)-2-({2-methyl-5-[(pyridin-2-yl)methoxy]-2H-indazol-3-yl}formamido)butanamide;

Cpd 234 - 4-fluoro-2-(hydroxymethyl)-2-({2-methyl-5-[(pyridin-2-yl)methoxy]-2H-indazol-3-yl}formamido)butanamide,

Cpd 235 - N-[2,2-difluoro-1-(hydroxymethyl)cyclopropyl]-2-methyl-5-[(pyridin-2-yl)methoxy]-2H-indazole-3-carboxamide,

Cpd 236 - N-[trans-2-(difluoromethyl)-1-(hydroxymethyl)cyclopropyl]-2-methyl-5-[(pyridin-2-yl)methoxy]-2H-indazole-3-carboxamide,

Cpd 237 - N-[cis-2-(difluoromethyl)-1-(hydroxymethyl)cyclopropyl]-2-methyl-5-[(pyridin-2-yl)methoxy]-2H-indazole-3-carboxamide,

Cpd 238 - N-[1-(1-cyclopropyl-1H-imidazol-2-yl)-2-hydroxyethyl]-2-methyl-5-[(pyridin-2-yl)methoxy]-2H-indazole-3-carboxamide,

Cpd 239 - N-[1-hydroxy-2-(1-methyl-1H-pyrazol-3-yl)propan-2-yl]-2-methyl-5-[(pyridin-2-yl)methoxy]-2H-indazole-3-carboxamide,

Cpd 240 - 4-hydroxy-3-({2-methyl-5-[(pyridin-2-yl)methoxy]-2H-indazol-3-yl}formamido)butanamide,

Cpd 241 - N-[2-hydroxy-1-(oxan-4-yl)ethyl]-2-methyl-5-[(pyridin-2-yl)methoxy]-2H-indazole-3-carboxamide,

Cpd 242 - N-{1-hydroxy-3-[2-(trifluoromethyl)-1H-imidazol-1-yl]propan-2-yl}-2-methyl-5-[(pyridin-2-yl)methoxy]-2H-indazole-3-carboxamide,

Cpd 243 - N-[1-hydroxy-3-(pyrimidin-2-yl)propan-2-yl]-2-methyl-5-[(pyridin-2-yl)methoxy]-2H-indazole-3-carboxamide,

Cpd 244 - N-[3,3-difluoro-1-hydroxy-3-((pyridin-2-yl))propan-2-yl]-2-methyl-5-[(pyridin-2-yl)methoxy]-2H-indazole-3-carboxamide;

Cpd 245 - 2-methyl-5-[(pyridin-2-yl)methoxy]-N-(4,4,4-trifluoro-2-hydroxybutyl)-2H-indazole-3-carboxamide,

Cpd 246 - 2-methyl-5-[(pyridin-2-yl)methoxy]-N-[trans-4-(trifluoromethyl)pyrrolidin-3-yl]-2H-indazole-3-carboxamide,

Cpd 247 - 2-methyl-5-[(pyridin-2-yl)methoxy]-N-[cis-4-(trifluoromethyl)pyrrolidin-3-yl]-2H-indazole-3-carboxamide,

Cpd 248 - N-[3-(2,2-difluoroethyl)piperidin-3-yl]-2-methyl-5-[(pyridin-2-yl)methoxy]-2H-indazole-3-carboxamide,

Cpd 249 - N-(2-difluoromethyl-1-hydroxypropan-3-yl)-2-methyl-5-[(pyridin-2-yl)methoxy]-2H-indazole-3-carboxamide;

Cpd 250 - 2-methyl-5-[(pyridin-2-yl)methoxy]-N-(3,3-difluoro-1-hydroxy-2-methylpropan-2-yl)-2H-indazole-3-carboxamide;

Cpd 251 - N-[2-hydroxy-1-(1-methyl-1H-pyrazol-3-yl)ethyl]-2-methyl-5-[(pyridin-2-yl)methoxy]-2H-indazole-3-carboxamide,

Cpd 252 - N-[1-hydroxy-3-(pyridin-2-yl)propan-2-yl]-2-methyl-5-[(pyridin-2-yl)methoxy]-2H-indazole-3-carboxamide,

Cpd 253 - N-[3-(hydroxymethyl)-2-oxopyrrolidin-3-yl]-2-methyl-5-[(pyridin-2-yl)methoxy]-2H-indazole-3-carboxamide,

Cpd 254 - 2-methyl-5-[(pyridin-2-yl)methoxy]-N-(1,1,1-trifluoro-3-hydroxypropan-2-yl)-2H-indazole-3-carboxamide,

Cpd 255 - 2-methyl-5-[(pyridin-2-yl)methoxy]-N-(4,4,4-trifluoro-1-hydroxy-2-methylbutan-2-yl)-2H-indazole-3-carboxamide,

Cpd 256 - 9-[(2-fluorophenyl)methoxy]-1H,2H,3H,4H-pyrazino[1,2-b]indazol-1-one,

Cpd 257 - 9-(benzyloxy)-1H,2H,3H,4H-pyrazino[1,2-b]indazol-1-one,

Cpd 258 - N-(1-hydroxy-3-methoxy-2-methylpropan-2-yl)-2-methyl-5-[(pyridin-2-yl)methoxy]-2H-indazole-3-carboxamide,

Cpd 259 - N-(1,3-dihydroxypropan-2-yl)-2-methyl-5-[(pyridin-2-yl)methoxy]-2H-indazole-3-carboxamide,

Cpd 260 - 2-(1,3-dihydroxypropan-2-yl)-9-[(2-fluorophenyl)methoxy]-1H,2H,3H,4H-pyrazino[1,2-b]indazol-1-one,

Cpd 261 - 9-[(2-fluorophenyl)methoxy]-2-(2-hydroxyethyl)-1H,2H,3H,4H-pyrazino[1,2-b]indazol-1-one,

Cpd 262 - N-(1,3-dihydroxypropan-2-yl)-5-[(2-fluorophenyl)methoxy]-2-methyl-2H-indazole-3-carboxamide,

[0111] The indazole derivatives according to the invention is for use in the treatment of pain which is preferably selected from nociceptive pain, inflammatory pain, and neuropathic pain. More preferably, the pain is post-operative pain. The indazole derivatives according to the invention are also for use in the treatment of epilepsy.

[0112] In some embodiments, the indazole derivatives are selected from the group consisting of compounds 1 – 262 shown in table 1 below, including stereoisomers and pharmaceutically acceptable salts thereof:

Table 1: Exemplary indazole derivatives

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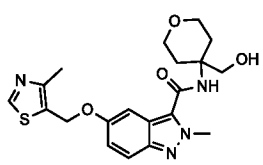
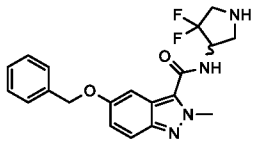
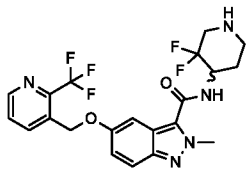
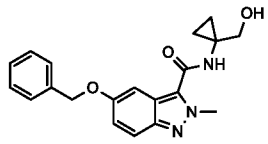
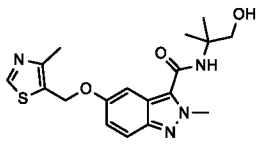
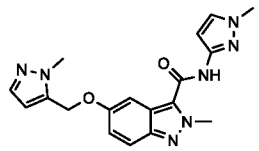
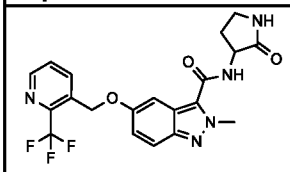
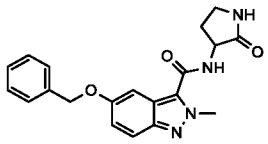
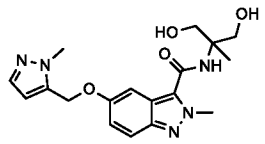
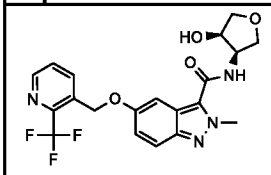
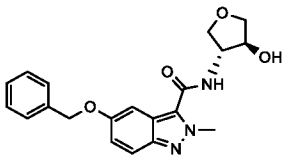
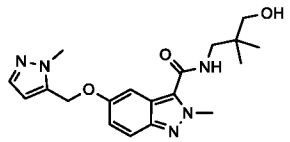
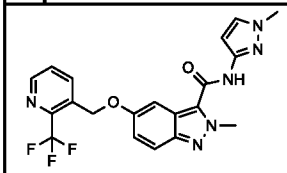
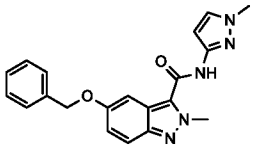
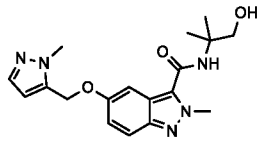
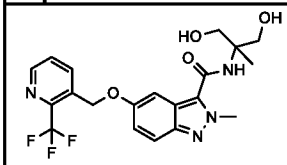
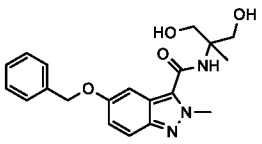
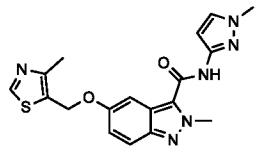
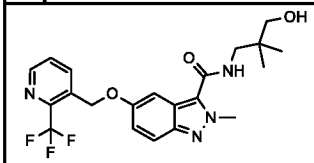
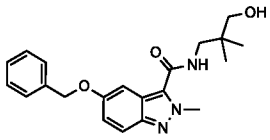
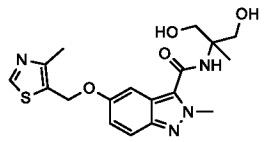
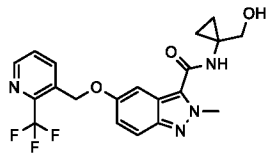
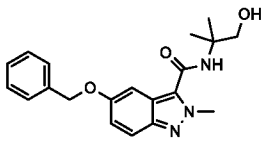
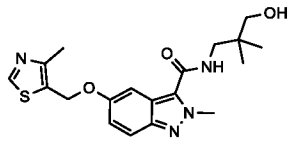
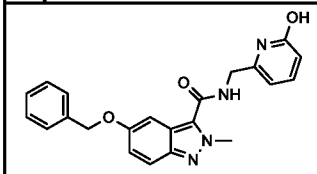
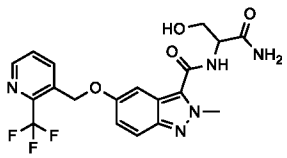
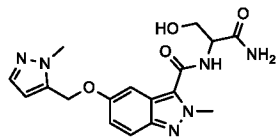
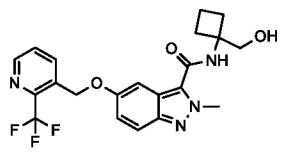
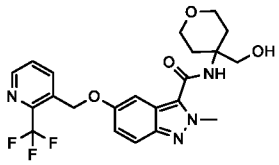
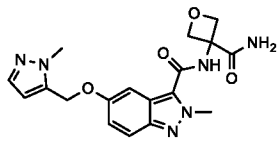
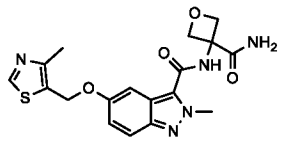
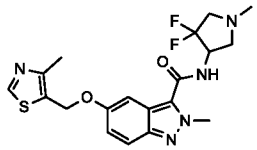
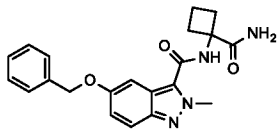
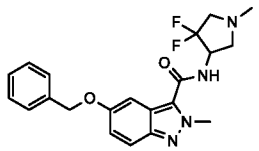
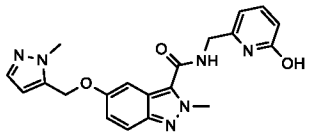
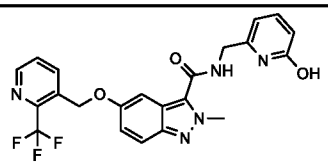
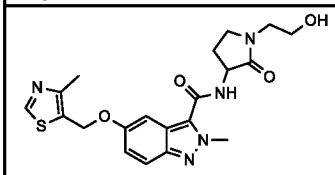
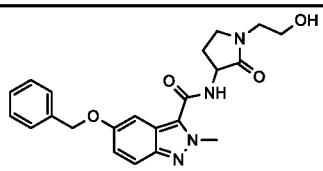
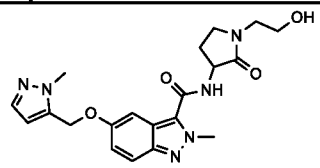
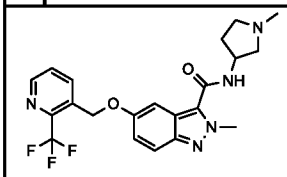
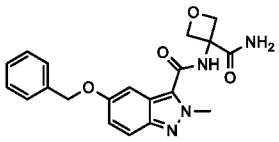
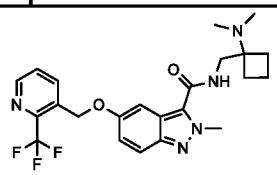
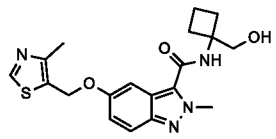
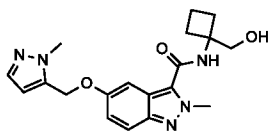
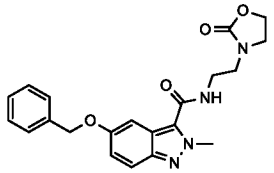
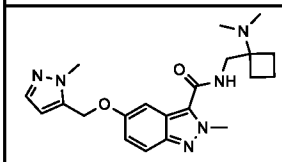
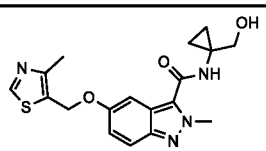
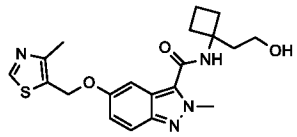
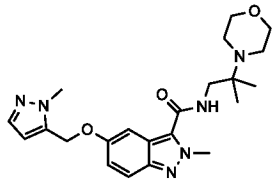
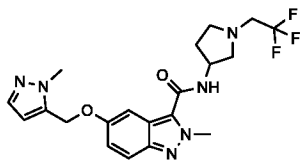
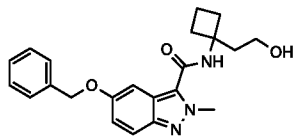
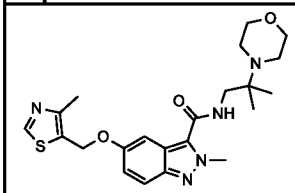
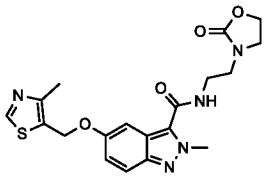
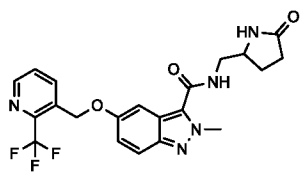
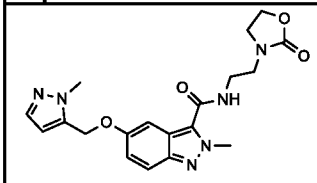
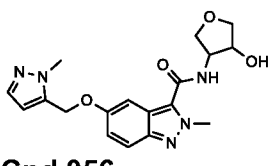
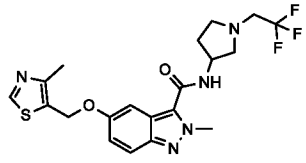
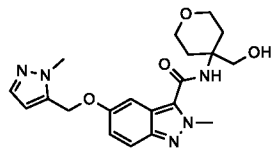
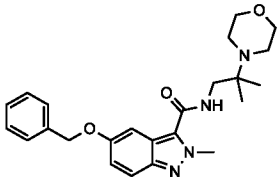
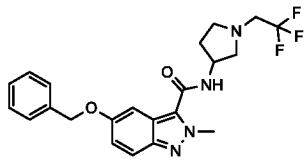
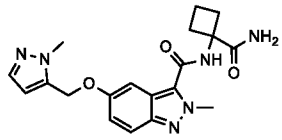
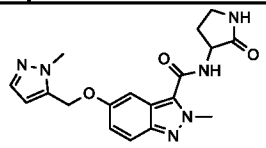
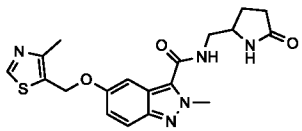
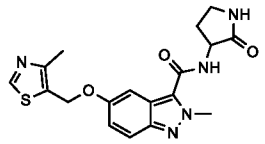
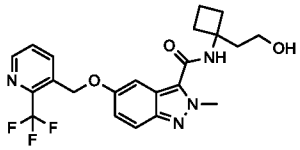
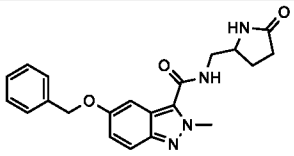
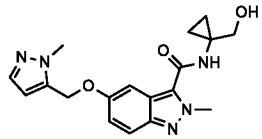
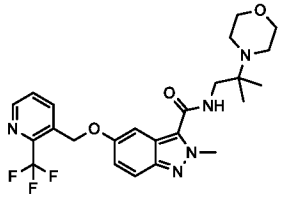
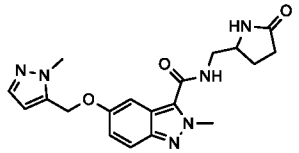
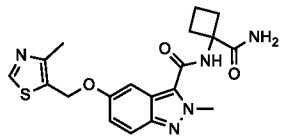
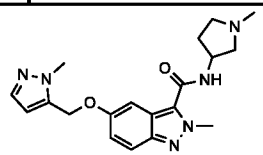
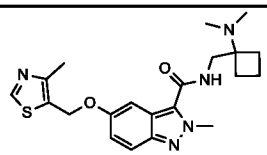
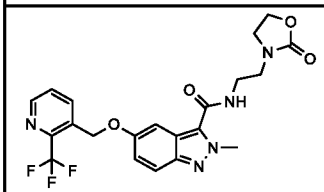
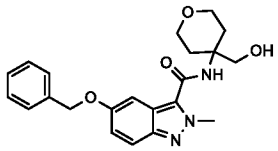
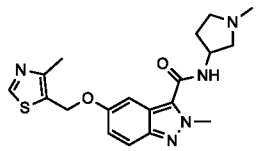
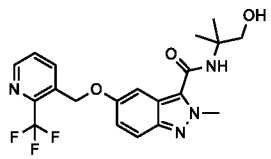
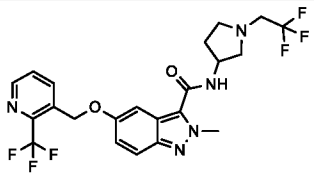
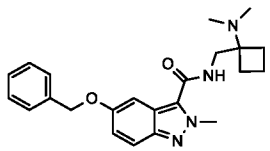
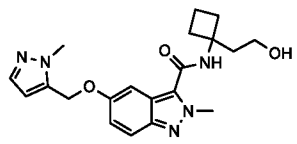
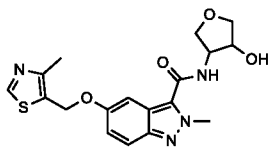
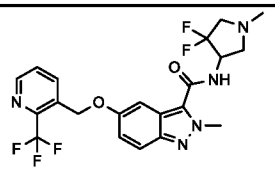
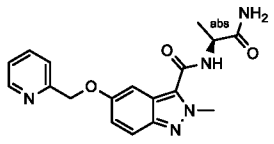
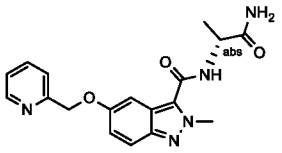
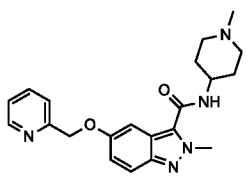
 **Cpd 001**	 **Cpd 002**	 **Cpd 003**

 Cpd 004	 Cpd 005	 Cpd 006
 Cpd 007	 Cpd 008	 Cpd 009
 Cpd 010	 Cpd 011	 Cpd 012
 Cpd 013	 Cpd 014	 Cpd 015
 Cpd 016	 Cpd 017	 Cpd 018
 Cpd 019	 Cpd 020	 Cpd 021
 Cpd 022	 Cpd 023	 Cpd 024
 Cpd 025	 Cpd 026	 Cpd 027
 Cpd 028	 Cpd 029	 Cpd 030

 Cpd 031	 Cpd 032	 Cpd 033
 Cpd 034	 Cpd 035	 Cpd 036
 Cpd 037	 Cpd 038	 Cpd 039
 Cpd 040	 Cpd 041	 Cpd 042
 Cpd 043	 Cpd 044	 Cpd 045
 Cpd 046	 Cpd 047	 Cpd 048
 Cpd 049	 Cpd 050	 Cpd 051
 Cpd 052	 Cpd 053	 Cpd 054
 Cpd 055	 Cpd 056	 Cpd 057

 Cpd 058	 Cpd 059	 Cpd 060
 Cpd 061	 Cpd 062	 Cpd 063
 Cpd 064	 Cpd 065	 Cpd 066
 Cpd 067	 Cpd 068	 Cpd 069
 Cpd 070	 Cpd 071	 Cpd 072
 Cpd 073	 Cpd 074	 Cpd 075
 Cpd 076	 Cpd 077	 Cpd 078
 Cpd 079	 Cpd 080	 Cpd 081
 Cpd 082	 Cpd 083	

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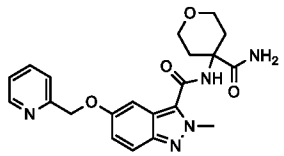
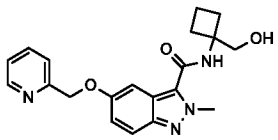
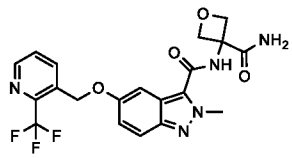
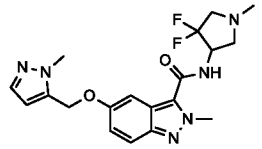
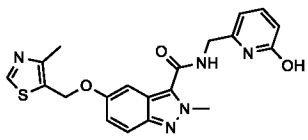
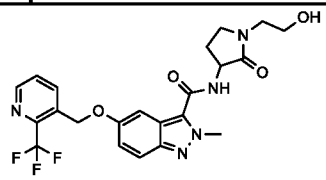
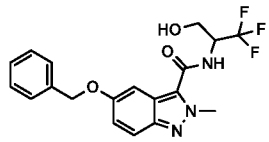
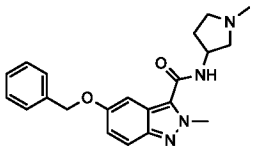
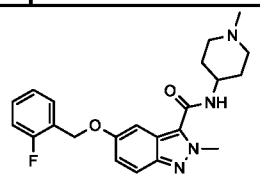
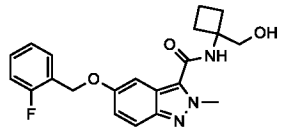
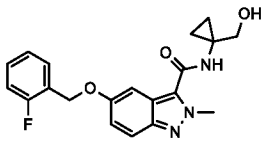
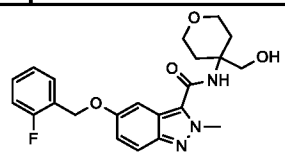
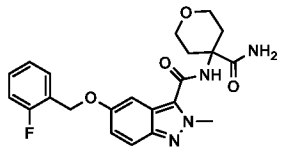
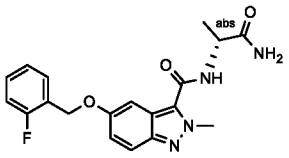
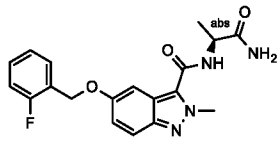
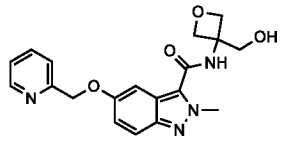
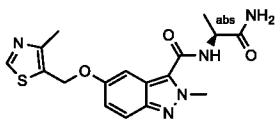
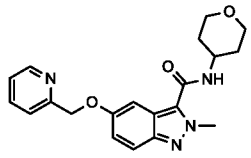
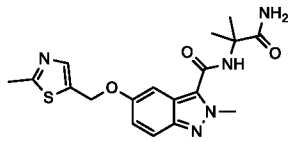
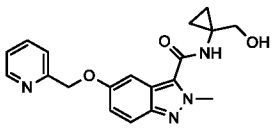
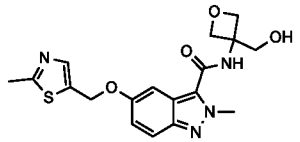
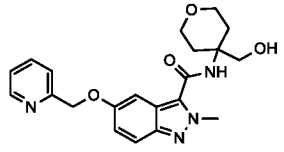
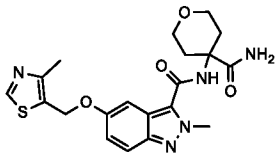
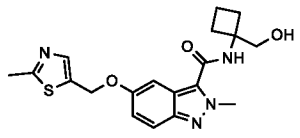
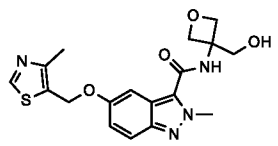
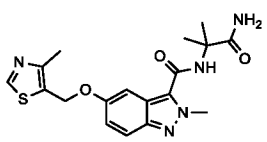
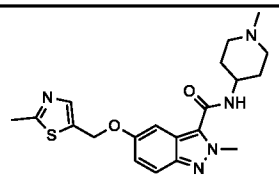
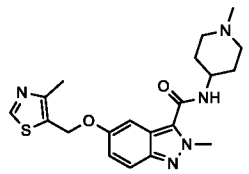
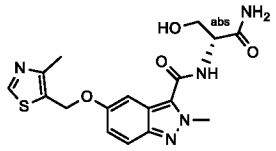
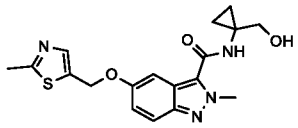
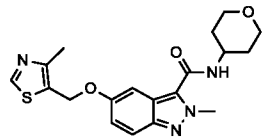
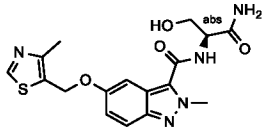
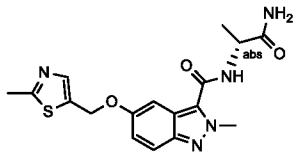
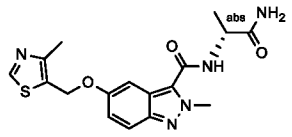
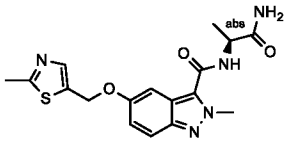
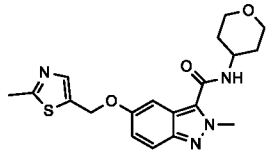
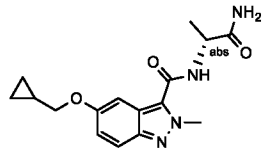
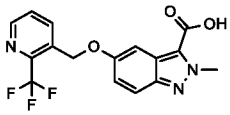
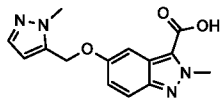
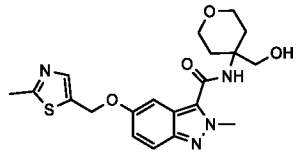
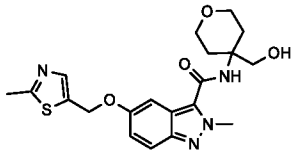
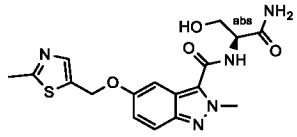
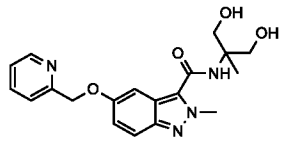
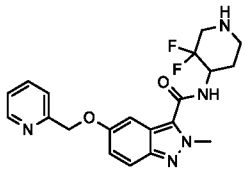
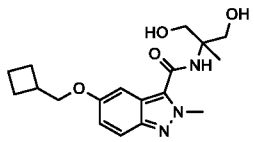
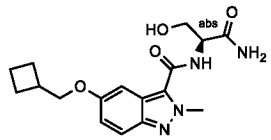
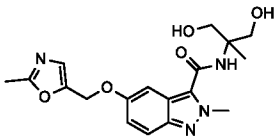
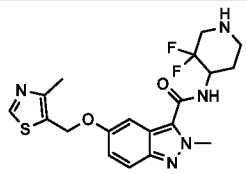
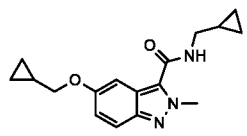
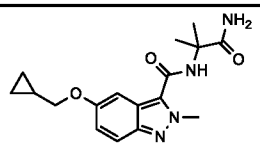
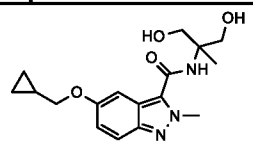
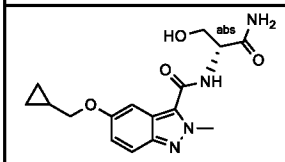
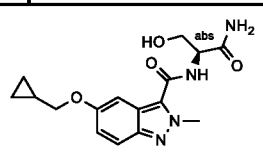
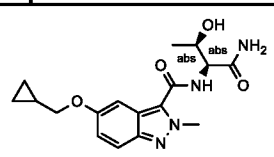
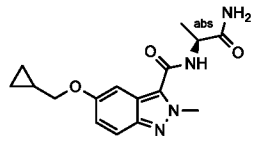
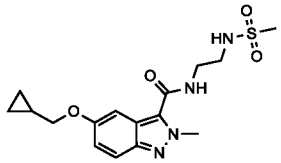
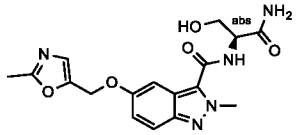
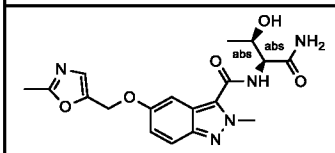
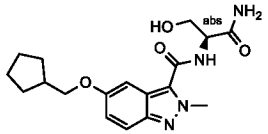
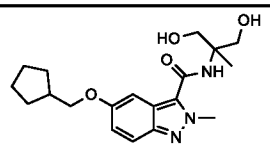
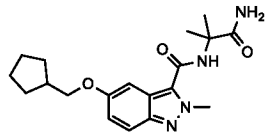
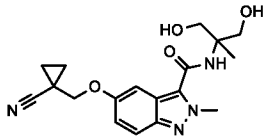
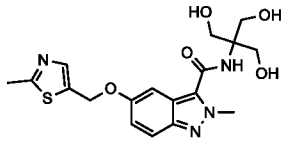
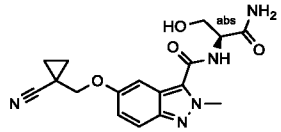
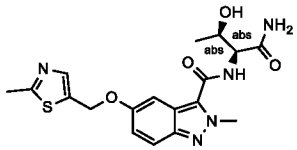
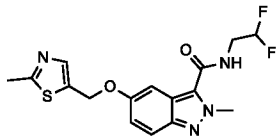
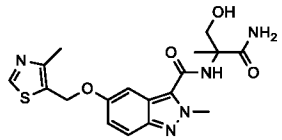
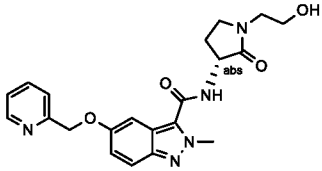
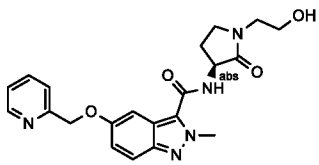
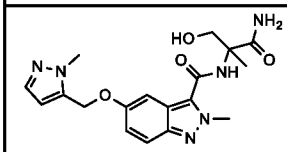
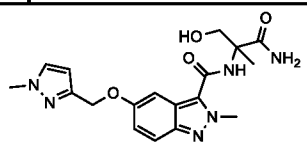
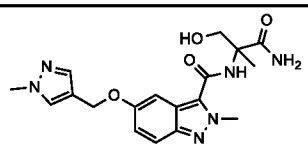
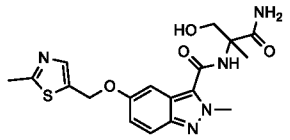
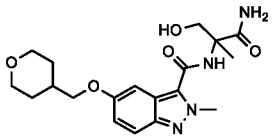
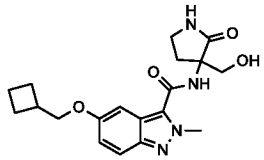
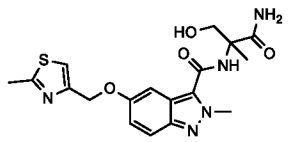
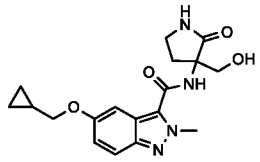
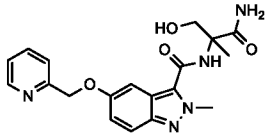
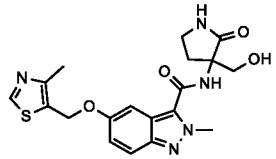
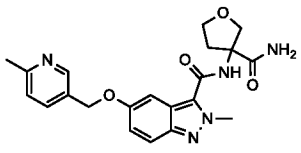
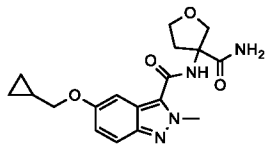
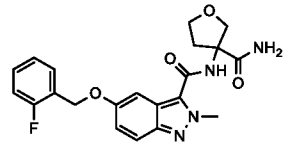
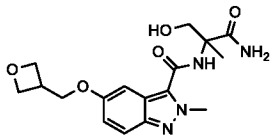
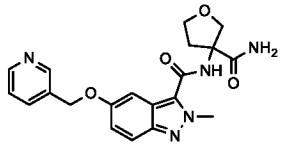
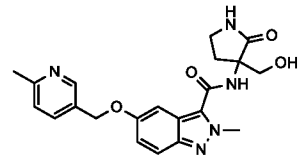
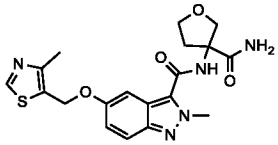
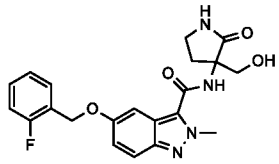
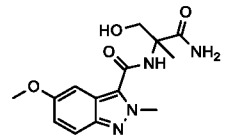
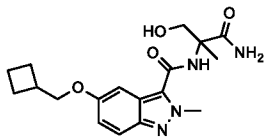
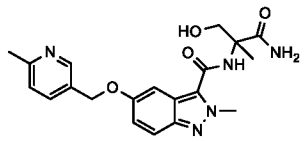
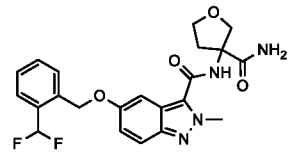
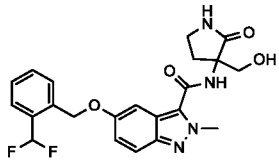
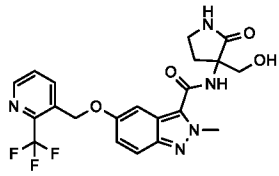
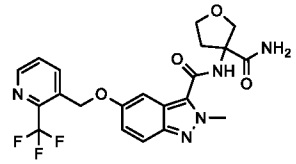
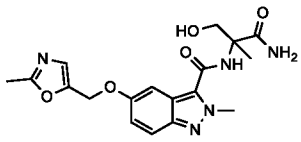
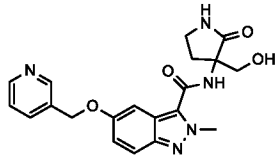
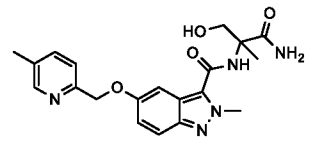
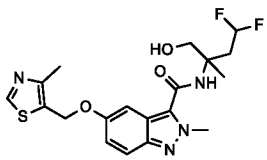
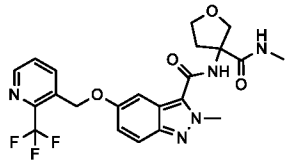
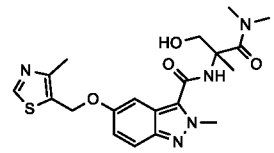
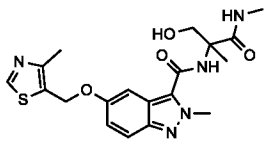
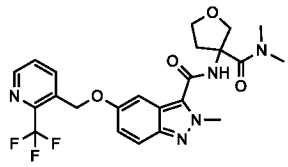
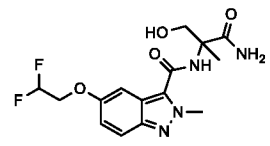
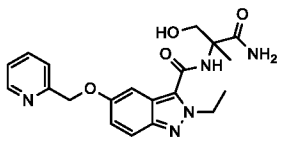
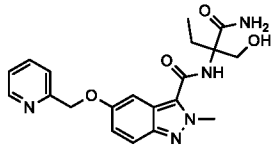
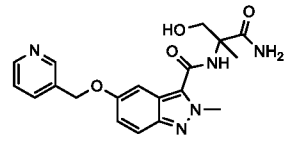
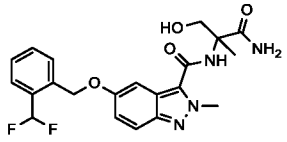
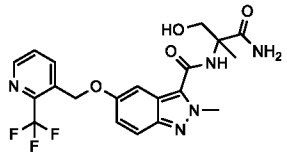
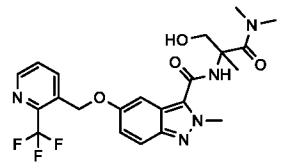
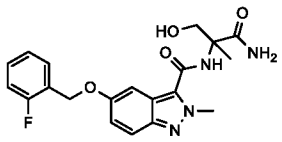
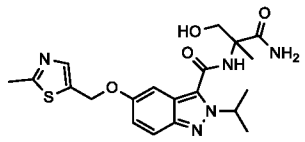
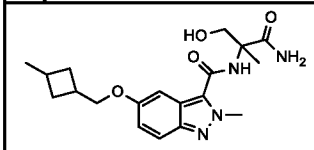
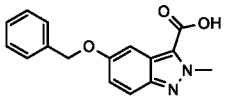
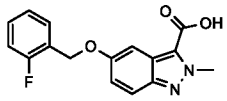
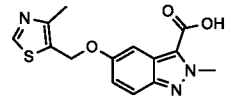
 Cpd 085	 Cpd 086	 Cpd 087
 Cpd 088	 Cpd 089	 Cpd 090
 Cpd 091	 Cpd 092	 Cpd 093
 Cpd 094	 Cpd 095	 Cpd 096
 Cpd 097	 Cpd 098	 Cpd 099
 Cpd 100	 Cpd 101	 Cpd 102
 Cpd 103	 Cpd 104	 Cpd 105
 Cpd 106	 Cpd 107	 Cpd 108
 Cpd 109	 Cpd 110	 Cpd 111

 Cpd 112	 Cpd 113	 Cpd 114
 Cpd 115	 Cpd 116	 Cpd 117
 Cpd 118	 Cpd 119	 Cpd 120
 Cpd 121	 Cpd 122	 Cpd 123
 Cpd 124	 Cpd 125	 Cpd 126
 Cpd 127	 Cpd 128	 Cpd 129
 Cpd 130	 Cpd 131	 Cpd 132
 Cpd 133	 Cpd 134	 Cpd 135
 Cpd 136	 Cpd 137	 Cpd 138

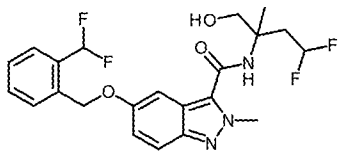
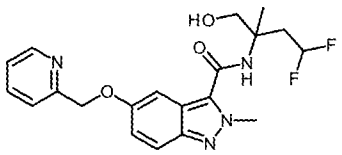
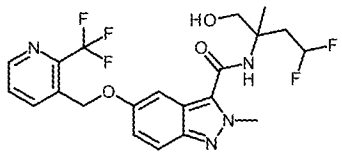
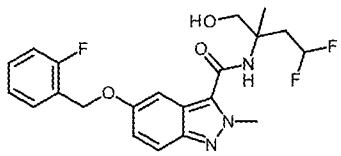
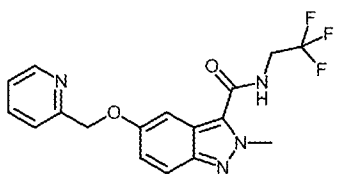
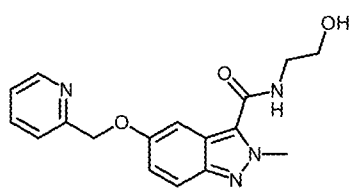
 Cpd 139	 Cpd 140	 Cpd 141
 Cpd 142	 Cpd 143	 Cpd 144
 Cpd 145	 Cpd 146	 Cpd 147
 Cpd 148	 Cpd 149	 Cpd 150
 Cpd 151	 Cpd 152	 Cpd 153
 Cpd 154	 Cpd 155	 Cpd 156
 Cpd 157	 Cpd 158	 Cpd 159
 Cpd 160	 Cpd 161	 Cpd 162
 Cpd 163	 Cpd 164	 Cpd 165

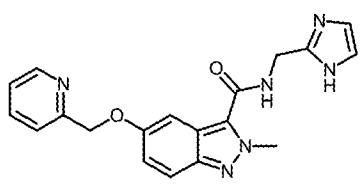
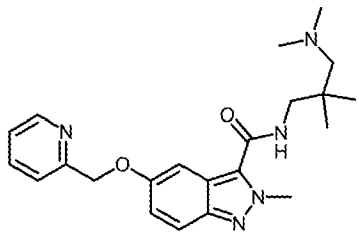
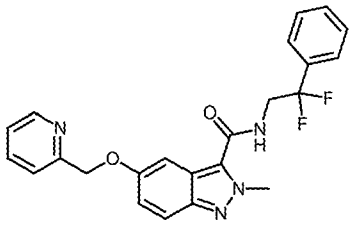
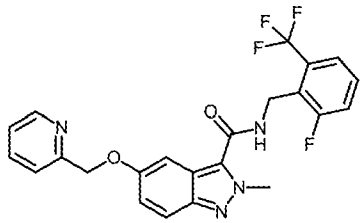
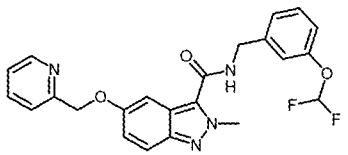
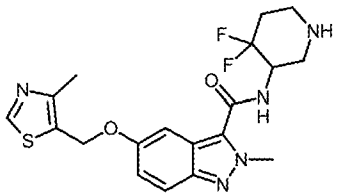
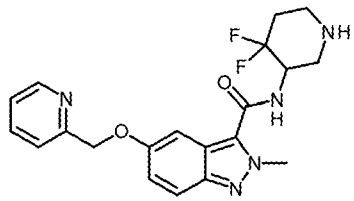
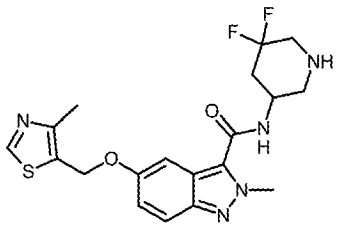
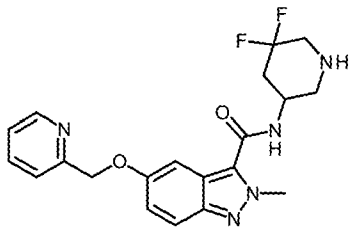
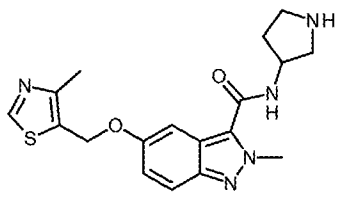
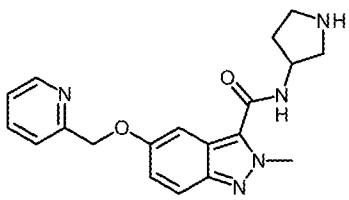
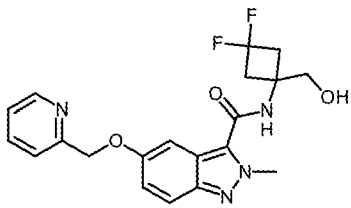
 Cpd 166	 Cpd 167	 Cpd 168
 Cpd 169	 Cpd 170	 Cpd 171
 Cpd 172	 Cpd 173	 Cpd 174
 Cpd 175	 Cpd 176	 Cpd 177
 Cpd 178	 Cpd 179	 Cpd 180
 Cpd 181	 Cpd 182	 Cpd 183
 Cpd 184	 Cpd 185	 Cpd 186
 Cpd 187	 Cpd 188	 Cpd 189
 Cpd 190	 Cpd 191	 Cpd 192

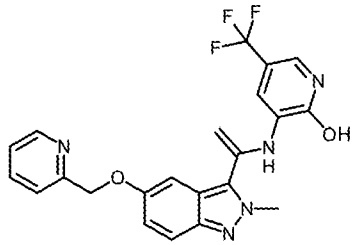
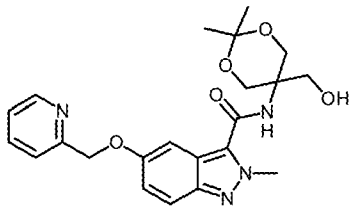
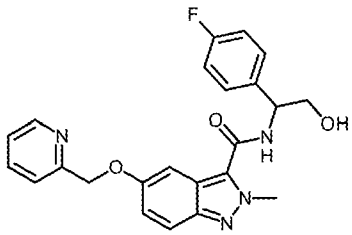
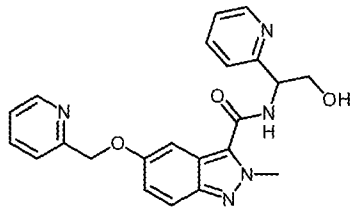
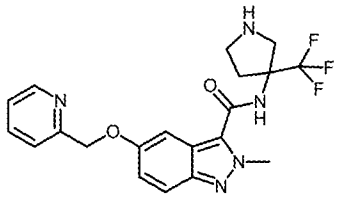
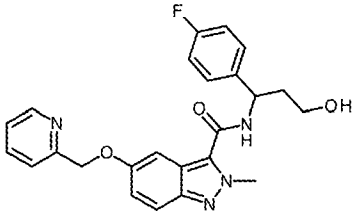
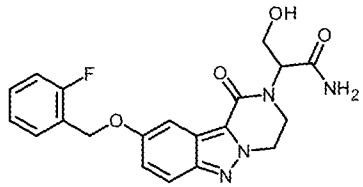
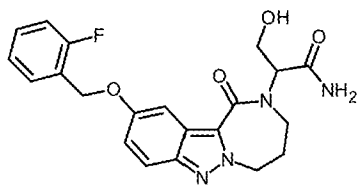
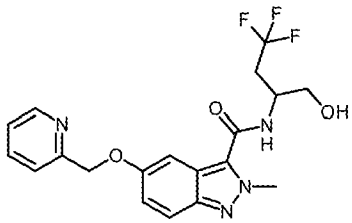
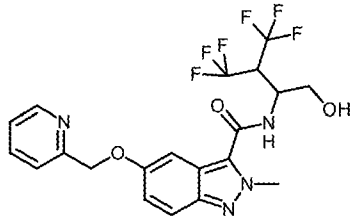
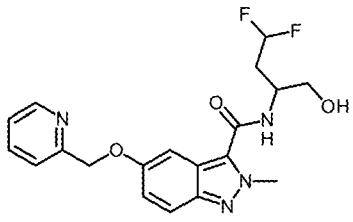
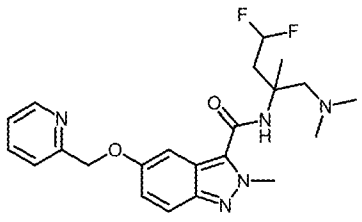
 Cpd 193	 Cpd 194	 Cpd 195
 Cpd 196	 Cpd 197	 Cpd 198
 Cpd 199		

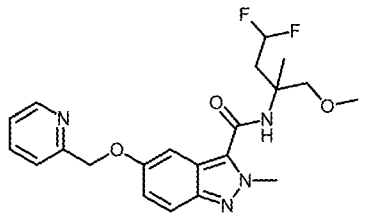
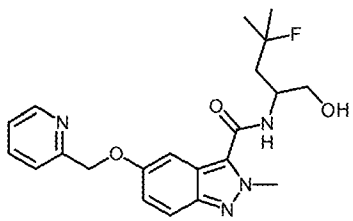
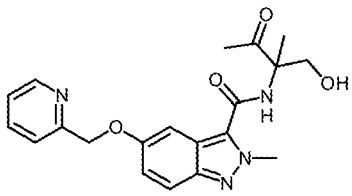
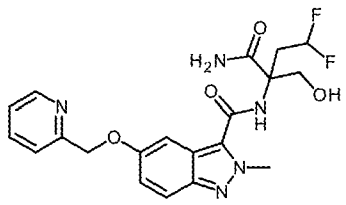
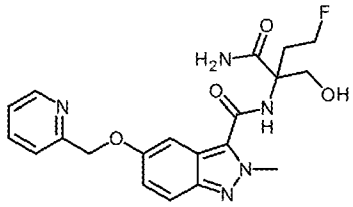
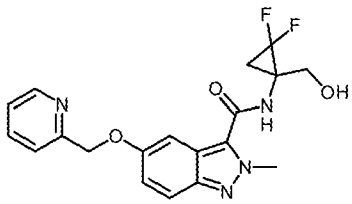
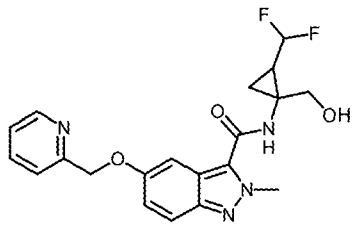
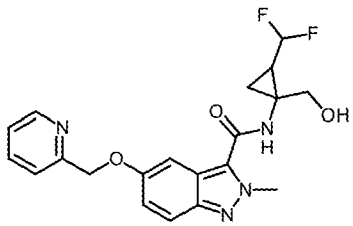
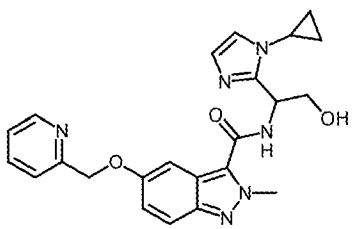
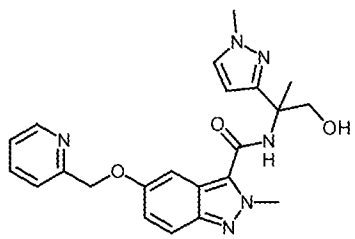
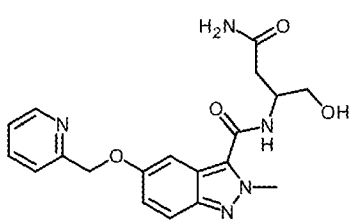
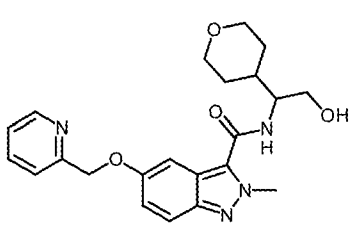
[0113] In some embodiments, the indazole derivatives are selected from the group consisting of compounds 200 – 262 shown in table 2 below, including stereoisomers and pharmaceutically acceptable salts thereof:

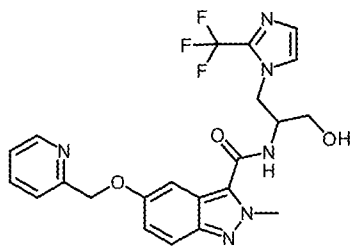
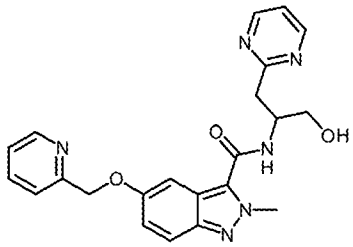
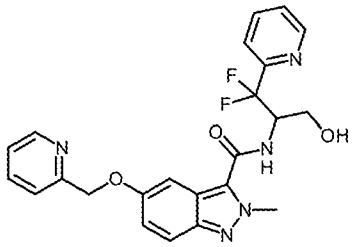
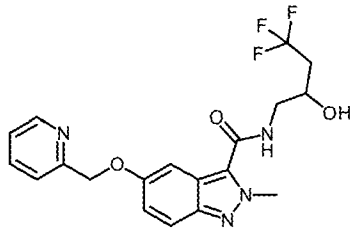
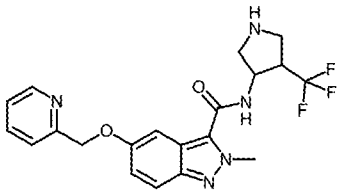
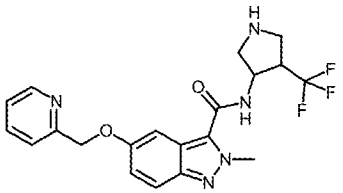
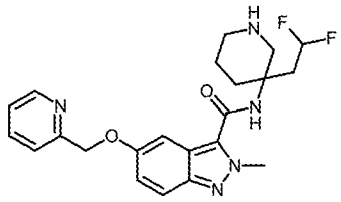
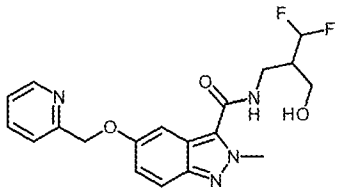
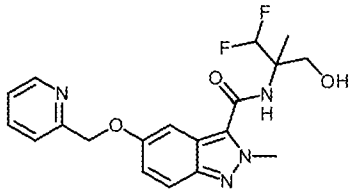
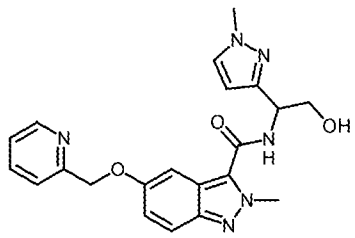
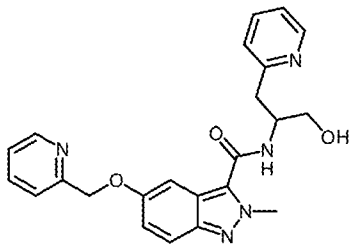
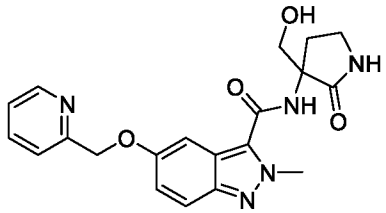
Table 2: Exemplary Indazole derivatives

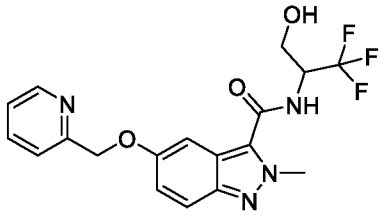
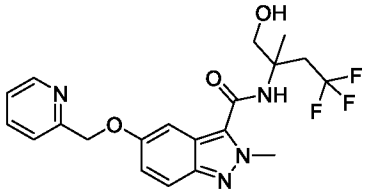
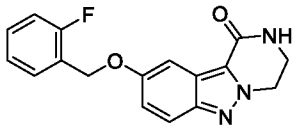
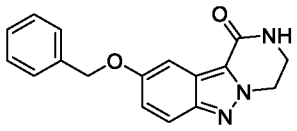
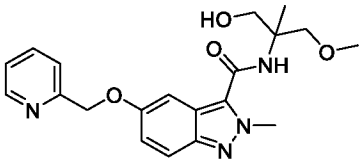
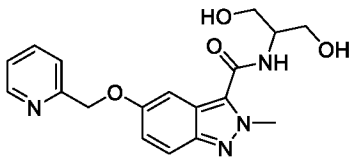
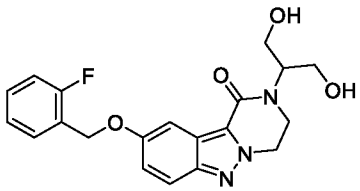
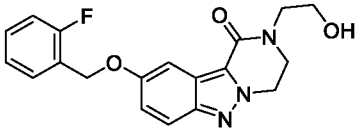
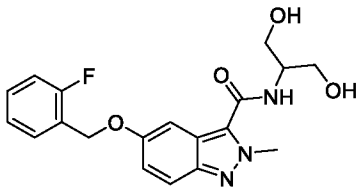
Structure and **Compound CODE**	Structure and **Compound CODE**	Structure and **Compound CODE**
 **Cmd 200**	 **Cpd 201**	 **Cpd 202**
 **Cpd 203**	 **Cpd 204**	 **Cpd 205**

 Cpd 206	 Cpd 207	 Cpd 208
 Cpd 209	 Cpd 210	 Cpd 211
 Cpd 212	 Cpd 213	 Cpd 214
 Cpd 215	 Cpd 216	 Cpd 217

 Cpd 218	 Cpd 219	 Cpd 220
 Cpd 221	 Cpd 222	 Cpd 223
 Cpd 224	 Cpd 225	 Cpd 226
 Cpd 227	 Cpd 228	 Cpd 229

 Cpd 230	 Cpd 231	 Cpd 232
 Cpd 233	 Cpd 234	 Cpd 235
 Cpd 236 (trans isomer)	 Cpd 237 (cis isomer)	 Cpd 238
 Cpd 239	 Cpd 240	 Cpd 241

 Cpd 242	 Cpd 243	 Cpd 244
 Cpd 245	 Cpd 246 (trans isomer)	 Cpd 247 (cis isomer)
 Cpd 248	 Cpd 249	 Cpd 250
 Cpd 251	 Cpd 252	 Cpd 253

 Cpd 254	 Cpd 255	 Cpd 256
 Cpd 257	 Cpd 258	 Cpd 259
 Cpd 260	 Cpd 261	 Cpd 262

[0114] All definitions, embodiments and meanings of **Q**, **T**, **U**, **V**, R^1, R^2, R^3, R^4, R^5, $R^{5'}$, R^6, R^7, and R^8 including the disclosed substituents also analogously apply the indazole derivatives according to the invention, including but not limited to (a-1), (a-2), (a-3), (b-1), (b-2), and (b-3), which are not necessarily restricted for use in the treatment of pain. Thus, this aspect of the invention relates to the indazole derivatives as such, compositions comprising the indazole derivatives, medicaments comprising the indazole derivatives, and the indazole derivatives for use in the prevention and/or treatment of TRPM3 mediated disorders such as pain and/or inflammatory hypersensitivity and/or epilepsy; and/or for counteracting pain and/or inflammatory hypersensitivity and/or epilepsy. Preferably, the pain is selected from nociceptive pain, inflammatory pain, and neuropathic pain. More preferably, the pain is post-operative pain.

[0115] In some embodiments of the invention, the indazole derivative is selected from the group consisting of cpd 001 to cpd 199 as mentioned above and the physiologically acceptable salts thereof.

[0116] In some embodiments of the invention, the indazole derivative is selected from the group consisting of cpd 200 to cpd 262 as mentioned above and the physiologically acceptable salts thereof.

[0117] Another aspect of the invention relates to a pharmaceutical composition or a medicament comprising a compound according to the invention as described above.

[0118] Reference throughout this specification to "one embodiment" or "an embodiment"

means that a particular feature, structure or characteristic described in connection with the embodiment is included in at least one embodiment of the invention. Thus, appearances of the phrases "in one embodiment" or "in an embodiment" in various places throughout this specification are not necessarily all referring to the same embodiment, but may. Furthermore, the particular features, structures or characteristics may be combined in any suitable manner, as would be apparent to one of ordinary skill in the art from this disclosure, in one or more embodiments. Also, embodiments described for an aspect of the invention may be used for another aspect of the invention and can be combined. Where an indefinite or definite article is used when referring to a singular noun e.g., "a" or "an", "the", this includes a plural of that noun unless something else is specifically stated.

[0119] Similarly, it should be appreciated that in the description of exemplary embodiments of the invention, various features of the invention are sometimes grouped together in a single embodiment, figure, or description thereof for the purpose of streamlining the disclosure and aiding in the understanding of one or more of the various inventive aspects.

[0120] In each of the following definitions, the number of carbon atoms represents the maximum number of carbon atoms generally optimally present in the substituent or linker; it is understood that where otherwise indicated in the present application, the number of carbon atoms represents the optimal maximum number of carbon atoms for that particular substituent or linker.

[0121] The term “leaving group” or “LG” as used herein means a chemical group which is susceptible to be displaced by a nucleophile or cleaved off or hydrolyzed in basic or acidic conditions. In a particular embodiment, a leaving group is selected from a halogen atom (e.g., Cl, Br, I) or a sulfonate (e.g., mesylate, tosylate, triflate).

[0122] The term "protecting group" refers to a moiety of a compound that masks or alters the properties of a functional group or the properties of the compound as a whole. The chemical substructure of a protecting group varies widely. One function of a protecting group is to serve as intermediates in the synthesis of the parental drug substance. Chemical protecting groups and strategies for protection/deprotection are well known in the art. See: "Protective Groups in Organic Chemistry", Theodora W. Greene (John Wiley & Sons, Inc., New York, 1991. Protecting groups are often utilized to mask the reactivity of certain functional groups, to assist in the efficiency of desired chemical reactions, e.g., making and breaking chemical bonds in an ordered and planned fashion. Protection of functional groups of a compound alters other physical properties besides the reactivity of the protected functional group, such as the polarity, lipophilicity (hydrophobicity), and other properties which can be measured by common analytical tools. Chemically protected intermediates may themselves be biologically active or inactive.

[0123] Protected compounds may also exhibit altered, and in some cases, optimized

properties in vitro and in vivo, such as passage through cellular membranes and resistance to enzymatic degradation or sequestration. In this role, protected compounds with intended therapeutic effects may be referred to as prodrugs. Another function of a protecting group is to convert the parental drug into a prodrug, whereby the parental drug is released upon conversion of the prodrug in vivo. Because active prodrugs may be absorbed more effectively than the parental drug, prodrugs may possess greater potency in vivo than the parental drug. Protecting groups are removed either in vitro, in the instance of chemical intermediates, or in vivo, in the case of prodrugs. With chemical intermediates, it is not particularly important that the resulting products after deprotection, e.g., alcohols, be physiologically acceptable, although in general it is more desirable if the products are pharmacologically innocuous.

[0124] The term “heteroatom(s)” as used herein means an atom selected from nitrogen, which can be quaternized or present as an oxide; oxygen; and sulfur, including oxidized sulfurs including, sulfoxide and sulfone, and in some cases sulfonate. In certain instances, the compounds and/or synthetic intermediates may include heteroatoms such as boron, phosphorous, and silicon.

[0125] The term “alkyl, saturated or unsaturated” as used herein encompasses saturated alkyl as well as unsaturated alkyl such as alkenyl, alkynyl, and the like. The term “alkyl” as used herein means normal, secondary, or tertiary, linear or branched hydrocarbon with no site of unsaturation. Examples are methyl, ethyl, 1-propyl (n-propyl), 2-propyl (iPr), 1-butyl, 2-methyl-1-propyl(i-Bu), 2-butyl (s-Bu), 2-dimethyl-2-propyl (t-Bu), 1-pentyl (n-pentyl), 2-pentyl, 3-pentyl, 2-methyl-2-butyl, 3-methyl-2-butyl, 3-methyl-1-butyl, 2-methyl-1-butyl, 1-hexyl, 2-hexyl, 3-hexyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 3-methyl-3-pentyl, 2-methyl-3-pentyl, 2,3-dimethyl-2-butyl, and 3,3-dimethyl-2-butyl. The term “alkenyl” as used herein means normal, secondary or tertiary, linear or branched hydrocarbon with at least one site (usually 1 to 3, preferably 1) of unsaturation, namely a carbon-carbon, sp2 double bond. Examples include, but are not limited to: ethylene or vinyl (-CH=CH_2), allyl (-CH_2CH=CH_2), and 5-hexenyl (-$CH_2CH_2CH_2CH_2$CH=CH_2). The double bond may be in the cis or trans configuration. The term “alkynyl” as used herein means normal, secondary, tertiary, linear or branched hydrocarbon with at least one site (usually 1 to 3, preferably 1) of unsaturation, namely a carbon-carbon, sp triple bond. Examples include, but are not limited to: ethynyl (-C≡CH), and 1-propynyl (propargyl, -CH_2C≡CH).

[0126] The term “alkylene, saturated or unsaturated” as used herein encompasses saturated alkylene as well as unsaturated alkylene such as alkenylene, alkynylene, alkenynylene and the like. The term "alkylene" as used herein means saturated, linear or branched chain hydrocarbon radical having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkane. Typical alkylene radicals include, but are not limited to: methylene (-CH_2-), 1,2-ethyl (-CH_2CH_2-), 1,3-

propyl (-$CH_2CH_2CH_2$-), 1,4-butyl (-$CH_2CH_2CH_2CH_2$-), and the like. The term "alkenylene" as used herein means linear or branched chain hydrocarbon radical with at least one site (usually 1 to 3, preferably 1) of unsaturation, namely a carbon-carbon, sp2 double bond, and having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkene. The term "alkynylene" as used herein means linear or branched chain hydrocarbon radical with at least one site (usually 1 to 3, preferably 1) of unsaturation, namely a carbon-carbon, sp triple bond, and having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkyne.

[0127] The term “heteroalkyl, saturated or unsaturated” as used herein encompasses saturated heteroalkyl as well as unsaturated heteroalkyl such as heteroalkenyl, heteroalkynyl, heteroalkenynyl and the like. The term “heteroalkyl” as used herein means linear or branched chain alkyl wherein one or more carbon atoms (usually 1, 2 or 3) are replaced by a heteroatom, i.e., an oxygen, nitrogen or sulfur atom, with the proviso that said chain may not contain two adjacent O atoms or two adjacent S atoms. This means that one or more -CH_3 of said alkyl can be replaced by -NH_2 and/or that one or more -CH_2- of said alkyl can be replaced by -NH-, -O- or -S-. The S atoms in said chains may be optionally oxidized with one or two oxygen atoms, to afford sulfoxides and sulfones, respectively. Furthermore, the heteroalkyl groups in the indazole derivatives of the invention can contain an oxo or thio group at any carbon or heteroatom that will result in a stable compound. Exemplary heteroalkyl groups include, but are not limited to, alcohols, alkyl ethers (such as for example -methoxy, -ethoxy, -butoxy…), primary, secondary, and tertiary alkyl amines, amides, ketones, esters, alkyl sulfides, and alkyl sulfones. The term “heteroalkenyl” means linear or branched chain alkenyl wherein one or more carbon atoms (usually 1, 2 or 3) are replaced by an oxygen, nitrogen or sulfur atom, with the proviso that said chain may not contain two adjacent O atoms or two adjacent S atoms. The term heteroalkenyl thus comprises imines, -O-alkenyl, -NH-alkenyl, -N(alkenyl)$_2$, -N(alkyl)(alkenyl), and -S-alkenyl. The term “heteroalkynyl” as used herein means linear or branched chain alkynyl wherein one or more carbon atoms (usually 1, 2 or 3) are replaced by an oxygen, nitrogen or sulfur atom, with the proviso that said chain may not contain two adjacent O atoms or two adjacent S atoms. The term heteroalkynyl thus comprises -cyano, -O-alkynyl, -NH-alkynyl, -N(alkynyl)$_2$, -N(alkyl)(alkynyl), -N(alkenyl)(alkynyl), and -S-alkynyl.

[0128] The term “heteroalkylene, saturated or unsaturated” as used herein encompasses saturated heteroalkylene as well as unsaturated heteroalkylene such as heteroalkenylene, heteroalkynylene, heteroalkenynylene and the like. The term “heteroalkylene” as used herein means linear or branched chain alkylene wherein one or more carbon atoms (usually 1, 2 or 3) are replaced by a heteroatom, i.e., an oxygen, nitrogen or sulfur atom, with the proviso that said chain may not contain two adjacent O atoms or two adjacent S atoms. The term

"heteroalkenylene" as used herein means linear or branched chain alkenylene wherein one or more carbon atoms (usually 1, 2 or 3) are replaced by an oxygen, nitrogen or sulfur atom, with the proviso that said chain may not contain two adjacent O atoms or two adjacent S atoms. The term "heteroalkynylene" as used herein means linear or branched chain alkynylene wherein one or more carbon atoms (usually 1, 2 or 3) are replaced by an oxygen, nitrogen or sulfur atom, with the proviso that said chain may not contain two adjacent O atoms or two adjacent S atoms.

[0129] The term "cycloalkyl, saturated or unsaturated" as used herein encompasses saturated cycloalkyl as well as unsaturated cycloalkyl such as cycloalkenyl, cycloalkynyl and the like. The term "cycloalkyl" as used herein and unless otherwise stated means a saturated cyclic hydrocarbon radical, such as for instance cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, norbornyl, fenchyl, decalinyl, adamantyl and the like. The term "cycloalkenyl" as used herein means a non-aromatic cyclic hydrocarbon radical with at least one site (usually 1 to 3, preferably 1) of unsaturation, namely a carbon-carbon, sp2 double bond. Examples include, but are not limited to cyclopentenyl and cyclohexenyl. The double bond may be in the cis or trans configuration. The term "cycloalkynyl" as used herein means a non-aromatic cyclic hydrocarbon radical with at least one site (usually 1 to 3, preferably 1) of unsaturation, namely a carbon-carbon, sp triple. An example is cyclohept-1-yne. Fused systems of a cycloalkyl ring with a heterocycloalkyl ring are considered as heterocycloalkyl irrespective of the ring that is bound to the core structure. Fused systems of a cycloalkyl ring with an aryl ring are considered as aryl irrespective of the ring that is bound to the core structure. Fused systems of a cycloalkyl ring with a heteroaryl ring are considered as heteroaryl irrespective of the ring that is bound to the core structure.

[0130] The term "heterocycloalkyl, saturated or unsaturated" as used herein encompasses saturated heterocycloalkyl as well as unsaturated non-aromatic heterocycloalkyl including at least one heteroatom, i.e., an N, O, or S as ring member. The term "heterocycloalkyl" as used herein and unless otherwise stated means "cycloalkyl" wherein one or more carbon atoms (usually 1, 2 or 3) are replaced by an oxygen, nitrogen or sulfur atom, with the proviso that said chain may not contain two adjacent O atoms or two adjacent S atoms. The term "heterocycloalkenyl" as used herein and unless otherwise stated means "cycloalkenyl" wherein one or more carbon atoms (usually 1, 2 or 3) are replaced by an oxygen, nitrogen or sulfur atom, with the proviso that said chain may not contain two adjacent O atoms or two adjacent S atoms. The term "heterocycloalkynyl" as used herein and unless otherwise stated means "cycloalkynyl" wherein one or more carbon atoms (usually 1, 2 or 3) are replaced by an oxygen, nitrogen or sulfur atom, with the proviso that said chain may not contain two adjacent O atoms or two adjacent S atoms. Examples of saturated and unsaturated heterocycloalkyl include but are not limited to azepane, 1,4-oxazepane, azetane, azetidine, aziridine, azocane, diazepane,

dioxane, dioxolane, dithiane, dithiolane, imidazolidine, isothiazolidine, isoxalidine, morpholine, oxazolidine, oxepane, oxetane, oxirane, piperazine, piperidine, pyrazolidine, pyrrolidine, quinuclidine, tetrahydrofuran, tetrahydropyran, tetrahydrothiopyran, thiazolidine, thietane, thiirane, thiolane, thiomorpholine, indoline, dihydrobenzofuran, dihydrobenzothiophene, 1,1-dioxothiacyclohexane, 2-azaspiro[3.3]heptane, 2-oxaspiro[3.3]heptane, 7-azaspiro[3.5]nonane, 8-azabicyclo[3.2.1]octane, 9-azabicyclo[3.3.1]nonane, hexahydro-1H-pyrrolizine, hexahydrocyclopenta[c]pyrrole, octahydrocyclopenta[c]pyrrole, and octahydropyrrolo[1,2-a]pyrazine. Further heterocycloalkyls in the meaning of the invention are described in Paquette, Leo A. "Principles of Modern Heterocyclic Chemistry" (W.A. Benjamin, New York, 1968), particularly Chapters 1, 3, 4, 6, 7, and 9; "The Chemistry of Heterocyclic Compounds, A series of Monographs" (John Wiley & Sons, New York, 1950 to present), in particular Volumes 13, 14, 16, 19, and 28; Katritzky, Alan R., Rees, C.W. and Scriven, E. "Comprehensive Heterocyclic Chemistry" (Pergamon Press, 1996); and J. Am. Chem. Soc. (1960) 82:5566. When the heterocycloalkyl contains no nitrogen as ring member, it is typically bonded through carbon. When the heterocycloalkyl contains nitrogen as ring member, it may be bonded through nitrogen or carbon. Fused systems of heterocycloalkyl ring with a cycloalkyl ring are considered as heterocycloalkyl irrespective of the ring that is bound to the core structure. Fused systems of a heterocycloalkyl ring with an aryl ring are considered as heterocycloalkyl irrespective of the ring that is bound to the core structure. Fused systems of a heterocycloalkyl ring with a heteroaryl ring are considered as heteroaryl irrespective of the ring that is bound to the core structure.

[0131] The term "aryl" as used herein means an aromatic hydrocarbon. Typical aryl groups include, but are not limited to 1 ring, or 2 or 3 rings fused together, radicals derived from benzene, naphthalene, anthracene, biphenyl, and the like. Fused systems of an aryl ring with a cycloalkyl ring are considered as aryl irrespective of the ring that is bound to the core structure. Fused systems of an aryl ring with a heterocycloalkyl ring are considered as heterocycloalkyl irrespective of the ring that is bound to the core structure. Thus, indoline, dihydrobenzofuran, dihydrobenzothiophene and the like are considered as heterocycloalkyl according to the invention. Fused systems of an aryl ring with a heteroaryl ring are considered as heteroaryl irrespective of the ring that is bound to the core structure.

[0132] The term “heteroaryl” as used herein means an aromatic ring system including at least one heteroatom, i.e., N, O, or S as ring member of the aromatic ring system. Examples of heteroaryl include but are not limited to benzimidazole, benzisoxazole, benzoazole, benzodioxole, benzofuran, benzothiadiazole, benzothiazole, benzothiophene, carbazole, cinnoline, dibenzofuran, furane, furazane, imidazole, imidazopyridine, indazole, indole, indolizine, isobenzofuran, isoindole, isoquinoline, isothiazole, isoxazole, naphthyridine, oxadiazole, oxazole, oxindole, phthalazine, purine, pyrazine, pyrazole, pyridazine, pyridine,

pyrimidine, pyrrole, quinazoline, quinoline, quinoxaline, tetrazole, thiadiazole, thiazole, thiophene, triazine, triazole, and [1,2,4]triazolo[4,3-a]pyrimidine.

[0133] By further way of example, carbon bonded heterocyclic rings are bonded at position 2, 3, 4, 5, or 6 of a pyridine, position 3, 4, 5, or 6 of a pyridazine, position 2, 4, 5, or 6 of a pyrimidine, position 2, 3, 5, or 6 of a pyrazine, position 2, 3, 4, or 5 of a furan, tetrahydrofuran, thiophene, pyrrole or tetrahydropyrrole, position 2, 4, or 5 of an oxazole, imidazole or thiazole, position 3, 4, or 5 of an isoxazole, pyrazole, or isothiazole, position 2 or 3 of an aziridine, position 2, 3, or 4 of an azetidine, position 2, 3, 4, 5, 6, 7, or 8 of a quinoline or position 1, 3, 4, 5, 6, 7, or 8 of an isoquinoline.

[0134] Carbon bonded heterocycles include 2-pyridyl, 3-pyridyl, 4-pyridyl, 5-pyridyl, 6-pyridyl, 3-pyridazinyl, 4-pyridazinyl, 5-pyridazinyl, 6-pyridazinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl, 2-pyrazinyl, 3-pyrazinyl, 5-pyrazinyl, 6-pyrazinyl, 2-thiazolyl, 4-thiazolyl, or 5-thiazolyl. By way of example, nitrogen bonded heterocyclic rings are bonded at position 1 of an aziridine, azetidine, pyrrole, pyrrolidine, 2-pyrroline, 3-pyrroline, imidazole, imidazolidine, 2-imidazoline, 3-imidazoline, pyrazole, pyrazoline, 2-pyrazoline, 3-pyrazoline, piperidine, piperazine, indole, indoline, 1H-indazole, position 2 of an isoindole, or isoindoline, position 4 of a morpholine, and position 9 of a carbazole, or ß-carboline. Nitrogen bonded heterocycles include 1-aziridyl, 1-azetedyl, 1-pyrrolyl, 1-imidazolyl, 1-pyrazolyl, and 1-piperidinyl. Further heteroaryls in the meaning of the invention are described in Paquette, Leo A. "Principles of Modern Heterocyclic Chemistry" (W.A. Benjamin, New York, 1968), particularly Chapters 1, 3, 4, 6, 7, and 9; "The Chemistry of Heterocyclic Compounds, A series of Monographs" (John Wiley & Sons, New York, 1950 to present), in particular Volumes 13, 14, 16, 19, and 28; Katritzky, Alan R., Rees, C.W. and Scriven, E. "Comprehensive Heterocyclic Chemistry" (Pergamon Press, 1996); and J. Am. Chem. Soc. (1960) 82:5566.

[0135] As used herein with respect to a substituting group, and unless otherwise stated, the terms “monosubstituted”, "disubstituted", "trisubstituted", "polysubstituted" and the like means chemical structures defined herein, wherein the respective moiety is substituted with one or more substituents, meaning that one or more hydrogen atoms of said moiety are each independently replaced with a substituent. For example, -C_{1-6}-alkyl that may be polysubstituted with -F includes -CH_2F, -CHF_2, -CF_3, -CH_2CF_3, CF_2CF_3, and the like. Likewise, -C_{1-6}-alkyl that may be polysubstituted with substituents independently of one another selected from -F and -Cl includes -CH_2F, -CHF_2, -CF_3, -CH_2CF_3, CF_2CF_3, -CH_2Cl, -$CHCl_2$, -CCl_3, -CH_2CCl_3, CCl_2CCl_3, -CHClF, -$CClF_2$, -CCl_2CF_3, -CF_2CCl_3, -$CClFCCl_2F$, and the like. Any substituent designation that is found in more than one site in a compound of this invention shall be independently selected.

[0136] As used herein and unless otherwise stated, the term “solvate” includes any combination which may be formed by a derivative of this invention with a suitable inorganic

solvent (e.g., hydrates) or organic solvent, such as but not limited to alcohols, ketones, esters, ethers, nitriles and the like.

[0137] The term “subject” as used herein, refers to an animal including humans, preferably a mammal, most preferably a human, who has been the object of treatment, observation or experiment.

[0138] The term “therapeutically effective amount” as used herein, means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes alleviation or partial alleviation of the symptoms of the disease or disorder being treated.

[0139] The term “composition” as used herein is intended to encompass a product comprising the specified ingredients in the therapeutically effective amounts, as well as any product which results, directly or indirectly, from combinations of the specified ingredients in the specified amounts.

[0140] The term “antagonist” or “inhibitor” as used herein refers to a compound capable of producing, depending on the circumstance, a functional antagonism of the TRPM3 ion channel, including competitive antagonists, non-competitive antagonists, desensitizing agonists, and partial agonists. In general, “antagonists” and “inhibitors” can be understood to modulate TRPM3.

[0141] For purposes of the invention, the term “TRPM3-modulated” is used to refer to the condition of being affected by the modulation of the TRPM3 ion channel, including the state of being mediated by the TRPM3 ion channel.

[0142] The term “TRPM3 mediated disorder” as used herein refers to disorders or diseases for which the use of an antagonist or modulator of TRPM3 would prevent, treat, (partially) alleviate or improve the symptoms and consist of pain and inflammatory hypersensitivity condition and epilepsy. According to the International Association for the Study of Pain and for the purpose of the invention, pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. Preferably, the TRPM3 mediated disorder is pain which is preferably selected from nociceptive pain, inflammatory pain, and neuropathic pain. More preferably, the pain is post-operative pain. For the purpose of the invention, the term "inflammatory hypersensitivity" is used to refer to a condition that is characterized by one or more hallmarks of inflammation, including edema, erythema, hyperthermia and pain, and/or by an exaggerated physiologic or pathophysiologic response to one or more than one type of stimulation, including thermal, mechanical and/or chemical stimulation.

[0143] The indazole derivatives of the invention have been shown to be or are understood to be antagonists or modulators of TRPM3 and the invention therefore provides the compounds

as such, the compounds for use as a medicine, more specifically for use as a medicine in the prevention or treatment of TRPM3 mediated disorders in a subject with a therapeutically effective amount of a indazole derivative of the invention.

[0144] In an embodiment of the invention, the indazole derivative of the invention is the sole pharmacologically active compound to be administered for therapy. In another embodiment of the invention, the indazole derivative of the invention may be employed in combination with other therapeutic agents for the treatment or prophylaxis of TRPM3 mediated disorders. The invention therefore also relates to the use of a composition comprising:

- one or more compounds of the formulae and embodiments herein, and
- one or more further therapeutic or preventive agents that are used for the prevention or treatment of TRPM3 mediated disorders as biologically active agents in the form of a combined preparation for simultaneous, separate or sequential use.

[0145] The pharmaceutical composition or combined preparation according to this invention may contain indazole derivatives of the invention over a broad content range depending on the contemplated use and the expected effect of the preparation. Generally, the content of the indazole derivatives of the invention of the combined preparation is within the range of 0.1 to 99.9% by weight, preferably from 1 to 99% by weight, more preferably from 5 to 95% by weight.

[0146] In view of the fact that, when several active ingredients are used in combination, they do not necessarily bring out their joint therapeutic effect directly at the same time in the mammal to be treated, the corresponding composition may also be in the form of a medical kit or package containing the two ingredients in separate but adjacent repositories or compartments. In the latter context, each active ingredient may therefore be formulated in a way suitable for an administration route different from that of the other ingredient, e.g., one of them may be in the form of an oral or parenteral formulation whereas the other is in the form of an ampoule for intravenous injection or an aerosol.

[0147] Those of skill in the art will also recognize that the indazole derivatives of the invention may exist in many different protonation states, depending on, among other things, the pH of their environment. While the structural formulae provided herein depict the compounds in only one of several possible protonation states, it will be understood that these structures are illustrative only, and that the invention is not limited to any particular protonation state - any and all protonated forms of the compounds are intended to fall within the scope of the invention.

[0148] The terms "pharmaceutically acceptable salts" or “physiologically acceptable salts” as used herein means the therapeutically active non-toxic salt forms which the compounds of formulae herein are able to form. Therefore, the compounds of this invention optionally comprise salts of the compounds herein, especially pharmaceutically acceptable non-toxic salts containing, for example, Na^+, Li^+, K^+, Ca^{2+} and Mg^{2+}. Such salts may include those derived by combination of appropriate cations such as alkali and alkaline earth metal ions or

ammonium and quaternary amino ions with an acid anion moiety, typically a carboxylic acid. The indazole derivatives of the invention may bear multiple positive or negative charges. The net charge of the indazole derivatives of the invention may be either positive or negative. Any associated counter ions are typically dictated by the synthesis and/or isolation methods by which the compounds are obtained. Typical counter ions include, but are not limited to ammonium, sodium, potassium, lithium, halides, acetate, trifluoroacetate, etc., and mixtures thereof. It will be understood that the identity of any associated counter ion is not a critical feature of the invention, and that the invention encompasses the compounds in association with any type of counter ion. Moreover, as the compounds can exist in a variety of different forms, the invention is intended to encompass not only forms of the compounds that are in association with counter ions (e.g., dry salts), but also forms that are not in association with counter ions (e.g., aqueous or organic solutions). Metal salts typically are prepared by reacting the metal hydroxide with a compound of this invention. Examples of metal salts which are prepared in this way are salts containing Li^+, Na^+, and K^+. A less soluble metal salt can be precipitated from the solution of a more soluble salt by addition of the suitable metal compound. In addition, salts may be formed from acid addition of certain organic and inorganic acids to basic centers, typically amines, or to acidic groups. Examples of such appropriate acids include, for instance, inorganic acids such as hydrohalogen acids, e.g. hydrochloric or hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like; or organic acids such as, for example, acetic, propanoic, hydroxyacetic, 2-hydroxypropanoic, 2-oxopropanoic, lactic, pyruvic, oxalic (i.e. ethanedioic), malonic, succinic (i.e. butanedioic acid), maleic, fumaric, malic, tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, p-toluenesulfonic, cyclohexanesulfamic, salicylic (i.e. 2-hydroxybenzoic), p-aminosalicylic and the like. Furthermore, this term also includes the solvates which the compounds of formulae herein as well as their salts are able to form, such as for example hydrates, alcoholates and the like. Finally, it is to be understood that the compositions herein comprise indazole derivatives of the invention in their unionized, as well as zwitterionic form, and combinations with stoichiometric amounts of water as in hydrates.

[0149] Also included within the scope of this invention are the salts of the parental compounds with one or more amino acids, especially the naturally-occurring amino acids found as protein components. The amino acid typically is one bearing a side chain with a basic or acidic group, e.g., lysine, arginine or glutamic acid, or a neutral group such as glycine, serine, threonine, alanine, isoleucine, or leucine.

[0150] The indazole derivatives of the invention also include physiologically acceptable salts thereof. Examples of physiologically acceptable salts of the indazole derivatives of the invention include salts derived from an appropriate base, such as an alkali metal (for example, sodium), an alkaline earth (for example, magnesium), ammonium and $NX4^+$ (wherein X is $-C_{1-}$

$_{6}$-alkyl). Physiologically acceptable salts of a hydrogen atom or an amino group include salts of organic carboxylic acids such as acetic, benzoic, lactic, fumaric, tartaric, maleic, malonic, malic, isethionic, lactobionic and succinic acids; organic sulfonic acids, such as methanesulfonic, ethanesulfonic, benzenesulfonic and p-toluenesulfonic acids; and inorganic acids, such as hydrochloric, sulfuric, phosphoric and sulfamic acids. Physiologically acceptable salts of a compound containing a hydroxy group include the anion of said compound in combination with a suitable cation such as Na^+ and $NX4^+$ (wherein X typically is independently selected from -H or a -C_{1-4}-alkyl group). However, salts of acids or bases which are not physiologically acceptable may also find use, for example, in the preparation or purification of a physiologically acceptable compound. All salts, whether or not derived form a physiologically acceptable acid or base, are within the scope of the invention.

[0151] As used herein and unless otherwise stated, the term "enantiomer" means each individual optically active form of an indazole derivative of the invention, having an optical purity or enantiomeric excess (as determined by methods standard in the art) of at least 80% (i.e., at least 90% of one enantiomer and at most 10% of the other enantiomer), preferably at least 90% and more preferably at least 98%.

[0152] The term "isomers" as used herein means all possible isomeric forms, including tautomeric and stereochemical forms, which the compounds of formulae herein may possess, but not including position isomers. Typically, the structures shown herein exemplify only one tautomeric or resonance form of the compounds, but the corresponding alternative configurations are contemplated as well. Unless otherwise stated, the chemical designation of compounds denotes the mixture of all possible stereochemically isomeric forms, said mixtures containing all diastereomers and enantiomers (since the compounds of formulae herein may have at least one chiral center) of the basic molecular structure, as well as the stereochemically pure or enriched compounds. More particularly, stereogenic centers may have either the R- or S-configuration, and multiple bonds may have either cis- or trans-configuration.

[0153] Pure isomeric forms of the said compounds are defined as isomers substantially free of other enantiomeric or diastereomeric forms of the same basic molecular structure. In particular, the term "stereoisomerically pure" or “chirally pure" relates to compounds having a stereoisomeric excess of at least about 80% (i.e., at least 90% of one isomer and at most 10% of the other possible isomers), preferably at least 90%, more preferably at least 94% and most preferably at least 97%. The terms "enantiomerically pure" and "diastereomerically pure" should be understood in a similar way, having regard to the enantiomeric excess, respectively the diastereomeric excess, of the mixture in question.

[0154] Separation of stereoisomers is accomplished by standard methods known to those in the art. One enantiomer of an indazole derivative of the invention can be separated substantially free of its opposing enantiomer by a method such as formation of diastereomers

using optically active resolving agents ("Stereochemistry of Carbon Compounds," (1962) by E. L. Eliel, McGraw Hill; Lochmuller, C. H., (1975) J. Chromatogr., 113:(3) 283-302). Separation of isomers in a mixture can be accomplished by any suitable method, including: (1) formation of ionic, diastereomeric salts with chiral compounds and separation by fractional crystallization or other methods, (2) formation of diastereomeric compounds with chiral derivatizing reagents, separation of the diastereomers, and conversion to the pure enantiomers, or (3) enantiomers can be separated directly under chiral conditions. Under method (1), diastereomeric salts can be formed by reaction of enantiomerically pure chiral bases such as brucine, quinine, ephedrine, strychnine, a-methyl-b-phenylethylamine (amphetamine), and the like with asymmetric compounds bearing acidic functionality, such as carboxylic acid and sulfonic acid. The diastereomeric salts may be induced to separate by fractional crystallization or ionic chromatography. For separation of the optical isomers of amino compounds, addition of chiral carboxylic or sulfonic acids, such as camphorsulfonic acid, tartaric acid, mandelic acid, or lactic acid can result in formation of the diastereomeric salts. Alternatively, by method (2), the substrate to be resolved may be reacted with one enantiomer of a chiral compound to form a diastereomeric pair (Eliel, E. and Wilen, S. (1994) Stereochemistry of Organic Compounds, John Wiley & Sons, Inc., p. 322). Diastereomeric compounds can be formed by reacting asymmetric compounds with enantiomerically pure chiral derivatizing reagents, such as menthyl derivatives, followed by separation of the diastereomers and hydrolysis to yield the free, enantiomerically enriched compound. A method of determining optical purity involves making chiral esters, such as a menthyl ester or Mosher ester, a-methoxy-a-(trifluoromethyl)phenyl acetate (Jacob III. (1982) J. Org. Chem. 47:4165), of the racemic mixture, and analyzing the NMR spectrum for the presence of the two atropisomeric diastereomers. Stable diastereomers can be separated and isolated by normal- and reverse-phase chromatography following methods for separation of atropisomeric naphthyl-isoquinolines (Hoye, T., WO 96/15111).Under method (3), a racemic mixture of two asymmetric enantiomers is separated by chromatography using a chiral stationary phase. Suitable chiral stationary phases are, for example, polysaccharides, in particular cellulose or amylose derivatives. Commercially available polysaccharide based chiral stationary phases are ChiralCel® CA, OA, OB5, OC5, OD, OF, OG, OJ and OK, and Chiralpak® AD, AS, OP(+) and OT(+). Appropriate eluents or mobile phases for use in combination with said polysaccharide chiral stationary phases are hexane and the like, modified with an alcohol such as ethanol, isopropanol and the like. ("Chiral Liquid Chromatography" (1989) W. J. Lough, Ed. Chapman and Hall, New York; Okamoto, (1990) "Optical resolution of dihydropyridine enantiomers by High-performance liquid chromatography using phenylcarbamates of polysaccharides as a chiral stationary phase", J. of Chromatogr. 513:375-378).

[0155] The terms cis and trans are used herein in accordance with Chemical Abstracts

nomenclature and include reference to the position of the substituents on a ring moiety. The absolute stereochemical configuration of the compounds of the formulae described herein may easily be determined by those skilled in the art while using well-known methods such as, for example, X-ray diffraction.

[0156] When a compound is crystallized from a solution or slurry, it can be crystallized in a different arrangement lattice of spaces (this property is called "polymorphism") to form crystals with different crystalline forms, each of which is known as "polymorphs". The term “Polymorph” as used herein, therefore, refers to a crystal form of a compound of Formula (I), where the molecules are localized in the three-dimensional lattice sites. Different polymorphs of the compound of Formula (I) may be different from each other in one or more physical properties, such as solubility and dissolution rate, true specific gravity, crystal form, accumulation mode, flowability and/or solid state stability. etc.

[0157] Indazole derivatives of the invention and their physiologically acceptable salts (hereafter collectively referred to as the active ingredients) may be administered by any route appropriate to the condition to be treated, suitable routes including oral, rectal, nasal, topical (including ocular, buccal and sublingual), vaginal and parenteral (including subcutaneous, intramuscular, intranasal, intravenous, intraarterial, intradermal, intrathecal and epidural). The preferred route of administration may vary with for example the condition of the recipient.

[0158] The therapeutically effective amount of the preparation of the compound(s), especially for the treatment of TRPM3 mediated disorders in humans and other mammals or in animals, preferably is a TRPM3 ion channel inhibiting amount of the compounds as defined herein and corresponds to an amount which ensures a plasma level of between 1µg/ml and 100 mg/ml.

[0159] Suitable dosages of the compounds or compositions of the invention should be used to treat or prevent the TRPM3 mediated disorders in a subject. Depending upon the pathologic condition to be treated and the patient’s condition, the said effective amount may be divided into several sub-units per day or may be administered at more than one day intervals.

[0160] The invention further provides (pharmaceutical) compositions comprising one or more indazole derivatives of the invention, more in particular of all the Formula (I) and other formulas and embodiments described herein and the more particular aspects or embodiments thereof. Furthermore, the invention provides the compounds or (pharmaceutical) compositions of the invention, more in particular of all the Formula (I) and other formulas and embodiments described herein and the more particular aspects or embodiments thereof, for use as a medicine, more in particular for use in the treatment of pain. The TRPM3 mediated disorders are selected from pain and an inflammatory hypersensitivity condition and epilepsy.

[0161] The indazole derivatives of the invention may be formulated with conventional carriers and excipients, which will be selected in accord with ordinary practice. Tablets will contain excipients, glidants, fillers, binders and the like. Aqueous formulations are prepared in sterile

form, and when intended for delivery by other than oral administration generally will be isotonic. Formulations optionally contain excipients such as those set forth in the "Handbook of Pharmaceutical Excipients" (1986).

[0162] Subsequently, the term "pharmaceutically acceptable carrier" as used herein means any material or substance with which the active ingredient is formulated in order to facilitate its application or dissemination to the locus to be treated, for instance by dissolving, dispersing or diffusing the said composition, and/or to facilitate its storage, transport or handling without impairing its effectiveness. The pharmaceutically acceptable carrier may be a solid or a liquid or a gas which has been compressed to form a liquid, i.e., the compositions of this invention can suitably be used as concentrates, emulsions, solutions, granulates, dusts, sprays, aerosols, suspensions, ointments, creams, tablets, pellets or powders.

[0163] Suitable pharmaceutical carriers for use in the said pharmaceutical compositions and their formulation are well known to those skilled in the art, and there is no particular restriction to their selection within the invention. They may also include additives such as wetting agents, dispersing agents, stickers, adhesives, emulsifying agents, surface-active agents, solvents, coatings, antibacterial and antifungal agents, isotonic agents and the like, provided the same are consistent with pharmaceutical practice, i.e., carriers and additives which do not create permanent damage to mammals. The pharmaceutical compositions of the invention may be prepared in any known manner, for instance by homogeneously mixing, coating and/or grinding the active ingredients, in a one-step or multi-steps procedure, with the selected carrier material and, where appropriate, the other additives such as surface-active agents. may also be prepared by micronisation, for instance in view to obtain them in the form of microspheres usually having a diameter of about 1 to 10 gm, namely for the manufacture of microcapsules for controlled or sustained release of the active ingredients.

[0164] While it is possible for the indazole derivatives to be administered alone it is preferable to present them as pharmaceutical formulations. The formulations, both for veterinary and for human use, of the invention comprise at least one active ingredient, as above described, together with one or more pharmaceutically acceptable carriers therefore and optionally other therapeutic ingredients. The carrier(s) optimally are "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. The formulations include those suitable for oral, rectal, nasal, topical (including buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural) administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Such methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association the active

ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

[0165] Formulations of the invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

[0166] A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein. For infections of the eye or other external tissues e.g., mouth and skin, the formulations are optionally applied as a topical ointment or cream containing the active ingredient(s) in an amount of, for example, 0.075 to 20% w/w (including active ingredient(s) in a range between 0.1% and 20% in increments of 0.1% w/w such as 0.6% w/w, 0.7% w/w, etc.), preferably 0.2 to 15% w/w and most preferably 0.5 to 10% w/w. When formulated in an ointment, the active ingredients may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base. If desired, the aqueous phase of the cream base may include, for example, at least 30% w/w of a polyhydric alcohol, i.e., an alcohol having two or more hydroxyl groups such as propylene glycol, butane 1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol (including PEG400) and mixtures thereof. The topical formulations may desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethylsulfoxide and related analogs.

[0167] The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier (otherwise known as an emulgent), it desirably comprises a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Optionally, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations.

[0168] The choice of suitable oils or fats for the formulation is based on achieving the desired

cosmetic properties, since the solubility of the active compound in most oils likely to be used in pharmaceutical emulsion formulations is very low. Thus, the cream should optionally be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters known as Crodamol CAP may be used, the last three being preferred esters. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils can be used.

[0169] Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent for the active ingredient. The active ingredient is optionally present in such formulations in a concentration of 0.5 to 20%, advantageously 0.5 to 10% particularly about 1.5% w/w. Formulations suitable for topical administration in the mouth include lozenges comprising the active ingredient in a flavored basis, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

[0170] Formulations for rectal administration may be presented as a suppository with a suitable base comprising for example cocoa butter or a salicylate. Formulations suitable for nasal administration wherein the carrier is a solid include a coarse powder having a particle size for example in the range 20 to 500 microns (including particle sizes in a range between 20 and 500 microns in increments of 5 microns such as 30 microns, 35 microns, etc.), which is administered in the manner in which snuff is taken, i.e. by rapid inhalation through the nasal passage from a container of the powder held close up to the nose. Suitable formulations wherein the carrier is a liquid, for administration as for example a nasal spray or as nasal drops, include aqueous or oily solutions of the active ingredient. Formulations suitable for aerosol administration may be prepared according to conventional methods and may be delivered with other therapeutic agents.

[0171] Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

[0172] Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening

agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

[0173] Preferred unit dosage formulations are those containing a daily dose or unit daily sub-dose, as herein above recited, or an appropriate fraction thereof, of an active ingredient.

[0174] It should be understood that in addition to the ingredients particularly mentioned above the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

[0175] Indazole derivatives of the invention can be used to provide controlled release pharmaceutical formulations containing as active ingredient one or more indazole derivatives of the invention ("controlled release formulations") in which the release of the active ingredient can be controlled and regulated to allow less frequency dosing or to improve the pharmacokinetic or toxicity profile of a given invention compound. Controlled release formulations adapted for oral administration in which discrete units comprising one or more indazole derivatives of the invention can be prepared according to conventional methods.

[0176] Another embodiment of this invention relates to various precursor or “prodrug” forms of the indazole derivatives of the invention. It may be desirable to formulate the indazole derivatives of the invention in the form of a chemical species which itself is not significantly biologically-active, but which when delivered to the animal, mammal or human will undergo a chemical reaction catalyzed by the normal function of the body, inter alia, enzymes present in the stomach or in blood serum, said chemical reaction having the effect of releasing a compound as defined herein. The term “prodrug” thus relates to these species which are converted in vivo into the active pharmaceutical ingredient.

[0177] The prodrugs of the indazole derivatives of the invention can have any form suitable to the formulator, for example, esters are non-limiting common pro-drug forms. In the present case, however, the pro-drug may necessarily exist in a form wherein a covalent bond is cleaved by the action of an enzyme present at the target locus. For example, a C-C covalent bond may be selectively cleaved by one or more enzymes at said target locus and, therefore, a pro-drug in a form other than an easily hydrolysable precursor, inter alia an ester, an amide, and the like, may be used. The counterpart of the active pharmaceutical ingredient in the pro-drug can have different structures such as an amino acid or peptide structure, alkyl chains, sugar moieties and others as known in the art.

[0178] For the purpose of the invention the term “therapeutically suitable pro-drug” is defined herein as “a compound modified in such a way as to be transformed in vivo to the

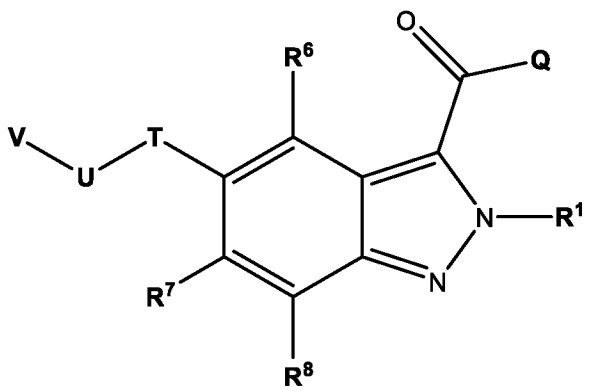
therapeutically active form, whether by way of a single or by multiple biological transformations, when in contact with the tissues of the animal, mammal or human to which the pro-drug has been administered, and without undue toxicity, irritation, or allergic response, and achieving the intended therapeutic outcome ".

[0179] More specifically the term "prodrug", as used herein, relates to an inactive or significantly less active derivative of a compound such as represented by the structural formulae herein described, which undergoes spontaneous or enzymatic transformation within the body in order to release the pharmacologically active form of the compound. For a comprehensive review, reference is made to Rautio J. et al. ("Prodrugs: design and clinical applications" Nature Reviews Drug Discovery, 2008, doi: 10.1038/nrd2468).

[0180] Representative indazole derivatives of the invention can be synthesized in accordance with the general synthetic methods described below and illustrated in the schemes that follow. Since the schemes are an illustration, the invention should not be construed as being limited by the specific chemical reaction and specific conditions described in the schemes and examples. The various starting material used in the schemes are commercially available or may be prepared by methods well within the skill persons versed in the art. The variables are as defined herein and within the skill of persons verses in the art.

[0181] Exemplary embodiments of the invention are summarized as Clauses 1 to 51 hereinafter:

1. A compound of formula (I), a stereo-isomeric form, a physiologically acceptable salt, solvate and/or polymorph thereof



(I)

preferably, the compound of formula (I), a stereo-isomeric form, a physiologically acceptable salt, solvate and/or polymorph thereof, optionally for use in the treatment of pain or epilepsy or in methods of treating pain or epilepsy;

wherein

R^1 represents -F, -Cl, -Br, -I, -CN, -R^W, -OR^W, -OC(=O)R^W, -N$R^W R^X$, -NR^WC(=O)R^X, -SR^W, -S(=O)R^W, -S(=O)$_2R^W$, -C(=O)R^W, -C(=O)OR^W, or -C(=O)N$R^W R^X$;

Q represents -O$\mathbf{R}^2$ or -N$\mathbf{R}^3\mathbf{R}^4$;

$\mathbf{R}^2$ represents -$\mathbf{R}^Y$;

$\mathbf{R}^3$ represents -OH or -$\mathbf{R}^Y$;

$\mathbf{R}^4$ represents -$\mathbf{R}^Y$ or -S(=O)$_2\mathbf{R}^Y$;

or $\mathbf{R}^3$ and $\mathbf{R}^4$ together form a 4, 5, 6, 7 or 8 membered heterocycle containing 1 to 3 heteroatoms selected from N, O and S, saturated or unsaturated, unsubstituted or mono- or polysubstituted;

T represents -O- and **U** represents -C$\mathbf{R}^5\mathbf{R}^{5'}$-; or **T** represents -C$\mathbf{R}^5\mathbf{R}^{5'}$- and **U** represents -O-;

$\mathbf{R}^5$ and $\mathbf{R}^{5'}$ independently of one another represent -$\mathbf{R}^Y$;

$\mathbf{R}^6$, $\mathbf{R}^7$ and $\mathbf{R}^8$ independently of one another represent -F, -Cl, -Br, -I, -CN, -NO$_2$, -SF$_5$, -$\mathbf{R}^W$, -O$\mathbf{R}^W$, -OC(=O)$\mathbf{R}^W$, -N$\mathbf{R}^W\mathbf{R}^X$, -N$\mathbf{R}^W$C(=O)$\mathbf{R}^X$, -S$\mathbf{R}^W$, -S(=O)$\mathbf{R}^W$, -S(=O)$_2\mathbf{R}^W$, -C(=O)$\mathbf{R}^W$, -C(=O)O$\mathbf{R}^W$, or -C(=O)N$\mathbf{R}^W\mathbf{R}^X$;

V represents 3-14-membered heterocycloalkyl, saturated or unsaturated; 3-14-membered cycloalkyl, saturated or unsaturated; 5-14-membered aryl, C_1-C_6 alkyl; or 5-14-membered heteroaryl; in each case unsubstituted, mono- or polysubstituted with substituents independently of one another selected from -F, -Cl, -Br, -I, -CF$_3$, -CF$_2$H, C_1-C_6 alkyl, -CN, -NO, -NO$_2$, =O, =S, -SF$_5$, -$\mathbf{R}^Y$, -O$\mathbf{R}^Y$, -OC(=O)$\mathbf{R}^Y$, -N$\mathbf{R}^Y\mathbf{R}^Z$, -N$\mathbf{R}^Y$C(=O)$\mathbf{R}^Z$, -S$\mathbf{R}^Y$, -S(=O)$\mathbf{R}^Y$, -S(=O)$_2\mathbf{R}^Y$, -C(=O)$\mathbf{R}^Y$, -C(=O)O$\mathbf{R}^Y$, or -C(=O)N$\mathbf{R}^Y\mathbf{R}^Z$;

wherein

$\mathbf{R}^W$ and $\mathbf{R}^X$ independently of one another in each case independently represent

-H;

-C_1-C_6-alkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted;

-C_1-C_6-heteroalkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted;

3-14-membered cycloalkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted; wherein said 3-14-membered cycloalkyl is optionally connected through -C_1-C_6-alkylene- or -C_1-C_6-heteroalkylene-, in each case saturated or unsaturated, unsubstituted, mono- or polysubstituted; or

3-14-membered heterocycloalkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted; wherein said 3-14-membered heterocycloalkyl is optionally connected through -C_1-C_6-alkylene- or -C_1-C_6-heteroalkylene-, in each case saturated or unsaturated, unsubstituted, mono- or polysubstituted;

$\mathbf{R}^Y$ and $\mathbf{R}^Z$ independently of one another in each case independently represent

-H;

-C_1-C_6-alkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted;

-C_1-C_6-heteroalkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted;

3-14-membered cycloalkyl, saturated or unsaturated, unsubstituted, mono- or

polysubstituted; wherein said 3-14-membered cycloalkyl is optionally connected through -C_1-C_6-alkylene- or -C_1-C_6-heteroalkylene-, in each case saturated or unsaturated, unsubstituted, mono- or polysubstituted;

3-14-membered heterocycloalkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted; wherein said 3-14-membered heterocycloalkyl is optionally connected through -C_1-C_6-alkylene- or -C_1-C_6-heteroalkylene-, in each case saturated or unsaturated, unsubstituted, mono- or polysubstituted;

6-14-membered aryl, unsubstituted, mono- or polysubstituted; wherein said 6-14-membered aryl is optionally connected through -C_1-C_6-alkylene- or -C_1-C_6-heteroalkylene-, in each case saturated or unsaturated, unsubstituted, mono- or polysubstituted; or

5-14-membered heteroaryl, unsubstituted, mono- or polysubstituted; wherein said 5-14-membered heteroaryl is optionally connected through -C_1-C_6-alkylene- or -C_1-C_6-heteroalkylene-, in each case saturated or unsaturated, unsubstituted, mono- or polysubstituted;

or $\mathbf{R^Y}$ and $\mathbf{R^Z}$ together form a 4, 5, 6, 7 or 8 membered heterocycle containing 1 to 3 heteroatoms selected from N, O and S, saturated or unsaturated, unsubstituted or mono- or polysubstituted;

and wherein "mono- or polysubstituted" in each case independently means substituted with one or more substituents independently of one another selected from -F, -Cl, -Br, -I, -CN, -C_{1-6}-alkyl, -CF_3, -CF_2H, -CFH_2, -CF_2Cl, -$CFCl_2$, -C_{1-6}-alkylene-CF_3, -C_{1-6}-alkylene-CF_2H, -C_{1-6}-alkylene-CFH_2, -C_{1-6}-alkylene-O-CF_3, -C_{1-6}-alkylene-O-CF_2H, -C_{1-6}-alkylene-O-CFH_2, -C_{1-6}-alkylene-NH-C_{1-6}-alkylene-CF_3, -C_{1-6}-alkylene-N(C_{1-6}-alkyl)-C_{1-6}-alkylene-CF_3, -C(=O)-C_{1-6}-alkyl, -C_{1-6}-alkylene-C(=O)-C_{1-6}-alkyl, -C(=O)OH, -C_{1-6}-alkylene-C(=O)-OH, -C(=O)-OC_{1-6}-alkyl, -C_{1-6}-alkylene-C(=O)-OC_{1-6}-alkyl, -C(=O)O-C_{1-6}-alkylene-CF_3, -C(=O)-NH_2, -C_{1-6}-alkylene-C(=O)-NH_2, -C(=O)-NH(C_{1-6}-alkyl), -C_{1-6}-alkylene-C(=O)-NH(C_{1-6}-alkyl), -C(=O)-N(C_{1-6}-alkyl)$_2$, -C_{1-6}-alkylene-C(=O)-N(C_{1-6}-alkyl)$_2$, -C(=O)-NH(OH), -C_{1-6}-alkylene-C(=O)-NH(OH), -OH, -C_{1-6}-alkylene-OH, =O, -OCF_3, -OCF_2H, -$OCFH_2$, -OCF_2Cl, -$OCFCl_2$, -O-C_{1-6}-alkyl, -C_{1-6}-alkylene-O-C_{1-6}-alkyl, -O-C_{1-6}-alkylene-O-C_{1-6}-alkyl, -O-C_{1-6}-alkylene-NH_2, -O-C_{1-6}-alkylene-NH-C_{1-6}-alkyl, -O-C_{1-6}-alkylene-N(C_{1-6}-alkyl)$_2$, -O-C(=O)-C_{1-6}-alkyl, -C_{1-6}-alkylene-O-C(=O)-C_{1-6}-alkyl, -O-C(=O)-O-C_{1-6}-alkyl, -C_{1-6}-alkylene-O-C(=O)-O-C_{1-6}-alkyl, -O-C(=O)-NH(C_{1-6}-alkyl), -C_{1-6}-alkylene-O-C(=O)-NH(C_{1-6}-alkyl), -O-C(=O)-N(C_{1-6}-alkyl)$_2$, -C_{1-6}-alkylene-O-C(=O)-N(C_{1-6}-alkyl)$_2$, -O-S(=O)$_2$-NH_2, -C_{1-6}-alkylene-O-S(=O)$_2$-NH_2, -O-S(=O)$_2$-NH(C_{1-6}-alkyl), -C_{1-6}-alkylene-O-S(=O)$_2$-NH(C_{1-6}-alkyl), -O-S(=O)$_2$-N(C_{1-6}-alkyl)$_2$, -C_{1-6}-alkylene-O-S(=O)$_2$-N(C_{1-6}-alkyl)$_2$, -NH_2, -NO, -NO_2, -C_{1-6}-alkylene-NH_2, -NH(C_{1-6}-alkyl), -N(3-14-membered cycloalkyl)(C_{1-6}-alkyl), -N(C_{1-6}-alkyl)-C_{1-6}-alkylene-OH, -N(H)-C_{1-6}-alkylene-OH, -C_{1-6}-alkylene-NH(C_{1-6}-

alkyl), -N(C_{1-6}-alkyl)$_2$, -C_{1-6}-alkylene-N(C_{1-6}-alkyl)$_2$, -NH-C(=O)-C_{1-6}-alkyl, -C_{1-6}-alkylene-NH-C(=O)-C_{1-6}-alkyl, -NH-C(=O)-O-C_{1-6}-alkyl, -C_{1-6}-alkylene-NH-C(=O)-O-C_{1-6}-alkyl, -NH-C(=O)-NH_2, -C_{1-6}-alkylene-NH-C(=O)-NH_2, -NH-C(=O)-NH(C_{1-6}-alkyl), -C_{1-6}-alkylene-NH-C(=O)-NH(C_{1-6}-alkyl), -NH-C(=O)-N(C_{1-6}-alkyl)$_2$, -C_{1-6}-alkylene-NH-C(=O)-N(C_{1-6}-alkyl)$_2$, -N(C_{1-6}-alkyl)-C(=O)-C_{1-6}-alkyl, -C_{1-6}-alkylene-N(C_{1-6}-alkyl)-C(=O)-C_{1-6}-alkyl, -N(C_{1-6}-alkyl)-C(=O)-O-C_{1-6}-alkyl, -C_{1-6}-alkylene-N(C_{1-6}-alkyl)-C(=O)-O-C_{1-6}-alkyl, -N(C_{1-6}-alkyl)-C(=O)-NH_2, -C_{1-6}-alkylene-N(C_{1-6}-alkyl)-C(=O)-NH_2, -N(C_{1-6}-alkyl)-C(=O)-NH(C_{1-6}-alkyl), -C_{1-6}-alkylene-N(C_{1-6}-alkyl)-C(=O)-NH(C_{1-6}-alkyl), -N(C_{1-6}-alkyl)-C(=O)-N(C_{1-6}-alkyl)$_2$, -C_{1-6}-alkylene-N(C_{1-6}-alkyl)-C(=O)-N(C_{1-6}-alkyl)$_2$, -NH-S(=O)$_2$OH, -C_{1-6}-alkylene-NH-S(=O)$_2$OH, -NH-S(=O)$_2$-C_{1-6}-alkyl, -C_{1-6}-alkylene-NH-S(=O)$_2$-C_{1-6}-alkyl, -NH-S(=O)$_2$-O-C_{1-6}-alkyl, -C_{1-6}-alkylene-NH-S(=O)$_2$-O-C_{1-6}-alkyl, -NH-S(=O)$_2$-NH_2, -C_{1-6}-alkylene-NH-S(=O)$_2$-NH_2, -NH-S(=O)$_2$-NH(C_{1-6}-alkyl), -C_{1-6}-alkylene-NH-S(=O)$_2$-NH(C_{1-6}-alkyl), -NH-S(=O)$_2$N(C_{1-6}-alkyl)$_2$, -C_{1-6}-alkylene-NH-S(=O)$_2$N(C_{1-6}-alkyl)$_2$, -N(C_{1-6}-alkyl)-S(=O)$_2$-OH, -C_{1-6}-alkylene-N(C_{1-6}-alkyl)-S(=O)$_2$-OH, -N(C_{1-6}-alkyl)-S(=O)$_2$-C_{1-6}-alkyl, -C_{1-6}-alkylene-N(C_{1-6}-alkyl)-S(=O)$_2$-C_{1-6}-alkyl, -N(C_{1-6}-alkyl)-S(=O)$_2$-O-C_{1-6}-alkyl, -C_{1-6}-alkylene-N(C_{1-6}-alkyl)-S(=O)$_2$-O-C_{1-6}-alkyl, -N(C_{1-6}-alkyl)-S(=O)$_2$-NH_2, -C_{1-6}-alkylene-N(C_{1-6}-alkyl)-S(=O)$_2$-NH_2, -N(C_{1-6}-alkyl)-S(=O)$_2$-NH(C_{1-6}-alkyl), -C_{1-6}-alkylene-N(C_{1-6}-alkyl)-S(=O)$_2$-NH(C_{1-6}-alkyl), -N(C_{1-6}-alkyl)-S(=O)$_2$-N(C_{1-6}-alkyl)$_2$, -C_{1-6}-alkylene-N(C_{1-6}-alkyl)-S(=O)$_2$-N(C_{1-6}-alkyl)$_2$, -SH, =S, -SF_5, -SCF_3, -SCF_2H, -$SCFH_2$, -S-C_{1-6}-alkyl, -C_{1-6}-alkylene-S-C_{1-6}-alkyl, -S(=O)-C_{1-6}-alkyl, -C_{1-6}-alkylene-S(=O)-C_{1-6}-alkyl, -S(=O)$_2$-C_{1-6}-alkyl, -C_{1-6}-alkylene-S(=O)$_2$-C_{1-6}-alkyl, -S(=O)$_2$-OH, -C_{1-6}-alkylene-S(=O)$_2$-OH, -S(=O)$_2$-O-C_{1-6}-alkyl, -C_{1-6}-alkylene-S(=O)$_2$-O-C_{1-6}-alkyl, -S(=O)$_2$-NH_2, -C_{1-6}-alkylene-S(=O)$_2$-NH_2, -S(=O)$_2$-NH(C_{1-6}-alkyl), -C_{1-6}-alkylene-S(=O)$_2$-NH(C_{1-6}-alkyl), -S(=O)$_2$-N(C_{1-6}-alkyl)$_2$, -C_{1-6}-alkylene-S(=O)$_2$-N(C_{1-6}-alkyl)$_2$, 3-14-membered cycloalkyl, -C_{1-6}-alkylene-(3-14-membered cycloalkyl), 3 to 14-membered heterocycloalkyl, -C_{1-6}-alkylene-(3 to 14-membered heterocycloalkyl), -phenyl, -C_{1-6}-alkylene-phenyl, 5 to 14-membered heteroaryl, -C_{1-6}-alkylene-(5 to 14-membered heteroaryl), -O-(3-14-membered cycloalkyl), -O-(3 to 14-membered heterocycloalkyl), -O-phenyl, -O-(5 to 14-membered heteroaryl), -C(=O)-(3-14-membered cycloalkyl), -C(=O)-(3 to 14-membered heterocycloalkyl), -C(=O)-phenyl, -C(=O)-(5 to 14-membered heteroaryl), -S(=O)$_2$-(3-14-membered cycloalkyl), -S(=O)$_2$-(3 to 14-membered heterocycloalkyl), -S(=O)$_2$-phenyl, -S(=O)$_2$-(5 to 14-membered heteroaryl).

2. The compound per se, or for use according to Clause 1, wherein **T** represents -O- and **U** represents -C$\mathbf{R^5R^{5'}}$-.

3. The compound per se, or for use according to Clause 1, wherein **T** represents -C$\mathbf{R^5R^{5'}}$- and **U** represents -O-.

4. The compound per se, or for use according to any one of Clauses 1 to 3, wherein **Q** represents -N**R**^{3}**R**^{4}.

5. The compound per se, or for use according to any one of Clauses 1 to 3, wherein **Q** represents -O**R**^{2}.

6. The compound per se, or for use according to any one of Clauses 1 to 5, wherein **V** represents 3-14-membered heterocycloalkyl, saturated or unsaturated; 3-14-membered cycloalkyl, saturated or unsaturated; 5-14-membered aryl; C_1-C_6 alkyl; or 5-14-membered heteroaryl; in each case unsubstituted, mono- or polysubstituted with substituents independently of one another selected from -F, -Cl, -Br, -I, -CF_3, -CF_2H, C_1-C_6 alkyl, -CN, -NO, -NO_2, =O, =S, -SF_5, -**R**^{Y}, -O**R**^{Y}, -OC(=O)**R**^{Y}, -N**R**^{Y}**R**^{Z}, -N**R**^{Y}C(=O)**R**^{Z}, -S**R**^{Y}, -S(=O)**R**^{Y}, -S(=O)$_2$**R**^{Y}, -C(=O)**R**^{Y}, -C(=O)O**R**^{Y}, or -C(=O)N**R**^{Y}**R**^{Z}.

7. The compound per se, or for use according to Clause 6, wherein the 5-14-membered heteroaryl is mono- or poly-substituted.

8. The compound per se, or for use according to Clause 6 or 7, wherein the 5-14-membered heteroaryl is selected from benzimidazole, benzisoxazole, benzoazole, benzodioxole, benzofuran, benzothiadiazole, benzothiazole, benzothiophene, carbazole, cinnoline, dibenzofuran, furane, furazane, imidazole, imidazopyridine, indazole, indole, indolizine, isobenzofuran, isoindole, isoquinoline, isothiazole, isoxazole, naphthyridine, oxadiazole, oxazole, oxindole, phthalazine, purine, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, pyrrole, quinazoline, quinoline, quinoxaline, tetrazole, thiadiazole, thiazole, thiophene, triazine, triazole, and [1,2,4]triazolo[4,3-a]pyrimidine; in each case unsubstituted, mono- or polysubstituted with substituents independently of one another selected from -F, -Cl, -Br, -I, CF_3, -CF_2H, C_1-C_6 alkyl, -CN, -NO, -NO_2, =O, =S, -SF_5, -**R**^{Y}, -O**R**^{Y}, -OC(=O)**R**^{Y}, -N**R**^{Y}**R**^{Z}, -N**R**^{Y}C(=O)**R**^{Z}, -S**R**^{Y}, -S(=O)**R**^{Y}, -S(=O)$_2$**R**^{Y}, -C(=O)**R**^{Y}, -C(=O)O**R**^{Y}, or -C(=O)N**R**^{Y}**R**^{Z}.

9. The compound per se, or for use according to any one of Clauses 6 to 8, wherein the 5-14-membered heteroaryl is selected from the group consisting of furane, thiophene, imidazole, pyrazole, oxazole, isoxazole, thiazole, triazole, pyridine, isoquinoline, benzothiazole, pyridazine, pyrimidine, imidazopyridine; in each case unsubstituted, mono- or polysubstituted with substituents independently of one another selected from -F, -Cl, -Br, -I, CF_3, -CF_2H, C_1-C_6 alkyl, -CN, -NO, -NO_2, =O, =S, -SF_5, -**R**^{Y}, -O**R**^{Y}, -OC(=O)**R**^{Y}, -N**R**^{Y}**R**^{Z}, -N**R**^{Y}C(=O)**R**^{Z}, -S**R**^{Y}, -S(=O)**R**^{Y}, -S(=O)$_2$**R**^{Y}, -C(=O)**R**^{Y}, -C(=O)O**R**^{Y}, or -C(=O)N**R**^{Y}**R**^{Z}.

10. The compound per se, or for use according to any one of Clauses 6 to 9, wherein the 5-14-membered heteroaryl is selected from the group consisting of furan-2-yl, furan-3-yl, thiophen-2-yl, thiophen-3-yl, pyrazol-3-yl, pyrazol-4-yl, pyrazol-5-yl, oxazol-5-yl, isoxazol-4-yl, thiazol-2-yl, thiazol-4-yl, thiazol-5-yl, 1,2,4-triazol-3-yl, 1,2,3-triazol-4-yl,

pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, isoquinolin-1-yl, isoquinolin-5-yl, benzo[d]thiazol-2-yl, pyridazin-3-yl, pyrimidin-5-yl, and imidazo[1,2-a]pyridin-6-yl; in each case unsubstituted, mono- or polysubstituted with substituents independently of one another selected from -F, -Cl, -Br, -I, CF_3, $-CF_2H$, C_1-C_6 alkyl, -CN, -NO, $-NO_2$, =O, =S, $-SF_5$, $-\mathbf{R}^Y$, $-O\mathbf{R}^Y$, $-OC(=O)\mathbf{R}^Y$, $-N\mathbf{R}^Y\mathbf{R}^Z$, $-N\mathbf{R}^YC(=O)\mathbf{R}^Z$, $-S\mathbf{R}^Y$, $-S(=O)\mathbf{R}^Y$, $-S(=O)_2\mathbf{R}^Y$, $-C(=O)\mathbf{R}^Y$, $-C(=O)O\mathbf{R}^Y$, or $-C(=O)N\mathbf{R}^Y\mathbf{R}^Z$.

11. The compound per se, or for use according to any one of Clauses 1 to 5, wherein **V** represents 3-14-membered heterocycloalkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted with substituents independently of one another selected from -F, -Cl, -Br, -I, CF_3, $-CF_2H$, C_1-C_6 alkyl, -CN, -NO, $-NO_2$, =O, =S, $-SF_5$, $-\mathbf{R}^Y$, $-O\mathbf{R}^Y$, $-OC(=O)\mathbf{R}^Y$, $-N\mathbf{R}^Y\mathbf{R}^Z$, $-N\mathbf{R}^YC(=O)\mathbf{R}^Z$, $-S\mathbf{R}^Y$, $-S(=O)\mathbf{R}^Y$, $-S(=O)_2\mathbf{R}^Y$, $-C(=O)\mathbf{R}^Y$, $-C(=O)O\mathbf{R}^Y$, or $-C(=O)N\mathbf{R}^Y\mathbf{R}^Z$.

12. The compound per se, or for use according to Clause 11, wherein the 3-14-membered heterocycloalkyl is selected from azepane, 1,4-oxazepane, azetane, azetidine, aziridine, azocane, diazepane, dioxane, dioxolane, dithiane, dithiolane, imidazolidine, isothiazolidine, isoxalidine, morpholine, oxazolidine, oxepane, oxetane, oxirane, piperazine, piperidine, pyrazolidine, pyrrolidine, quinuclidine, tetrahydrofuran, tetrahydropyran, tetrahydrothiopyran, thiazolidine, thietane, thiirane, thiolane, thiomorpholine, indoline, dihydrobenzofuran, dihydrobenzothiophene, 1,1-dioxothiacyclohexane, 2-azaspiro[3.3]heptane, 2-oxaspiro[3.3]heptane, 7-azaspiro[3.5]nonane, 8-azabicyclo[3.2.1]octane, 9-azabicyclo[3.3.1]nonane, hexahydro-1H-pyrrolizine, hexahydrocyclopenta[c]pyrrole, octahydrocyclopenta[c]pyrrole, and octahydropyrrolo[1,2-a]pyrazine; in each case unsubstituted, mono- or polysubstituted with substituents independently of one another selected from -F, -Cl, -Br, -I, CF_3, $-CF_2H$, C_1-C_6 alkyl, -CN, -NO, $-NO_2$, =O, =S, $-SF_5$, $-\mathbf{R}^Y$, $-O\mathbf{R}^Y$, $-OC(=O)\mathbf{R}^Y$, $-N\mathbf{R}^Y\mathbf{R}^Z$, $-N\mathbf{R}^YC(=O)\mathbf{R}^Z$, $-S\mathbf{R}^Y$, $-S(=O)\mathbf{R}^Y$, $-S(=O)_2\mathbf{R}^Y$, $-C(=O)\mathbf{R}^Y$, $-C(=O)O\mathbf{R}^Y$, or $-C(=O)N\mathbf{R}^Y\mathbf{R}^Z$.

13. The compound per se, or for use according to Clause 11 or 12, wherein the 3-14-membered heterocycloalkyl is oxane, or oxetanyl; in each case unsubstituted, mono- or polysubstituted with substituents independently of one another selected from -F, -Cl, -Br, -I, CF_3, $-CF_2H$, C_1-C_6 alkyl, -CN, -NO, $-NO_2$, =O, =S, $-SF_5$, $-\mathbf{R}^Y$, $-O\mathbf{R}^Y$, $-OC(=O)\mathbf{R}^Y$, $-N\mathbf{R}^Y\mathbf{R}^Z$, $-N\mathbf{R}^YC(=O)\mathbf{R}^Z$, $-S\mathbf{R}^Y$, $-S(=O)\mathbf{R}^Y$, $-S(=O)_2\mathbf{R}^Y$, $-C(=O)\mathbf{R}^Y$, $-C(=O)O\mathbf{R}^Y$, or $-C(=O)N\mathbf{R}^Y\mathbf{R}^Z$.

14. The compound per se, or for use according to any one of Clauses 11 to 13, wherein the 3-14-membered heterocycloalkyl is oxan-4-yl or oxetan-3-yl; in each case unsubstituted, mono- or polysubstituted with substituents independently of one another selected from -F, -Cl, -Br, -I, -CN, -NO, $-NO_2$, =O, =S, $-SF_5$, $-\mathbf{R}^Y$, $-O\mathbf{R}^Y$, $-OC(=O)\mathbf{R}^Y$, $-N\mathbf{R}^Y\mathbf{R}^Z$, $-N\mathbf{R}^YC(=O)\mathbf{R}^Z$, $-S\mathbf{R}^Y$, $-S(=O)\mathbf{R}^Y$, $-S(=O)_2\mathbf{R}^Y$, $-C(=O)\mathbf{R}^Y$, $-C(=O)O\mathbf{R}^Y$, or $-C(=O)N\mathbf{R}^Y\mathbf{R}^Z$.

15. The compound per se, or for use according to any one of clauses 1 to 5, wherein the 3-14-membered cycloalkyl, saturated or unsaturated, is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, or cyclodecyl including unfused or unbridged, fused, or bridged cycloalkyls; in each case unsubstituted, mono- or polysubstituted with substituents independently of one another selected from -F, -Cl, -Br, -I, , CF_3, $-CF_2H$, C_1-C_6 alkyl, -CN, -NO, $-NO_2$, =O, =S, $-SF_5$, $-\mathbf{R}^Y$, $-O\mathbf{R}^Y$, $-OC(=O)\mathbf{R}^Y$, $-N\mathbf{R}^Y\mathbf{R}^Z$, $-N\mathbf{R}^YC(=O)\mathbf{R}^Z$, $-S\mathbf{R}^Y$, $-S(=O)\mathbf{R}^Y$, $-S(=O)_2\mathbf{R}^Y$, $-C(=O)\mathbf{R}^Y$, $-C(=O)O\mathbf{R}^Y$, or $-C(=O)N\mathbf{R}^Y\mathbf{R}^Z$.

16. The compound per se, or for use according to any one of clauses 1 to 5, wherein the 5-14-membered aryl is phenyl or another 5-14 membered aryl unsubstituted, mono- or polysubstituted with substituents independently of one another selected from -F, -Cl, -Br, -I, CF_3, $-CF_2H$, C_1-C_6 alkyl, -CN, -NO, $-NO_2$, =O, =S, $-SF_5$, $-\mathbf{R}^Y$, $-O\mathbf{R}^Y$, $-OC(=O)\mathbf{R}^Y$, $-N\mathbf{R}^Y\mathbf{R}^Z$, $-N\mathbf{R}^YC(=O)\mathbf{R}^Z$, $-S\mathbf{R}^Y$, $-S(=O)\mathbf{R}^Y$, $-S(=O)_2\mathbf{R}^Y$, $-C(=O)\mathbf{R}^Y$, $-C(=O)O\mathbf{R}^Y$, or $-C(=O)N\mathbf{R}^Y\mathbf{R}^Z$.

17. The compound per se, or for use according to any one of clauses 1 to 6, wherein the C_1-C_6 alkyl or C_1-C_6 heteroalkyl representing **V** is saturated or unsaturated, unsubstituted, mono- or polysubstituted with substituents independently of one another selected from -F, -Cl, -Br, -I, CF_3, $-CF_2H$, C_1-C_6 alkyl, -CN, -NO, $-NO_2$, =O, =S, $-SF_5$, $-\mathbf{R}^Y$, $-O\mathbf{R}^Y$, $-OC(=O)\mathbf{R}^Y$, $-N\mathbf{R}^Y\mathbf{R}^Z$, $-N\mathbf{R}^YC(=O)\mathbf{R}^Z$, $-S\mathbf{R}^Y$, $-S(=O)\mathbf{R}^Y$, $-S(=O)_2\mathbf{R}^Y$, $-C(=O)\mathbf{R}^Y$, $-C(=O)O\mathbf{R}^Y$, or $-C(=O)N\mathbf{R}^Y\mathbf{R}^Z$.

18. The compound per se, or for use according to any one of the preceding Clauses, wherein **V** is unsubstituted, mono- or polysubstituted with substituents independently of one another selected from

-F, -Cl, -Br, -I, CF_3, $-CF_2H$, -CN, -C(=O)OH, $-NH_2$, $-NO_2$, -OH, =O, $-SF_5$;

$-C_{1\text{-}6}$-alkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted;

$-C(=O)O-C_{1\text{-}6}$-alkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted;

$-NHC_{1\text{-}6}$-alkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted;

$-N(C_{1\text{-}6}\text{-alkyl})_2$, saturated or unsaturated, unsubstituted, mono- or polysubstituted;

$-O-C_{1\text{-}6}$-alkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted;

$-S(=O)_2-C_{1\text{-}6}$-alkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted;

3-14-membered cycloalkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted; wherein said 3-14-membered cycloalkyl is optionally connected through $-C_1$-C_6-alkylene- or $-C_1$-C_6-heteroalkylene-, in each case saturated or unsaturated, unsubstituted, mono- or polysubstituted; or

3-14-membered heterocycloalkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted; wherein said 3-14-membered heterocycloalkyl is optionally connected through $-C_1$-C_6-alkylene- or $-C_1$-C_6-heteroalkylene-, in each case saturated or

unsaturated, unsubstituted, mono- or polysubstituted.

19. The compound per se, or for use according to any one of the preceding Clauses, wherein **V** is unsubstituted, mono- or polysubstituted with substituents independently of one another selected from

-OH, -F, -Cl, -Br, -I, -SH, $-CF_3$, $-CHF_2$, $-CH_2F$, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, SF_5, -CN, $-NO_2$, -C(=O)OH, $-NH_2$, $-N(CH_3)_2$, -cyclopropyl, or -O-cyclopropyl; preferably selected from -OH, -F, -Cl, -Br, -I, -SH, $-CF_3$, $-CHF_2$, $-CH_2F$, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, SF_5, -CN, $-NO_2$, -C(=O)OH, $-NH_2$, or $-N(CH_3)_2$;

$-C_{1-6}$-alkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted with substituents independently of one another , selected from the group consisting of -F, -Cl, -Br, -I, $-C_{1-6}$-alkyl, C_{2-6}-alkenyl, $-C_{2-6}$-alkynyl, -OH, =O, -SH, =S, -CN, $-CF_3$, $-CHF_2$, $-CH_2F$, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, SF_5, $-NO_2$, -C(=O)OH, $-NH_2$, C(=O)CHF_2, $-C(=O)NH_2$, and -cyclopropyl; preferably selected from the group consisting of -F, -Cl, -Br, -I, $-C_{1-6}$-alkyl, C_{2-6}-alkenyl, $-C_{2-6}$-alkynyl, -OH, =O, -SH, =S, -CN, $-CF_3$, $-CHF_2$, $-CH_2F$, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, SF_5, $-NO_2$, -C(=O)OH, $-NH_2$, C(=O)CHF_2, and $-C(=O)NH_2$;

$-C_{1-6}$-heteroalkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted with substituents independently of one another , selected from the group consisting of -F, -Cl, -Br, -I, $-C_{1-6}$-alkyl, C_{2-6}-alkenyl, $-C_{2-6}$-alkynyl, -OH, =O, -SH, =S, -CN, $-CF_3$, $-CHF_2$, $-CH_2F$, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, SF_5, $-NO_2$, -C(=O)OH, $-NH_2$, C(=O)CHF_2, and $-C(=O)NH_2$;

$-OC_{1-6}$-alkyl, unsubstituted, mono- or polysubstituted with substituents independently of one another , selected from the group consisting of -F, -Cl, -Br, -I, $-C_{1-6}$-alkyl, C_{2-6}-alkenyl, $-C_{2-6}$-alkynyl, -OH, =O, -SH, =S, -CN, $-CF_3$, $-CHF_2$, $-CH_2F$, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, SF_5, $-NO_2$, -C(=O)OH, $-NH_2$, C(=O)CHF_2, and $-C(=O)NH_2$;

$-O(C=O)C_{1-6}$-alkyl, unsubstituted, mono- or polysubstituted with substituents independently of one another , selected from the group consisting of -F, -Cl, -Br, -I, $-C_{1-6}$-alkyl, C_{2-6}-alkenyl, $-C_{2-6}$-alkynyl, -OH, =O, -SH, =S, -CN, $-CF_3$, $-CHF_2$, $-CH_2F$, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, SF_5, $-NO_2$, -C(=O)OH, $-NH_2$, C(=O)CHF_2, and $-C(=O)NH_2$;

$-C(=O)OC_{1-6}$-alkyl, unsubstituted, mono- or polysubstituted with substituents independently of one another , selected from the group consisting of -F, -Cl, -Br, -I, $-C_{1-6}$-alkyl, C_{2-6}-alkenyl, $-C_{2-6}$-alkynyl, -OH, =O, -SH, =S, -CN, $-CF_3$, $-CHF_2$, $-CH_2F$, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, SF_5, $-NO_2$, -C(=O)OH, $-NH_2$, C(=O)CHF_2, and $-C(=O)NH_2$;

3-14-membered cycloalkyl selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl; in each case unsubstituted, mono- or polysubstituted with substituents independently of one another , selected from the group consisting of -F, -Cl, -Br, -I, $-C_{1-6}$-alkyl, C_{2-6}-alkenyl, $-C_{2-6}$-alkynyl, -OH, =O, -SH, =S, -CN, $-CF_3$, $-CHF_2$, $-CH_2F$, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, SF_5, $-NO_2$, -C(=O)OH, $-NH_2$, C(=O)CHF_2,

and -C(=O)NH_2;

3-14-membered heterocycloalkyl selected from the group consisting of azepane, 1,4-oxazepane, azetane, azetidine, aziridine, azocane, diazepane, dioxane, dioxolane, dithiane, dithiolane, imidazolidine, isothiazolidine, isoxalidine, morpholine, oxazolidine, oxepane, oxetane, oxirane, piperazine, piperidine, pyrazolidine, pyrrolidine, quinuclidine, tetrahydrofuran, tetrahydropyran, tetrahydrothiopyran, thiazolidine, thietane, thiirane, thiolane, thiomorpholine, indoline, dihydrobenzofuran, dihydrobenzothiophene, 1,1-dioxothiacyclohexane, 2-azaspiro[3.3]heptane, 2-oxaspiro[3.3]heptane, 7-azaspiro[3.5]-nonane, 8-azabicyclo[3.2.1]octane, 9-azabicyclo[3.3.1]nonane, hexahydro-1H-pyrrolizine, hexahydrocyclopenta[c]pyrrole, octahydrocyclopenta[c]pyrrole, and octahydropyrrolo[1,2-a]pyrazine, in each case unsubstituted, mono- or polysubstituted with substituents independently of one another , selected from the group consisting of -F, -Cl, -Br, -I, -C_{1-6}-alkyl, C_{2-6}-alkenyl, -C_{2-6}-alkynyl, -OH, =O, -SH, =S, -CN, -CF_3, -CHF_2, -CH_2F, -OCF_3, -$OCHF_2$, -OCH_2F, SF_5, -NO_2, -C(=O)OH, -NH_2, C(=O)CHF_2, and -C(=O)NH_2.

20. The compound per se, or for use according to any one of the preceding Clauses, wherein **V** is unsubstituted, mono- or polysubstituted with substituents independently of one another selected from -F, -Cl, -CN, -OH, =O, -C_{1-6}-alkyl, -CHF_2, -CF_3, -C_{1-6}-alkylene-NH_2, -C_{1-6}-alkylene-NHC(=O)O-C_{1-6}-alkyl, -C_{1-6}-alkylene-OH, -C_{1-6}-alkylene-NHC(=O)-O-C_{1-6}-alkyl, -C(=O)O-C_{1-6}-alkyl, -N(C_{1-6}-alkyl)$_2$, -OC_{1-6}-alkyl, -OCF_3, -O-C_{1-6}-alkylene-N(C_{1-6}-alkyl)$_2$, -S(=O)$_2$-C_{1-6}-alkyl, -azetidine, -C_{1-6}-alkylene-O-tetrahydropyran, or -piperazine substituted with -C_{1-6}-alkyl; or represents oxetanyl, unsubstituted, mono- or polysubstituted.

21. The compound per se, or for use according to any one of the preceding Clauses, wherein **V** is

(i) unsubstituted;

(ii) monosubstituted;

(iii) disubstituted;

(iv) trisubstituted; or

(v) tetrasubstituted.

22. The compound per se, or for use according to any one of the preceding Clauses, wherein $\mathbf{R^1}$ represents

-H, -F, -Cl, -Br, -I;

-C_{1-6}-alkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted; -O-C_{1-6}-alkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted;

-C(=O)C_{1-6}-alkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted;

-C(=O)OC_{1-6}-alkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted;

-C(=O)NHC$_{1-6}$-alkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted;
-C(=O)N(C$_{1-6}$-alkyl)$_2$, saturated or unsaturated, unsubstituted, mono- or polysubstituted;
-S(=O)C$_{1-6}$-alkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted;
-S(=O)$_2$-C$_{1-6}$-alkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted;
-C$_1$-C$_6$-heteroalkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted; or
3-14-membered cycloalkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted; wherein said 3-14-membered cycloalkyl is optionally connected through -C$_1$-C$_6$-alkylene- or -C$_1$-C$_6$-heteroalkylene-, in each case saturated or unsaturated, unsubstituted, mono- or polysubstituted.

23. The compound per se, or for use according to any one of the preceding Clauses, wherein **R^1** represents -H, -F, -Cl, -Br, -I, -C$_{1-6}$-alkyl, -O-C$_{1-6}$-alkyl, -C$_{1-6}$-alkylene-O-C$_{1-6}$-alkyl, -C$_{1-6}$-alkylene-NH(C$_{1-6}$-alkyl), -C$_{1-6}$-alkylene-N(C$_{1-6}$-alkyl)$_2$, -CF$_3$, -CF$_2$H, -CFH$_2$, -CF$_2$Cl, -CFCl$_2$, -C$_{1-6}$-alkylene-CF$_3$, -C$_{1-6}$-alkylene-CF$_2$H, -C$_{1-6}$-alkylene-CFH$_2$, -C$_{1-6}$-alkylene-NH-C$_{1-6}$-alkylene-CF$_3$, -C$_{1-6}$-alkylene-N(C$_{1-6}$-alkyl)-C$_{1-6}$-alkylene-CF$_3$, -C(=O)C$_{1-6}$-alkyl, -C(=O)OC$_{1-6}$-alkyl, -C(=O)NHC$_{1-6}$-alkyl, -C(=O)N(C$_{1-6}$-alkyl)$_2$, -S(=O)-C$_{1-6}$-alkyl, -S(=O)$_2$-C$_{1-6}$-alkyl, -O-C$_{1-6}$-alkyl, -cyclopropyl unsubstituted, cyclobutyl unsubstituted, cyclopentyl unsubstituted or cyclohexyl unsubstituted.

24. The compound per se, or for use according to any one of the preceding Clauses, wherein **R^1** represents -H, -C$_{1-6}$-alkyl, -C$_{1-6}$-alkylene-O-C$_{1-6}$-alkyl, -CH$_2$F, -CHF$_2$, -CF$_3$, -cyclopentyl, unsubstituted, or -cyclopropyl, unsubstituted; preferably wherein **R^1** represents -H, -C$_{1-6}$-alkyl, -C$_{1-6}$-alkylene-O-C$_{1-6}$-alkyl, -CH$_2$F, -CHF$_2$, -CF$_3$, or -cyclopentyl, unsubstituted.

25. The compound per se, or for use according to any one of the preceding Clauses, wherein **R^1** represents -CH$_2$F, -CHF$_2$, -CH$_3$, or -cyclopropyl, unsubstituted; preferably wherein **R^1** represents -CH$_2$F, -CHF$_2$, -CH$_3$, or -CH$_2$CH$_3$.

26. The compound per se, or for use according to any one of the preceding Clauses, wherein **R^2** represents
-H;
-C$_1$-C$_6$-alkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted;
-C$_1$-C$_6$-heteroalkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted;
3-14-membered cycloalkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted; wherein said 3-14-membered cycloalkyl is optionally connected through -C$_1$-C$_6$-alkylene- or -C$_1$-C$_6$-heteroalkylene-, in each case saturated or unsaturated, unsubstituted, mono- or polysubstituted; or
3-14-membered heterocycloalkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted; wherein said 3-14-membered heterocycloalkyl is optionally connected through -C$_1$-C$_6$-alkylene- or -C$_1$-C$_6$-heteroalkylene-, in each case saturated or

unsaturated, unsubstituted, mono- or polysubstituted.

27. The compound per se, or for use according to any one of the preceding Clauses, wherein $\mathbf{R^2}$ represents -H, -C_{1-6}-alkyl, -C_{1-6}-alkylene-O-C_{1-6}-alkyl, -C_{1-6}-alkylene-NH(C_{1-6}-alkyl), -C_{1-6}-alkylene-N(C_{1-6}-alkyl)$_2$, -CF_3, -CF_2H, -CFH_2, -CF_2Cl, -$CFCl_2$, -C_{1-6}-alkylene-CF_3, -C_{1-6}-alkylene-CF_2H, -C_{1-6}-alkylene-CFH_2, -C_{1-6}-alkylene-NH-C_{1-6}-alkylene-CF_3, or -C_{1-6}-alkylene-N(C_{1-6}-alkyl)-C_{1-6}-alkylene-CF_3.

28. The compound per se, or for use according to any one of the preceding Clauses, wherein $\mathbf{R^2}$ represents -H or -C_{1-6}-alkyl.

29. The compound per se, or for use according to any one of the preceding Clauses, wherein $\mathbf{R^3}$ represents

-H;

-OH;

-C_1-C_6-alkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted; or

-C_1-C_6-heteroalkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted.

30. The compound per se, or for use according to any one of the preceding Clauses, wherein $\mathbf{R^3}$ represents -H, -OH, -C_{1-6}-alkyl, -C_{1-6}-alkylene-OH, -C_{1-6}-alkylene-O-C_{1-6}-alkyl, -C_{1-6}-alkylene-NH_2, -C_{1-6}-alkylene-NH(C_{1-6}-alkyl), -C_{1-6}-alkylene-N(C_{1-6}-alkyl)$_2$, -CF_3, -CF_2H, -CFH_2, -CF_2Cl, -$CFCl_2$, -C_{1-6}-alkylene-CF_3, -C_{1-6}-alkylene-CF_2H, -C_{1-6}-alkylene-CFH_2, -C_{1-6}-alkylene-NH-C_{1-6}-alkylene-CF_3, or -C_{1-6}-alkylene-N(C_{1-6}-alkyl)-C_{1-6}-alkylene-CF_3.

31. The compound per se, or for use according to any one of the preceding Clauses, wherein $\mathbf{R^3}$ represents -H, -OH, or -C_{1-6}-alkyl, saturated, unsubstituted or monosubstituted with -OH.

32. The compound per se, or for use according to any one of the preceding Clauses, wherein $\mathbf{R^4}$ represents

-H;

-S(=O)C_{1-6}-alkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted;

-S(=O)$_2$-C_{1-6}-alkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted;

-C_1-C_6-alkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted;

-C_1-C_6-heteroalkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted;

3-14-membered cycloalkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted; wherein said 3-14-membered cycloalkyl is optionally connected through -C_1-C_6-alkylene- or -C_1-C_6-heteroalkylene-, in each case saturated or unsaturated, unsubstituted, mono- or polysubstituted;

3-14-membered heterocycloalkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted; wherein said 3-14-membered heterocycloalkyl is optionally connected through -C_1-C_6-alkylene- or -C_1-C_6-heteroalkylene-, in each case saturated or unsaturated, unsubstituted, mono- or polysubstituted;

6-14-membered aryl, unsubstituted, mono- or polysubstituted; wherein said 6-14-membered aryl is optionally connected through -C_1-C_6-alkylene- or -C_1-C_6-heteroalkylene-, in each case saturated or unsaturated, unsubstituted, mono- or polysubstituted; or

5-14-membered heteroaryl, unsubstituted, mono- or polysubstituted; wherein said 5-14-membered heteroaryl is optionally connected through -C_1-C_6-alkylene- or -C_1-C_6-heteroalkylene-, in each case saturated or unsaturated, unsubstituted, mono- or polysubstituted.

33. The compound per se, or for use according to any one of the preceding Clauses, wherein **R^4** represents

-S(=O)$_2$$C_{1-6}$-alkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted with substituents independently of one another selected from the group consisting of -F, -Cl, -C_{1-6}-alkyl, -C_{1-6}-alkylene-CF_3, -OH, =O, -OC_{1-6}-alkyl, -C_{1-6}-alkylene-OH, -C_{1-6}-alkylene-O-C_{1-6}-alkyl, -NH_2, -NHC_{1-6}-alkyl, -N(C_{1-6}-alkyl)$_2$, -NHC(=O)O-C_{1-6}-alkyl, -N(C_{1-6}-alkyl)C(=O)O-C_{1-6}-alkyl, -C_{1-6}-alkylene-NHC(=O)O-C_{1-6}-alkyl, -C_{1-6}-alkylene-NH_2, -C_{1-6}-alkylene-NH-C_{1-6}-alkyl, -C_{1-6}-alkylene-N(C_{1-6}-alkyl)$_2$, -C_{1-6}-alkylene-NH-C_{1-6}-alkylene-CF_3, -C(=O)-C_{1-6}-alkyl, -C(=O)OH, -C(=O)O-C_{1-6}-alkyl, -C(=O)O-C_{1-6}-alkylene-CF_3, -C(=O)NH_2, -C(=O)NH(C_{1-6}-alkyl), -C(=O)N(C_{1-6}-alkyl)$_2$, -S(=O)$_2$$C_{1-6}$-alkyl, -phenyl, -$C_{1-6}$-alkylene-phenyl, 3-14-membered heterocycloalkyl, saturated or unsaturated, unsubstituted; and 5-14-membered heteroaryl, unsubstituted;

-S(=O)$_2$(3-14-membered cycloalkyl), wherein said 3-14-membered cycloalkyl is selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl, in each case saturated or unsaturated, unsubstituted, mono- or polysubstituted with substituents independently of one another selected from the group consisting of -F, -Cl, -C_{1-6}-alkyl, -C_{1-6}-alkylene-CF_3, -OH, =O, -OC_{1-6}-alkyl, -C_{1-6}-alkylene-OH, -C_{1-6}-alkylene-O-C_{1-6}-alkyl, -NH_2, -NHC_{1-6}-alkyl, -N(C_{1-6}-alkyl)$_2$, -NHC(=O)O-C_{1-6}-alkyl, -N(C_{1-6}-alkyl)C(=O)O-C_{1-6}-alkyl, -C_{1-6}-alkylene-NHC(=O)O-C_{1-6}-alkyl, -C_{1-6}-alkylene-NH_2, -C_{1-6}-alkylene-NH-C_{1-6}-alkyl, -C_{1-6}-alkylene-N(C_{1-6}-alkyl)$_2$, -C_{1-6}-alkylene-NH-C_{1-6}-alkylene-CF_3, -C(=O)-C_{1-6}-alkyl, -C(=O)OH, -C(=O)O-C_{1-6}-alkyl, -C(=O)O-C_{1-6}-alkylene-CF_3, -C(=O)NH_2, -C(=O)NH(C_{1-6}-alkyl), -C(=O)N(C_{1-6}-alkyl)$_2$, -S(=O)$_2$$C_{1-6}$-alkyl, -phenyl, -$C_{1-6}$-alkylene-phenyl, 3-14-membered heterocycloalkyl, saturated or unsaturated, unsubstituted; and 5-14-membered heteroaryl, unsubstituted;

-C_{1-6}-alkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted with substituents independently of one another selected from the group consisting of -F, -Cl, -C_{1-6}-alkyl, -C_{1-6}-alkylene-CF_3, -OH, =O, -OC_{1-6}-alkyl, -C_{1-6}-alkylene-OH, -C_{1-6}-alkylene-O-C_{1-6}-alkyl, -NH_2, -NHC_{1-6}-alkyl, -N(C_{1-6}-alkyl)$_2$, -NHC(=O)O-C_{1-6}-alkyl, -N(C_{1-6}-alkyl)C(=O)O-C_{1-6}-alkyl, -C_{1-6}-alkylene-NHC(=O)O-C_{1-6}-alkyl, -C_{1-6}-alkylene-NH_2, -C_{1-6}-

alkylene-NH-C_{1-6}-alkyl, -C_{1-6}-alkylene-N(C_{1-6}-alkyl)$_2$, -C_{1-6}-alkylene-NH-C_{1-6}-alkylene-CF_3, -C(=O)-C_{1-6}-alkyl, -C(=O)OH, -C(=O)O-C_{1-6}-alkyl, -C(=O)O-C_{1-6}-alkylene-CF_3, -C(=O)NH_2, -C(=O)NH(C_{1-6}-alkyl), -C(=O)N(C_{1-6}-alkyl)$_2$, -S(=O)$_2$$C_{1-6}$-alkyl, -phenyl, -$C_{1-6}$-alkylene-phenyl, 3-14-membered heterocycloalkyl, saturated or unsaturated, unsubstituted; and 5-14-membered heteroaryl, unsubstituted;

3-14-membered cycloalkyl or -C_{1-6}-alkylene-(3-14-membered cycloalkyl), wherein -C_{1-6}-alkylene- is unsubstituted or monosubstituted with -OH, wherein said 3-14-membered cycloalkyl is selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl, in each case saturated or unsaturated, in each case unsubstituted, mono- or polysubstituted with substituents independently of one another selected from the group consisting of -F, -Cl, -C_{1-6}-alkyl, -C_{1-6}-alkylene-CF_3, -OH, =O, -OC_{1-6}-alkyl, -C_{1-6}-alkylene-OH, -C_{1-6}-alkylene-O-C_{1-6}-alkyl, -NH_2, -NHC_{1-6}-alkyl, -N(C_{1-6}-alkyl)$_2$, -NHC(=O)O-C_{1-6}-alkyl, -N(C_{1-6}-alkyl)C(=O)O-C_{1-6}-alkyl, -C_{1-6}-alkylene-NHC(=O)O-C_{1-6}-alkyl, -C_{1-6}-alkylene-NH_2, -C_{1-6}-alkylene-NH-C_{1-6}-alkyl, -C_{1-6}-alkylene-N(C_{1-6}-alkyl)$_2$, -C_{1-6}-alkylene-NH-C_{1-6}-alkylene-CF_3, -C(=O)-C_{1-6}-alkyl, -C(=O)OH, -C(=O)O-C_{1-6}-alkyl, -C(=O)O-C_{1-6}-alkylene-CF_3, -C(=O)NH_2, -C(=O)NH(C_{1-6}-alkyl), -C(=O)N(C_{1-6}-alkyl)$_2$, -S(=O)$_2$$C_{1-6}$-alkyl, -phenyl, -$C_{1-6}$-alkylene-phenyl, 3-14-membered heterocycloalkyl, saturated or unsaturated, unsubstituted; and 5-14-membered heteroaryl, unsubstituted;

3-14-membered heterocycloalkyl or -C_{1-6}-alkylene-(3-14-membered heterocycloalkyl), wherein -C_{1-6}-alkylene- is unsubstituted or monosubstituted with -OH, wherein said 3-14-membered heterocycloalkyl in each case is selected from the group consisting of azepane, 1,4-oxazepane, azetane, azetidine, aziridine, azocane, diazepane, dioxane, dioxolane, dithiane, dithiolane, imidazolidine, isothiazolidine, isoxalidine, morpholine, oxazolidine, oxepane, oxetane, oxirane, piperazine, piperidine, pyrazolidine, pyrrolidine, quinuclidine, tetrahydrofuran, tetrahydropyran, tetrahydrothiopyran, thiazolidine, thietane, thiirane, thiolane, thiomorpholine, indoline, dihydrobenzofuran, dihydrobenzothiophene, 1,1-dioxothiacyclohexane, 2-azaspiro[3.3]heptane, 2-oxaspiro[3.3]heptane, 7-azaspiro[3.5]nonane, 8-azabicyclo[3.2.1]octane, 9-azabicyclo[3.3.1]nonane, hexahydro-1H-pyrrolizine, hexahydrocyclopenta[c]pyrrole, octahydrocyclopenta[c]pyrrole, and octahydropyrrolo[1,2-a]pyrazine; in each case unsubstituted, mono- or polysubstituted with substituents independently of one another selected from the group consisting of -F, -Cl, -C_{1-6}-alkyl, -C_{1-6}-alkylene-CF_3, -OH, =O, -OC_{1-6}-alkyl, -C_{1-6}-alkylene-OH, -C_{1-6}-alkylene-O-C_{1-6}-alkyl, -NH_2, -NHC_{1-6}-alkyl, -N(C_{1-6}-alkyl)$_2$, -NHC(=O)O-C_{1-6}-alkyl, -N(C_{1-6}-alkyl)C(=O)O-C_{1-6}-alkyl, -C_{1-6}-alkylene-NHC(=O)O-C_{1-6}-alkyl, -C_{1-6}-alkylene-NH_2, -C_{1-6}-alkylene-NH-C_{1-6}-alkyl, -C_{1-6}-alkylene-N(C_{1-6}-alkyl)$_2$, -C_{1-6}-alkylene-NH-C_{1-6}-alkylene-CF_3, -C(=O)-C_{1-6}-alkyl, -C(=O)OH, -C(=O)O-C_{1-6}-alkyl, -

$C(=O)O$-C_{1-6}-alkylene-CF_3, $-C(=O)NH_2$, $-C(=O)NH(C_{1-6}$-alkyl), $-C(=O)N(C_{1-6}$-alkyl$)_2$, $-S(=O)_2C_{1-6}$-alkyl, -phenyl, $-C_{1-6}$-alkylene-phenyl, 3-14-membered heterocycloalkyl, saturated or unsaturated, unsubstituted; and 5-14-membered heteroaryl, unsubstituted; -phenyl unsubstituted, mono- or polysubstituted with substituents independently of one another selected from the group consisting of -F, -Cl, -CN, $-C_{1-6}$-alkyl, $-C_{1-6}$-alkylene-CF_3, -OH, =O, $-OC_{1-6}$-alkyl, $-C_{1-6}$-alkylene-OH, $-C_{1-6}$-alkylene-O-C_{1-6}-alkyl, $-NH_2$, $-NHC_{1-6}$-alkyl, $-N(C_{1-6}$-alkyl$)_2$, $-NHC(=O)O$-C_{1-6}-alkyl, $-N(C_{1-6}$-alkyl$)C(=O)O$-C_{1-6}-alkyl, $-C_{1-6}$-alkylene-$NHC(=O)O$-C_{1-6}-alkyl, $-C_{1-6}$-alkylene-NH_2, $-C_{1-6}$-alkylene-NH-C_{1-6}-alkyl, $-C_{1-6}$-alkylene-$N(C_{1-6}$-alkyl$)_2$, $-C_{1-6}$-alkylene-NH-C_{1-6}-alkylene-CF_3, $-C(=O)$-C_{1-6}-alkyl, -C(=O)OH, $-C(=O)O$-C_{1-6}-alkyl, $-C(=O)O$-C_{1-6}-alkylene-CF_3, $-C(=O)NH_2$, $-C(=O)NH(C_{1-6}$-alkyl), $-C(=O)N(C_{1-6}$-alkyl$)_2$, $-S(=O)_2C_{1-6}$-alkyl, -phenyl, $-C_{1-6}$-alkylene-phenyl, 3-14-membered heterocycloalkyl, saturated or unsaturated, unsubstituted; and 5-14-membered heteroaryl, unsubstituted;

5-14-membered heteroaryl or $-C_{1-6}$-alkylene-(5-14-membered heteroaryl), wherein $-C_{1-6}$-alkylene- is unsubstituted or monosubstituted with -OH, wherein said 5-14-membered heteroaryl in each case is selected from the group consisting of benzimidazole, benzisoxazole, benzoazole, benzodioxole, benzofuran, benzothiadiazole, benzothiazole, benzothiophene, carbazole, cinnoline, dibenzofuran, furane, furazane, imidazole, imidazopyridine, indazole, indole, indolizine, isobenzofuran, isoindole, isoquinoline, isothiazole, isoxazole, naphthyridine, oxadiazole, oxazole, oxindole, phthalazine, purine, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, pyrrole, quinazoline, quinoline, quinoxaline, tetrazole, thiadiazole, thiazole, thiophene, triazine, triazole, and [1,2,4]triazolo[4,3-a]pyrimidine; in each case unsubstituted, mono- or polysubstituted with substituents independently of one another selected from the group consisting of -F, -Cl, -CN, $-C_{1-6}$-alkyl, $-C_{1-6}$-alkylene-CF_3, -OH, =O, $-OC_{1-6}$-alkyl, $-C_{1-6}$-alkylene-OH, $-C_{1-6}$-alkylene-O-C_{1-6}-alkyl, $-NH_2$, $-NHC_{1-6}$-alkyl, $-N(C_{1-6}$-alkyl$)_2$, $-NHC(=O)O$-C_{1-6}-alkyl, $-N(C_{1-6}$-alkyl$)C(=O)O$-C_{1-6}-alkyl, $-C_{1-6}$-alkylene-$NHC(=O)O$-C_{1-6}-alkyl, $-C_{1-6}$-alkylene-NH_2, $-C_{1-6}$-alkylene-NH-C_{1-6}-alkyl, $-C_{1-6}$-alkylene-$N(C_{1-6}$-alkyl$)_2$, $-C_{1-6}$-alkylene-NH-C_{1-6}-alkylene-CF_3, $-C(=O)$-C_{1-6}-alkyl, -C(=O)OH, $-C(=O)O$-C_{1-6}-alkyl, $-C(=O)O$-C_{1-6}-alkylene-CF_3, $-C(=O)NH_2$, $-C(=O)NH(C_{1-6}$-alkyl), $-C(=O)N(C_{1-6}$-alkyl$)_2$, $-S(=O)_2C_{1-6}$-alkyl, -phenyl, $-C_{1-6}$-alkylene-phenyl, 3-14-membered heterocycloalkyl, saturated or unsaturated, unsubstituted; and 5-14-membered heteroaryl, unsubstituted.

34. The compound per se, or for use according to any one of the preceding Clauses, wherein $\mathbf{R^4}$ represents

-H;

$-S(=O)_2C_{1-6}$-alkyl, saturated, unsubstituted, monosubstituted or polysubstituted with -F;

$-S(=O)_2$(3-14-membered cycloalkyl), saturated, unsubstituted;

-C_{1-6}-alkyl, saturated, unsubstituted, monosubstituted or disubstituted with substituents independently of one another selected from the group consisting of -OH, -OC_{1-6}-alkyl, -$N(C_{1-6}$-alkyl$)_2$, -C_{1-6}-alkylene-NH_2, -C_{1-6}-alkylene-NH-C_{1-6}-alkyl, -phenyl unsubstituted;

3-14-membered cycloalkyl or -C_{1-6}-alkylene-(3-14-membered cycloalkyl), wherein -C_{1-6}-alkylene- is unsubstituted or monosubstituted with -OH, wherein said 3-14-membered cycloalkyl is saturated, unsubstituted, monosubstituted or disubstituted with substituents independently of one another selected from the group consisting of -C_{1-6}-alkyl, -C_{1-6}-alkylene-NH_2, -C_{1-6}-alkylene-NH-C_{1-6}-alkylene-CF_3, -C_{1-6}-alkylene-OH, -C_{1-6}-alkylene-NHC(=O)O-C_{1-6}-alkyl, -OH, -OC_{1-6}-alkyl, -NH_2, -$N(C_{1-6}$-alkyl$)_2$, -NHC(=O)O-C_{1-6}-alkyl;

3-14-membered heterocycloalkyl or -C_{1-6}-alkylene-(3-14-membered heterocycloalkyl), wherein -C_{1-6}-alkylene- is unsubstituted or monosubstituted with -OH, wherein said 3-14-membered heterocycloalkyl in each case is selected from azetane, 1,4-oxazepane, pyrrolidine, piperidine, azepane, diazepane, tetrahydrofuran, tetrahydropyran, oxetane, morpholine, piperazine, hexahydrocyclopenta[c]pyrrole, octahydrocyclopenta[c]pyrrole, octahydropyrrolo[1,2-a]pyrazine, 8-azabicyclo[3.2.1]octane, 9-azabicyclo[3.3.1]nonane, quinuclidine, hexahydro-1H-pyrrolizine, 2-oxaspiro[3.3]heptane, 2-azaspiro[3.3]heptane, 7-azaspiro[3.5]nonane, 1,1-dioxothiacyclohexane, in each case unsubstituted, mono- or polysubstituted with substituents independently of one another selected from the group consisting of -F, -OH, =O, -C_{1-6}-alkyl, -C_{1-6}-alkylene-CF_3, -C_{1-6}-alkylene-OH, -C_{1-6}-alkylene-O-C_{1-6}-alkyl, -NH_2, -$N(C_{1-6}$-alkyl$)_2$, -C_{1-6}-alkylene-NH_2, -C_{1-6}-alkylene-$N(C_{1-6}$-alkyl$)_2$, -C(=O)-C_{1-6}-alkyl, -C(=O)OH, -C(=O)O-C_{1-6}-alkyl, -C(=O)O-C_{1-6}-alkylene-CF_3, -$C(=O)NH_2$, -C(=O)NH(C_{1-6}-alkyl), -$S(=O)_2C_{1-6}$-alkyl, oxetanyl, pyrimidinyl, -C_{1-6}-alkylene-phenyl;

-phenyl unsubstituted;

5-14-membered heteroaryl or -C_{1-6}-alkylene-(5-14-membered heteroaryl), wherein -C_{1-6}-alkylene- is unsubstituted or monosubstituted with -OH, wherein said 5-14-membered heteroaryl in each case is selected from the group consisting of pyridine, pyridazine, pyrazine, pyrazole, isoxazole, triazole, and [1,2,4]triazolo[4,3-a]pyrimidine, in each case unsubstituted, monosubstituted or disubstituted with substituents independently of one another selected from the group consisting of -C_{1-6}-alkyl, -OH.

35. The compound per se, or for use according to any one of the preceding Clauses, wherein $\mathbf{R^3}$ and $\mathbf{R^4}$ together form a 5- or 6-membered heterocycle containing 1 or 2 heteroatoms selected from N, O and S, saturated or unsaturated, unsubstituted or mono- or polysubstituted.

36. The compound per se, or for use according to any one of the preceding Clauses, wherein $\mathbf{R^3}$ and $\mathbf{R^4}$ together form a heterocycle selected from the group consisting of pyrrolidine, piperidine, morpholine, and piperazine, in each case unsubstituted, mono- or

polysubstituted with substituents independently of one another selected from the group consisting of -C_{1-6}-alkyl, -NH_2, -$NHCH_3$, -$N(CH_3)_2$, -C(=O)NH-C_{1-6}-alkyl, -C(=O)N(C_{1-6}-alkyl)$_2$, -C(=O)O-C_{1-6}-alkyl, -NHC(=O)O-C_{1-6}-alkyl, -pyridyl unsubstituted, and 1,2,4-oxadiazole unsubstituted or monosubstituted with -C_{1-6}-alkyl.

37. The compound per se, or for use according to any one of the preceding Clauses, wherein **R**^{3} and **R**^{4} together form a

pyrrolidine ring, unsubstituted or monosubstituted with -$N(CH_3)_2$;

piperidine ring, unsubstituted or monosubstituted with a substituent selected from the group consisting of -C_{1-6}-alkyl, -NH_2, -$N(CH_3)_2$, -C(=O)NH-C_{1-6}-alkyl, -C(=O)O-C_{1-6}-alkyl, -NHC(=O)O-C_{1-6}-alkyl, and 1,2,4-oxadiazole unsubstituted or monosubstituted with -C_{1-6}-alkyl;

morpholine ring, unsubstituted; or

piperazine ring, unsubstituted or N-substituted with a substituent selected from the group consisting of -C_{1-6}-alkyl and -pyridyl unsubstituted.

38. The compound per se, or for use according to one any one of the preceding Clauses, wherein **R**^{5} and **R**$^{5'}$ independently of one another represent

-H;

-C_1-C_6-alkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted;

-C_1-C_6-heteroalkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted;

3-14-membered cycloalkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted; wherein said 3-14-membered cycloalkyl is optionally connected through -C_1-C_6-alkylene- or -C_1-C_6-heteroalkylene-, in each case saturated or unsaturated, unsubstituted, mono- or polysubstituted.

39. The compound per se, or for use according to any one of the preceding Clauses, wherein **R**^{5} and **R**$^{5'}$ independently of one another represent -H, -C_1-C_6-alkyl, or -C_1-C_6-alkylene-N(C_1-C_6-alkyl)$_2$.

40. The compound per se, or for use according to any one of the preceding Clauses, wherein at least one of **R**^{5} and **R**$^{5'}$ does not represent -H.

41. The compound per se, or for use according to any one of the preceding Clauses, wherein **R**^{6}, **R**^{7} and **R**^{8} independently of one another represent

-H;

-F, -Cl, -Br, -I, -OH, -SH, -SF_5, -CN, -NO_2, -C(=O)OH, -NH_2;

-C_{1-6}-alkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted;

-O-C_{1-6}-alkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted;

-NHC_{1-6}-alkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted;

-N(C_{1-6}-alkyl)$_2$, saturated or unsaturated, unsubstituted, mono- or polysubstituted;

-C(=O)OC_{1-6}-alkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted;

-OC(=O)C_{1-6}-alkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted;

-C_{1-6}-heteroalkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted.

42. The compound per se, or for use according to any one of the preceding Clauses, wherein **R^6**, **R^7** and **R^8** independently of one another represent

-H, -F, -Cl, -Br, -I, -OH, -SH, -SF_5, -CN, -NO_2, -C(=O)OH, -NH_2,

-C_{1-6}-alkyl, -CF_3, -CHF_2, -CH_2F,

-O-C_{1-6}-alkyl, -OCF_3, -$OCHF_2$, -OCH_2F,

-NHC_{1-6}-alkyl unsubstituted or substituted with one or more substituents independently of one another selected from -OH, =O, -F, -Cl, -Br, -I, -SH, =S, -CN, -CF_3, -CHF_2, -CH_2F, -OCF_3, -$OCHF_2$, -OCH_2F, SF_5, -NO_2, -C(=O)OH, -NH_2, and -C(=O)NH_2;

-N(C_{1-6}-alkyl)$_2$ unsubstituted or substituted with one or more substituents independently of one another selected from -OH, =O, -F, -Cl, -Br, -I, -SH, =S, -CN, -CF_3, -CHF_2, -CH_2F, -OCF_3, -$OCHF_2$, -OCH_2F, SF_5, -NO_2, -C(=O)OH, -NH_2, and -C(=O)NH_2;

-C(=O)OC_{1-6}-alkyl unsubstituted or substituted with one or more substituents independently of one another selected from -OH, =O, -F, -Cl, -Br, -I, -SH, =S, -CN, -CF_3, -CHF_2, -CH_2F, -OCF_3, -$OCHF_2$, -OCH_2F, SF_5, -NO_2, -C(=O)OH, -NH_2, and -C(=O)NH_2;

-OC(=O)C_{1-6}-alkyl unsubstituted or substituted with one or more substituents independently of one another selected from -OH, =O, -F, -Cl, -Br, -I, -SH, =S, -CN, -CF_3, -CHF_2, -CH_2F, -OCF_3, -$OCHF_2$, -OCH_2F, SF_5, -NO_2, -C(=O)OH, -NH_2, and -C(=O)NH_2; or

-C_{1-6}-heteroalkyl unsubstituted or substituted with one or more substituents independently of one another selected from -OH, =O, -F, -Cl, -Br, -I, -SH, =S, -CN, -CF_3, -CHF_2, -CH_2F, -OCF_3, -$OCHF_2$, -OCH_2F, SF_5, -NO_2, -C(=O)OH, -NH_2, and -C(=O)NH_2.

43. The compound per se, or for use according to any one of the preceding Clauses, wherein **R^6** represents -H, -F, -Cl, -CN, or -C_1-C_6-alkyl.

44. The compound per se, or for use according to any one of the preceding Clauses, wherein **R^6** does not represent -H.

45. The compound per se, or for use according to any one of the preceding Clauses, wherein **R^7** represents -H, -F, -Cl, -CN, or -C_1-C_6-alkyl.

46. The compound per se, or for use according to any one of the preceding Clauses, wherein **R^7** does not represent -H.

47. The compound per se, or for use according to any one of the preceding Clauses, wherein **R^8** represents -H, -F, -Cl, -CN, or -C_1-C_6-alkyl.

48. The compound per se, or for use according to any one of the preceding Clauses, wherein **R^8** does not represent -H.

49. The compound per se, or for use according to any one of the preceding Clauses, wherein

(i) **R^6**, **R^7** and **R^8** each represent -H; or

(ii) two of **R**^{6}, **R**^{7} and **R**^{8} represent -H and the other of **R**^{6}, **R**^{7} and **R**^{8} represents -F, -Cl, -CN, or -CH_3; or

(iii) one of **R**^{6}, **R**^{7} and **R**^{8} represents -H and the other of **R**^{6}, **R**^{7} and **R**^{8} independently of one another represent -F, -Cl, -CN, or -CH_3.

50. The compound per se, or for use according to any one of the preceding Clauses, which is selected from the group consisting of cpd 001 to cpd 199, or cpd 200 to 262, as mentioned above and the physiologically acceptable salts thereof.

51. The compound per se, or for use according to any one of the preceding Clauses, wherein the pain is selected from nociceptive pain, inflammatory pain, and neuropathic pain.

52. The compound per se, or for use according to any one of the preceding Clauses, wherein the pain is post-operative pain.

53. A compound of formula (I), a stereo-isomeric form, a physiologically acceptable salt, solvate and/or polymorph thereof, as defined in any one of the preceding Clauses, wherein

(a-1) **Q** represents -N**R**^{3}**R**^{4}; **R**^{1} represents **R**^{W} ; and **R**^{W} represents -C_1-C_6-alkyl - and/or

(a-2) **Q** represents -N**R**^{3}**R**^{4}; and at least one of **R**^{5} and **R**$^{5'}$ represents -H; and/or

(a-3) **Q** represents -N**R**^{3}**R**^{4} ; and **R**^{6} represents -H; and/or

(a-4) **Q** represents -N**R**^{3}**R**^{4} ; and **R**^{8} represents -H;

or

(b-1)

(b-1) Q represents -N**R**^{3}**R**^{4}; and **R**^{1} represents -CH_2F, -CHF_2, -CF_3, -CN, -methyl, -ethyl, -propyl or -cyclopropyl; and/or

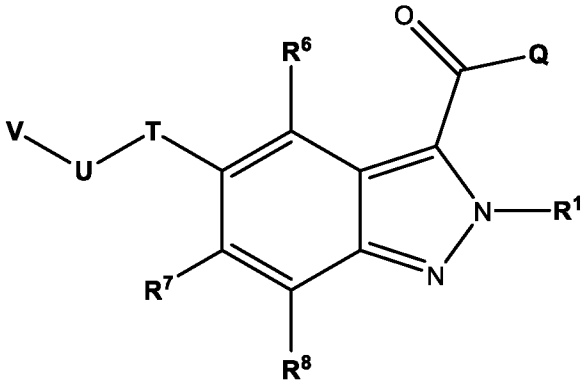
(b-2) Q represents -N**R**^{3}**R**^{4}; and at least one of **R**^{5} and **R**$^{5'}$ does not represent -H; and/or

(b-3) Q represents -N**R**^{3}**R**^{4}; and **R**^{3} represents -H.

54. A pharmaceutical composition or a medicament comprising a compound according to any one of the preceding Clauses.

Further exemplary embodiments of the invention are summarized as Items 1 to 70 hereinafter:

1. A compound of formula (I), a stereo-isomeric form, a physiologically acceptable salt, solvate and/or polymorph thereof



(I)

wherein

R^1 represents -F, -Cl, -Br, -I, -CN, -R^W, -OR^W, -OC(=O)R^W, -N$R^W R^X$, -NR^WC(=O)R^X, -SR^W, -S(=O)R^W, -S(=O)$_2R^W$, -C(=O)R^W, -C(=O)OR^W, or -C(=O)N$R^W R^X$;

Q represents -OR^2 or -NR^3R^4;

R^2 represents -R^Y;

R^3 represents -OH or -R^Y;

R^4 represents -R^Y or -S(=O)$_2R^Y$;

or R^3 and R^4 together form a 4, 5, 6, 7 or 8 membered heterocycle containing 1 to 3 heteroatoms selected from N, O and S, saturated or unsaturated, unsubstituted or mono- or polysubstituted;

T represents -O- and **U** represents -C$R^5R^{5'}$-; or **T** represents -C$R^5R^{5'}$- and **U** represents -O-;

R^5 and $R^{5'}$ independently of one another represent -R^Y;

R^6, R^7 and R^8 independently of one another represent -F, -Cl, -Br, -I, -CN, -NO_2, -SF_5, -R^W, -OR^W, -OC(=O)R^W, -N$R^W R^X$, -NR^WC(=O)R^X, -SR^W, -S(=O)R^W, -S(=O)$_2R^W$, -C(=O)R^W, -C(=O)OR^W, or -C(=O)N$R^W R^X$;

V represents 3-14-membered heterocycloalkyl, saturated or unsaturated; 3-14-membered cycloalkyl, saturated or unsaturated; 5-14-membered aryl; C_1-C_6 alkyl or 5-14-membered heteroaryl; in each case unsubstituted, mono- or polysubstituted with substituents independently of one another selected from -F, -Cl, -Br, -I, -CF_3, -CF_2H, C_1-C_6 alkyl, -CN, -NO, -NO_2, =O, =S, -SF_5, -R^Y, -OR^Y, -OC(=O)R^Y, -N$R^Y R^Z$, -NR^YC(=O)R^Z, -SR^Y, -S(=O)R^Y, -S(=O)$_2R^Y$, -C(=O)R^Y, -C(=O)OR^Y, or -C(=O)N$R^Y R^Z$;

wherein

R^W and R^X independently of one another and in each case independently represent

-H;

-C_1-C_6-alkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted;

-C_1-C_6-heteroalkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted;

3-14-membered cycloalkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted; wherein said 3-14-membered cycloalkyl is optionally connected through -C_1-C_6-alkylene- or -C_1-C_6-heteroalkylene-, in each case saturated or unsaturated, unsubstituted, mono- or polysubstituted; or

3-14-membered heterocycloalkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted; wherein said 3-14-membered heterocycloalkyl is optionally connected through -C_1-C_6-alkylene- or -C_1-C_6-heteroalkylene-, in each case saturated or unsaturated, unsubstituted, mono- or polysubstituted;

$\mathbf{R^Y}$ and $\mathbf{R^Z}$ independently of one another and in each case independently represent

-H;

-C_1-C_6-alkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted;

-C_1-C_6-heteroalkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted;

3-14-membered cycloalkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted; wherein said 3-14-membered cycloalkyl is optionally connected through -C_1-C_6-alkylene- or -C_1-C_6-heteroalkylene-, in each case saturated or unsaturated, unsubstituted, mono- or polysubstituted;

3-14-membered heterocycloalkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted; wherein said 3-14-membered heterocycloalkyl is optionally connected through -C_1-C_6-alkylene- or -C_1-C_6-heteroalkylene-, in each case saturated or unsaturated, unsubstituted, mono- or polysubstituted;

6-14-membered aryl, unsubstituted, mono- or polysubstituted; wherein said 6-14-membered aryl is optionally connected through -C_1-C_6-alkylene- or -C_1-C_6-heteroalkylene-, in each case saturated or unsaturated, unsubstituted, mono- or polysubstituted; or

5-14-membered heteroaryl, unsubstituted, mono- or polysubstituted; wherein said 5-14-membered heteroaryl is optionally connected through -C_1-C_6-alkylene- or -C_1-C_6-heteroalkylene-, in each case saturated or unsaturated, unsubstituted, mono- or polysubstituted;

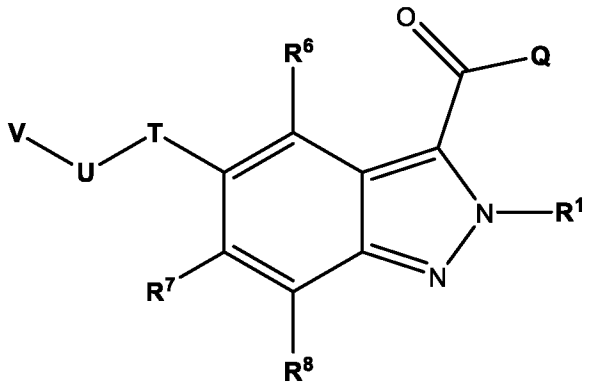
or $\mathbf{R^Y}$ and $\mathbf{R^Z}$ together form a 4, 5, 6, 7 or 8 membered heterocycle containing 1 to 3 heteroatoms selected from N, O and S, saturated or unsaturated, unsubstituted or mono- or polysubstituted;

and wherein "mono- or polysubstituted" in each case independently means substituted with one or more substituents independently of one another selected from -F, -Cl, -Br, -I, -CN, -C_{1-6}-alkyl, -CF_3, -CF_2H, -CFH_2, -CF_2Cl, -$CFCl_2$, -C_{1-6}-alkylene-CF_3, -C_{1-6}-alkylene-

CF_2H, -C_{1-6}-alkylene-CFH_2, -C_{1-6}-alkylene-O-CF_3, -C_{1-6}-alkylene-O-CF_2H, -C_{1-6}-alkylene-O-CFH_2, -C_{1-6}-alkylene-NH-C_{1-6}-alkylene-CF_3, -C_{1-6}-alkylene-N(C_{1-6}-alkyl)-C_{1-6}-alkylene-CF_3, -C(=O)-C_{1-6}-alkyl, -C_{1-6}-alkylene-C(=O)-C_{1-6}-alkyl, -C(=O)OH, -C_{1-6}-alkylene-C(=O)-OH, -C(=O)-OC_{1-6}-alkyl, -C_{1-6}-alkylene-C(=O)-OC_{1-6}-alkyl, -C(=O)O-C_{1-6}-alkylene-CF_3, -C(=O)-NH_2, -C_{1-6}-alkylene-C(=O)-NH_2, -C(=O)-NH(C_{1-6}-alkyl), -C_{1-6}-alkylene-C(=O)-NH(C_{1-6}-alkyl), -C(=O)-N(C_{1-6}-alkyl)$_2$, -C_{1-6}-alkylene-C(=O)-N(C_{1-6}-alkyl)$_2$, -C(=O)-NH(OH), -C_{1-6}-alkylene-C(=O)-NH(OH), -OH, -C_{1-6}-alkylene-OH, =O, -OCF_3, -OCF_2H, -$OCFH_2$, -OCF_2Cl, -$OCFCl_2$, -O-C_{1-6}-alkyl, -C_{1-6}-alkylene-O-C_{1-6}-alkyl, -O-C_{1-6}-alkylene-O-C_{1-6}-alkyl, -O-C_{1-6}-alkylene-NH_2, -O-C_{1-6}-alkylene-NH-C_{1-6}-alkyl, -O-C_{1-6}-alkylene-N(C_{1-6}-alkyl)$_2$, -O-C(=O)-C_{1-6}-alkyl, -C_{1-6}-alkylene-O-C(=O)-C_{1-6}-alkyl, -O-C(=O)-O-C_{1-6}-alkyl, -C_{1-6}-alkylene-O-C(=O)-O-C_{1-6}-alkyl, -O-C(=O)-NH(C_{1-6}-alkyl), -C_{1-6}-alkylene-O-C(=O)-NH(C_{1-6}-alkyl), -O-C(=O)-N(C_{1-6}-alkyl)$_2$, -C_{1-6}-alkylene-O-C(=O)-N(C_{1-6}-alkyl)$_2$, -O-S(=O)$_2$-NH_2, -C_{1-6}-alkylene-O-S(=O)$_2$-NH_2, -O-S(=O)$_2$-NH(C_{1-6}-alkyl), -C_{1-6}-alkylene-O-S(=O)$_2$-NH(C_{1-6}-alkyl), -O-S(=O)$_2$-N(C_{1-6}-alkyl)$_2$, -C_{1-6}-alkylene-O-S(=O)$_2$-N(C_{1-6}-alkyl)$_2$, -NH_2, -NO, -NO_2, -C_{1-6}-alkylene-NH_2, -NH(C_{1-6}-alkyl), -N(3-14-membered cycloalkyl)(C_{1-6}-alkyl), -N(C_{1-6}-alkyl)-C_{1-6}-alkylene-OH, -N(H)-C_{1-6}-alkylene-OH, -C_{1-6}-alkylene-NH(C_{1-6}-alkyl), -N(C_{1-6}-alkyl)$_2$, -C_{1-6}-alkylene-N(C_{1-6}-alkyl)$_2$, -NH-C(=O)-C_{1-6}-alkyl, -C_{1-6}-alkylene-NH-C(=O)-C_{1-6}-alkyl, -NH-C(=O)-O-C_{1-6}-alkyl, -C_{1-6}-alkylene-NH-C(=O)-O-C_{1-6}-alkyl, -NH-C(=O)-NH_2, -C_{1-6}-alkylene-NH-C(=O)-NH_2, -NH-C(=O)-NH(C_{1-6}-alkyl), -C_{1-6}-alkylene-NH-C(=O)-NH(C_{1-6}-alkyl), -NH-C(=O)-N(C_{1-6}-alkyl)$_2$, -C_{1-6}-alkylene-NH-C(=O)-N(C_{1-6}-alkyl)$_2$, -N(C_{1-6}-alkyl)-C(=O)-C_{1-6}-alkyl, -C_{1-6}-alkylene-N(C_{1-6}-alkyl)-C(=O)-C_{1-6}-alkyl, -N(C_{1-6}-alkyl)-C(=O)-O-C_{1-6}-alkyl, -C_{1-6}-alkylene-N(C_{1-6}-alkyl)-C(=O)-O-C_{1-6}-alkyl, -N(C_{1-6}-alkyl)-C(=O)-NH_2, -C_{1-6}-alkylene-N(C_{1-6}-alkyl)-C(=O)-NH_2, -N(C_{1-6}-alkyl)-C(=O)-NH(C_{1-6}-alkyl), -C_{1-6}-alkylene-N(C_{1-6}-alkyl)-C(=O)-NH(C_{1-6}-alkyl), -N(C_{1-6}-alkyl)-C(=O)-N(C_{1-6}-alkyl)$_2$, -C_{1-6}-alkylene-N(C_{1-6}-alkyl)-C(=O)-N(C_{1-6}-alkyl)$_2$, -NH-S(=O)$_2$OH, -C_{1-6}-alkylene-NH-S(=O)$_2$OH, -NH-S(=O)$_2$-C_{1-6}-alkyl, -C_{1-6}-alkylene-NH-S(=O)$_2$-C_{1-6}-alkyl, -NH-S(=O)$_2$-O-C_{1-6}-alkyl, -C_{1-6}-alkylene-NH-S(=O)$_2$-O-C_{1-6}-alkyl, -NH-S(=O)$_2$-NH_2, -C_{1-6}-alkylene-NH-S(=O)$_2$-NH_2, -NH-S(=O)$_2$-NH(C_{1-6}-alkyl), -C_{1-6}-alkylene-NH-S(=O)$_2$-NH(C_{1-6}-alkyl), -NH-S(=O)$_2$N(C_{1-6}-alkyl)$_2$, -C_{1-6}-alkylene-NH-S(=O)$_2$N(C_{1-6}-alkyl)$_2$, -N(C_{1-6}-alkyl)-S(=O)$_2$-OH, -C_{1-6}-alkylene-N(C_{1-6}-alkyl)-S(=O)$_2$-OH, -N(C_{1-6}-alkyl)-S(=O)$_2$-C_{1-6}-alkyl, -C_{1-6}-alkylene-N(C_{1-6}-alkyl)-S(=O)$_2$-C_{1-6}-alkyl, -N(C_{1-6}-alkyl)-S(=O)$_2$-O-C_{1-6}-alkyl, -C_{1-6}-alkylene-N(C_{1-6}-alkyl)-S(=O)$_2$-O-C_{1-6}-alkyl, -N(C_{1-6}-alkyl)-S(=O)$_2$-NH_2, -C_{1-6}-alkylene-N(C_{1-6}-alkyl)-S(=O)$_2$-NH_2, -N(C_{1-6}-alkyl)-S(=O)$_2$-NH(C_{1-6}-alkyl), -C_{1-6}-alkylene-N(C_{1-6}-alkyl)-S(=O)$_2$-NH(C_{1-6}-alkyl), -N(C_{1-6}-alkyl)-S(=O)$_2$-N(C_{1-6}-alkyl)$_2$, -C_{1-6}-alkylene-N(C_{1-6}-alkyl)-S(=O)$_2$-N(C_{1-6}-alkyl)$_2$, -SH, =S, -SF_5, -SCF_3, -SCF_2H, -$SCFH_2$, -S-C_{1-6}-alkyl, -C_{1-6}-alkylene-S-C_{1-6}-alkyl, -S(=O)-C_{1-6}-alkyl, -C_{1-6}-alkylene-S(=O)-C_{1-6}-alkyl, -S(=O)$_2$-C_{1-6}-alkyl, -C_{1-6}-alkylene-S(=O)$_2$-C_{1-6}-alkyl, -S(=O)$_2$-OH, -C_{1-6}-alkylene-S(=O)$_2$-OH, -S(=O)$_2$-

O-C_{1-6}-alkyl, -C_{1-6}-alkylene-S(=O)$_2$-O-C_{1-6}-alkyl, -S(=O)$_2$-NH_2, -C_{1-6}-alkylene-S(=O)$_2$-NH_2, -S(=O)$_2$-NH(C_{1-6}-alkyl), -C_{1-6}-alkylene-S(=O)$_2$-NH(C_{1-6}-alkyl), -S(=O)$_2$-N(C_{1-6}-alkyl)$_2$, -C_{1-6}-alkylene-S(=O)$_2$-N(C_{1-6}-alkyl)$_2$, 3-14-membered cycloalkyl, -C_{1-6}-alkylene-(3-14-membered cycloalkyl), 3 to 14-membered heterocycloalkyl, -C_{1-6}-alkylene-(3 to 14-membered heterocycloalkyl), -phenyl, -C_{1-6}-alkylene-phenyl, 5 to 14-membered heteroaryl, -C_{1-6}-alkylene-(5 to 14-membered heteroaryl), -O-(3-14-membered cycloalkyl), -O-(3 to 14-membered heterocycloalkyl), -O-phenyl, -O-(5 to 14-membered heteroaryl), -C(=O)-(3-14-membered cycloalkyl), -C(=O)-(3 to 14-membered heterocycloalkyl), -C(=O)-phenyl, -C(=O)-(5 to 14-membered heteroaryl), -S(=O)$_2$-(3-14-membered cycloalkyl), -S(=O)$_2$-(3 to 14-membered heterocycloalkyl), -S(=O)$_2$-phenyl, -S(=O)$_2$-(5 to 14-membered heteroaryl).

2. The compound of formula (I), a stereo-isomeric form, a physiologically acceptable salt, solvate and/or polymorph thereof, preferably according to item 1,



wherein

Q represents -OR^2 or -NR^3R^4;

T represents -O-;

U represents –$CR^5R^{5'}$-;

V represents H or R^4

R^1 represents -H, R^9, -O-C_{1-6}-alkyl, -C_{1-6}-alkylene-CF_3, -C_{1-6}-alkylene-CF_2H, -C_{1-6}-alkylene-CFH_2, -C_{1-6}-alkylene-NH-C_{1-6}-alkylene-CF_3, -C_{1-6}-alkylene-N(C_{1-6}-alkyl)-C_{1-6}-alkylene-CF_3, -S(=O)-C_{1-6}-alkyl, -S(=O)$_2$-C_{1-6}-alkyl, cyclopropyl unsubstituted, cyclobutyl unsubstituted, cyclopentyl unsubstituted or cyclohexyl unsubstituted;

R^2 represents hydrogen or R^9;

R^3 represents -H, R^9, -OH, -C_{1-6}-alkylene-CF_3, -C_{1-6}-alkylene-CF_2H, -C_{1-6}-alkylene-CFH_2, -C_{1-6}-alkylene-NH-C_{1-6}-alkylene-CF_3, or -C_{1-6}-alkylene-N(C_{1-6}-alkyl)-C_{1-6}-alkylene-CF_3;

R^4 represents $R^{4'}$ or -SO_2-$R^{4'}$, wherein

$R^{4'}$ represents -R^9, -R^{cycl} or -R^{10}-R^{cycl}; and

R^{cycl} represents

3-14-membered cycloalkyl, saturated or unsaturated

4-14-membered heterocycloalkyl, saturated or unsaturated, with one or more N, O or S atom in the heterocycloalkyl ring

6-14-membered aryl, or

5-14-membered heteroaryl with one or more N, O or S in the heteroaryl ring; or

R^1 and R^3 together may form a group $-R^{10}-$; or

R^3 and R^4 together may form a group $-R^{10}-$; and

R^5, $R^{5'}$, R^6, R^7 and R^8 independently of each other represent hydrogen or R^9; and

R^{cycl} may be substituted by R^9 and the cycloalkyl rings and the heterocycloalkyl rings of R^{cycl} independently of each other may be substituted by =O or =S; and

R^9 represents $-C_{1-6}$-alkyl or $-C_{1-6}$-heteroalkyl with one or more N, O or S in the chain; and

R^{10} represents $-C_{1-6}$-alkylen- or $-C_{1-6}$-heteroalkylen- with one or more N, O or S in the chain; and wherein

R^9 and R^{10} may be straight or branched, saturated or unsaturated; and

R^9 , R^{10} and R^{cycl} may be substituted by R^{11}; and

R^{11} is selected from the list consisting of -OR, $-NR_2$, halogen, -CN, -COOR, $-CO-NR_2$, -CONR(OR), -O-CO-O-C_{1-6}-alkyl, -NR-C(=O)-R, -NR-C(=O)-O-R, $-NR-C(=O)-N(R)_2$, $-O-S(=O)_2-NR_2$, $-N(R)-S(=O)_2OR$, $-N(R)-S(=O)_2NR_2$, -SR, -S(=O)-R, $-S(=O)_2-OR$, $-S(=O)_2-NR_2$, -NO, $-NO_2$, $-C_{1-6}$-alkylen-OR, $-C_{1-6}$-alkylen-NR_2 wherein the residues R may be independently of each other H or $-C_{1-6}$-alkyl, and wherein

all groups R^9 to R^{11} and R^{cycl} may be selected independently of each other and may be selected in each case independently.

3. The compound of any one of the preceding items, wherein R^1 represents a straight or branched alkyl with 1 to 6 carbon atoms, which may be substituted by halogen, -OR, $-CONR_2$ or $-NR_2$, wherein the residues R independently of each other represent H or C_{1-6}-alkyl.

4. The compound of any one of the preceding items, wherein R^3 represent hydrogen or R^9.

5. The compound of any one of the preceding items, wherein

Q represents OR^2 or $-NR^3R^4$;

T represents -O-;

U represents $-CR^5R^{5'}-$;

V represents H or R^4

R^1 represents a straight or branched alkyl with 1 to 6 carbon atoms, which may be substituted by halogen, -OR, -$CONR_2$ or -NR_2, wherein the residues R independently of each other represent H or C_{1-6}-alkyl;

R^2 and R^3 represent hydrogen or R^9;

R^4 represents $R^{4'}$ or -SO_2-$R^{4'}$, wherein

$R^{4'}$ represents -R^9, -R^{cycl} or -R^{10}-R^{cycl}; and

R^{cycl} represents

3-14-membered cycloalkyl, saturated or unsaturated

4-14-membered heterocycloalkyl, saturated or unsaturated, with one or more N, O or S atom in the heterocycloalkyl ring,

6-14-membered aryl, or

5-14-membered heteroaryl with one or more N, O or S in the heteroaryl ring; or

R^1 and R^3 together may form a group -R^{10}-; and

R^5, $R^{5'}$, R^6, R^7 and R^8 independently of each other represent hydrogen or R^9; and

R^{cycl} may be substituted by R^9 and the cycloalkyl rings and the heterocycloalkyl rings of R^{cycl} independently of each other may be substituted by =O or =S; and

R^9 represents -C_{1-6}-alkyl or -C_{1-6}-heteroalkyl with one or more N, O or S in the chain; and

R^{10} represents -C_{1-6}-alkylen- or -C_{1-6}-heteroalkylen- with one or more N, O or S in the chain; and wherein

R^9 and R^{10} may be straight or branched, saturated or unsaturated; and

R^9 , R^{10} and R^{cycl} may be substituted by R^{11}; and

R^{11} is selected from the list consisting of -OR, -NR_2, halogen, -CN, -COOR, -CO-NR_2, -CONR(OR), -O-CO-O-C_{1-6}-alkyl, -NR-C(=O)-R, -NR-C(=O)-O-R, -NR-C(=O)-$N(R)_2$, -O-$S(=O)_2$-NR_2, -N(R)-$S(=O)_2$OR, -N(R)-$S(=O)_2NR_2$, -SR, -S(=O)-R, -$S(=O)_2$-OR, -$S(=O)_2$-NR_2, -NO, -NO_2, -C_{1-6}-alkylen-OR, -C_{1-6}-alkylen-NR_2 wherein the residues R may be independently of each other H or -C_{1-6}-alkyl, and wherein

all groups R^9 to R^{11} and R^{cycl} may be selected independently of each other and may be selected in each case independently.

6. The compound of any one of the preceding items, wherein V represents H, -R^9 or -R^{cycl}.

7. The compound of any one of the preceding items, wherein R^5, $R^{5'}$, R^6, R^7 and R^8 independently of each other represent hydrogen or C_{1-3}-alkyl.

8. The compound of any one of the preceding items, wherein R^5, $R^{5'}$, R^6, R^7 and R^8 independently of each other represent hydrogen or methyl.

9. The compound of any one of the preceding items, wherein

Q represents OR^2 or $-NR^3R^4$;

T represents -O-;

U represents $–CR^5R^{5'}$-;

V represents H, $-R^9$ or $-R^{cycl}$;

R^1 represents $-C_{1-6}$-alkyl, which may be substituted by halogen, -OH, OR, $-CONR_2$ or $-NR_2$, wherein the residues R independently of each other represent H or $-C_{1-6}$-alkyl;

R^2 and R^3 represent hydrogen or methyl;

R^4 represents $R^{4'}$ or $-SO_2-R^{4'}$, wherein

$R^{4'}$ represents $-R^9$, $-R^{cycl}$ or $-R^{10}-R^{cycl}$; and

R^{cycl} represents

3-14-membered cycloalkyl, saturated or unsaturated

4-14-membered heterocycloalkyl, saturated or unsaturated, with one or more N, O or S atom in the heterocycloalkyl ring

6-14-membered aryl, or

5-14-membered heteroaryl with one or more N, O or S in the heteroaryl ring; or

R^1 and R^3 together may form a group $-R^{10}$-; and

R^5, $R^{5'}$, R^6, R^7 and R^8 independently of each other represent hydrogen or methyl; and

R^{cycl} may be substituted by R^9 and the cycloalkyl rings and the heterocycloalkyl rings of R^{cycl} independently of each other may be substituted by =O or =S; and

R^9 represents $-C_{1-6}$-alkyl or $-C_{1-6}$-heteroalkyl with one or more N, O or S in the chain; and

R^{10} represents $-C_{1-6}$-alkylen- or $-C_{1-6}$-heteroalkylen- with one or more N, O or S in the chain; and wherein

R^9 and R^{10} may be straight or branched, saturated or unsaturated; and

R^9 , R^{10} and R^{cycl} may be substituted by R^{11}; and

R^{11} is selected from the list consisting of -OR, $-NR_2$, halogen, -CN, -COOR, $-CO-NR_2$, -CONR(OR), -O-CO-O-C_{1-6}-alkyl, -NR-C(=O)-R, -NR-C(=O)-O-R, -NR-C(=O)-$N(R)_2$, -O-$S(=O)_2-NR_2$, -N(R)-$S(=O)_2$OR, -N(R)-$S(=O)_2NR_2$, -SR, -S(=O)-R, $-S(=O)_2$-OR, $-S(=O)_2-NR_2$, -NO, $-NO_2$, $-C_{1-6}$-alkylen-OR, $-C_{1-6}$-alkylen-NR_2 wherein the residues R may be independently of each other H or $-C_{1-6}$-alkyl, and wherein

all groups R^9 to R^{11} and R^{cycl} may be selected independently of each other and may be selected in each case independently.

10. The compound of any one of the preceding items, wherein R^5 and $R^{5'}$ represent hydrogen.

11. The compound of any one of the preceding items, wherein R^1 and R^3 together form a group $-R^{10}-$.

12. The compound of any one of the preceding items, wherein R^4 represents $R^{4'}$ or $-SO_2-C_{1-6}$-alkyl.

13. The compound of any one of the preceding items, wherein V represents H, C_{1-6}-alkyl or $-R^{cycl}$.

14. The compound of any one of the preceding items, wherein

Q represents OR^2 or $-NR^3R^4$;
T represents -O-;
U represents $–CH_2-$;
V represents H, C_{1-6}-alkyl or $-R^{cycl}$; wherein R^{cycl} of group V may be substituted by at least one group selected from the list consisting of $-COO-C_{1-6}$-alkyl, $-CO-NR_2$, -CN, halogen or C_{1-6}-alkyl, wherein R represents independently of each other H or $-C_{1-6}$-alkyl and the alkyl groups in the group V may be substituted by one or more halogen atoms;
R^1 represents $-C_{1-6}$-alkyl, which may be substituted by halogen, -OH, $-CONR_2$ or $-NR_2$, wherein the residues R independently of each other represent H or $-C_{1-6}$-alkyl;
R^2 and R^3 represent hydrogen or methyl;
R^4 represents $-SO_2-C_{1-6}$-alkyl, $-R^9$, $-R^{cycl}$ or $-R^{10}-R^{cycl}$; and
R^{cycl} represents
3-14-membered cycloalkyl, saturated or unsaturated
4-14-membered heterocycloalkyl, saturated or unsaturated, with one or more N, O or S atom in the heterocycloalkyl ring
6-14-membered aryl, or
5-14-membered heteroaryl with one or more N, O or S in the heteroaryl ring; and
R^1 and R^3 together may form a group $-R^{10}-$, which may be substituted by R^{11}; and
R^6, R^7 and R^8 independently of each other represent hydrogen or methyl; and
R^{cycl} may be substituted by R^9 and the cycloalkyl rings and the heterocycloalkyl rings of R^{cycl} independently of each other may be substituted by =O or =S; and
R^9 represents $-C_{1-6}$-alkyl or $-C_{1-6}$-heteroalkyl with one or more N, O or S in the chain; and
R^{10} represents $-C_{1-6}$-alkylen- or $-C_{1-6}$-heteroalkylen- with one or more N, O or S in the chain; and wherein
R^9 and R^{10} may be straight or branched, saturated or unsaturated; and

R^9 , R^{10} and R^{cycl} of R^4 may be substituted by R^{11}; and

R^{11} is selected from the list consisting of -OR, -NR_2, halogen, -CN, -COOR, -CO-NR_2, -CONR(OR), -O-CO-O-C_{1-6}-alkyl, -NR-C(=O)-R, -NR-C(=O)-O-R, -NR-C(=O)-$N(R)_2$, -O-$S(=O)_2$-NR_2, -N(R)-$S(=O)_2$OR, -N(R)-$S(=O)_2NR_2$, -SR, -S(=O)-R, -$S(=O)_2$-OR, -$S(=O)_2$-NR_2, -NO, -NO_2, -C_{1-6}-alkylen-OR, -C_{1-6}-alkylen-NR_2 wherein the residues R may be independently of each other H or -C_{1-6}-alkyl, and wherein

all groups R^9 to R^{11} and R^{cycl} may be selected independently of each other and may be selected in each case independently.

15. The compound of any one of the preceding items, wherein R^6, R^7 and R^8 independently of each other represent hydrogen.

16. The compound of any one of the preceding items, wherein R^2 represents hydrogen.

17. The compound of any one of the preceding items, wherein R^3 represents hydrogen.

18. The compound of any one of the preceding items, wherein R^2 and R^3 represent hydrogen.

19. The compound of any one of the preceding items, wherein R^2, R^3, R^5, $R^{5'}$, R^6, R^7 and R^8 independently of each other represent hydrogen.

20. The compound of any one of the preceding items, wherein R^1 represents -C_{1-6}-alkyl.

21. The compound of any one of the preceding items, wherein R^1 and R^3 together form a group that represents straight or branched -C_{1-4}-alkylen- or -C_{1-4}-heteroalkylen- with one or more N, O or S in the chain, which may be unsaturated and may be substituted by R^{11}.

22. The compound of any one of the preceding items, wherein R^1 and R^3 together form a group that represents straight or branched -C_{1-3}-alkylen- or -C_{1-3}-heteroalkylen- with one or more N, O or S in the chain, which may be unsaturated and may be substituted by R^{11}.

23. The compound of any one of the preceding items, wherein

Q represents OR^2 or –NR^3R^4;

T represents -O-;

U represents -CH_2-;

V represents H, C_{1-6}-alkyl or -R^{cycl}; wherein R^{cycl} of group V may be substituted by at least one group selected from the list consisting of -COO-C_{1-6}-alkyl, -CO-NR_2, -CN, halogen or C_{1-6}-alkyl, wherein R represents independently of each other H or -C_{1-6}-alkyl and the alkyl groups in the group V may be substituted by one or more halogen atoms;

R^1 represents -C_{1-6}-alkyl;

R^2 represents hydrogen;

R^3 represents hydrogen;

R^4 represents -SO_2-C_{1-6}-alkyl, -R^9, -R^{cycl} or -R^{10}-R^{cycl}; and

R^{cycl} represents

3-6-membered cycloalkyl, saturated or unsaturated

4-7-membered heterocycloalkyl, saturated or unsaturated, with one or more N, O or S atom in the heterocycloalkyl ring

6-membered aryl, or

6-membered heteroaryl with one or more N, O or S in the heteroaryl ring; and

R^1 and R^3 together may form a group that represents -C_{1-3}-alkylen- or a -C_{1-3}-heteroalkylen- with one or more N, O or S in the chain, which may be unsaturated and may be substituted by R^{11}; and

R^6, R^7 and R^8 independently of each other represent hydrogen or methyl; and

R^{cycl} may be substituted by R^9 and the cycloalkyl rings and the heterocycloalkyl rings of R^{cycl} independently of each other may be substituted by =O or =S; and

R^9 represents -C_{1-6}-alkyl or a -C_{1-6}-heteroalkyl with one or more N, O or S in the chain; and

R^{10} represents -C_{1-6}-alkylen- or a -C_{1-6}-heteroalkylen- with one or more N, O or S in the chain; and wherein

R^9 and R^{10} may be straight or branched, saturated or unsaturated; and

R^9 , R^{10} and R^{cycl} of R^4 may be substituted by R^{11}; and

groups R^{11} are independently of each other selected from the list consisting of -OR, -NR_2, halogen, -CN, -COOR, -CO-NR_2, -CONR(OR), -O-CO-O-C_{1-6}-alkyl, -NR-C(=O)-R, -NR-C(=O)-O-R, -NR-C(=O)-$N(R)_2$, -O-$S(=O)_2$-NR_2, -N(R)-$S(=O)_2$OR, -N(R)-$S(=O)_2NR_2$, -SR, -S(=O)-R, -$S(=O)_2$-OR, -$S(=O)_2$-NR_2, -NO, -NO_2, -C_{1-6}-alkylen-OR, -C_{1-6}-alkylen-NR_2 wherein the residues R may be independently of each other H or -C_{1-6}-alkyl.

24. The compound of any one of the preceding items, wherein R^9 represents -C_{1-6}-alkyl, straight or branched.

25. The compound of any one of the preceding items, wherein R^9 represents -C_{1-6}-alkyl, straight or branched and R^{10} represents -C_{1-6}-alkylen-, straight or branched.

26. The compound of any one of the preceding items, wherein R^9 represents a straight or branched alkyl with 1 to 6 carbon atoms.

27. The compound of any one of the preceding items, wherein R^{10} represents a straight or branched alkanediyl with 1 to 6 carbon atoms.

28. The compound of any one of the preceding items, wherein R^{10} represents a straight or branched alkanediyl with 1 to 3 carbon atoms.

29. The compound of any one of the preceding items, wherein

Q represents OR^2 or $–NR^3R^4$;
T represents -O-;
U represents -CH_2-;
V represents H, C_{1-6}-alkyl or -R^{cycl}; wherein R^{cycl} of group V may be substituted by at least one group selected from the list consisting of -CN, halogen or a C_{1-3}-alkyl and all alkyl groups in the group V may be substituted by one or more halogen atoms;
R^1 represents -C_{1-3}-alkyl;
R^2 represents hydrogen;
R^3 represents hydrogen;
R^4 represents -SO_2-C_{1-6}-alkyl, -R^9, -R^{cycl} or -R^{10}-R^{cycl}; and
R^{cycl} represents
3-6-membered cycloalkyl, saturated or unsaturated
4-7-membered heterocycloalkyl, saturated or unsaturated, with one or more N, O or S atom in the heterocycloalkyl ring
6-membered aryl, or
6-membered heteroaryl with one or more N, O or S in the heteroaryl ring; and
R^1 and R^3 together may form a group that represents -C_{1-3}-alkylen- or a -C_{1-3}-heteroalkylen- with one or more N, O or S in the chain, which may be unsaturated and may be substituted by R^{11}; and
R^6, R^7 and R^8 represent hydrogen; and
R^{cycl} may be substituted by R^9 and the cycloalkyl rings and the heterocycloalkyl rings of R^{cycl} independently of each other may be substituted by =O or =S; and
R^9 represents C_{1-6} alkyl; and

R^{10} represents -C_{1-3}-alkylen; and

wherein R^9 and R^{10} may be straight or branched, saturated or unsaturated; and

R^9 ,R^{10} and R^{cycl} of R^4 may be substituted by R^{11}; and

groups R^{11} are independently of each other selected from the list consisting of OH, halogen, a C_{1-3}-alkyl group or a –$CONR_2$ group, wherein R may be independently of each other H or a C_{1-3}-alkyl group.

30. The compound of any one of the preceding items, wherein R^{cycl} comprises 1, 2 or 3 heteroatoms.

31. The compound of any one of the preceding items, wherein R^{cycl} comprises 1 or 2 heteroatoms.

32. The compound of any one of the preceding items, wherein R^1 and R^3 together form a group that represents a straight or branched alkanediyl or alkenediyl with 1 to 3 carbon atoms, which may not be substituted or may be substituted by Halogen, C_{1-6}-alkyl or $CONR_2$, wherein the residues R may be independently of each other H or a C_{1-3}-alkyl.

33. The compound of any one of the preceding items, wherein R^1 and R^3 together form a group that represents a straight or branched alkanediyl or alkenediyl with 1 to 3 carbon atoms.

34. The compound of any one of the preceding items, wherein R^9 represents a straight or branched alkyl with 1 to 3 carbon atoms.

35. The compound of any one of the preceding items, wherein

Q represents OR^2 or –NR^3R^4;

T represents -O-;

U represents -CH_2-;

V represents

H;

C_{1-3}-alkyl which may be substituted with at least one halogen;

3-6 membered cycloalkyl, which may be substituted with a -CN group;

4-6-membered heterocycloalkyl, comprising one oxygen atom in the heterocycloalkyl ring;

6-membered aryl, which may be substituted with at least one halogen or with a

C_{1-3}-alkyl group, wherein the C_{1-3}-alkyl group may be substituted by at least one halogen atom;

5-6-membered heteroaryl with one or more N, O or S atom in the heteroaryl ring, wherein the heteroaryl ring may be substituted with a C_{1-3}-alkyl group which may be substituted by at least one halogen atom;

R^1 represents -C_{1-3}-alkyl;

R^2 represents hydrogen;

R^3 represents hydrogen;

R^4 represents

-SO_2-C_{1-3}-alkyl;

C_{1-6} alkyl which may be substituted by OH, F or -$CONR_2$, wherein residues R are independently from each other hydrogen or C_{1-3} alkyl;

3-6-membered cycloalkyl which may be substituted by C_{1-3}-alkylene-OH or -$CONH_2$;

C_{1-3}-alkylene-3-6-membered cycloalkyl which may be substituted by a C_{1-3}-alkyl or a -N(C_{1-6} alkyl)$_2$ group;

4-7-membered heterocycloalkyl with one or more N or O atom in the heterocycloalkyl ring and wherein the heterocycloalkyl ring may be substituted by =O, halogen or -$CONR_2$ wherein the residues R independently of each other represent H or C_{1-3}-alkyl or the cycloalkyl ring may be substituted by a C_{1-3} alkyl group, which may be substituted by at least one of OH or halogen;

C_{1-4}-alkylene-4-7-membered heterocycloalkyl with one or more N, O in the heterocycloalkyl ring, wherein the heterocycloalkyl group may be substituted by C_{1-3} alkyl or =O;

5-7-membered heteroaryl with one or more N, O or S in the heteroaryl ring, wherein the heteroaryl ring may be substituted by C_{1-6} alkyl or OH; or a

C_{1-3}-alkylene-5-6-membered heteroaryl, with one or more N, O or S in the heteroaryl ring wherein the heteroaryl ring may be substituted by OH; or wherein

R^1 and R^3 together form a group that represents a straight or branched alkanediyl or alkenediyl with 1 to 3 carbon atoms; and wherein

R^6, R^7 and R^8 represent hydrogen.

36. The compound of any one of the preceding items, wherein

Q represents OR^2 or $–NR^3R^4$;

T represents -O-;

U represents -CH_2-;

V represents

H;

C_{1-3}-alkyl which may be substituted with at least one fluorine atom;

3-6 membered cycloalkyl, which may be substituted with a -CN group;

4-6-membered heterocycloalkyl, comprising one oxygen atom in the heterocycloalkyl ring;

6-membered aryl, which may be substituted with at least one fluorine atom or with a C_{1-3}-alkyl group, wherein the C_{1-3}-alkyl group may be substituted by at least one fluorine atom;

5-6-membered heteroaryl with one or more N, O or S atom in the heteroaryl ring, wherein the heteroaryl ring may be substituted with a C_{1-3}-alkyl group which may be substituted by at least one fluorine atom;

R^1 represents -C_{1-3}-alkyl;

R^2 represents hydrogen;

R^3 represents hydrogen;

R^4 represents

-SO_2-C_{1-3}-alkyl;

C_{1-6} alkyl which may be substituted by OH, F or -$CONR_2$, wherein residues R are independently from each other hydrogen or methyl;

3-6-membered cycloalkyl which may be substituted by C_{1-3}-alkylene-OH or -$CONH_2$;

C_{1-3}-alkylene-3-6-membered cycloalkyl which may be substituted by a C_{1-3}-alkyl or a -NMe_2 group;

4-7-membered heterocycloalkyl with one or more N or O atom in the heterocycloalkyl ring and wherein the heterocycloalkyl ring may be substituted by =O, F or -$CONR_2$ wherein the residues R independently of each other represent H or C_{1-3}-alkyl or the cycloalkyl ring may be substituted by a C_{1-3} alkyl group, wherein the C_{1-3} alkyl group may be substituted by at least one of OH or fluorine;

C_{1-4}-alkylene-4-7-membered heterocycloalkyl with one or more N, O in the heterocycloalkyl ring, wherein the heterocycloalkyl group may be substituted by C_{1-3} alkyl or =O;

5-7-membered heteroaryl with one or more N, O or S in the with one or more N, O or S in the heteroaryl ring, wherein heteroaryl ring may be substituted by methyl or OH; or a

C_{1-3}-alkylene-5-6-membered heteroaryl with one or more N, O or S in the heteroaryl ring, wherein the heteroaryl ring may be substituted by OH; or wherein

R^1 and R^3 together form a group that represents a straight or branched alkanediyl with 1 to 3 carbon atoms; and wherein

R^6, R^7 and R^8 represent hydrogen.

37. The compound of any one of the preceding items, wherein R^1 and R^3 together form a group that represents a group selected from -CH_2-CH_2- and -CH_2-CH_2-CH_2-.

38. The compound of any one of the preceding items, wherein

Q represents OR^2 or $–NR^3R^4$;

T represents -O-;

U represents $-CH_2-$;

V represents

H;

methyl which may be substituted with at least one fluorine atom;

3-5-membered cycloalkyl, which may be substituted with a -CN group;

4-6-membered heterocycloalkyl, comprising one oxygen atom in the heterocycloalkyl ring;

phenyl, which may be substituted with at least one fluorine atom or with a methyl group, wherein the methyl group may be substituted by at least one fluorine atom;

1,3-thiazole or 1H-pyrazole which may be substituted with a methyl group; or

pyridine, which may be substituted with a methyl group, and wherein the hydrogen atoms of the methyl group may be substituted by at least one fluorine atom;

R^1 represents $-C_{1-3}$-alkyl;

R^2 represents hydrogen;

R^3 represents hydrogen;

R^4 represents

$-SO_2Me$;

C_{1-5} alkyl which may be substituted by OH, F or $-CONR_2$, or $-NHS(=O)_2$-Me, wherein the residues R are independently from each other hydrogen or methyl;

3-4-membered cycloalkyl which may be substituted by $-CH_2OH$, $-CH_2CH_2OH$ or $-CONH_2$;

C_{1-3}-alkylene-3-4-membered cycloalkyl which may be substituted by a methyl or a $-NMe_2$ group;

4-6-membered heterocycloalkyl with one or more N or O atom in the heterocycloalkyl ring which may be a lactam ring and wherein the heterocycloalkyl ring may be substituted by F or $-CONR_2$ wherein the residues R independently of each other represent H or methyl or the heterocycloalkyl ring may be substituted by a C_{1-2} alkyl group, wherein the C_{1-2} alkyl group may be substituted by at least one of OH or F;

C_{1-3}-alkylene-5-6-membered heterocycloalkyl with one or more N or O in the heterocycloalkyl ring, which may be a lactam ring and wherein the heterocycloalkyl group may be substituted by methyl;

5-6-membered heteroaryl with one or more N in the heteroaryl ring, wherein the heteroaryl ring may be substituted by methyl or OH; or a

C_{1-3}-alkylen group which is substituted by a pyridine ring, wherein the pyridine ring may be substituted by OH; or wherein

R^1 and R^3 together form a group that represents a group selected from $-CH_2-CH_2-$ and $-CH_2-CH_2-CH_2-$; and wherein

R^6, R^7 and R^8 represent hydrogen.

39. The compound of any one of the preceding items, wherein R^1 and R^3 together form a group $-CH_2-CH_2-$.

40. The compound of any one of the preceding items, wherein

Q represents OR^2 or $-NR^3R^4$;

T represents -O-;

U represents $-CH_2-$;

V represents

H;

methyl which is substituted with two fluorine atoms;

3-4-membered cycloalkyl, which may be substituted with a -CN group;

4-6-membered heterocycloalkyl, comprising one oxygen atom in the heterocycloalkyl ring;

phenyl, which may be substituted with one fluorine atom or with a methyl group, wherein two of the hydrogen atoms of the methyl group are substituted with two fluorine atoms;

1,3-thiazole or 1H-pyrazole which are substituted with a methyl group; or

pyridine, which may be substituted with a methyl group, and wherein the hydrogen atoms of the methyl group may be substituted by three fluorine atoms;

R^1 represents $-C_{1-3}$-alkyl;

R^2 represents hydrogen;

R^3 represents hydrogen;

R^4 represents

$-SO_2Me$;

C_{1-5} alkyl which may be substituted by up to three OH, up to three F, $-CONR_2$, or $-NHS(=O)_2-Me$, wherein residues R are independently from each other hydrogen or methyl;

3-4-membered cycloalkyl substituted by $-CH_2OH$, $-CH_2CH_2OH$ or $-CONH_2$;

C_{1-3}-alkylene-3-4-membered cycloalkyl substituted by a methyl or a $-NMe_2$ group;

4-5-membered heterocycloalkyl with one or more N or O atom in the heterocycloalkyl ring and which may be a lactam ring and wherein the heterocycloalkyl ring may be substituted by F, $-CONR_2$, wherein the residues R independently of each other represent H or methyl or

the heterocycloalkyl ring may be substituted by a C_{1-2} alkyl group, wherein the C_{1-2} alkyl group may be substituted by OH, F;

C_{1-3}-alkylene-5-6-membered heterocycloalkyl with one or more N, O in the heterocycloalkyl ring, which may be a lactam and wherein the heterocycloalkyl ring may be substituted by methyl;

5-6-membered heteroaryl with one or more N in the heteroaryl ring, wherein the heteroaryl ring may be substituted by methyl or OH; or a

C_{1-3}-alkylen group which is substituted by a pyridine ring, wherein the pyridine ring is substituted by OH; or wherein

R^1 and R^3 together form a group $-CH_2-CH_2-$; and wherein

R^6, R^7 and R^8 represent hydrogen.

41. The compound of any one of the preceding items, wherein R^1 and R^4 are not connected to form a heterocycle.

42. The compound of any one of the preceding items, wherein R^{cycl} comprises 1 heteroatom.

43. The compound of item 1, wherein $\mathbf{R^3}$ represents -H.

44. . The compound of item 43, wherein $\mathbf{R^4}$ represents a residue other than -H.

45. The compound of any one of the preceding items, wherein $\mathbf{R^1}$ represents -methyl or ethyl.

46. The compound of any one of items 1 and 43 to 45, wherein **T** represents -O- and **U** represents $-C\mathbf{R^5R^{5'}}-$.

47. The compound of any one of the preceding items, wherein the $\mathbf{R^Y}$ representing each of $\mathbf{R^5}$ and $\mathbf{R^{5'}}$ is H.

48. The compound of one of the preceding items, wherein **V** represents (i) 5-14-membered heteroaryl selected from benzimidazole, benzisoxazole, benzoazole, benzodioxole, benzofuran, benzothiadiazole, benzothiazole, benzothiophene, carbazole, cinnoline, dibenzofuran, furane, furazane, imidazole, imidazopyridine, indazole, indole, indolizine, isobenzofuran, isoindole, isoquinoline, isothiazole, isoxazole, naphthyridine, oxadiazole, oxazole, oxindole, phthalazine, purine, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, pyrrole, quinazoline, quinoline, quinoxaline, tetrazole, thiadiazole, thiazole, thiophene, triazine, triazole, and [1,2,4]triazolo[4,3-a]pyrimidine; in each case

unsubstituted, mono- or polysubstituted with substituents independently of one another selected from -F, -Cl, -CN, -OH, =O, -C_{1-6}-alkyl, -CHF_2, -CF_3, -C_{1-6}-alkylene-NH_2, -C_{1-6}-alkylene-NHC(=O)O-C_{1-6}-alkyl, -C_{1-6}-alkylene-OH, -C_{1-6}-alkylene-CHF_2, -C_{1-6}-alkylene-CF_3, -C_{1-6}-alkylene-cyclopropyl, -cyclopropyl, -O-cyclopropyl, -C_{1-6}-alkylene-NHC(=O)-O-C_{1-6}-alkyl, -C(=O)O-C_{1-6}-alkyl, -N(C_{1-6}-alkyl)$_2$, -OC_{1-6}-alkyl, -OCF_3, -O-C_{1-6}-alkylene-N(C_{1-6}-alkyl)$_2$, -S(=O)$_2$-C_{1-6}-alkyl, -azetidine, -C_{1-6}-alkylene-O-tetrahydropyran, or -piperazine substituted with -C_{1-6}-alkyl; particularly in each case unsubstituted, mono- or polysubstituted with substituents independently of one another selected from -F, -Cl, -CN, -OH, =O, -C_{1-6}-alkyl, -CHF_2, -CF_3, -C_{1-6}-alkylene-NH_2, -C_{1-6}-alkylene-NHC(=O)O-C_{1-6}-alkyl, -C_{1-6}-alkylene-OH, -C_{1-6}-alkylene-NHC(=O)-O-C_{1-6}-alkyl, -C(=O)O-C_{1-6}-alkyl, -N(C_{1-6}-alkyl)$_2$, -OC_{1-6}-alkyl, -OCF_3, -O-C_{1-6}-alkylene-N(C_{1-6}-alkyl)$_2$, -S(=O)$_2$-C_{1-6}-alkyl, -azetidine, -C_{1-6}-alkylene-O-tetrahydropyran, or -piperazine substituted with -C_{1-6}-alkyl; or represents (ii) -oxetanyl, unsubstituted, mono- or polysubstituted.

49. The compound of any one of items 1 to 47, wherein the 3-14-membered cycloalkyl, saturated or unsaturated within the definition of **V** is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, or cyclodecyl including unfused or unbridged, fused, or bridged cycloalkyls; in each case unsubstituted, mono- or polysubstituted with substituents independently of one another selected from -F, -Cl, -Br, -I, , CF_3, -CF_2H, C_1-C_6 alkyl, -CN, -NO, -NO_2, =O, =S, -SF_5, -$\mathbf{R^Y}$, -O$\mathbf{R^Y}$, -OC(=O)$\mathbf{R^Y}$, -N$\mathbf{R^Y}$$\mathbf{R^Z}$, -N$\mathbf{R^Y}$C(=O)$\mathbf{R^Z}$, -S$\mathbf{R^Y}$, -S(=O)$\mathbf{R^Y}$, -S(=O)$_2$$\mathbf{R^Y}$, -C(=O)$\mathbf{R^Y}$, -C(=O)O$\mathbf{R^Y}$, or -C(=O)N$\mathbf{R^Y}$$\mathbf{R^Z}$.

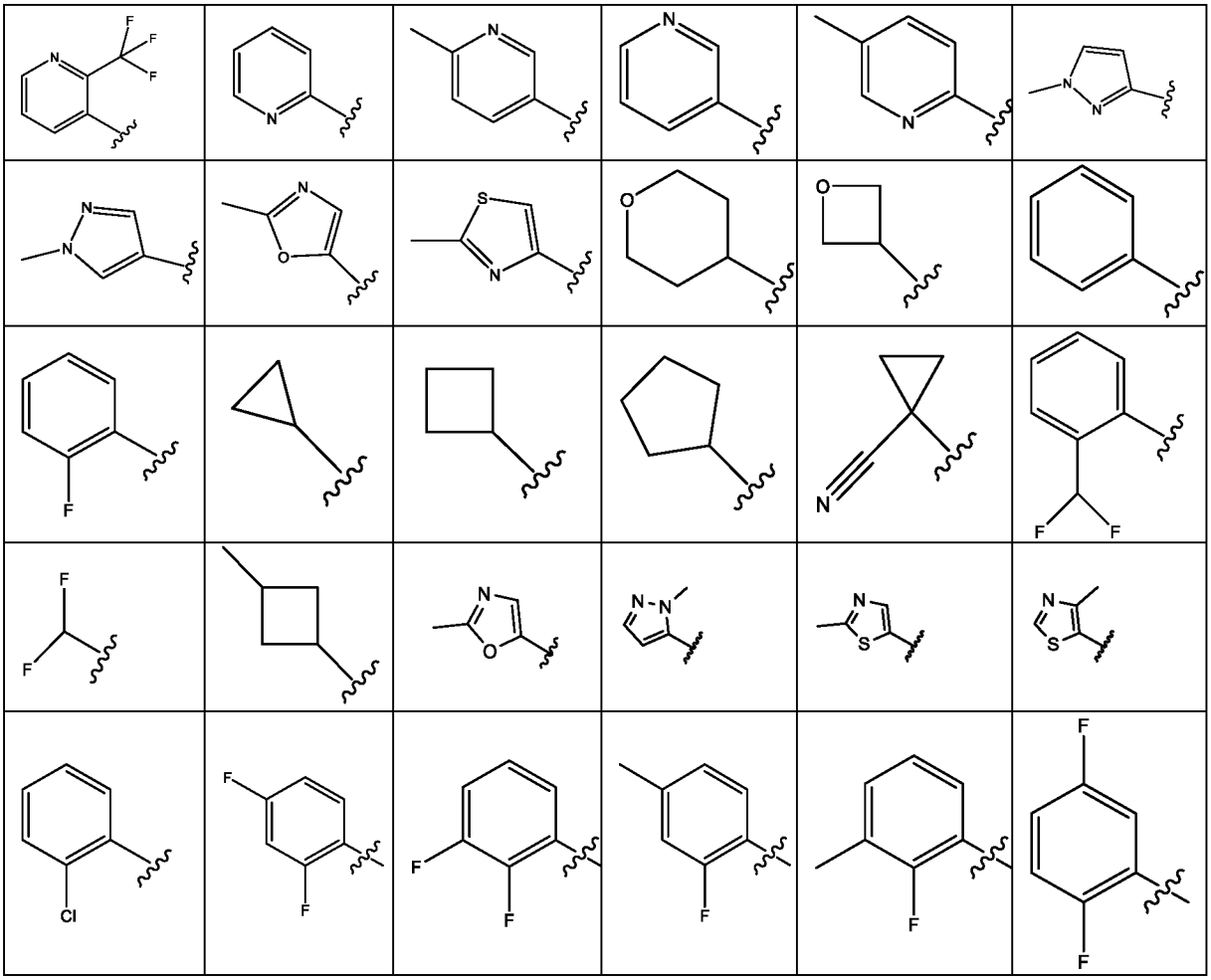
50. The compound of any one of items 1 to 47 wherein the 5-14-membered aryl within the definition of **V** is phenyl or another 5-14-membered aryl, unsubstituted, mono- or polysubstituted with substituents independently of one another selected from -F, -Cl, -Br, -I, CF_3, -CF_2H, C_1-C_6 alkyl, -CN, -NO, -NO_2, =O, =S, -SF_5, -$\mathbf{R^Y}$, -O$\mathbf{R^Y}$, -OC(=O)$\mathbf{R^Y}$, -N$\mathbf{R^Y}$$\mathbf{R^Z}$, -N$\mathbf{R^Y}$C(=O)$\mathbf{R^Z}$, -S$\mathbf{R^Y}$, -S(=O)$\mathbf{R^Y}$, -S(=O)$_2$$\mathbf{R^Y}$, -C(=O)$\mathbf{R^Y}$, -C(=O)O$\mathbf{R^Y}$, or -C(=O)N$\mathbf{R^Y}$$\mathbf{R^Z}$.

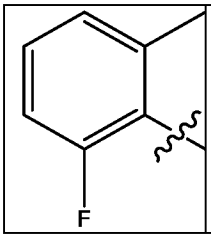
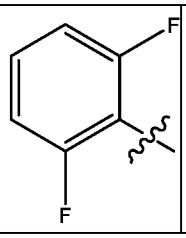
51. The compound of any one of items 1 to 47 wherein the 3-14-membered heterocycloalkyl within the definition of **V** is selected from azepane, 1,4-oxazepane, azetane, azetidine, aziridine, azocane, diazepane, dioxane, dioxolane, dithiane, dithiolane, imidazolidine, isothiazolidine, isoxalidine, morpholine, oxazolidine, oxane, oxepane, oxetane, oxirane, piperazine, piperidine, pyrazolidine, pyrrolidine, quinuclidine, tetrahydrofurane, tetrahydropyrane, tetrahydrothiopyrane, thiazolidine, thietane, thiirane, thiolane, thiomorpholine, indoline, dihydrobenzofuran, dihydrobenzo-thiophene, 1,1-dioxothia-

cyclohexane, 2-azaspiro[3.3]heptane, 2-oxaspiro[3.3]heptane, 7-azaspiro[3.5]nonane, 8-azabicyclo[3.2.1]octane, 9-azabicyclo[3.3.1]nonane, hexahydro-1H-pyrrolizine, hexahydro-cyclopenta[c]pyrrole, octahydro-cyclopenta[c]pyrrole, and octahydro-pyrrolo[1,2-a]pyrazine; in each case unsubstituted, mono- or polysubstituted with substituents independently of one another selected from -F, -Cl, -Br, -I, CF_3, $-CF_2H$, C_1-C_6 alkyl, -CN, -NO, $-NO_2$, =O, =S, $-SF_5$, $-\mathbf{R}^Y$, $-O\mathbf{R}^Y$, $-OC(=O)\mathbf{R}^Y$, $-N\mathbf{R}^Y\mathbf{R}^Z$, $-N\mathbf{R}^YC(=O)\mathbf{R}^Z$, $-S\mathbf{R}^Y$, $-S(=O)\mathbf{R}^Y$, $-S(=O)_2\mathbf{R}^Y$, $-C(=O)\mathbf{R}^Y$, $-C(=O)O\mathbf{R}^Y$, or $-C(=O)N\mathbf{R}^Y\mathbf{R}^Z$.

52. The compound of any one of items 1 to 47 wherein **V** represents C_1-C_6 alkyl or C_1-C_6 heteroalkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted with substituents independently of one another selected from -F, -Cl, -Br, -I, CF_3, $-CF_2H$, C_1-C_6 alkyl, -CN, -NO, $-NO_2$, =O, =S, $-SF_5$, $-\mathbf{R}^Y$, $-O\mathbf{R}^Y$, $-OC(=O)\mathbf{R}^Y$, $-N\mathbf{R}^Y\mathbf{R}^Z$, $-N\mathbf{R}^YC(=O)\mathbf{R}^Z$, $-S\mathbf{R}^Y$, $-S(=O)\mathbf{R}^Y$, $-S(=O)_2\mathbf{R}^Y$, $-C(=O)\mathbf{R}^Y$, $-C(=O)O\mathbf{R}^Y$, or $-C(=O)N\mathbf{R}^Y\mathbf{R}^Z$.

53. The compound of any one of items 1 to 47 wherein **V** is a residue selected from the group consisting of:



54. The compound according to any one of the preceding items, wherein R^1 represents -H, -F, -Cl, -Br, -I, -C_{1-6}-alkyl, -O-C_{1-6}-alkyl, -C_{1-6}-alkylene-O-C_{1-6}-alkyl, -C_{1-6}-alkylene-NH(C_{1-6}-alkyl), -C_{1-6}-alkylene-N(C_{1-6}-alkyl)$_2$, -CF_3, -CF_2H, -CFH_2, -CF_2Cl, -$CFCl_2$, -C_{1-6}-alkylene-CF_3, -C_{1-6}-alkylene-CF_2H, -C_{1-6}-alkylene-CFH_2, -C_{1-6}-alkylene-NH-C_{1-6}-alkylene-CF_3, -C_{1-6}-alkylene-N(C_{1-6}-alkyl)-C_{1-6}-alkylene-CF_3, -C(=O)C_{1-6}-alkyl, -C(=O)OC_{1-6}-alkyl, -C(=O)NH_2, -C(=O)NHC_{1-6}-alkyl, -C(=O)N(C_{1-6}-alkyl)$_2$, -S(=O)-C_{1-6}-alkyl, -S(=O)$_2$-C_{1-6}-alkyl, -O-C_{1-6}-alkyl, -cyclopropyl unsubstituted, cyclobutyl unsubstituted, cyclopentyl unsubstituted or cyclohexyl unsubstituted.

55. The compound according to any one of the preceding items, wherein R^3 represents -H, -OH, -C_{1-6}-alkyl, -C_{1-6}-alkylene-OH, -C_{1-6}-alkylene-O-C_{1-6}-alkyl, -C_{1-6}-alkylene-NH_2, -C_{1-6}-alkylene-NH(C_{1-6}-alkyl), -C_{1-6}-alkylene-N(C_{1-6}-alkyl)$_2$, -CF_3, -CF_2H, -CFH_2, -CF_2Cl, -$CFCl_2$, -C_{1-6}-alkylene-CF_3, -C_{1-6}-alkylene-CF_2H, -C_{1-6}-alkylene-CFH_2, -C_{1-6}-alkylene-NH-C_{1-6}-alkylene-CF_3, or -C_{1-6}-alkylene-N(C_{1-6}-alkyl)-C_{1-6}-alkylene-CF_3.

56. The compound according to any one of any one of the preceding items, wherein R^4 represents

-H;

-S(=O)$_2$$C_{1-6}$-alkyl, saturated, unsubstituted, monosubstituted or polysubstituted with -F;

-S(=O)$_2$(3-14-membered cycloalkyl), saturated, unsubstituted;

-C_{1-6}-alkyl, saturated, unsubstituted mono- or polysubstituted ;

3-14-membered cycloalkyl or -C_{1-6}-alkylene-(3-14-membered cycloalkyl), each unsubstituted, mono- or polysubstituted;

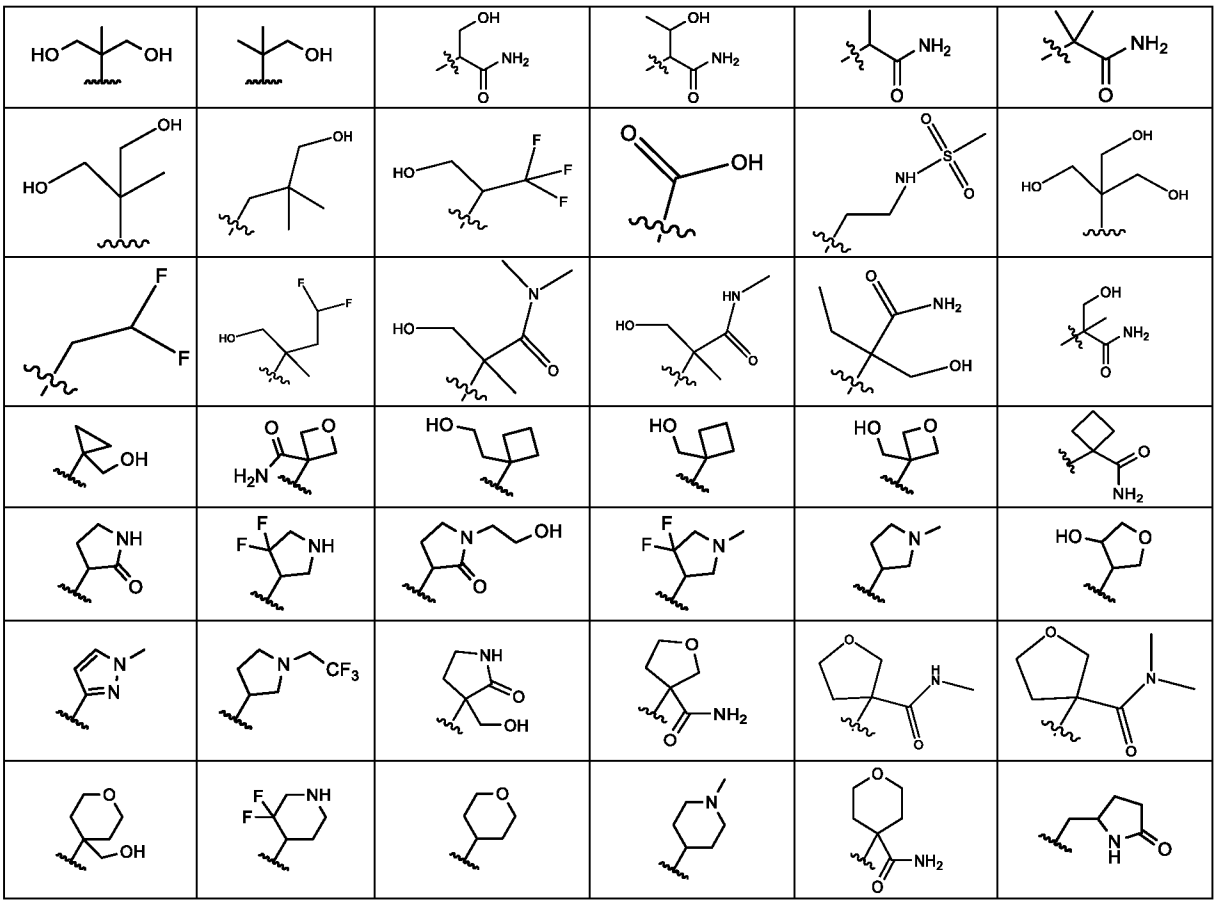
3-14-membered heterocycloalkyl or -C_{1-6}-alkylene-(3-14-membered heterocycloalkyl), unsubstituted, mono- or polysubstituted;

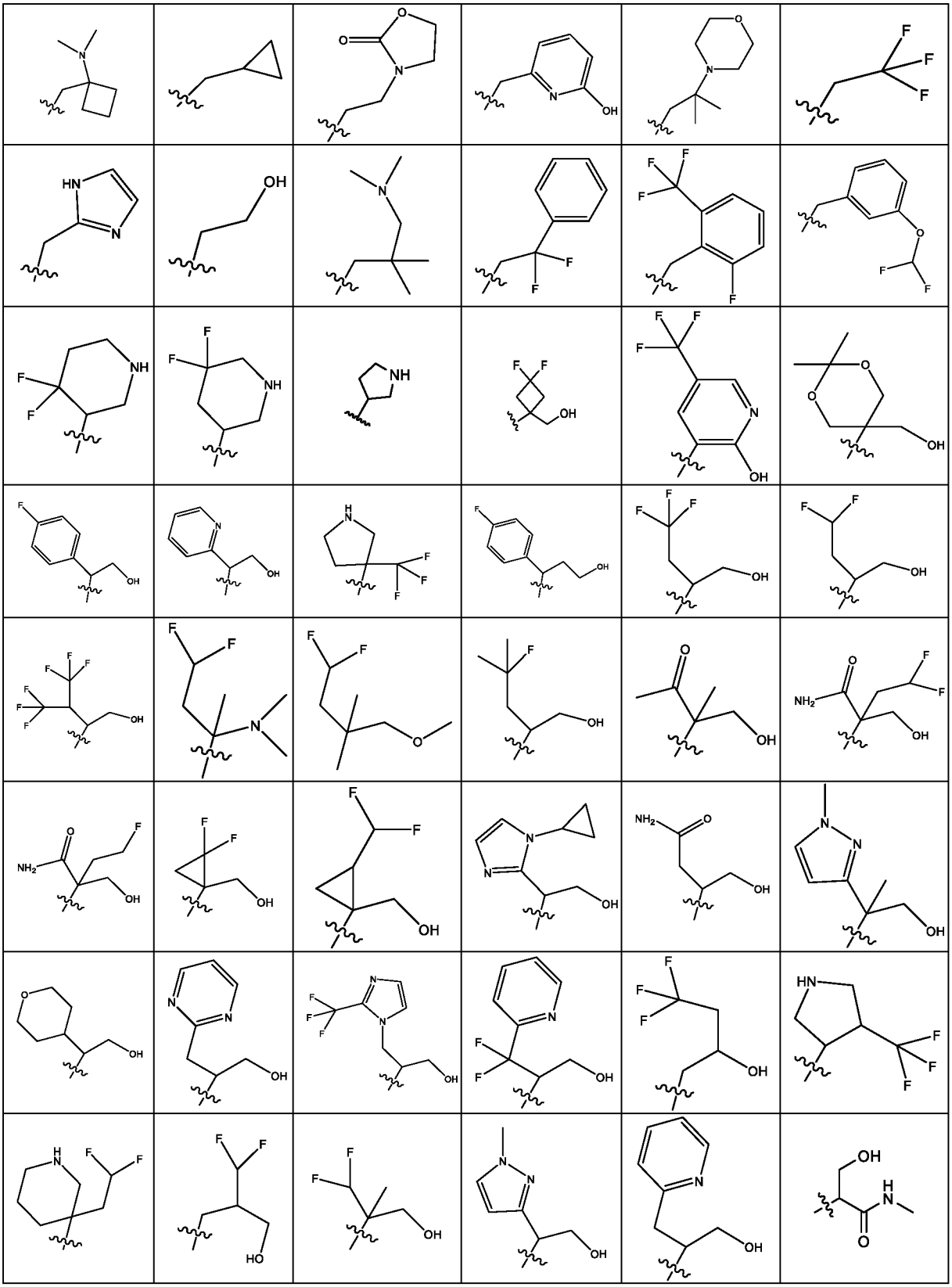
-phenyl, or -C_{1-6}-alkylene-phenyl, each unsubstituted, mono- or polysubstituted; or

5-14-membered heteroaryl or -C_{1-6}-alkylene-(5-14-membered heteroaryl), each unsubstituted, mono- or polysubstituted.

57. The compound according to any one of any one of the preceding items wherein **R**^{4} represents a 3-14-membered cycloalkyl (preferably a 3, 4, 5 or 6-membered cycloalkyl), saturated or unsaturated, unsubstituted, mono- or polysubstituted; wherein said 3-14-membered cycloalkyl is connected through -C_1-C_6-alkylene-, saturated or unsaturated, unsubstituted, mono- or polysubstituted; or a 3-14-membered heterocycloalkyl (preferably a 4, 5 or 6-membered heterocycloalkyl), saturated or unsaturated, unsubstituted, mono- or polysubstituted; wherein said 3-14-membered heterocycloalkyl is connected through -C_1-C_6-alkylene-, saturated or unsaturated, unsubstituted, mono- or polysubstituted; or a 6-14-membered aryl (preferably a 6-membered aryl), unsubstituted, mono- or polysubstituted; wherein said 6-14-membered aryl is connected through -C_1-C_6-alkylene-, saturated or unsaturated, unsubstituted, mono- or polysubstituted; or a 5-14-membered heteroaryl (preferably a 5 or 6-membered heteroaryl), unsubstituted, mono- or polysubstituted; wherein said 5-14-membered heteroaryl is connected through -C_1-C_6-alkylene-, saturated or unsaturated, unsubstituted, mono- or polysubstituted.

58. The compound according to any one of any one of the preceding items wherein **R**^{3} is H and **R**^{4} is a residue selected from the group consisting of:





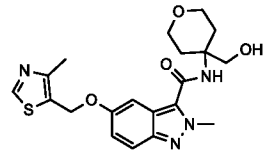
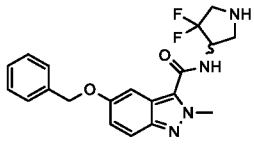
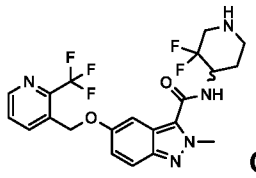
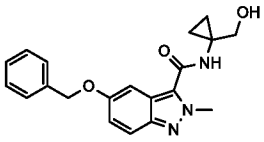
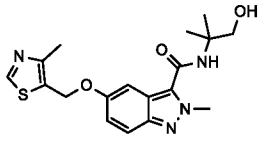
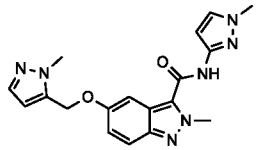
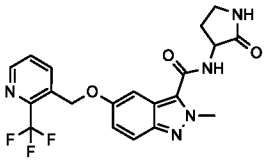
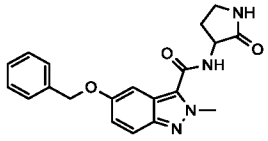
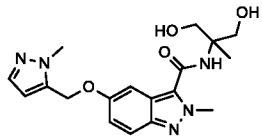
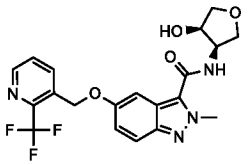
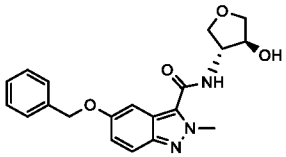
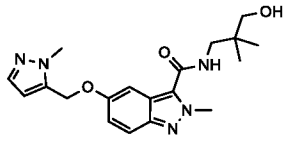
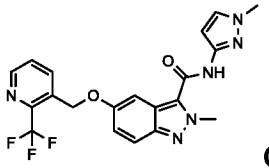
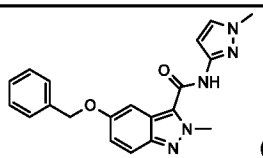
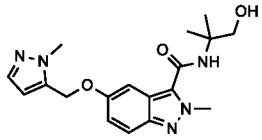
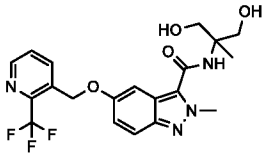
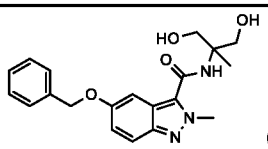
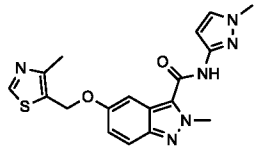
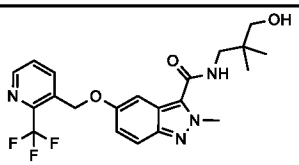
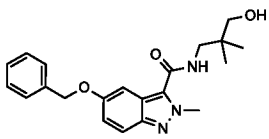
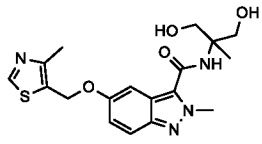
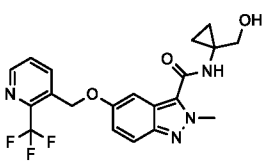
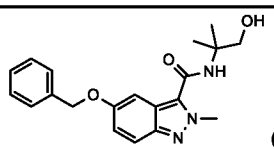
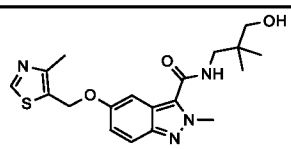
59. The compound of any one of the preceding items wherein R^3 and R^4 together form a heterocycle selected from the group consisting of pyrrolidine, piperidine, morpholine, and

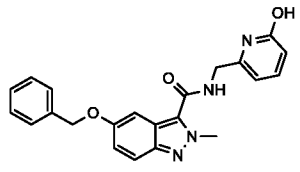
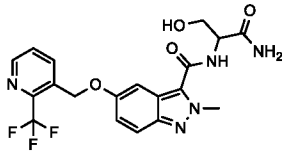
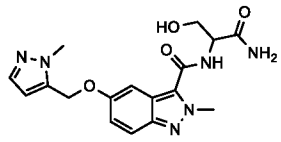
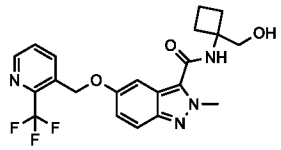
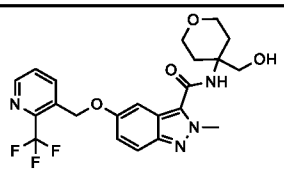
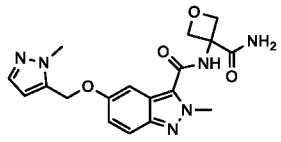
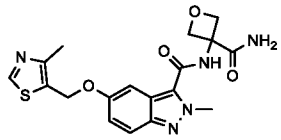
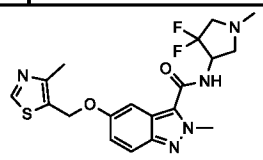
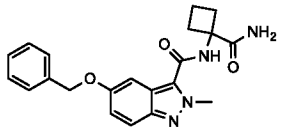
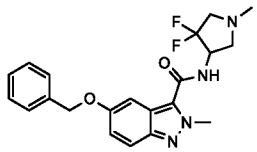
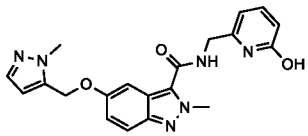
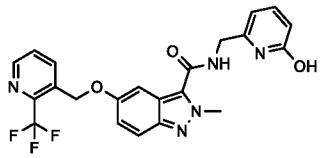
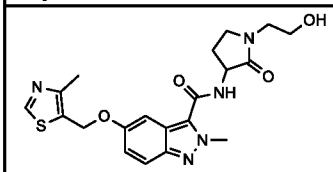
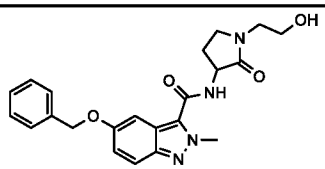
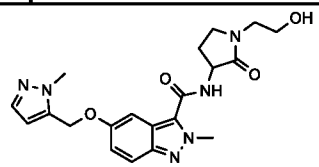
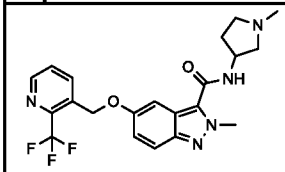
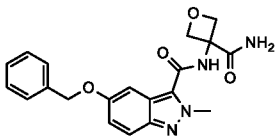
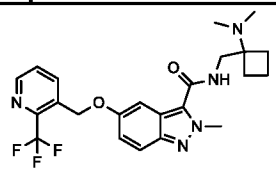
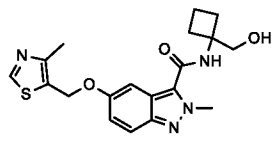
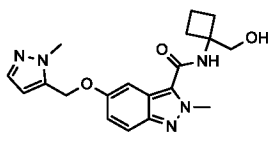
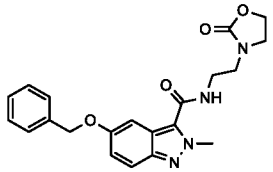
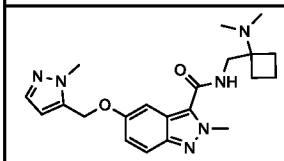
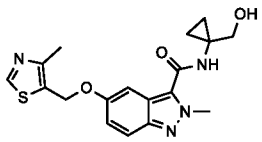
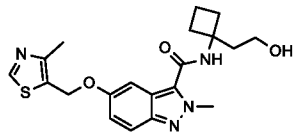
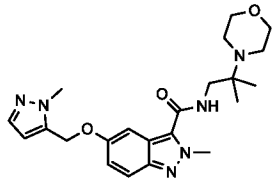
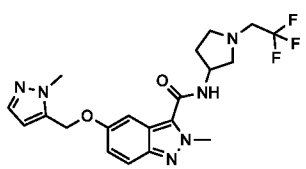
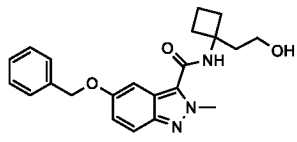
piperazine, in each case unsubstituted, mono- or polysubstituted with substituents independently of one another selected from the group consisting of -F, -C_{1-6}-alkyl, -NH_2, -$NHCH_3$, -$N(CH_3)_2$, -C(=O)NH-C_{1-6}-alkyl, -C(=O)N(C_{1-6}-alkyl)$_2$, -C(=O)O-C_{1-6}-alkyl, -NHC(=O)O-C_{1-6}-alkyl, -pyridyl unsubstituted, and 1,2,4-oxadiazole unsubstituted or monosubstituted with -C_{1-6}-alkyl.

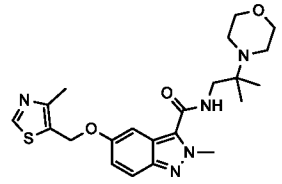
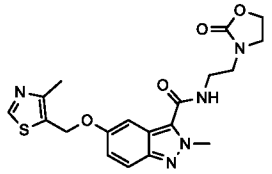
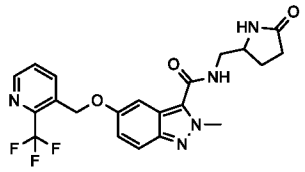
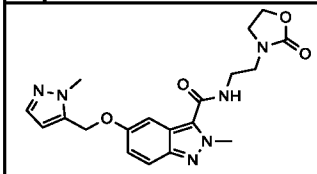
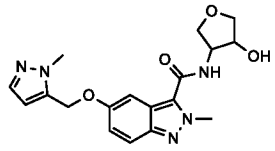
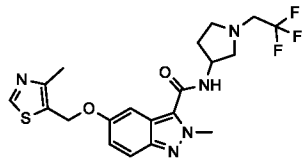
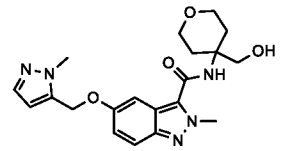
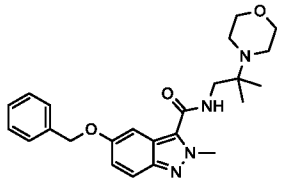
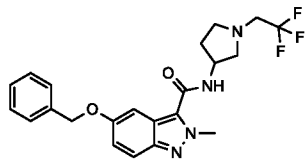
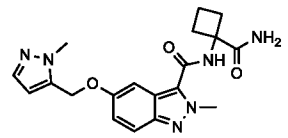
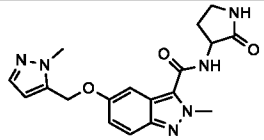
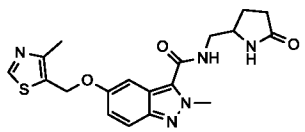
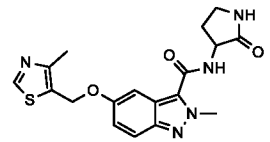
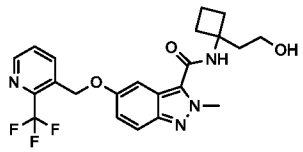
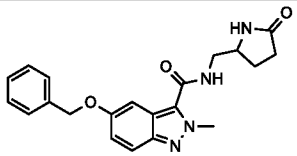
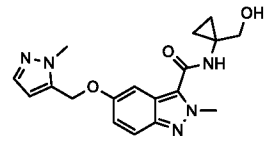
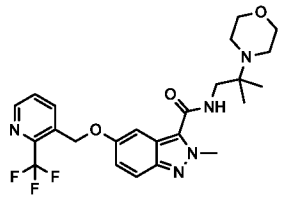
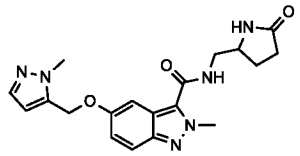
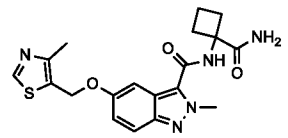
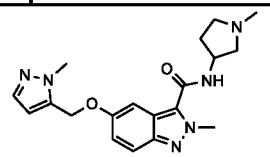
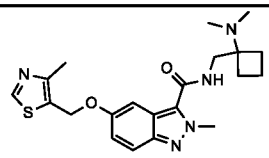
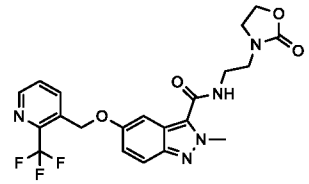
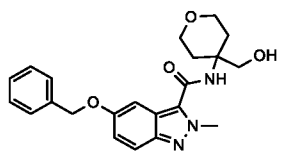
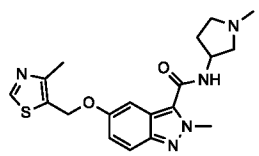
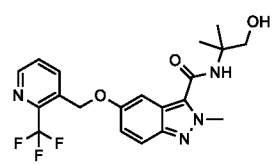
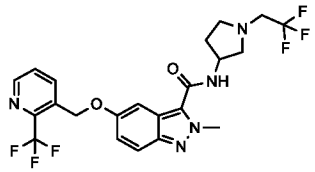
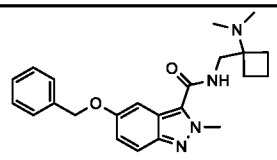
60. The compound of any one of the preceding items, wherein **R^5** and **$R^{5'}$** independently of one another represent
-H;
-C_1-C_6-alkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted;
-C_1-C_6-heteroalkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted;
3-14-membered cycloalkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted; wherein said 3-14-membered cycloalkyl is optionally connected through -C_1-C_6-alkylene- or -C_1-C_6-heteroalkylene-, in each case saturated or unsaturated, unsubstituted, mono- or polysubstituted.

61. The compound according to any one of any one of the preceding items, wherein **R^6**, **R^7** and **R^8** independently of one another represent
-H, -F, -Cl, -Br, -I, -OH, -SH, -SF_5, -CN, -NO_2, -C(=O)OH, -NH_2,
-C_{1-6}-alkyl, -CF_3, -CHF_2, -CH_2F,
-O-C_{1-6}-alkyl, -OCF_3, -$OCHF_2$, -OCH_2F,
-NHC_{1-6}-alkyl unsubstituted or substituted with one or more substituents independently of one another selected from -OH, =O, -F, -Cl, -Br, -I, -SH, =S, -CN, -CF_3, -CHF_2, -CH_2F, -OCF_3, -$OCHF_2$, -OCH_2F, SF_5, -NO_2, -C(=O)OH, -NH_2, and -C(=O)NH_2;
-N(C_{1-6}-alkyl)$_2$ unsubstituted or substituted with one or more substituents independently of one another selected from -OH, =O, -F, -Cl, -Br, -I, -SH, =S, -CN, -CF_3, -CHF_2, -CH_2F, -OCF_3, -$OCHF_2$, -OCH_2F, SF_5, -NO_2, -C(=O)OH, -NH_2, and -C(=O)NH_2;
-C(=O)OC_{1-6}-alkyl unsubstituted or substituted with one or more substituents independently of one another selected from -OH, =O, -F, -Cl, -Br, -I, -SH, =S, -CN, -CF_3, -CHF_2, -CH_2F, -OCF_3, -$OCHF_2$, -OCH_2F, SF_5, -NO_2, -C(=O)OH, -NH_2, and -C(=O)NH_2;
-OC(=O)C_{1-6}-alkyl unsubstituted or substituted with one or more substituents independently of one another selected from -OH, =O, -F, -Cl, -Br, -I, -SH, =S, -CN, -CF_3, -CHF_2, -CH_2F, -OCF_3, -$OCHF_2$, -OCH_2F, SF_5, -NO_2, -C(=O)OH, -NH_2, and -C(=O)NH_2;
or
-C_{1-6}-heteroalkyl unsubstituted or substituted with one or more substituents independently of one another selected from -OH, =O, -F, -Cl, -Br, -I, -SH, =S, -CN, -CF_3, -CHF_2, -CH_2F, -OCF_3, -$OCHF_2$, -OCH_2F, SF_5, -NO_2, -C(=O)OH, -NH_2, and -C(=O)NH_2.

62. The compound of any one of the preceding items, which is selected from the group consisting of compounds 001 – 199 as shown in the table below:

Structure and **Compound CODE**	Structure and **Compound CODE**	Structure and **Compound CODE**
 **Cpd 001**	 **Cpd 002**	 **Cpd 003**
 **Cpd 004**	 **Cpd 005**	 **Cpd 006**
 **Cpd 007**	 **Cpd 008**	 **Cpd 009**
 **Cpd 010**	 **Cpd 011**	 **Cpd 012**
 **Cpd 013**	 **Cpd 014**	 **Cpd 015**
 **Cpd 016**	 **Cpd 017**	 **Cpd 018**
 **Cpd 019**	 **Cpd 020**	 **Cpd 021**
 **Cpd 022**	 **Cpd 023**	 **Cpd 024**

 Cpd 025	 Cpd 026	 Cpd 027
 Cpd 028	 Cpd 029	 Cpd 030
 Cpd 031	 Cpd 032	 Cpd 033
 Cpd 034	 Cpd 035	 Cpd 036
 Cpd 037	 Cpd 038	 Cpd 039
 Cpd 040	 Cpd 041	 Cpd 042
 Cpd 043	 Cpd 044	 Cpd 045
 Cpd 046	 Cpd 047	 Cpd 048
 Cpd 049	 Cpd 050	 Cpd 051

 Cpd 052	 Cpd 053	 Cpd 054
 Cpd 055	 Cpd 056	 Cpd 057
 Cpd 058	 Cpd 059	 Cpd 060
 Cpd 061	 Cpd 062	 Cpd 063
 Cpd 064	 Cpd 065	 Cpd 066
 Cpd 067	 Cpd 068	 Cpd 069
 Cpd 070	 Cpd 071	 Cpd 072
 Cpd 073	 Cpd 074	 Cpd 075
		 Cpd 078

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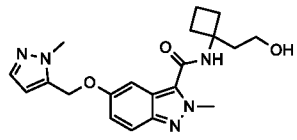
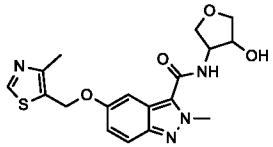
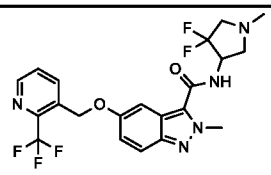
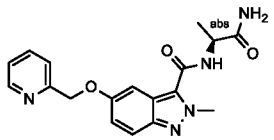
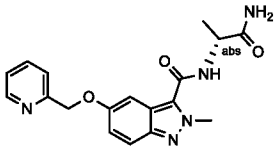
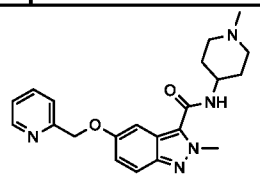
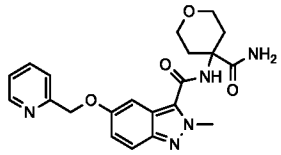
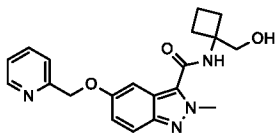
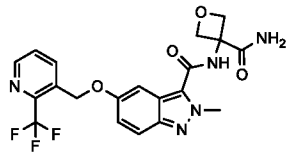
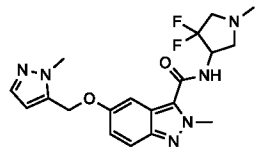
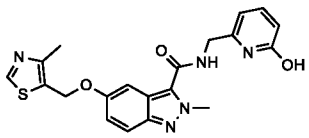
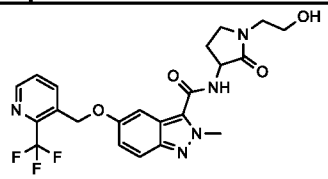
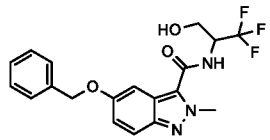
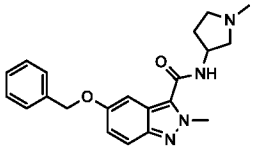
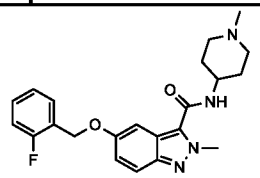
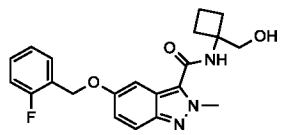
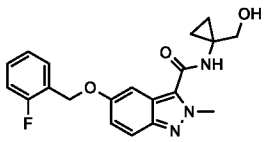
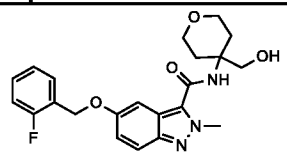
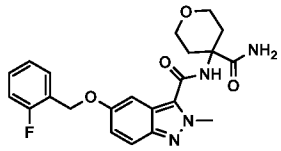
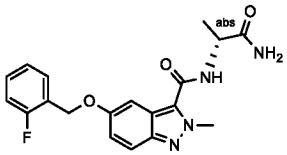
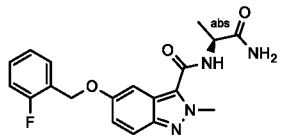
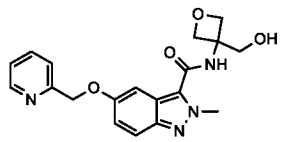
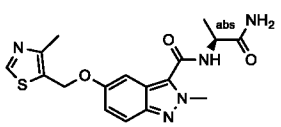
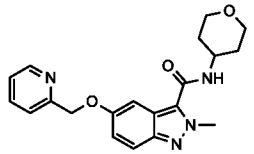
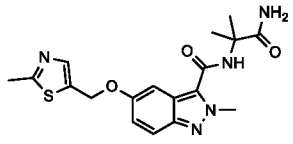
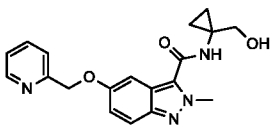
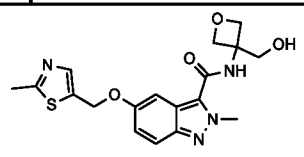
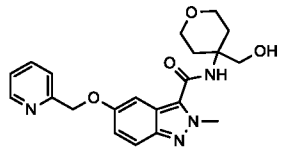
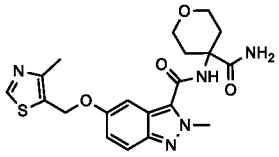
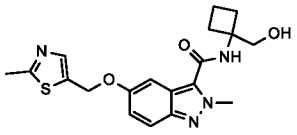
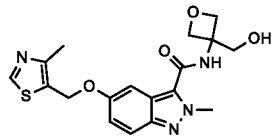
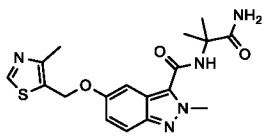
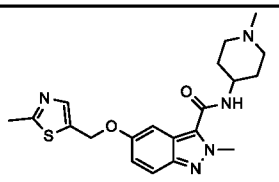
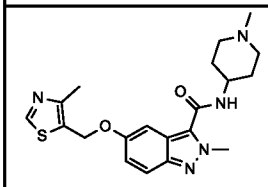
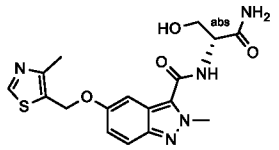
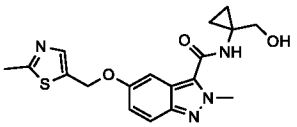
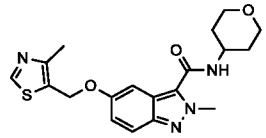
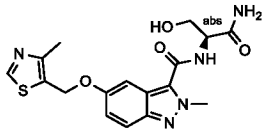
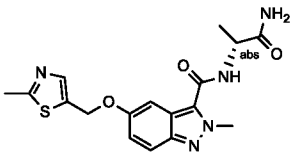
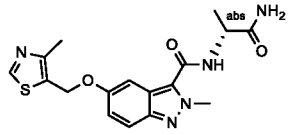
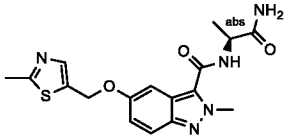
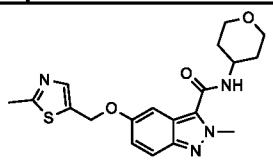
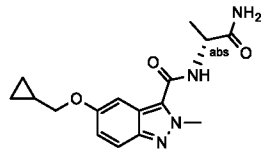
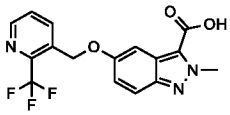
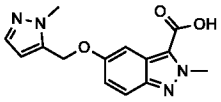
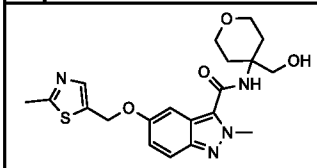
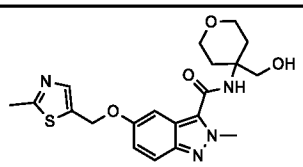
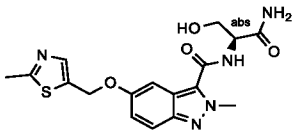
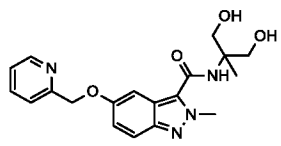
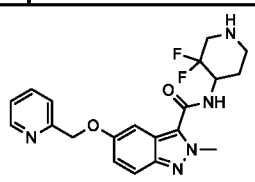
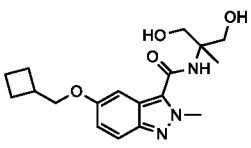
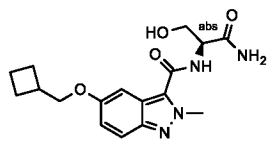
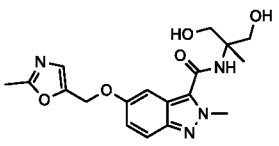
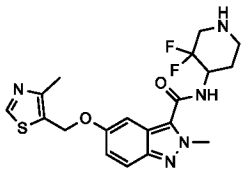
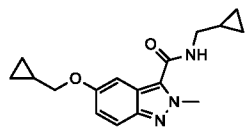
 Cpd 079	 Cpd 080	 Cpd 081
 Cpd 082	 Cpd 083	 Cpd 084
 Cpd 085	 Cpd 086	 Cpd 087
 Cpd 088	 Cpd 089	 Cpd 090
 Cpd 091	 Cpd 092	 Cpd 093
 Cpd 094	 Cpd 095	 Cpd 096
 Cpd 097	 Cpd 098	 Cpd 099
 Cpd 100	 Cpd 101	 Cpd 102
 Cpd 103	 Cpd 104	 Cpd 105

 Cpd 106	 Cpd 107	 Cpd 108
 Cpd 109	 Cpd 110	 Cpd 111
 Cpd 112	 Cpd 113	 Cpd 114
 Cpd 115	 Cpd 116	 Cpd 117
 Cpd 118	 Cpd 119	 Cpd 120
 Cpd 121	 Cpd 122	 Cpd 123
 Cpd 124	 Cpd 125	 Cpd 126
 Cpd 127	 Cpd 128	 Cpd 129
 Cpd 130	 Cpd 131	 Cpd 132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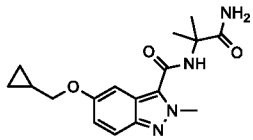
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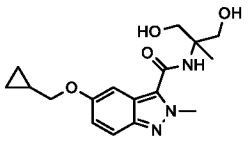
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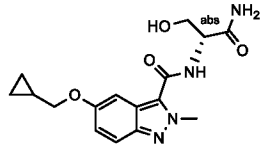
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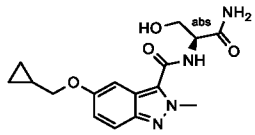
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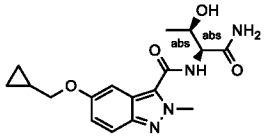
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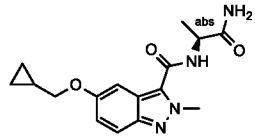
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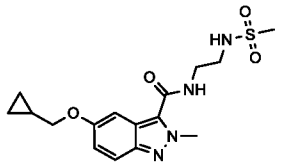
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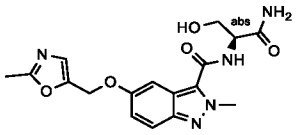
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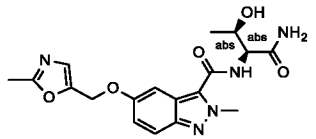
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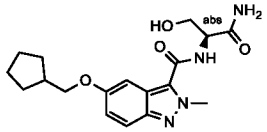
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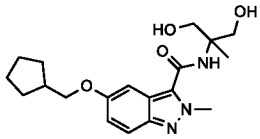
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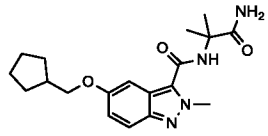
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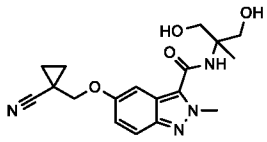
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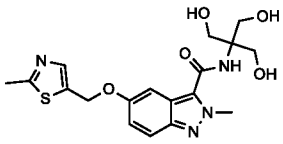
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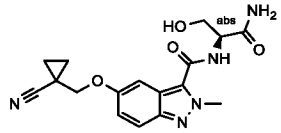
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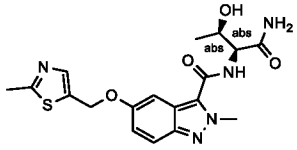
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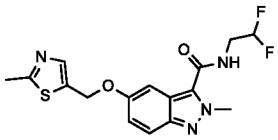
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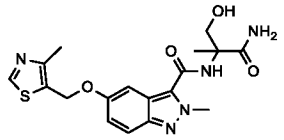
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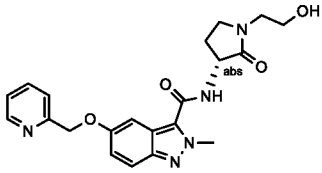
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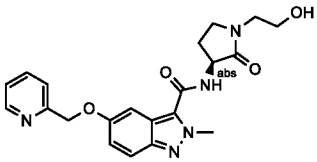
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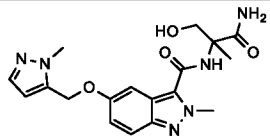
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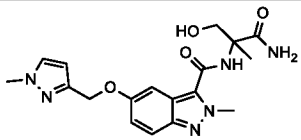
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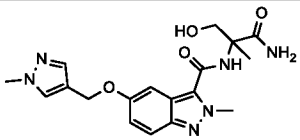
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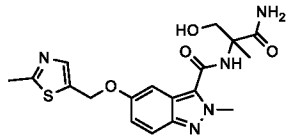
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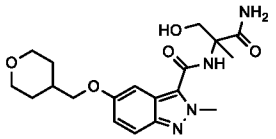
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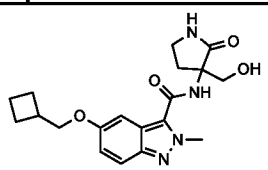
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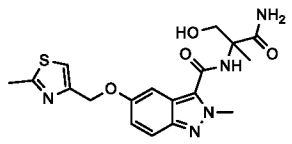
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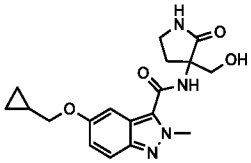
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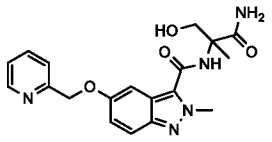
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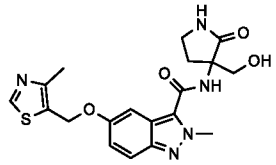
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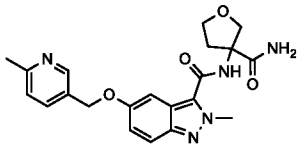
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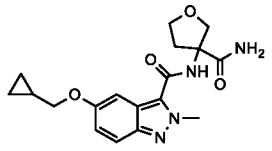
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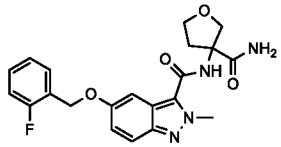
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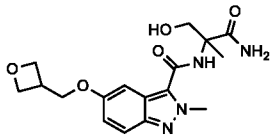
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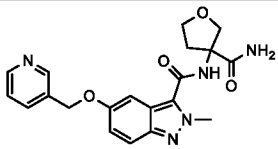
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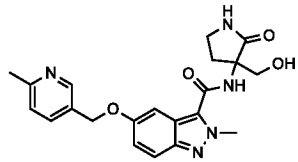
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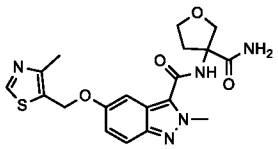
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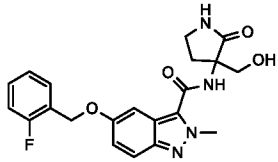
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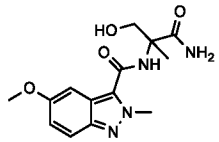
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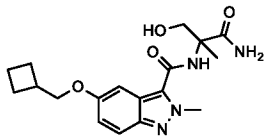
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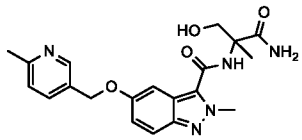
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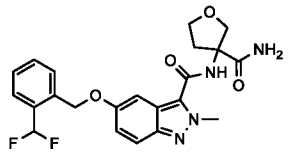
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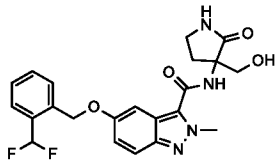
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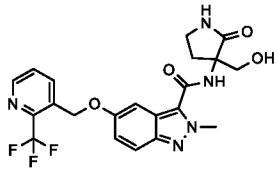
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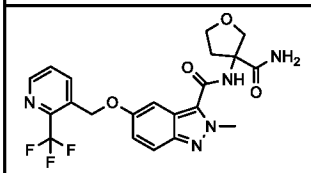
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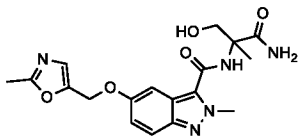
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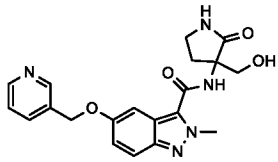
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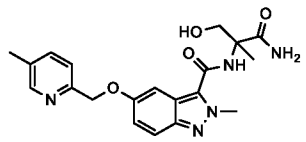
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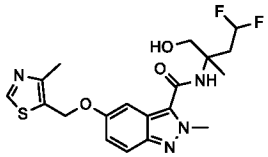
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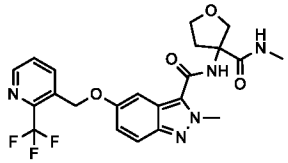
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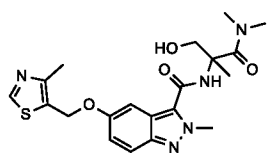
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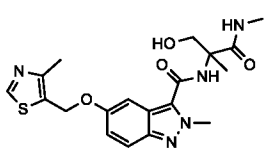
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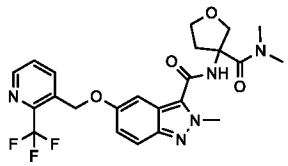
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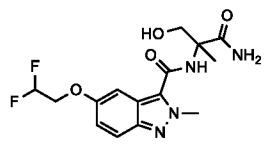
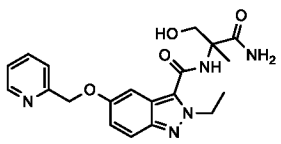
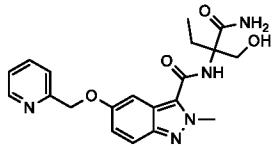
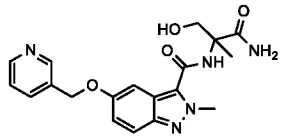
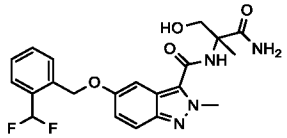
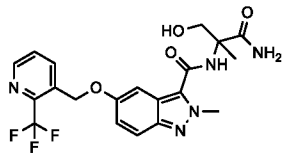
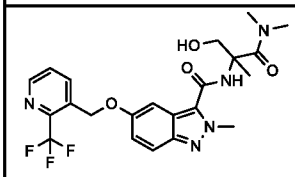
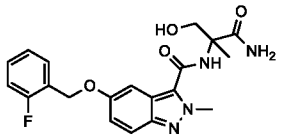
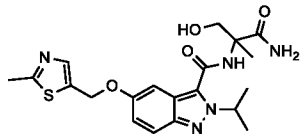
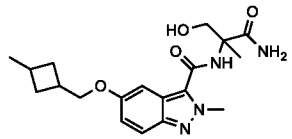
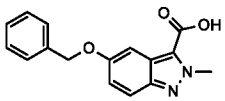
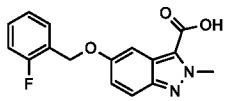
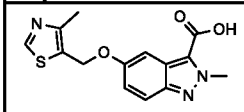
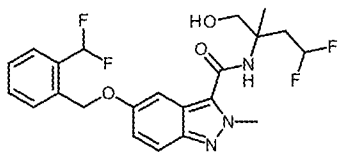
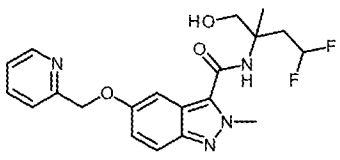
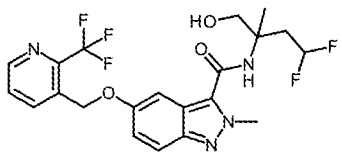
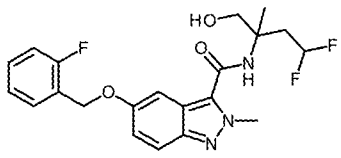
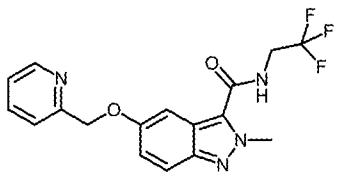
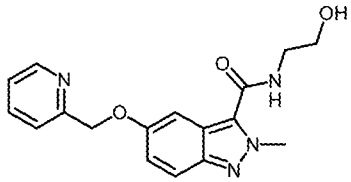
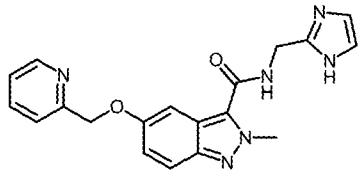
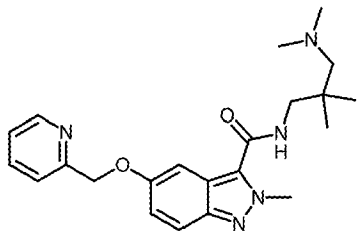
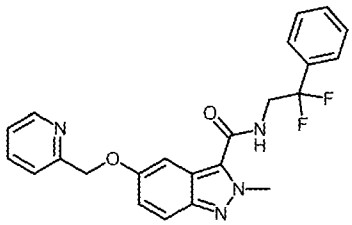
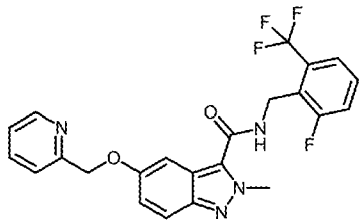
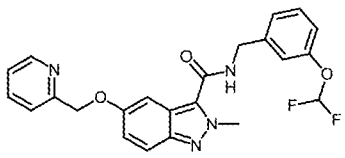
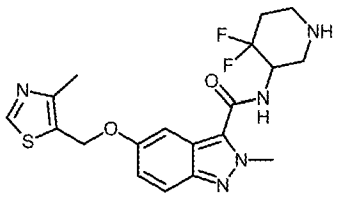
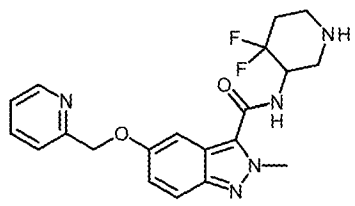
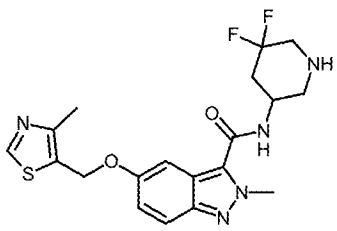
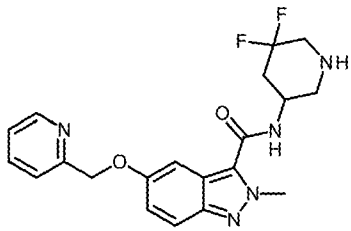
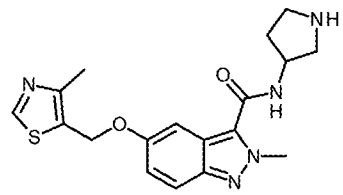
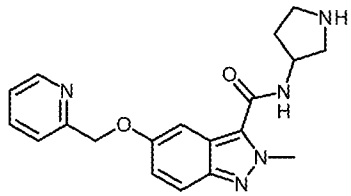
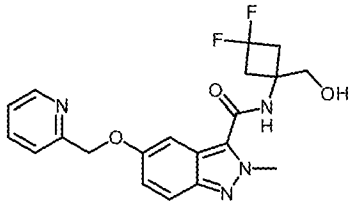
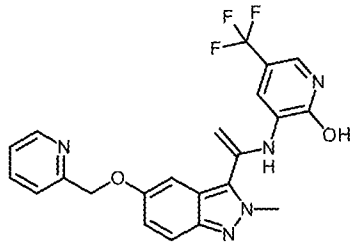
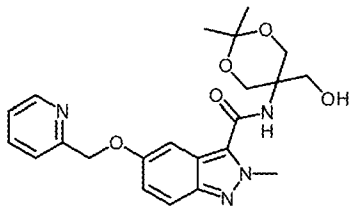
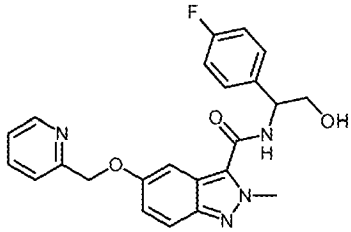
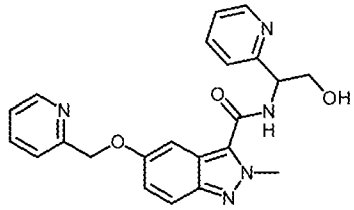
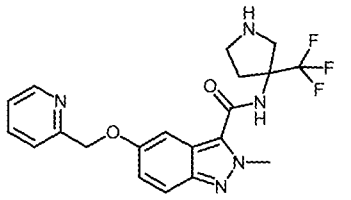
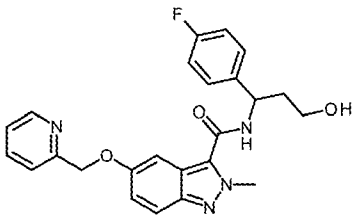
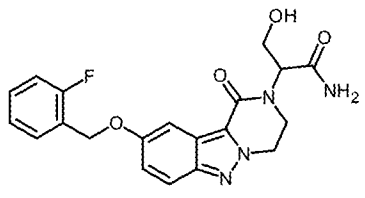
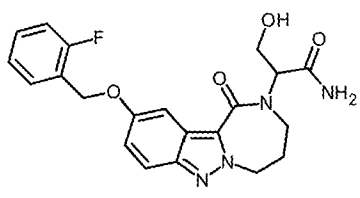
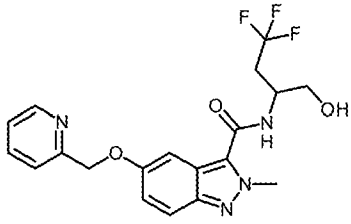
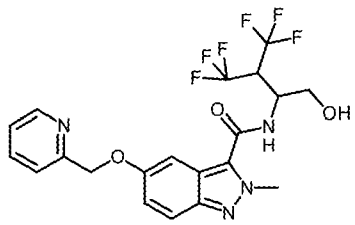
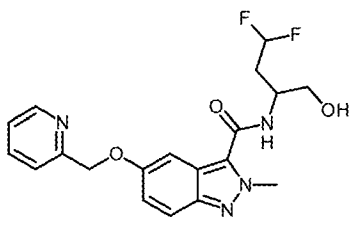
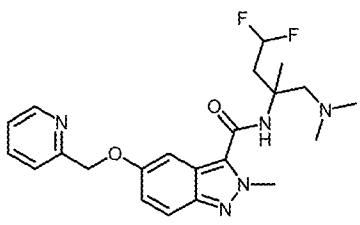
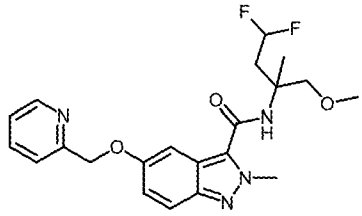
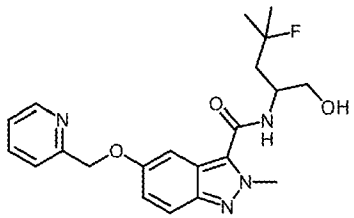
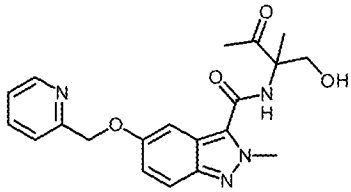
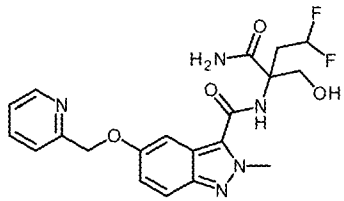
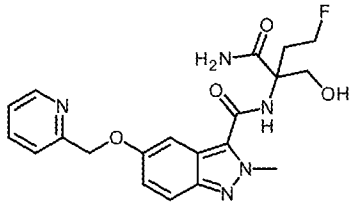
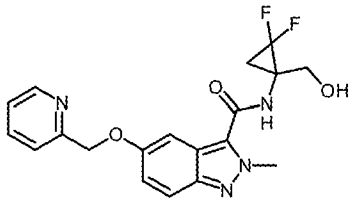
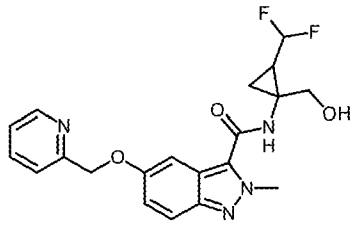
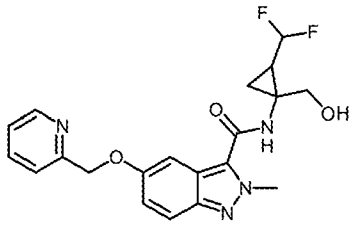
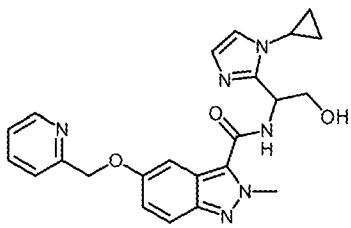
 Cpd 187	 Cpd 188	 Cpd 189
 Cpd 190	 Cpd 191	 Cpd 192
 Cpd 193	 Cpd 194	 Cpd 195
 Cpd 196	 Cpd 197	 Cpd 198
 Cpd 199		

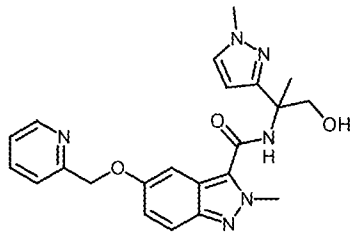
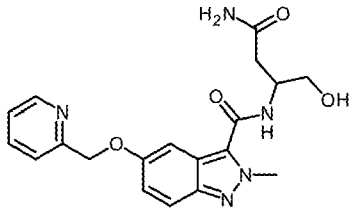
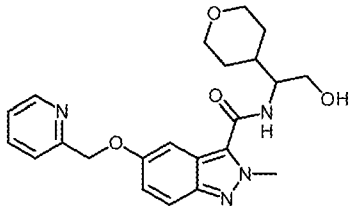
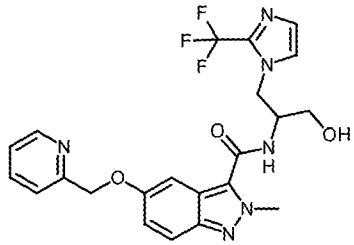
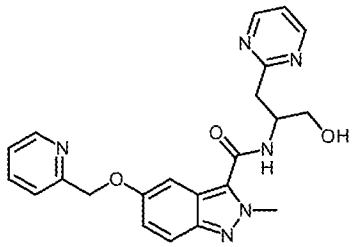
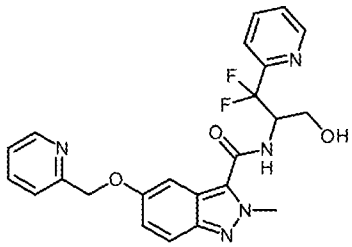
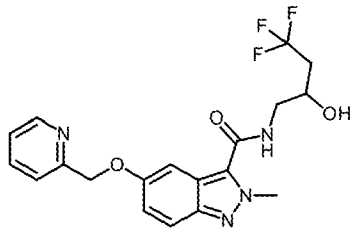
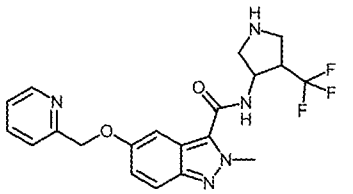
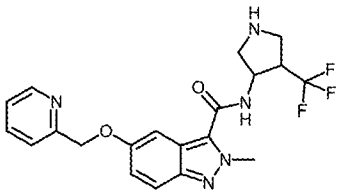
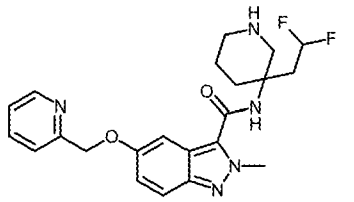
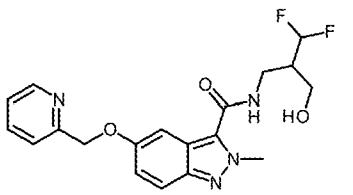
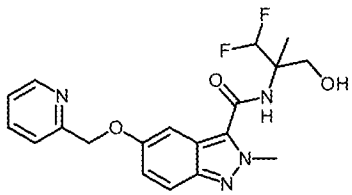
63. The compound of any one of the preceding items, which is selected from the group consisting of compounds 200 – 262 as shown in the table below:

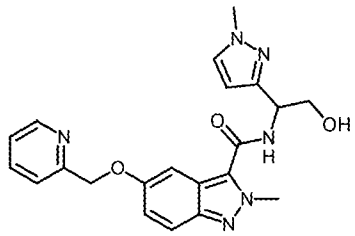
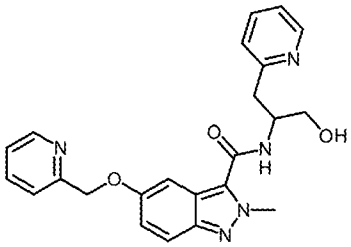
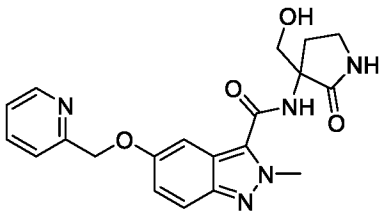
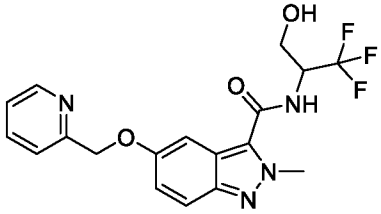
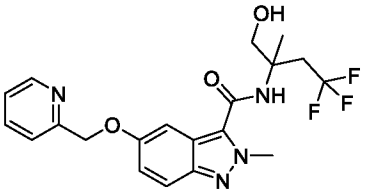
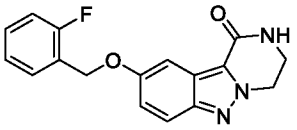
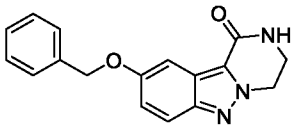
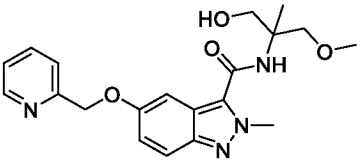
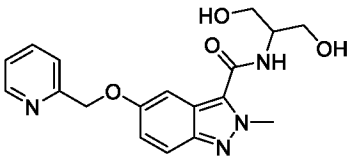
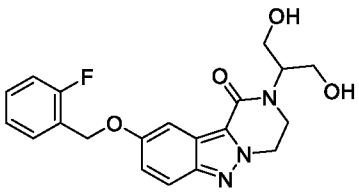
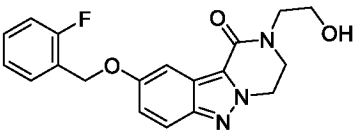
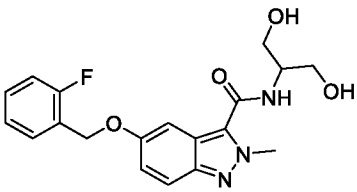
Structure and **Compound CODE**	Structure and **Compound CODE**	Structure and **Compound CODE**
 **Cmd 200**	 **Cpd 201**	 **Cpd 202**

 Cpd 203	 Cpd 204	 Cpd 205
 Cpd 206	 Cpd 207	 Cpd 208
 Cpd 209	 Cpd 210	 Cpd 211
 Cpd 212	 Cpd 213	 Cpd 214

 Cpd 215	 Cpd 216	 Cpd 217
 Cpd 218	 Cpd 219	 Cpd 220
 Cpd 221	 Cpd 222	 Cpd 223
 Cpd 224	 Cpd 225	 Cpd 226

 Cpd 227	 Cpd 228	 Cpd 229
 Cpd 230	 Cpd 231	 Cpd 232
 Cpd 233	 Cpd 234	 Cpd 235
 Cpd 236 (trans isomer)	 Cpd 237 (cis isomer)	 Cpd 238

 Cpd 239	 Cpd 240	 Cpd 241
 Cpd 242	 Cpd 243	 Cpd 244
 Cpd 245	 Cpd 246 (trans isomer)	 Cpd 247 (cis isomer)
 Cpd 248	 Cpd 249	 Cpd 250

 Cpd 251	 Cpd 252	 Cpd 253
 Cpd 254	 Cpd 255	 CPD 256
 Cpd 257	 Cpd 258	 Cpd 259
 Cpd 260	 Cpd 261	 Cpd 262

64. A pharmaceutical composition comprising a compound according to any one of the preceding items.

65. The compound according to any one of items 1 to 63 or the pharmaceutical composition according to item 64, for use in the treatment of pain.

66. The compound or the pharmaceutical composition for use in the treatment of pain according to item 65, wherein the pain is selected from nociceptive pain, inflammatory pain, and neuropathic pain; preferably post-operative pain.

67. A method of treating of pain comprising administering a compound according to any one of items 1 – 63, or a pharmaceutical composition according to item 64, to a subject in need thereof.

68. The method of item 67 wherein the pain is selected from nociceptive pain, inflammatory pain, and neuropathic pain; preferably post-operative pain.

69. The compound according to any one of items 1 to 63 or the pharmaceutical composition according to claim 64, for use in the treatment of epilepsy.

70. A method of treating of epilepsy comprising administering a compound according to any one of items 1 – 63, or a pharmaceutical composition according to any of items 64 or 69, to a subject in need thereof.

EXAMPLES

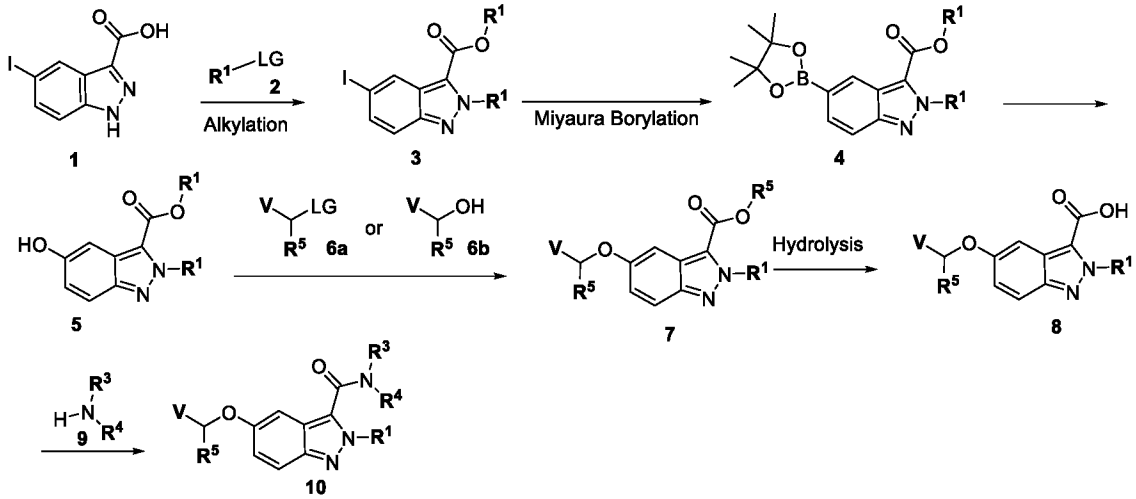
[0182] The following examples are provided for the purpose of illustrating the invention and by no means should be interpreted to limit the scope of the invention.

[0183] Representative compounds of the present invention can be synthesized in accordance with the general synthetic methods described below and illustrated in the schemes that follow. Since the schemes are an illustration, the invention should not be construed as being limited by the specific chemical reaction and specific conditions described in the schemes and examples. The various starting material used in the schemes are commercially available or may be prepared by methods well within the skill of persons versed in the art. The variables are as defined herein an within the skill of persons versed in the art.

[0184] Abbreviations used in the instant specification, particularly in the schemes and examples, are as follows: ABC – Aqueous solution of Ammonium Bicarbonate, ACN – acetonitrile, AcOH - Acetic acid, ADDP - 1,1'-(Azodicarbonyl)dipiperidide, aq. – Aqueous, AIBN – Azobisisobutyronitrile, CAN - Ceric ammonium nitrate, COMU - (1-Cyano-2-ethoxy-2-oxoethylidenaminooxy)dimethylamino-morpholino-carbenium , hexafluorophosphate, DABCO - 1,4-diazabicyclo[2.2.2]octane, DAST - Diethylaminosulfur trifluoride, DBU - 1,8-Diazabicyclo[5.4.0]undec-7-ene, DCC - N,N'-dicyclohexylcarbodiimide, DCM – Dichloromethane, DEAD - Diethyl azodicarboxylate, DIA – Diastereomer, DIAD – Diisopropyl azodicarboxylate, DEA – Diethylamine, DIPEA - Diisopropyl-ethyl amine, DME - 1,2-Dimethoxyethane, DMF - N,N-Dimethylformamide, DMSO – Dimethylsulfoxide, DPPA - Diphenylphosphoryl azide, DTBAD - tert-Butylazodicarboxylate, EDCI or EDC - 1-Ethyl-3-(3-dimethylaminopropyl)¬carbodiimide, En – Enantiomer, Et2O - Diethyl ether, EtOH –

Ethanol, EtOAc - Ethyl acetate, Eq. – Equivalent, FA - Formic acid, FCC - Flash column chromatography, h – Hour, HATU - O-(7-Azabenzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium hexafluorophosphate, HPLC - High performance liquid chromatography, IPA – isopropyl alcohol, LAH – Lithiumaluminiumhydrid, LG - Leaving group, MeOH – methanol, MgSO4 - Magnesium sulfate, min. – Minute, Ms – Methanesulfonyl, Na_2SO_4 - Sodium sulfate, NBS - N-Bromosuccinimide, nBuLi - n-Butyl lithium, NMP - 1-Methyl-2-pyrrolidinone, Pd(PPh3)4 - Tetrakis-(triphenylphosphine)-palladium(0), Pd2(dba)3 - Tris(dibenzylideneacetone)dipalladium, Pet ether - Petroleum ether, PPh3 – Triphenylphospine, PS-DIEA - Diisoprpropyl-ethyl amine supported on PolyStyrene, PS-PPh3 - Triphenylphospine supported on PolyStyrene, PyBop - Benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate, PTSA - p-Toluenesulfonic acid, RF: ratio of frontiers, RM - Reaction mixture, RP - Reverse phase, RT - Room temperature, sat. – Saturated, SEM - [2-(Trimethylsilyl)ethoxy]methyl acetal, SFC - Supercritical fluid chromatography, SPE - Solid Phase Extraction, TBDMS - Tert-Butyldimethylsilyl ether, TBAF - Tetrabutylammonium fluoride hydrate, TBAI - Tetrabutylammonium iodide, TEA – Triethylamine, THF - Tetrahydrofurane , TFA - Trifluoroacetic acid, TLC – thin layer chromatography, TPP – triphenyl phosphine, IPA – isopropyl alcohol, TMS – trimethyl silyl, T3P - Propylphosphonic anhydride.

[0185] The compounds of interest having a structure according to the general formula (A) and all other formulas described herein and embodiments thereof can be prepared as outlined in the general chemical scheme 1.

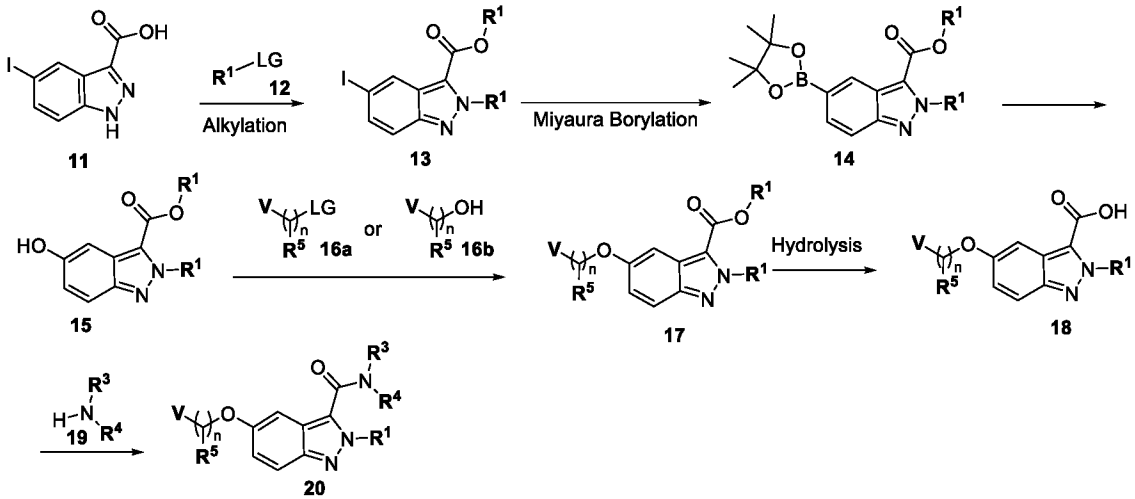


[0186]

[0187] Scheme 1: all **V**, $\mathbf{R^1}$, $\mathbf{R^3}$, $\mathbf{R^4}$ and $\mathbf{R^5}$ are as described for the compounds of the present invention. At each occurrence of R^5, up to two independent substituents are contemplated (i.e. R^5 and $R^{5'}$).

[0188] 5-Iodo-1H-indazole-3-carboxylic acid of formula **1** may be converted into intermediate of formula **3** via nucleophilic substitution using intermediates of formula 2 (commercially available or synthesized), wherein LG is a leaving group (e.g. halides, sulfonate ester, and the like), in the presence of a base (e.g., DIPEA, DBU, triethylamine, Cs_2CO_3, and the like) in a

polar solvent (e.g., acetonitrile, DMF, NMP, and the like), with or without a chelating agent (e.g., 18-crown-6, cis-anti-cis-dicyclohexano-18-crown-6, and the like) at a temperature ranging from 0 to 100°C. Compounds of formula **3** may be reacted under cross-coupling reaction conditions with a boron reagent (e.g. bis(pinacolato)diboron, and the like) in the presence of a metal catalyst (e.g. [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (II), and the like) and a base (e.g. K_2CO_3, potassium acetate, and the like) in a solvent (e.g. DMF, Dioxane, and the like) at a temperature from RT to Reflux to provide intermediates of formula **4**. Then, alcohol derivatives **5** may obtained via an oxidative cleavage of Boronic ester from intermediate **4** in presence of an oxidant (e.g. Oxone, and the like) and water in a solvent (e.g. Acetone, and the likes). Intermediates of formula **5** may then be converted into the desired compounds of formula **7** via nucleophilic substitution using intermediates of formula **6a** (commercially available or synthesized), wherein LG is a leaving group (e.g. halides, sulfonate ester, and the like), in the presence of a base (e.g., DIPEA, DBU, triethylamine, Cs_2CO_3, and the like) in a polar solvent (e.g., acetonitrile, DMF, NMP, and the like), with or without a chelating agent (e.g., 18-crown-6, cis-anti-cis-dicyclohexano-18-crown-6, and the like) at a temperature ranging from 0 to reflux. Alternatively, intermediates of formula **5** may instead be reacted with intermediates of formula **6b** (commercially available or synthesized) in the presence of an azodicarboxylate reagent (e.g., DEAD, DIAD, ADDP, and the like) and a phosphine (e.g., tributylphosphine, triphenylphosphine and the like) in a solvent (e.g., THF, toluene, and the like) at a temperature ranging from 0 to 100°C, to provide the desired compounds of formula **7**. Ester derivatives **7** may then be converted into the desired compounds of formula **8** via standard saponification reactions. The desired compounds of formula **10** may be obtained from acid derivatives of formula **8** by reaction with amine derivatives of formula **9** (commercially available or synthesized by procedures known in the art or as set forth in the examples below) under standard peptide coupling conditions (e.g. DCC, EDCI, HATU, PyBop and the like) in a polar aprotic solvent (e.g. DCM, DMF and the like). Alternatively, carboxylic acid derivatives of formula **8**, may be converted into acid chloride derivatives by procedures known to those skilled in the art or as set forth in the examples below, and then reacted with amines of formula **9** to obtain the desired compounds of formula **10** by procedures known to those skilled in the art or as set forth in the examples below.



[0189]

[0190] Scheme 2: all **V**, n, $\mathbf{R^1}$, $\mathbf{R^3}$, $\mathbf{R^4}$ and $\mathbf{R^5}$ are as described for the compounds of the present invention. At each occurrence of R^5, up to two independent substituents are contemplated (i.e. R^5 and $R^{5'}$). The integer n may range from 1 to 10 in some embodiments.

[0191] In an alternative embodiment, 5-Iodo-1H-indazole-3-carboxylic acid of formula **11** may be converted into intermediate of formula **13** via nucleophilic substitution using intermediates of formula **12** (commercially available or synthesized), wherein LG is a leaving group (e.g. halides, sulfonate ester, and the like), in the presence of a base (e.g., DIPEA, DBU, triethylamine, Cs_2CO_3, and the like) in a polar solvent (e.g., acetonitrile, DMF, NMP, and the like), with or without a chelating agent (e.g., 18-crown-6, cis-anti-cis-dicyclohexano-18-crown-6, and the like) at a temperature ranging from 0 to 100°C. Compounds of formula **13** may be reacted under cross-coupling reaction conditions with a boron reagent (e.g. bis(pinacolato)diboron, and the like) in the presence of a metal catalyst (e.g. [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (II), and the like) and a base (e.g. K_2CO_3, potassium acetate, and the like) in a solvent (e.g. DMF, Dioxane, and the like) at a temperature from RT to Reflux to provide intermediates of formula **14**. Then, alcohol derivatives **15** may obtained via an oxidative cleavage of Boronic ester from intermediate **14** in presence of an oxidant (e.g. Oxone, and the like) and water in a solvent (e.g. Acetone, and the likes). Intermediates of formula **15** may then be converted into the desired compounds of formula **17** via nucleophilic substitution using intermediates of formula **16a** (commercially available or synthesized), wherein LG is a leaving group (e.g. halides, sulfonate ester, and the like), in the presence of a base (e.g., DIPEA, DBU, triethylamine, Cs_2CO_3, and the like) in a polar solvent (e.g., acetonitrile, DMF, NMP, and the like), with or without a chelating agent (e.g., 18-crown-6, cis-anti-cis-dicyclohexano-18-crown-6, and the like) at a temperature ranging from 0 to reflux. Alternatively, intermediates of formula **15** may instead be reacted with intermediates of formula **16b** (commercially available or synthesized) in the presence of an azodicarboxylate reagent (e.g., DEAD, DIAD, ADDP, and the like) and a phosphine (e.g., tributylphosphine, triphenylphosphine and the like) in a solvent (e.g., THF, toluene, and the like) at a temperature ranging from 0 to 100°C, to provide the desired compounds of formula **17**. Ester derivatives **17**

may then be converted into the desired compounds of formula **18** via standard saponification reactions. The desired compounds of formula **20** may be obtained from acid derivatives of formula **18** by reaction with amine derivatives of formula **19** (commercially available or synthesized by procedures known in the art or as set forth in the examples below) under standard peptide coupling conditions (e.g. DCC, EDCI, HATU, PyBop and the like) in a polar aprotic solvent (e.g. DCM, DMF and the like). Alternatively, carboxylic acid derivatives of formula **18**, may be converted into acid chloride derivatives by procedures known to those skilled in the art or as set forth in the examples below, and then reacted with amines of formula **19** to obtain the desired compounds of formula **20** by procedures known to those skilled in the art or as set forth in the examples below.

Table 3: Exemplary compounds

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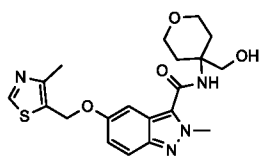
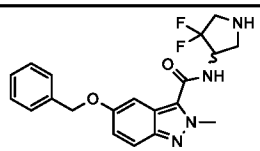
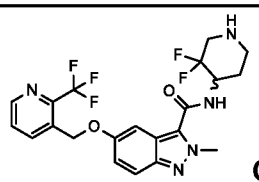
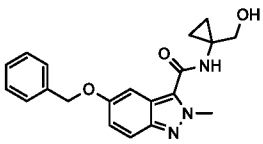
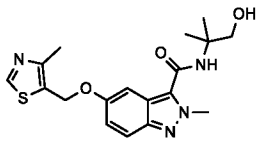
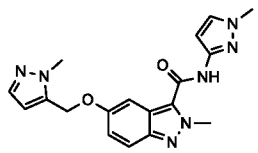
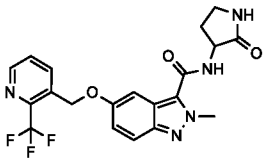
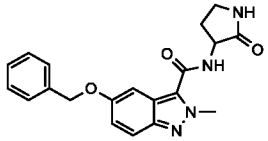
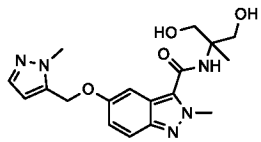
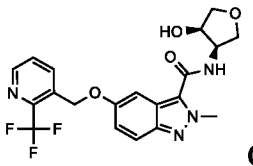
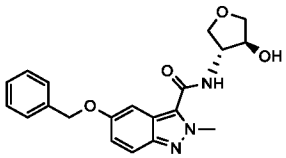
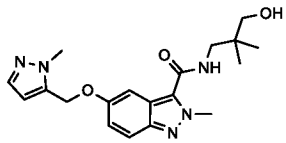
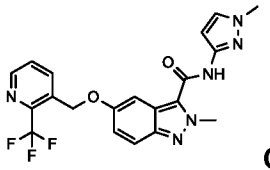
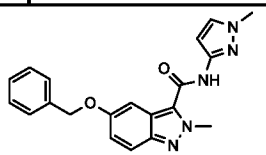
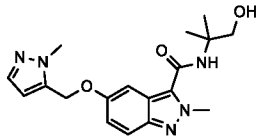
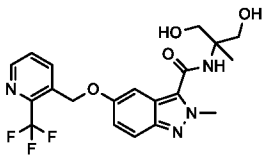
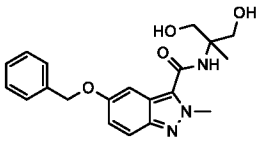
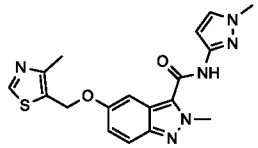
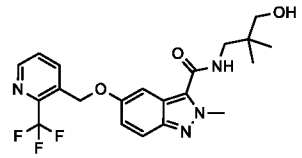
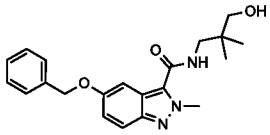
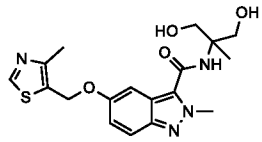
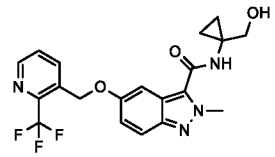
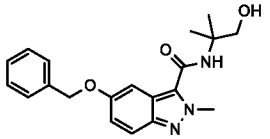
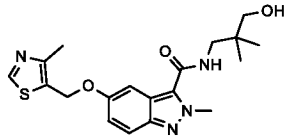
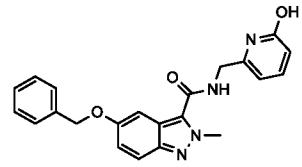
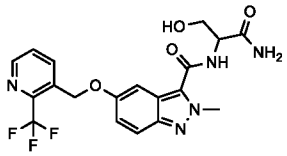
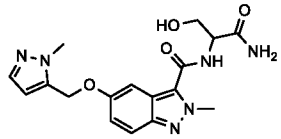
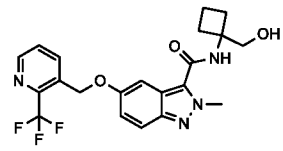
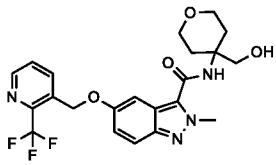
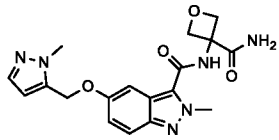
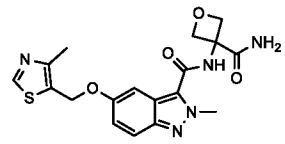
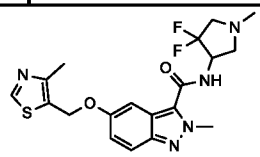
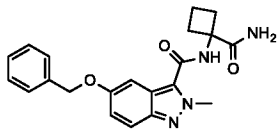
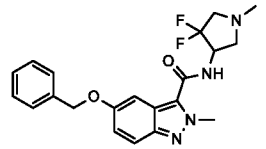
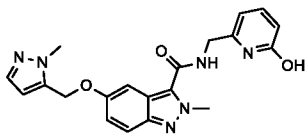
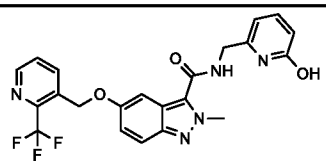
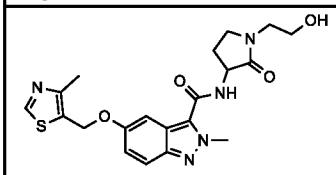
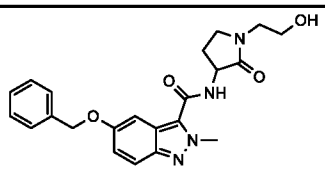
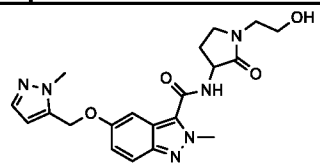
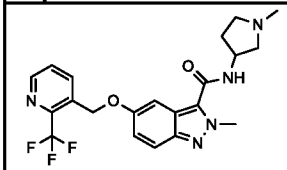
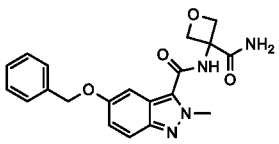
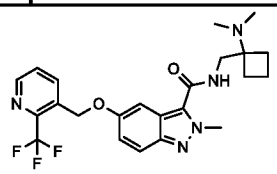
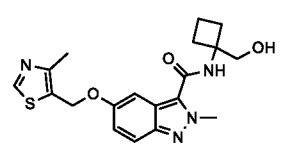
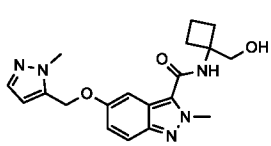
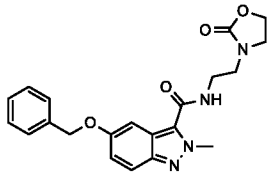
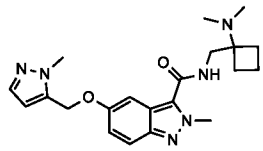
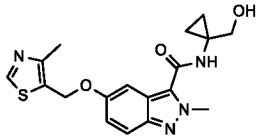
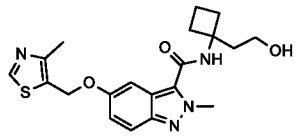
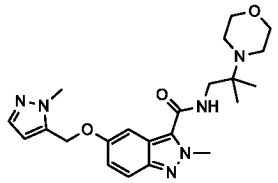
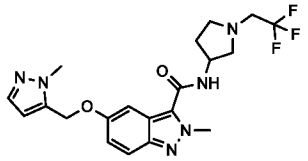
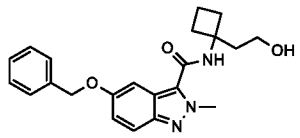
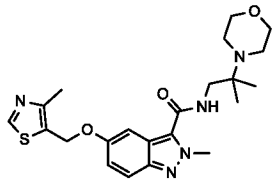
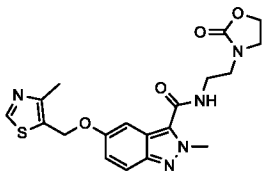
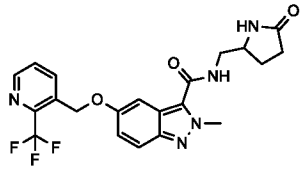
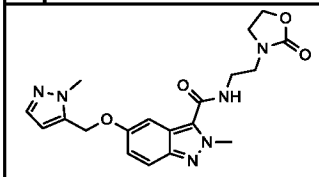
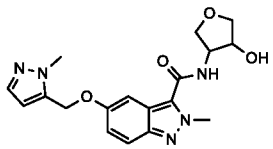
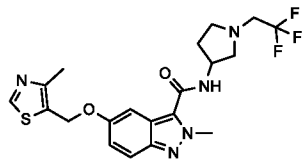
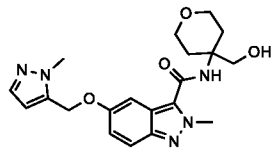
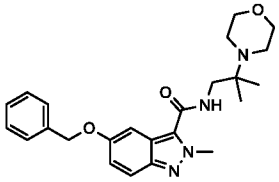
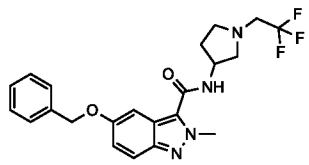
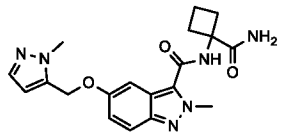
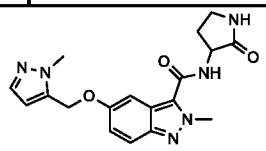
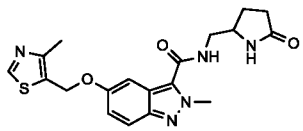
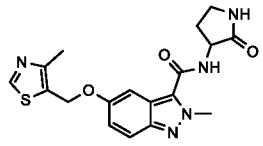
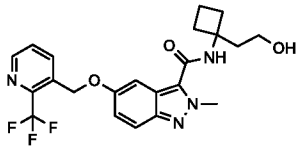
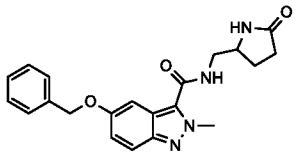
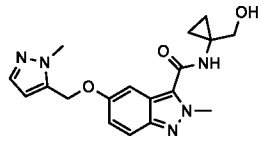
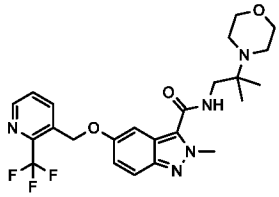
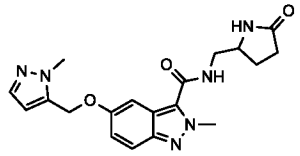
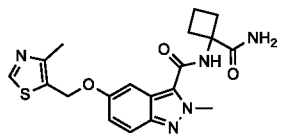
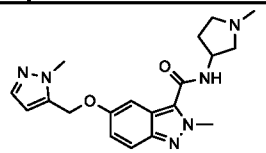
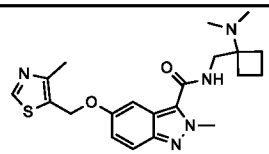
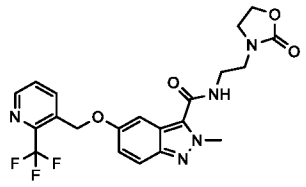
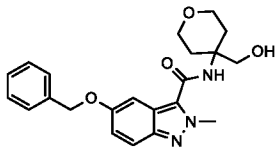
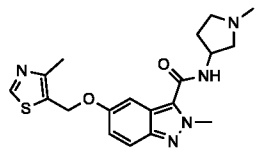
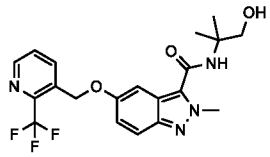
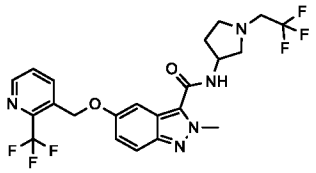
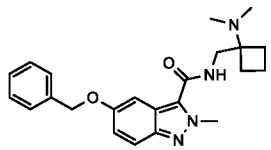
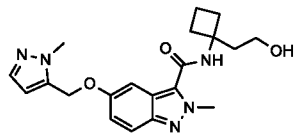
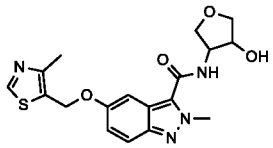
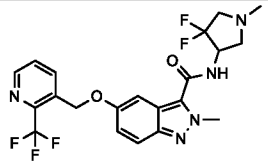
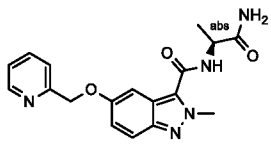
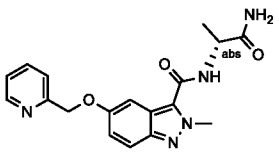
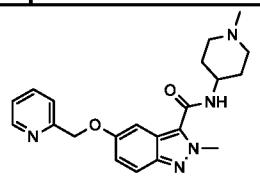
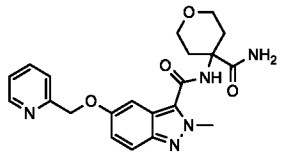
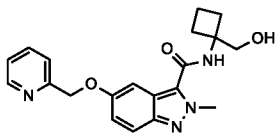
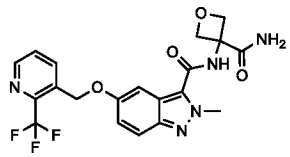
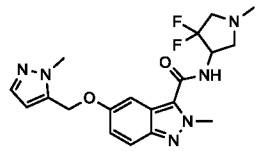
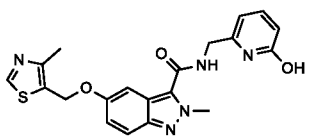
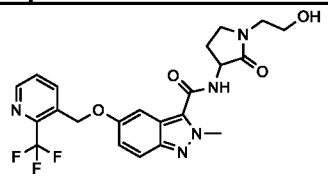
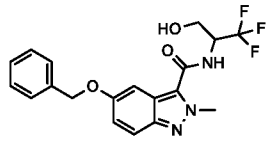
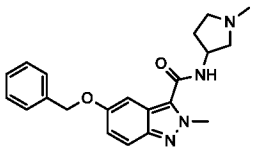
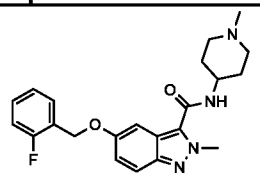
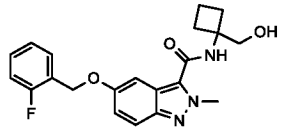
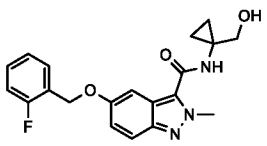
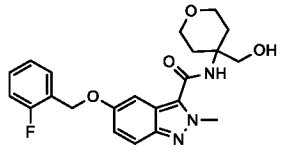
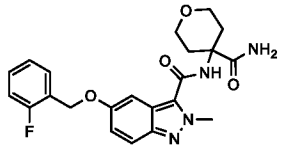
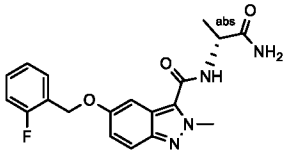
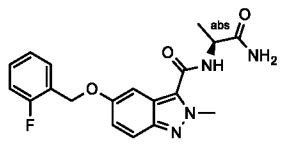
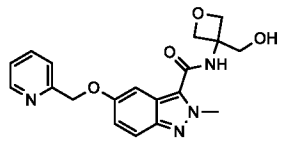
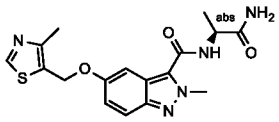
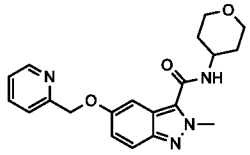
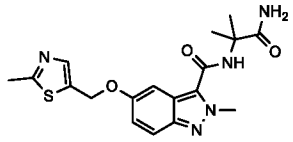
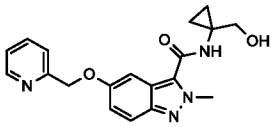
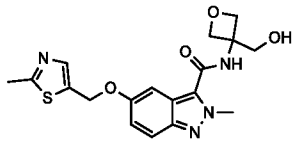
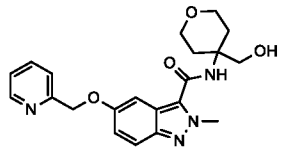
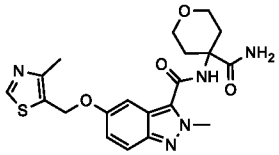
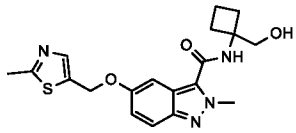
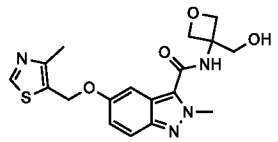
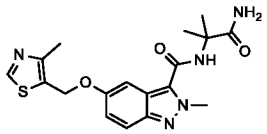
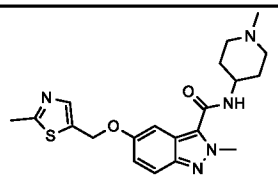
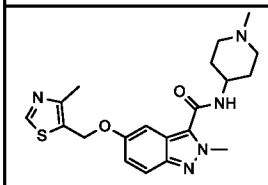
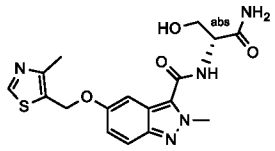
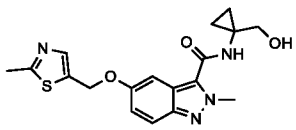
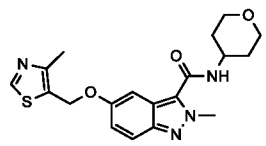
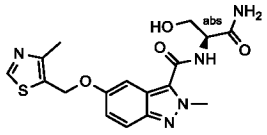
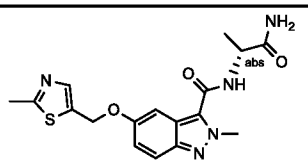
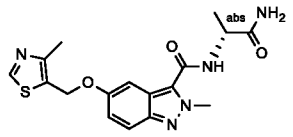
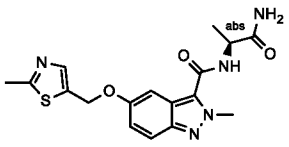
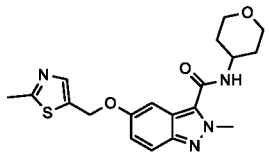
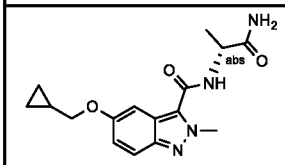
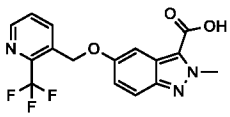
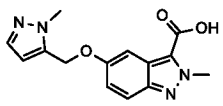
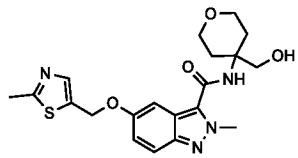
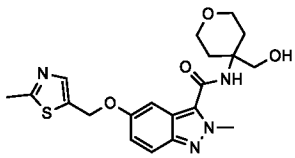
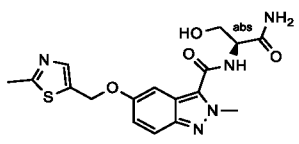
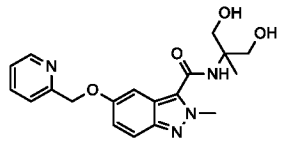
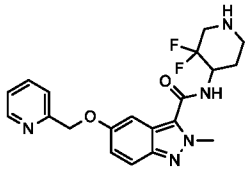
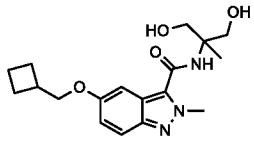
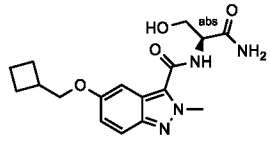
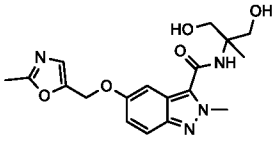
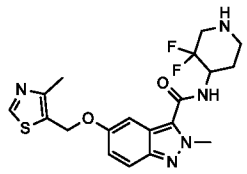
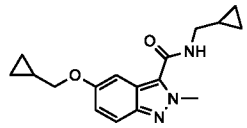
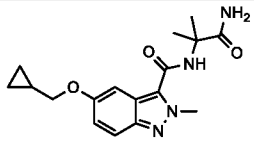
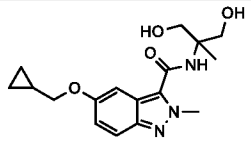
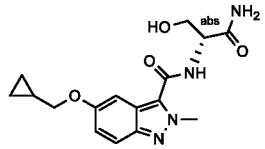
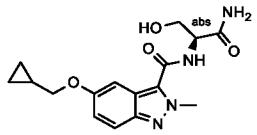
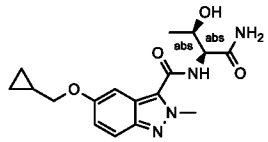
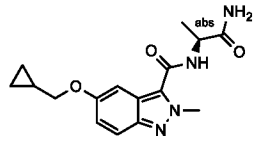
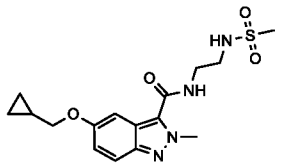
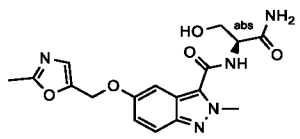
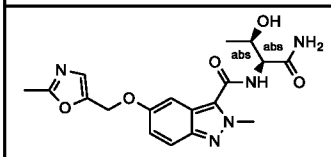
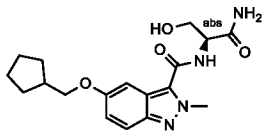
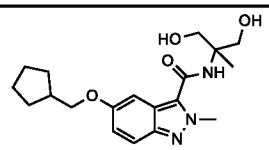
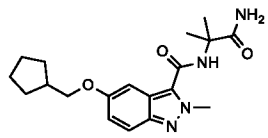
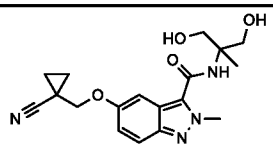
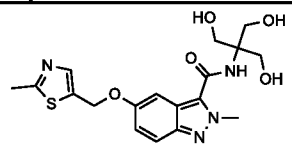
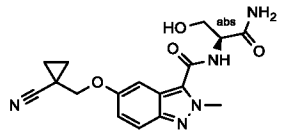
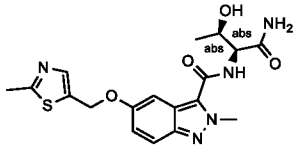
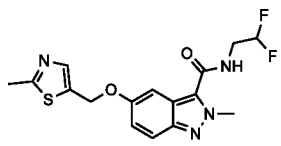
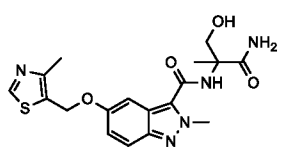
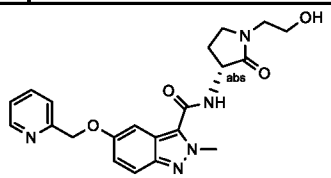
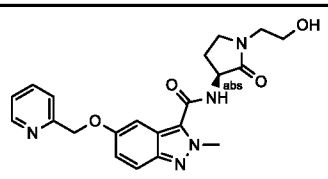
 **Cpd 001**	 **Cpd 002**	 **Cpd 003**
 **Cpd 004**	 **Cpd 005**	 **Cpd 006**
 **Cpd 007**	 **Cpd 008**	 **Cpd 009**
 **Cpd 010**	 **Cpd 011**	 **Cpd 012**
 **Cpd 013**	 **Cpd 014**	 **Cpd 015**
 **Cpd 016**	 **Cpd 017**	 **Cpd 018**

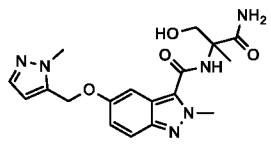
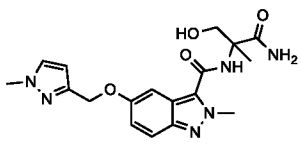
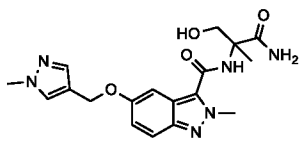
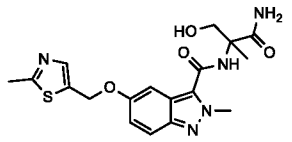
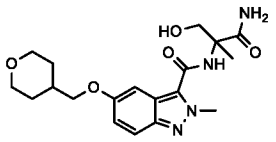
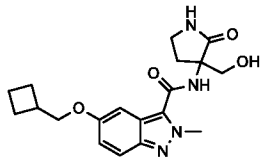
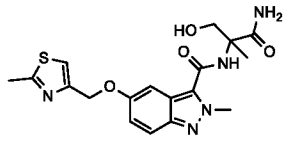
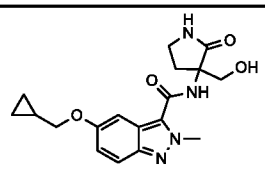
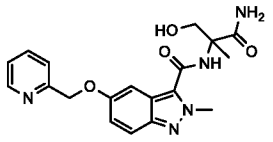
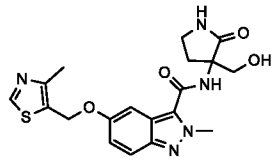
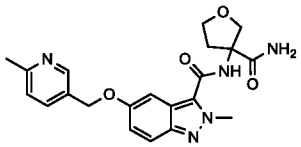
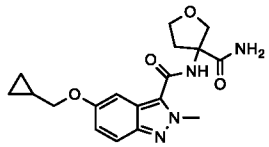
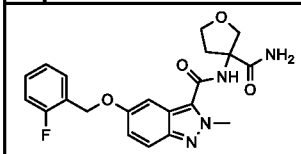
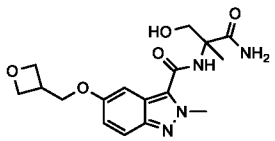
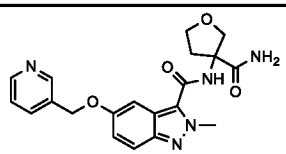
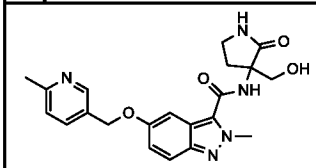
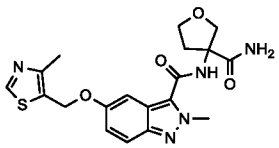
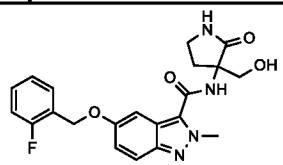
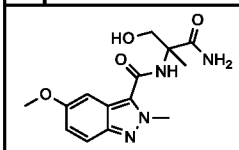
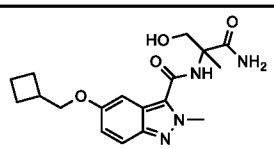
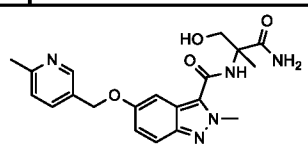
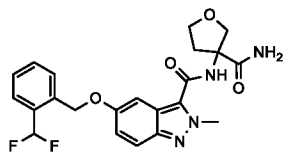
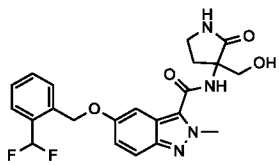
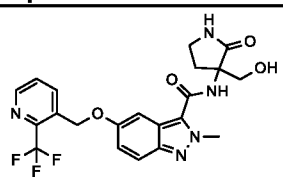
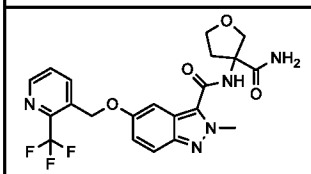
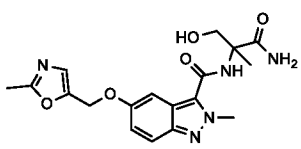
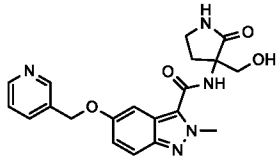
 Cpd 019	 Cpd 020	 Cpd 021
 Cpd 022	 Cpd 023	 Cpd 024
 Cpd 025	 Cpd 026	 Cpd 027
 Cpd 028	 Cpd 029	 Cpd 030
 Cpd 031	 Cpd 032	 Cpd 033
 Cpd 034	 Cpd 035	 Cpd 036
 Cpd 037	 Cpd 038	 Cpd 039
 Cpd 040	 Cpd 041	 Cpd 042
 Cpd 043	 Cpd 044	 Cpd 045

 Cpd 046	 Cpd 047	 Cpd 048
 Cpd 049	 Cpd 050	 Cpd 051
 Cpd 052	 Cpd 053	 Cpd 054
 Cpd 055	 Cpd 056	 Cpd 057
 Cpd 058	 Cpd 059	 Cpd 060
 Cpd 061	 Cpd 062	 Cpd 063
 Cpd 064	 Cpd 065	 Cpd 066
 Cpd 067	 Cpd 068	 Cpd 069
 Cpd 070	 Cpd 071	 Cpd 072

 Cpd 073	 Cpd 074	 Cpd 075
 Cpd 076	 Cpd 077	 Cpd 078
 Cpd 079	 Cpd 080	 Cpd 081
 Cpd 082	 Cpd 083	 Cpd 084
 Cpd 085	 Cpd 086	 Cpd 087
 Cpd 088	 Cpd 089	 Cpd 090
 Cpd 091	 Cpd 092	 Cpd 093
 Cpd 094	 Cpd 095	 Cpd 096
 Cpd 097	 Cpd 098	 Cpd 099

 Cpd 100	 Cpd 101	 Cpd 102
 Cpd 103	 Cpd 104	 Cpd 105
 Cpd 106	 Cpd 107	 Cpd 108
 Cpd 109	 Cpd 110	 Cpd 111
 Cpd 112	 Cpd 113	 Cpd 114
 Cpd 115	 Cpd 116	 Cpd 117
 Cpd 118	 Cpd 119	 Cpd 120
 Cpd 121	 Cpd 122	 Cpd 123
 Cpd 124	 Cpd 125	 Cpd 126

 Cpd 127	 Cpd 128	 Cpd 129
 Cpd 130	 Cpd 131	 Cpd 132
 Cpd 133	 Cpd 134	 Cpd 135
 Cpd 136	 Cpd 137	 Cpd 138
 Cpd 139	 Cpd 140	 Cpd 141
 Cpd 142	 Cpd 143	 Cpd 144
 Cpd 145	 Cpd 146	 Cpd 147
 Cpd 148	 Cpd 149	 Cpd 150
 Cpd 151	 Cpd 152	 Cpd 153

 Cpd 154	 Cpd 155	 Cpd 156
 Cpd 157	 Cpd 158	 Cpd 159
 Cpd 160	 Cpd 161	 Cpd 162
 Cpd 163	 Cpd 164	 Cpd 165
 Cpd 166	 Cpd 167	 Cpd 168
 Cpd 169	 Cpd 170	 Cpd 171
 Cpd 172	 Cpd 173	 Cpd 174
 Cpd 175	 Cpd 176	 Cpd 177
 Cpd 178	 Cpd 179	 Cpd 180

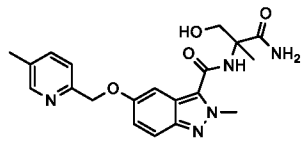
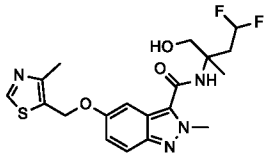
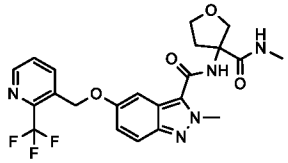
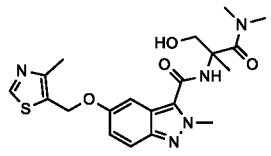
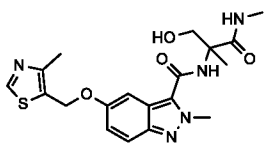
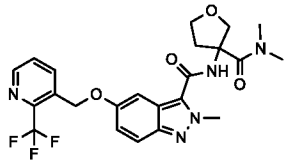
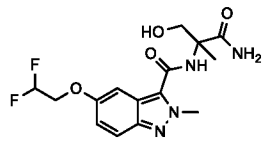
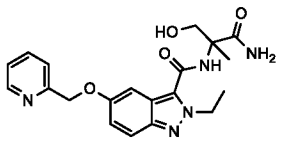
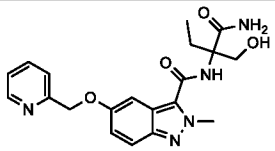
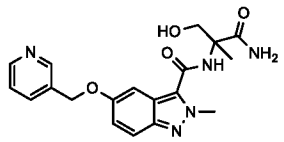
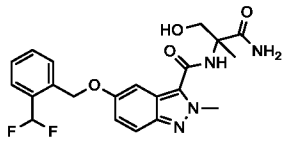
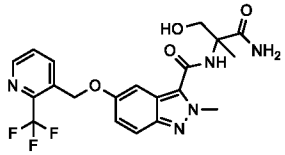
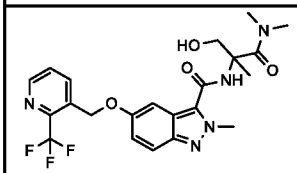
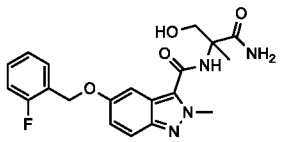
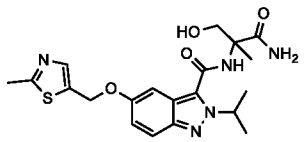
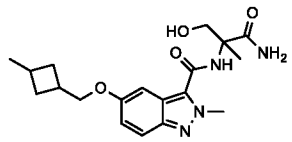
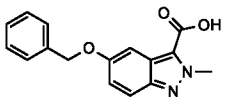
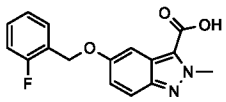
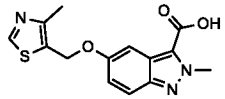
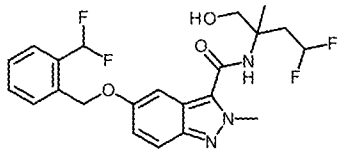
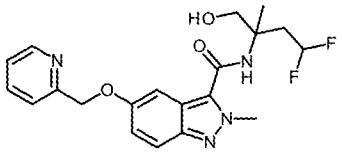
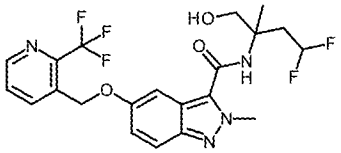
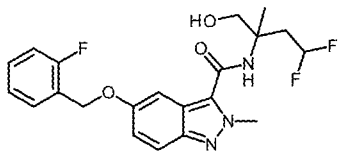
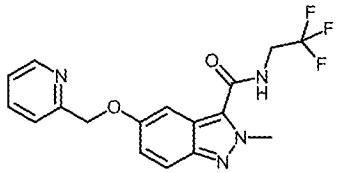
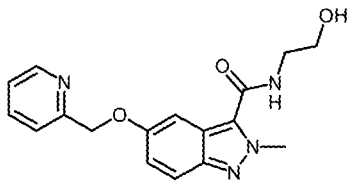
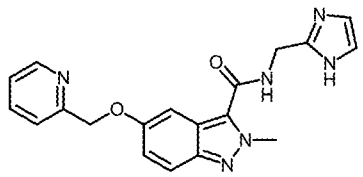
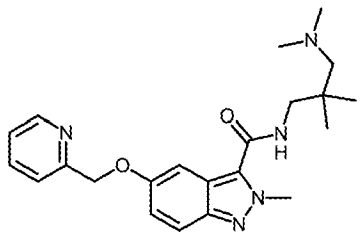
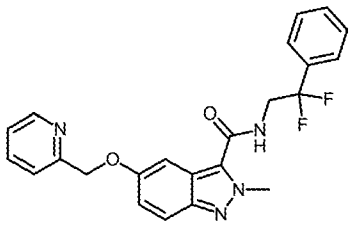
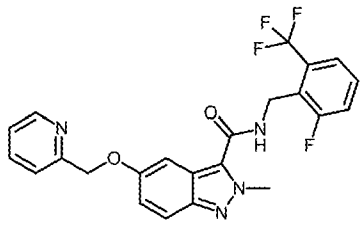
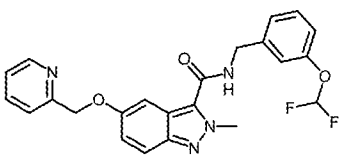
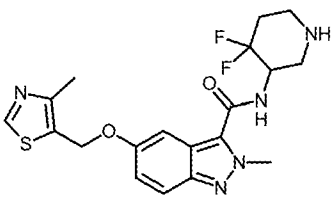
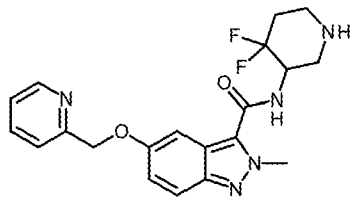
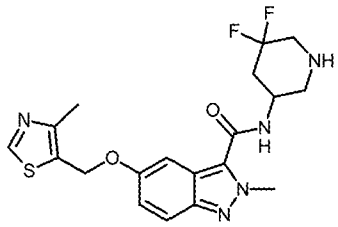
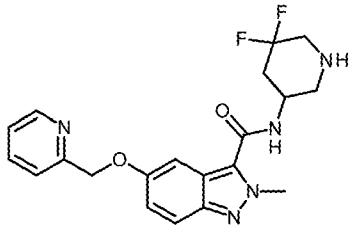
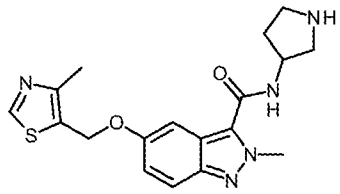
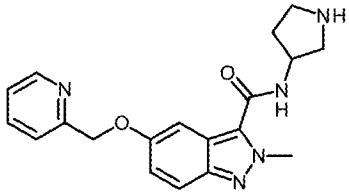
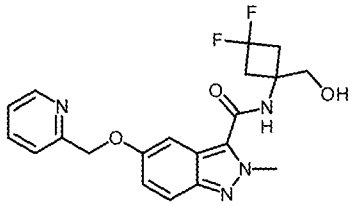
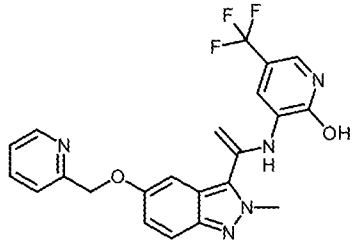
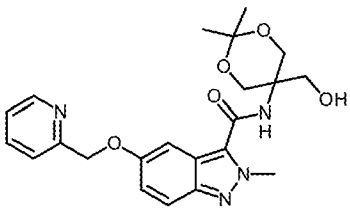
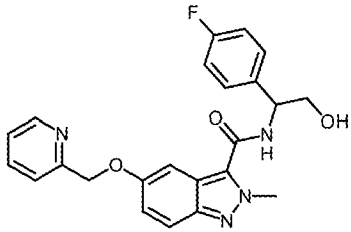
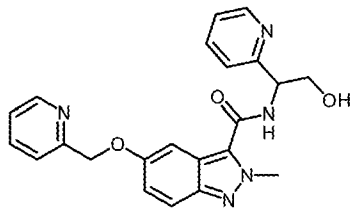
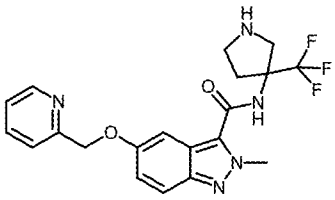
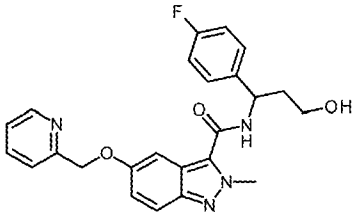
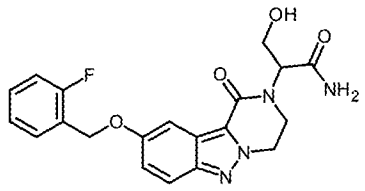
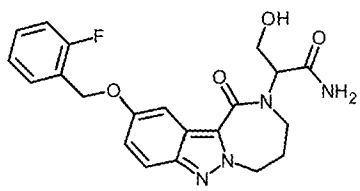
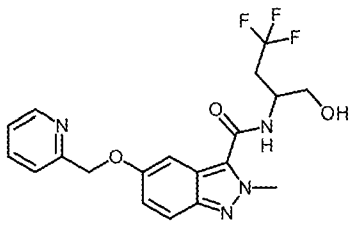
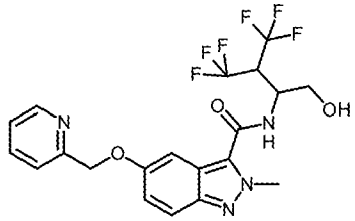
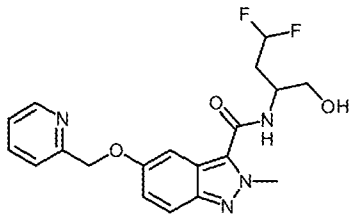
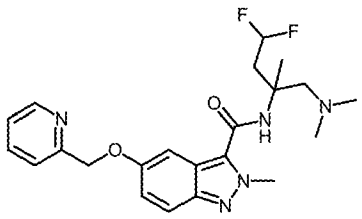
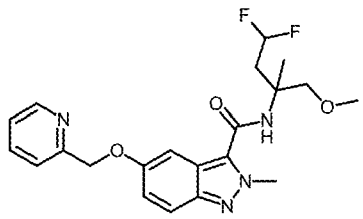
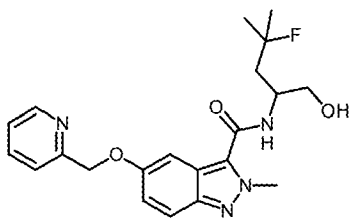
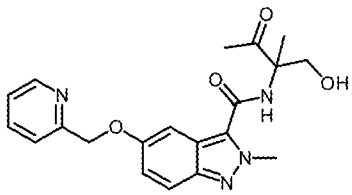
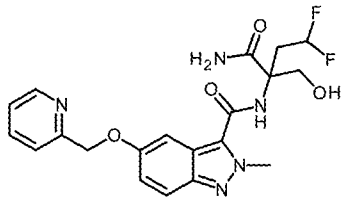
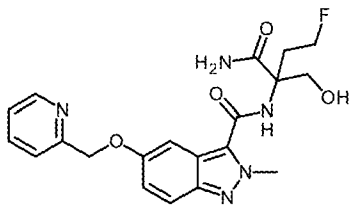
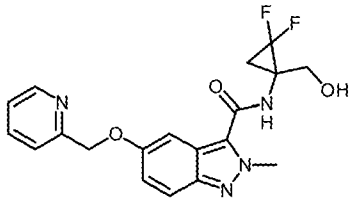
 Cpd 181	 Cpd 182	 Cpd 183
 Cpd 184	 Cpd 185	 Cpd 186
 Cpd 187	 Cpd 188	 Cpd 189
 Cpd 190	 Cpd 191	 Cpd 192
 Cpd 193	 Cpd 194	 Cpd 195
 Cpd 196	 Cpd 197	 Cpd 198
 Cpd 199		

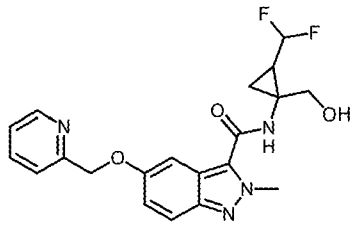
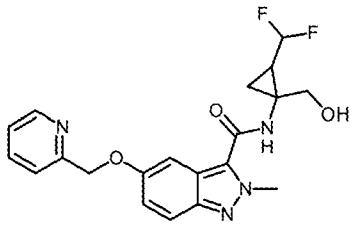
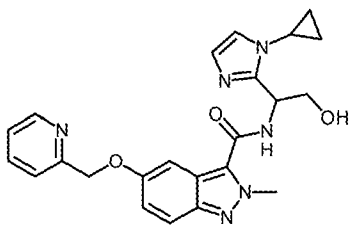
Table 4: Exemplary compounds

Structure and **Compound CODE**	Structure and **Compound CODE**	Structure and **Compound CODE**

 Cmd 200	 Cpd 201	 Cpd 202
 Cpd 203	 Cpd 204	 Cpd 205
 Cpd 206	 Cpd 207	 Cpd 208
 Cpd 209	 Cpd 210	 Cpd 211

 Cpd 212	 Cpd 213	 Cpd 214
 Cpd 215	 Cpd 216	 Cpd 217
 Cpd 218	 Cpd 219	 Cpd 220
 Cpd 221	 Cpd 222	 Cpd 223

 Cpd 224	 Cpd 225	 Cpd 226
 Cpd 227	 Cpd 228	 Cpd 229
 Cpd 230	 Cpd 231	 Cpd 232
 Cpd 233	 Cpd 234	 Cpd 235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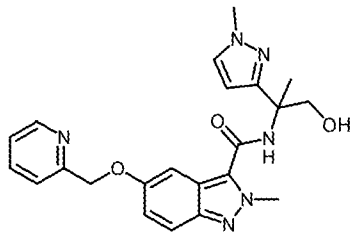	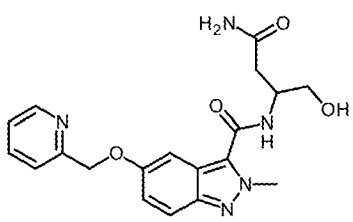	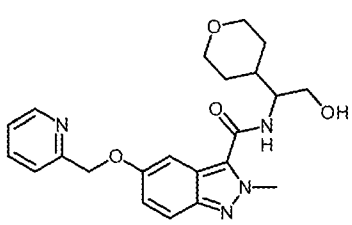
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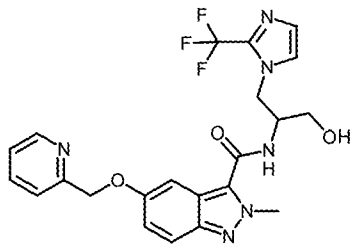	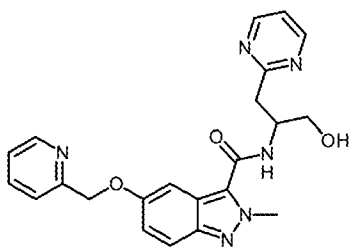	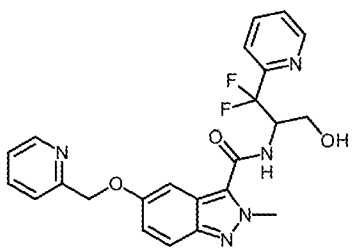
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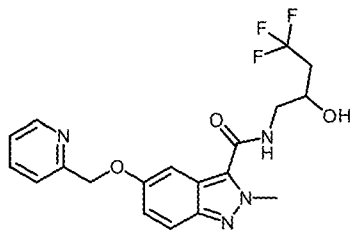	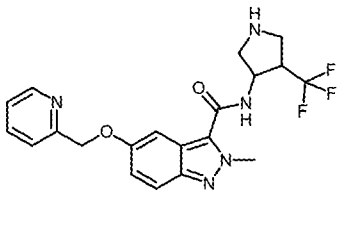	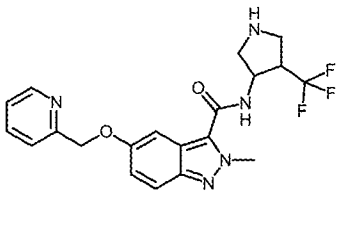
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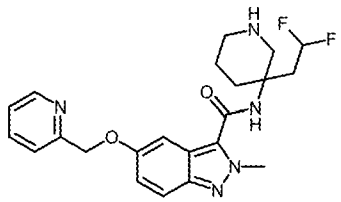
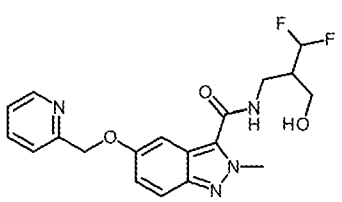
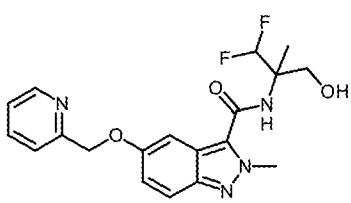
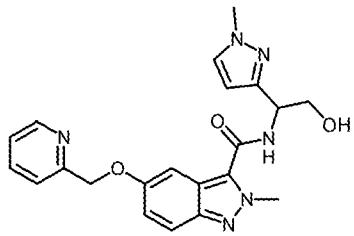
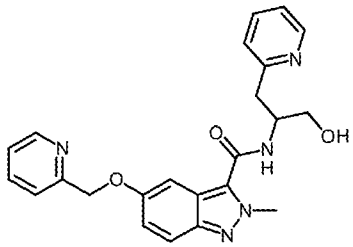
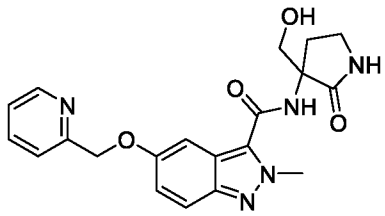
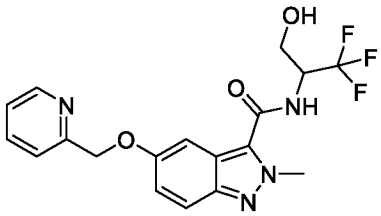
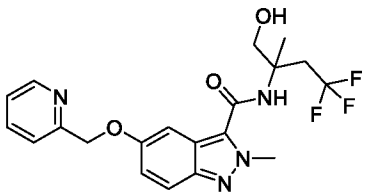
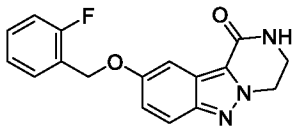
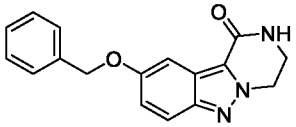
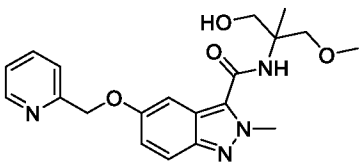
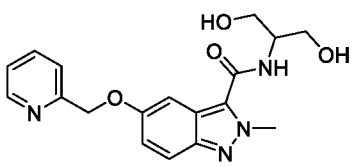
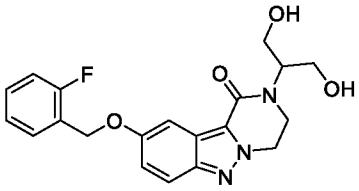
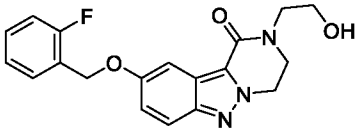
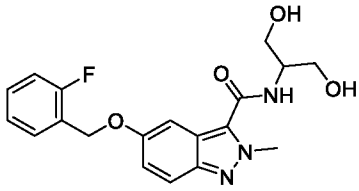
 Cpd 248	 Cpd 249	 Cpd 250
 Cpd 251	 Cpd 252	 Cpd 253
 Cpd 254	 Cpd 255	 Cpd 256
 Cpd 257	 Cpd 258	 Cpd 259
 Cpd 260	 Cpd 261	 Cpd 262

[0192]

[0193] The following examples are provided for the purpose of illustrating the present invention and by no means should be interpreted to limit the scope of the present invention.

[0194] Part A represent the preparation of the compounds whereas Part B represents the

pharmacological examples.

[0195] **Part A**

[0196] All starting materials which are not explicitly described were either commercially available (the details of suppliers such as for example ABCR, Apollo Scientific Combi-Blocks, Enamine, FluoroChem, MatrixScientific, Maybridge, Merck, TCI etc. can be found in the SciFinder® Database for example) or the synthesis thereof has already been described precisely in the specialist literature (experimental guidelines can be found in the Reaxys® Database or the SciFinder® Database respectively, for example) or can be prepared using the conventional methods known to the person skilled in the art.

[0197] The reactions were, if necessary, carried out under an inert amosphere (mostly argon and N_2). The number of equivalents of reagents and the amounts of solvents employed as well as the reaction temperatures and times can vary slightly between different reactions carried out by analogous methods. The work-up and purification methods were adapted according to the characteristic properties of each compound and can vary slightly for analogous methods. The yields of the compounds prepared are not optimized.

[0198] The indication „equivalents“ ("eq." or “eq” or “equiv.”) means molar equivalents, „RT“ or “rt” means room temperature T (23 ± 7 °C), „M“ are indications of concentration in mol/l, „sol.“ means solution, "conc." means concentrated. The mixing ratios of solvents are usually stated in the volume / volume ratio.

[0199] Key analytical characterization was carried out by means of ^{1}H-NMR spectroscopy and/or mass spectrometry (MS, m/z for $[M+H]^+$ and/or $[M-H]^-$) for all the exemplary compounds and selected intermediate products. In certain cases, where e.g. regioisomers and/or diatereomers could be/were formed during the reaction, additional analytics, such as, e.g. ^{13}C NMR and NOE (nuclear overhauser effect) NMR experiments were in some cases performed.

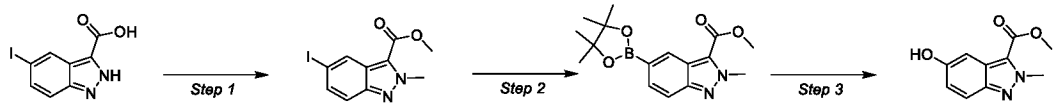
[0200] Analytical instruments employed were e.g. for NMR analysis a BRUKER 400MHz or a BRUKER 500MHz machine (Software Topspin), alternatively a BRUKER AVANCE 300MHz and 400Mhz was employed. For LC/MS analysis e.g. an Agilent 1290 infinity,Mass:6150 SQD(ESI/APCI) or an Agilent 1200 SERIES,Mass:6130 SQD(ESI/APCI) (Software Chemistation) was employed. Analytical HPLCs were measured e.g. on Waters (Software Empower), an Agilent-1200-ELSD (Software Chemistation) or an Agilent-1260 (Software OpenLAB). Analytical SFC were performed e.g. on a PIC solution (Software: SFC PICLAB ONLINE), a WATERS-X5 (Software MASSLYNX) or a WATERS-UPC2 (Empower).

[0201] Preparative HPLC were performed e.g. on a Waters 2998 (Software Empower) or a YMC (Software K-Prep). Preparative SFC were performed e.g. on a Waters,SFC- 200 (Software Chromscope or Super chrome), a Waters,SFC-80 (Super chrome) or a PIC,PIC-175 (Software S10-100).

[0202] Structures of example compounds that contain stereocenters are drawn and named

with absolute stereochemistry, if known. In case of unknown absolute stereochemistry the compounds can be either racemic, a mixture of diastereomers, a pure diastereomer of unknown stereochemistry, or a pure enantiomer of unknown stereochemistry. **Dia 1** and **Dia 2** means that diastereoisomers were separated but the stereochemistry is unknown. **En 1** and **En 2** means that both enantiomers were separated but the absolute configuration is unknown. No suffix given after the compound code means that a compound containing stereocenters was obtained as a racemic mixture or a mixture of diastereomers, respectively, unless the chemical name of the compound specifies the exact stereochemistry.

[0203] **Synthesis of methyl 5-hydroxy-2-methyl-2H-indazole-3-carboxylate (**Int-01**).**



Int-01

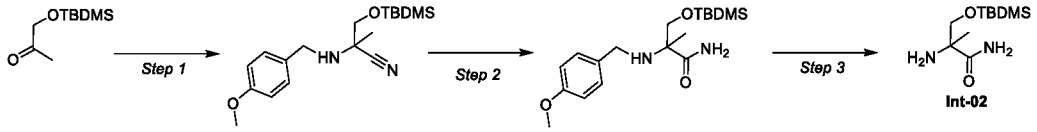
[0204] *Step 1* : To a stirred solution of 5-Iodo-1H-indazole-3-carboxylic acid (36 g, 0.12 mol) in DMF (500 ml) was added K_2CO_3 (86.38 g, 0.625 mol) followed by Methyl Iodide (23.5 ml, 0.375 mol) at RT. The RM was stirred at 80 0°C for 4h. The RM was filtered over celite bed, washed with EtOAc (3 x 100). Filtrate was poured into ice water, resulting aqueous extracted with EtOAc (3 x 700 ml). Combined organic layers were washed with water (2 x 350 ml), followed by brine (350 ml), dried over anhydrous Na_2SO_4 and concentrated to afford crude. The crude was purified FCC (using silica gel 100-200 mesh, 15 % EtOAc in hexane as eluent) to afford 5-Iodo-2-methyl-2H-indazole-3-carboxylic acid methyl ester. ^{1}H-NMR (400 MHz, CDCl3) δ [ppm]: 8.41 (s, 1H), 7.58-7.56 (dd, 1H), 7.52-7.50 (d, 1H), 4.48 (s, 3H), 4.03 (s, 3H).

[0205] *Step 2* : To a stirred solution of 5-Iodo-2-methyl-2H-indazole-3-carboxylic acid methyl ester (7.5 g, 0.023 mol) in 1,4-Dioxane (150 ml) was added Bis-pin (8.76 g, 0.0345 mol) followed by potassium acetate (6.77 g, 0.069 mol) at RT. The RM was degassed with nitrogen for 10 minutes, then Pd(dppf)Cl2. DCM adduct (0.56 g, 0.00069 mol) was added and heated at 110 °C for 16 h. The RM was filtered through celite bed, washed with EtOAc. Combined filtrate was concentrated to afford methyl 2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2H-indazole-3-carboxylate (7.5 g) as brown solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm]: 8.50 (s, 1H), 7.72 (s, 2H), 4.51 (s, 3H), 4.05 (s, 3H), 1.25 (s, 12H).

[0206] *Step 3* : To a stirred solution of methyl 2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2H-indazole-3-carboxylate (7.5 g, 0.023 mol) in Acetone (150 ml) was added solution of Oxone (14.13 g, 0.023 mol) in water (150 ml) drop-wise at 0°C. The RM was stirred at 0°C for 2h. The RM was diluted with EtOAc (200 ml). Two layers were separated; aqueous layer was extracted with EtOAc (200 ml). Combined organic layers were washed with water (150 ml), followed by brine (150 ml), dried over Na_2SO_4 and concentrated to afford crude. The crude was purified by FCC (using silica gel 100-200 mesh, 30% EA in hexane as eluent) to afford methyl 5-hydroxy-2-methyl-2H-indazole-3-carboxylate (**Int-01**) (2.6 g, 53%) as off white solid. ^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 9.66 (s, 1H), 7.62-7.60 (d, 1H), 7.16-7.15

(d, 1H), 6.96-6.93 (dd, 1H), 4.35 (s, 3H), 3.93 (s, 3H).

[0207] **Synthesis of 2-amino-3-((tert-butyldimethylsilyl)oxy)-2-methylpropanamide (**Int-02**).**



[0208] *Step* 1 : To a stirred solution of 1-(tert-Butyl-dimethyl-silanyloxy)-propan-2-one (25 g, 132.7 mmol) in EtOH (250ml) was added 4-methoxy benzylamine (19.08 ml, 146 mmol) at room temperature. Trimethylsillylcyanide (19.93 ml, 159.286 mmol) followed by ammonium chloride (2.13 g, 39.8 mmol) were added to the RM at RT. The RM was stirred at 80°C for 16 h. The RM was concentrated. The crude was partitioned between EtOAc and saturated sodium bicarbonate solution. Organic layer was washed with brine solution, dried over sodium sulphate and concentrated. The crude was purified on FCC (using 100-200 silica gel, eluted with 10% EtOAc-Hexane) to afford 3-(tert-Butyl-dimethyl-silanyloxy)-2-(4-methoxy-benzylamino)-2-methyl-propionitrile (25 g, 57%) as yellow liquid.^{1}H-NMR (400 MHz, DMSO) δ [ppm]: 7.25-7.23 (d, 2H), 6.68-6.86(d, 2H), 3.72-3.68(m, 6H), 3.51-3.48 (m, 1H), 1.36(s, 3H), 0.87 (s, 9H), 0.06 (s, 6H).

[0209] *Step 2* : To a stirred solution of 3-(tert-Butyl-dimethyl-silanyloxy)-2-(4-methoxy-benzylamino)-2-methyl-propionitrile (10 g, 29.9 mmol) in DMSO (100 ml) was added potassium carbonate (28.92 g, 209.243 mmol) at RT. Hydrogen peroxide (14.03 ml, 298.92 mmol) was added drop wise to the reaction at 0°C. The RM was stirred for 16 h at RT. The RM was quenched with ice cold water and extracted with MTBE. Organic part was dried over Na_2SO_4 and concentrated. Resultant crude material was purified on FCC (using 100-200 silica gel, eluted with 50% EtOAc-Hexane) to afford 3-(tert-Butyl-dimethyl-silanyloxy)-2-(4-methoxy-benzylamino)-2-methyl-propionamide (3.4 g, 33%) as oily liquid. ^{1}H-NMR (400 MHz, DMSO) δ [ppm]: 7.26-7.24 (d, 3H), 7.06 (s, 1H), 6.87-6.85 (d, 2H), 3.72 (s, 3H), 3.70-3.68 (m, 1H), 3.58-3.56 (m, 1H), 3.51-3.50 (d, 2H), 2.04 (m, 1H), 1.15 (s, 3H), 0.85 (s, 9H), 0.03 (s, 6H).

[0210] *Step 3* :To a stirred solution of -(tert-Butyl-dimethyl-silanyloxy)-2-(4-methoxy-benzylamino)-2-methyl-propionamide (3 g, 8.509 mmol) in MeOH (60 ml) was added palladium hydroxide (1.5 g) was added at RT. The RM was stirred for 4 h under H_2 gas balloon pressure at RT. The RM was filtered through celite bed, washed with 10% MeOH-DCM. Combine filtrate was concentrated to afford 2-amino-3-((tert-butyldimethylsilyl)oxy)-2-methylpropanamide (**Int-02**) (1.5 g, 76%) as off white solid. ^{1}H-NMR (400 MHz, DMSO) δ [ppm]: 7.25 (s, 1H), 6.95 (s, 1H), 3.77-3.74 (d, 1H), 3.70-3.68 (m, 1H), 3.27-3.24 (d, 1H), 1.82 (s, 2H), 1.04 (s, 3H), 0.85 (s, 9H), 0.02 (s, 6H).

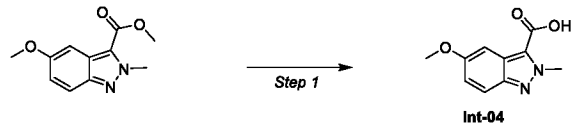
[0211] **Synthesis of 5-hydroxy-2-methyl-2H-indazole-3-carboxylic acid (**Int-03**).**



Int-03

[0212] *Step 1* : To a stirred solution of methyl 5-methoxy-2-methyl-2H-indazole-3-carboxylate (2.5 g, 11.36 mmol, 1.0 eq) in toluene (100 ml) was added AlCl3 (4.53 g, 34.09 mmol, 4 eq) at RT, then the reaction mixture was heated up to 110 °C for 2 h. Reaction progress was monitored by LCMS. The reaction mixture was distilled under vacuum to get crude, which was diluted with ice water (10 ml), then stirred for 10 min, filtered the solid precipitated was washed with diethyl ether to afford 5-hydroxy-2-methyl-2H-indazole-3-carboxylic acid (**Int-03**) (1.0 g, 47%, off-white solid). TLC system: 60% EtOAc/Pet ether; RF: 0.1.

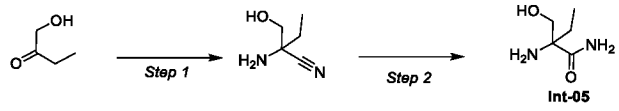
[0213] **Synthesis of 5-methoxy-2-methyl-2H-indazole-3-carboxylic acid (**Int-04**).**



Int-04

[0214] *Step 1* : To a stirred solution of methyl 5-methoxy-2-methyl-2H-indazole-3-carboxylate (500 mg, 2.27 mmol) in MeOH:THF (1:1; 20 mL) was added NaOH (900 mg, 22.72 mmol) in water (5 mL), at RT. The reaction mixture was stirred for 16 h at RT and reaction progress was monitored by TLC. The reaction mixture was concentrated under reduced pressure, diluted with water (20 mL), acidified to pH ~1 with 1N aq. HCl solution and stirred for 30 min. Solid precipitated was filtered and washed with water (10 mL), dried under vacuum to afford 55-methoxy-2-methyl-2H-indazole-3-carboxylic acid (**Int-04**) (350 mg, crude) as an off-white solid. TLC system: 40% Ethyl acetate in pet- ether; Rf: 0.21.

[0215] **Synthesis of 2-amino-2-(hydroxymethyl)butanamide (**Int-05**).**



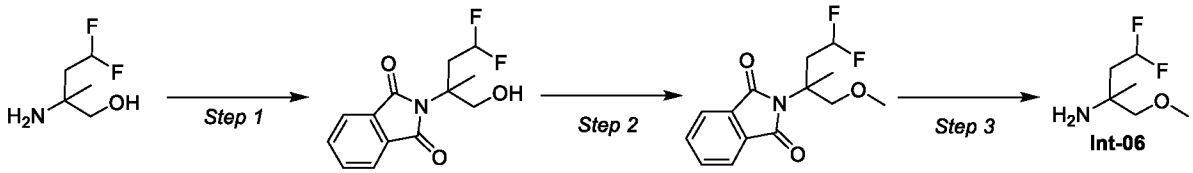
Int-05

[0216] *Step 1* : A mixture of sodium cyanide (4.45 g, 90.90 mmol), ammonium chloride (4.9 g, 90.90 mmol), and ammonia solution (7M in methanol, 120 mL) in methanol (65 ml) was stirred at RT and stirred for 10 min, then 1-hydroxybutan-2-one (4.0 g, 45.45 mmol) was added. The reaction mixture was stirred for 24 h at RT and filter through celite bed, celite bed was washed with methanol (50 mL). Combined filtrate was concentrated under vacuum. To the residue was added ethyl acetate (80 mL) and the mixture was filtered. The filtrate was concentrated under vacuum. The residue was co-distilled with dichloromethane (2 x 50 mL) to afford 2-amino-2-(hydroxymethyl)butanenitrile (4.2 g) as a pale yellow residue. TLC system: 100% Ethyl acetate; RF: 0.3.

[0217] *Step 2* : To a stirred solution of 2-amino-2-(hydroxymethyl)butanenitrile (2.0 g, 17.54 mmol) in ethanol (20 mL) cooled to 0 °C was added KOH (1.47 g, 26.31 mmol) followed by 30% H_2O_2 (2 mL) drop wise at 0 °C. Reaction mixture was stirred for 1 h at RT. The reaction progress was monitored by TLC and reaction mixture was concentrated under vacuum. The

crude was diluted with 10% methanol in dichloromethane (2 x 50 ml), stirred for 20 minutes and filtered. Filtrate was concentrated under reduced pressure to afford 2-amino-2-(hydroxymethyl)butanamide (**Int-05**) (1.8 g) as a thicky residue. TLC system: 10% Methanol in dichloromethane; RF: 0.1.

[0218] **Synthesis of Synthesis of 4,4-difluoro-1-methoxy-2-methylbutan-2-amine hydrochloride (**Int-06**).**



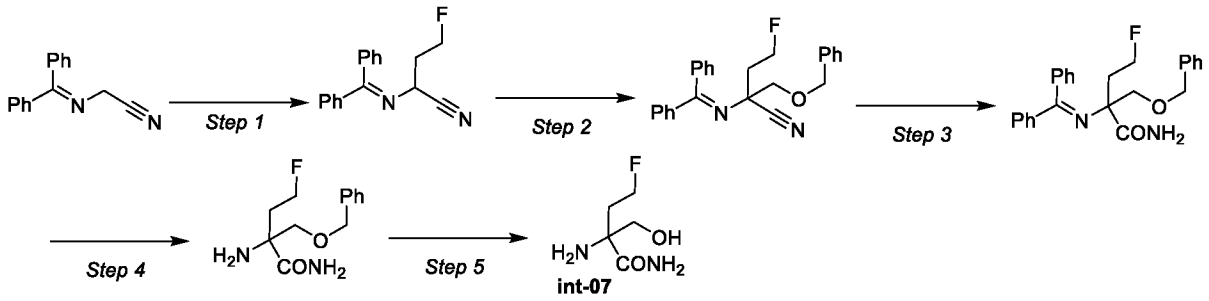
Step 1 : To a solution of 2-amino-4,4-difluoro-2-methylbutan-1-ol (2.5 g, 17.96 mmol) in toluene (25 mL) was added phthalic anhydride (2.66 g, 17.96 mmol). The RM was stirred at 120 °C for 24 h in a sealed tube. After consumption, the RM was concentrated under reduced pressure. The residue was purified by FCC on silica gel using 25% EtOAc in pet ether as an eluent to afford 2-(4,4-difluoro-1-hydroxy-2-methylbutan-2-yl)isoindoline-1,3-dione as a pale yellow gummy (2.0 g, yield: 41.34%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.79 – 7.84 (m, 2 H), 7.71 – 7.75 (m, 2 H), 6.06 – 6.37 (dt, 1 H), 4.03 – 4.12 (m, 2 H), 3.62 (t, 1 H), 2.87 – 3.00 (m, 1 H), 2.29 – 2.43 (m, 1 H), 1.66 (s, 3 H).

Step 2 : To a solution of 2-(4,4-difluoro-1-hydroxy-2-methylbutan-2-yl)isoindoline-1,3-dione (2.6 g, 9.657 mmol) in DMF (26 mL) were added NaH (60% in mineral oil) (463.51 mg, 19.313 mmol), Iodomethane (1.194 mL, 19.31 mmol) at 0 °C . The RM was stirred at RT for 2 h. After consumption, the RM was quenched with ice cold water (20 mL) and extracted with EtOAc (2 x 40 mL). Organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by FCC on silica gel using 25% EtOAc in pet ether as an eluent to afford 2-(4,4-difluoro-1-methoxy-2-methylbutan-2-yl)isoindoline-1,3-dione as a pale yellow gummy (1.1 g, yield: 40.21%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.76 – 7.81 (m, 2 H), 7.67 – 7.72 (m, 2 H), 5.87 – 6.17 (dt, 1 H), 3.99 (d, 1 H), 3.79 (d, 2 H), 3.36 (d, 3 H), 2.77 – 2.90 (m, 1 H), 2.40 – 2.53 (m, 1 H), 1.82 (s, 3 H).

Step 3 : To a solution of 2-(4,4-difluoro-1-methoxy-2-methylbutan-2-yl)isoindoline-1,3-dione (1.1 g, 3.883 mmol) in IPA (22 mL) and water (2.2 mL) was added $NaBH_4$ (733.9 mg, 19.41 mmol) at 0 °C. The RM was stirred at RT for 16 h. After completion, the RM was concentrated and the resulting residue was quenched with cold water (30 mL), extracted with EtOAc (2 X 30 mL). Organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was treated with 6N HCl (22 mL) and heated to 80 °C for 2 h. The RM was concentrated under reduced pressure and the obtained residue was triturated with diethyl ether (2 x 30 mL). The solid was filtered and dried under vacuum to afford 4,4-difluoro-1-methoxy-2-methylbutan-2-amine

hydrochloride (int-06) as an off white solid (650 mg, yield: 88.27%). 1H NMR (400 MHz, DMSO-D_6) δ ppm: 8.40 (s, 3 H), 6.20 – 6.50 (dt, 1 H), 3.43 (s, 2 H), 3.33 (s, 3 H), 2.19 – 2.30 (m, 2 H), 1.29 (s, 3 H).

[0219] **Synthesis of 2-amino-4-fluoro-2-(hydroxymethyl)butanamide (**Int-07**).**



Step 1 : To a solution of 2-((diphenylmethylene)amino)acetonitrile (5 g, 22.699 mmol) in THF (60 mL) were added n-BuLi, 2.5M solution in hexanes (13.61 mL, 34.049 mmol) at -78 °C. The RM was stirred for 15 min at -78°C. After 15 min, 1-Fluoro-2-iodoethane (3.949 g, 22.699 mmol) was added at 0 °C. The RM was stirred at 0 °C for 15 minutes. After completion, the RM was quenched with water (50 mL), extracted with EtOAc (2x 100 mL) Combined organic phases were washed with brine solution (20 mL), dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by FCC on silica gel using 15% EtOAc in pet. Ether as an eluent to afford tert-butyl 4-(hydroxymethyl)-2,2-dimethyloxazolidine-3-carboxylate as a pale yellow gummy (4.5 g, 74.44%).

Step 2 : To a solution of 2-((diphenylmethylene)amino)-4-fluorobutanenitrile (3.2 g, 12.016 mmol) in THF (25.0 mL) was added n-BuLi, 2.5M solution in hexanes, (9.61 mL, 24.031 mmol) at -78 °C. The RM was stirred for 15 min. After 15 min, (chloromethoxy)methyl)benzene (2.0 mL, 14.419 mmol) was added into the RM at -78 °C. The RM was stirred at 0 °C for 2 h. After completion, the RM was quenched with water (25 mL), extracted with EtOAc (2x 50 mL). Combined organic phases were washed with brine solution (20 mL), dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by FCC on silica gel using as eluent 15% EtOAc in pet ether to afford 2-((benzyloxy)methyl)-2-((diphenylmethylene)amino)-4-fluorobutanenitrile as a pale yellow gummy (1.5 g, yield: 32.30%).

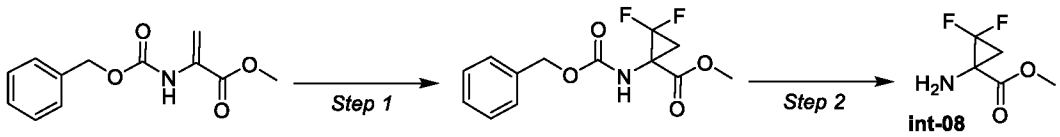
Step 3: To a solution of 2-((benzyloxy)methyl)-2-((diphenylmethylene)amino)-4-fluorobutanenitrile (3.3 g, 8.539 mmol) in MeOH (50 mL) and water (20 mL) were added LiOH monohydrate (1.254 g, 29.886 mmol) and H_2O_2 (50 wt% solution in water, stabilized) (4.3 mL, 17.078 mmol) at 0 °C. The RM was stirred at RT for 16 h. After completion, the RM was diluted with water (5 mL), extracted with EtOAc (2x 30 mL). The combined organic phases were washed with brine solution (20 mL), dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by FCC on silica gel using 15% EtOAc in Pet. Ether as an eluent to afford 2-((benzyloxy)methyl)-2-((diphenylmethylene)amino)-4-fluorobutanamide as a

pale yellow gummy (1.6 g, 46.33%). ^{1}H NMR (400 MHz, DMSO-D_6) δ ppm: 9.78 (s, 1 H), 7.58 (d, 2 H), 7.37 - 7.24 (m, 12 H), 7.15 - 7.13 (m, 2 H), 4.60 (m, 1 H), 4.53 - 4.46 (m, 1 H), 4.43 - 4.38 (m, 2 H), 3.55 (d, 1 H), 3.43 (d, 1 H), 1.77 - 1.71 (m, 1 H), 1.61 - 1.50 (m, 1 H).

Step 4: To a solution of 2-((benzyloxy)methyl)-2-((diphenylmethylene)amino)-4-fluorobutanamide (2.8 g, 6.922 mmol) in DCM (10 mL) was added TFA (10.5 mL, 138.44 mmol) at 0 °C. The RM was stirred at RT for 16 h. After completion, the RM was evaporated to dryness under reduced pressure. The residue was purified by FCC on silica gel using 10% MeOH in DCM as eluent to afford 2-amino-2-((benzyloxy)methyl)-4-fluorobutanamide as a brown gummy liquid (600 mg, 36%). ^{1}H NMR (400 MHz, DMSO-D6) δ ppm: 7.36 - 7.24 (m, 5 H), 7.12 (s, 1 H), 4.59 - 4.41 (m, 3 H), 3.63 (d, 1H), 3.27 (d, 1H), 1.99 - 1.76 (m, 3 H).

Step 5: To a solution of 2-amino-2-((benzyloxy)methyl)-4-fluorobutanamide (300 mg, 1.242 mmol) in EtOH (25.0 mL) was added 10% Palladium on activated carbon (264 mg, 2.484 mmol) at RT. The RM was stirred at RT for 16 h under hydrogen balloon pressure. The reaction mixture was filtered through celite pad, washed with MeOH (3 x 10 mL), filtrate was evaporated under vacuum to afford 2-amino-4-fluoro-2-(hydroxymethyl)butanamide (Int-07) as a white solid (170 mg, 91%). ^{1}H NMR (400 MHz, DMSO-D_6) δ ppm: 7.38 - 7.26 (m, 2 H), 7.13 (s, 1 H), 5.0 (s, 1 H), 4.61 - 4.41 (m, 2 H), 3.58 - 3.54 (m, 1 H), 2.01 - 1.94 (m, 1 H), 1.90 (s, 2 H),1.87 - 1.76 (m, 1 H)..

[0220] **Synthesis of methyl 1-amino-2,2-difluorocyclopropane-1-carboxylate hydrobromide (**Int-08**).**

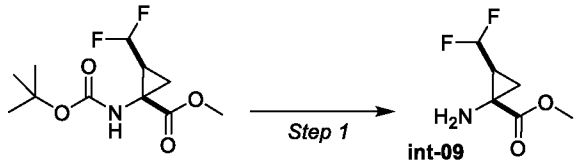


Step 1 : To z solution of methyl 2-(((benzyloxy)carbonyl)amino)acrylate (2.5 g, 10.627 mmol) in toluene (50 mL) was added NaF (44.61 mg, 1.063 mmol) at RT and heated to 110 °C. After 10 min, a solution of trimethylsilyl 2,2-difluoro-2-(fluorosulfonyl)acetate (5.236 mL, 26.56 mmol) in toluene (50 mL) was added dropwise over 4 h to the RM.. The RM was stirred at 110 °C for 18 h. After completion, the RM was cooled to 0 °C and quenched with sat Na_2CO_3 solution (70 mL), extracted with EtOAc (2 x 70 mL). The combined organic layers were washed with brine solution (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by FCC on silica gel using 15% EtOAc in pet ether as an eluent to afford methyl 1-(((benzyloxy)carbonyl)amino)-2,2-difluorocyclopropane-1-carboxylate as a pale yellow liquid (1.4 g, yield: 46.18%). ^{1}H NMR (400 MHz, CDCl3) δ ppm: 7.32 – 7.38 (m, 5 H), 5.57 (s, 1 H), 5.14 (s, 2 H), 3.77 (s, 3 H), 2.66 – 2.71 (m, 1 H), 1.75 – 1.95 (m, 1 H).

Step 2: Methyl 1-(((benzyloxy)carbonyl)amino)-2,2-difluorocyclopropane-1-carboxylate (1.4 g, 4.908 mmol) and HBr in acetic acid (33%) (7.5 mL) was stirred at RT for 2 h. After

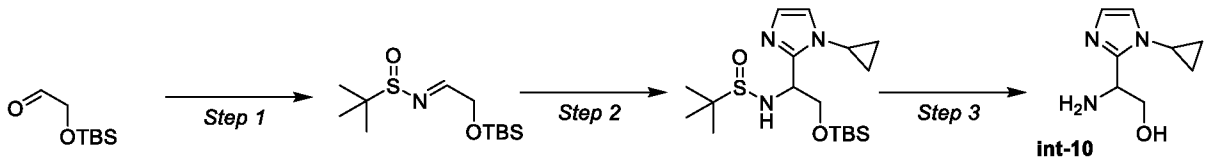
consumption, the RM was concentrated under reduced pressure and the obtained residue was triturated with diethyl ether (2 x 30 mL). The obtained solid was filtered and dried under vacuum to afford methyl 1-amino-2,2-difluorocyclopropane-1-carboxylate hydrobromide (Int-08) as a pale brown solid (1.0 g, Yield: 87.81%). ^{1}H NMR (400 MHz, DMSO-D_6) δ ppm: 9.15 (s, 2 H), 3.82 (s, 3 H), 2.69 – 2.78 (m, 1 H), 2.43 – 2.51 (m, 1 H).

[0221] **Synthesis of (cis-1-amino-2-(difluoromethyl)cyclopropyl)methanol hydrochloride (**Int-09**).**



Step 1 : To a solution of tert-butyl (cis-2-(difluoromethyl)-1-(hydroxymethyl)cyclopropyl)carbamate (880 mg, 3.318 mmol) in DCM (10 mL) was added 4 M HCl in Dioxane (5.0 mL) at RT. The RM was stirred at RT for 1 h. After consumption , the RM was concentrated under reduced pressure and the obtained residue was triturated with diethyl ether (2 x 20 mL). The residue was dried under vacuum to afford cis-1-amino-2-(difluoromethyl)cyclopropyl)methanol hydrochloride (Int-09) as pale yellow gummy (700 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 9.19 (s, 2 H), 6.00 – 5.70 (dt, 1 H), 3.70 (s, 3 H), 2.80- 2.70 (m, 1 H), 2.23- 2.18 (m, 1 H), 1.90- 1.86 (m, 1 H).

[0222] **Synthesis of 2-amino-2-(1-cyclopropyl-1H-imidazol-2-yl)ethan-1-ol hydrochloride (**Int-10**).**



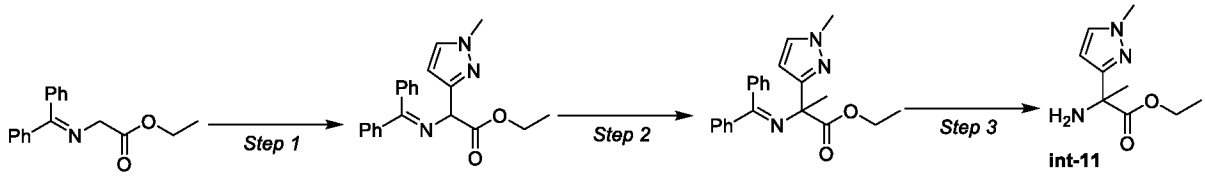
Step 1 : To a solution of 2-((tert-butyldimethylsilyl)oxy)acetaldehyde (2 g, 11.47 mmol) in DCM (30 mL) were added 2-methylpropane-2-sulfinamide (1.53 g, 12.62 mmol) and copper(II)sulphate (3.66 g, 22.94 mmol) at RT under N_2 atmosphere. The RM was stirred at RT for 12 h. After completion, the RM was filtered and rinsed with DCM (50 mL). The filtrate was concentrated under reduced pressure. The residue was purified by FCC on silica gel using 10% EtOAc in Pet. Ether as an eluent to afford (E/Z)-N-(2-((tert-butyldimethylsilyl)oxy)ethylidene)-2-methylpropane-2-sulfinamide as a pale yellow gum (1.5 g, yield: 47.11%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.96 (s, 1 H), 4.44 (s, 2H), 1.10 (s, 9H). 0.82 (s, 9H).

Step 2 : To a solution of 1-cyclopropyl-1H-imidazole (500 mg, 4.62 mmol) in THF (22 mL) was treated with nBuLi (5 mL, 2.5 M) drop wise at -78 °C. The RM was stirred for 2 h at -78°C. After 2 h, a solution of (E)-N-(2-((tert-butyldimethylsilyl)oxy)ethylidene)-2-

methylpropane-2-sulfinamide (1.54 g, 5.54 mmol) in THF (2 mL) was added drop wise to the RM. The RM was stirred for 1.5 h. After completion, the RM was quenched with sat. NH_4Cl (25 mL) at 0 °C, extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (30 mL) and concentrated to afford compound (1.5 g, 84%).

Step 3 :To q solution of N-(2-((tert-butyldimethylsilyl)oxy)-1-(1-cyclopropyl-1H-imidazol-2-yl)ethyl)-2-methylpropane-2-sulfinamide (1.3 g, 3.37 mmol) in 1,4-dioxane (10 mL) was added 4M HCl in 1,4-dioxane (5 mL) at 0°C. The RM was stirred at RT for 16 h. After consumption, the RM was concentrated under reduced pressure. The residue was triturated with DCM (2 x 5 mL) and dried under vacuum to afford 2-amino-2-(1-cyclopropyl-1H-imidazol-2-yl)ethan-1-ol hydrochloride (Int-10) as a brown gummy (800 mg, 88.71).

[0223] **Synthesis of ethyl 2-amino-2-(1-methyl-1H-pyrazol-3-yl)propanoate** (Int-11).

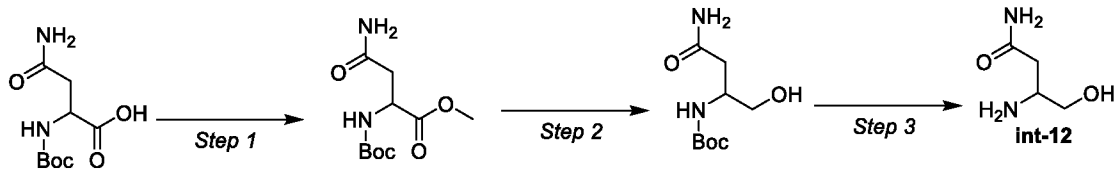


Step 1 :To a solution of ethyl 2-((diphenylmethylene)amino)acetate (5.0 g, 18.704 mmol), 3-bromo-1-methyl-1H-pyrazole (2.850 mL, 28.056 mmol) in toluene (50 mL, taken in 100 mL sealed tube) was added K_3PO_4 (11.907 g, 56.113 mmol). The RM was degassed with argon for 20 min. Pd(t-Bu3P)2 (955.87 mg, 1.870 mmol) was added at RT. The resulted RM was stirred at 100 °C for 16 h. After completion, the RM was diluted with cold water (100 mL), extracted with EtOAc (2 x 100 mL). Combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by FCC on silica gel using 12% EtOAc in pet ether as an eluent to afford ethyl 2-((diphenylmethylene)amino)-2-(1-methyl-1H-pyrazol-3-yl) acetate as a pale yellow gummy (2.5 g, yield: 38.47%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.68 - 7.71 (q, 2 H), 7.42 - 7.44 (m, 3 H), 7.36 - 7.38 (m, 1 H), 7.30 - 7.33 (m, 3 H), 7.17 - 7.20 (m, 2 H), 6.45 (d, 1 H), 5.34 (s, 1 H), 4.15 - 4.19 (m, 2 H), 3.84 (s, 3 H), 1.22 (t, 3 H).

Step 2: To a solution of ethyl 2-((diphenylmethylene)amino)-2-(1-methyl-1H-pyrazol-3-yl)acetate (1.8 g, 5.181 mmol,) in DMF (20 mL, taken in a sealed tube) was added NaH (60%) (621 mg, 15.543 mmol) portion wise at 0 °C. The RM was stirred for 30 min at 0 °C. After 30 min, Iodomethane (1.613 mL, 25.90 mmol) was added. The RM was stirred at RT for 16 h. After completion, the RM was quenched with cold water (50 mL), extracted with EtOAc (2 x 50 mL). Combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by FCC on silica gel using 20% EtOAc in pet ether as an eluent to afford ethyl 2-((diphenylmethylene)amino)-2-(1-methyl-1H-pyrazol-3-yl)propanoate as a pale brown gummy (1.0 g, yield: 53.40%). ^{1}H NMR (400 MHz, DMSO-D_6) δ ppm: 7.48 - 7.52 (m, 3 H), 7.34 - 7.42 (m, 6 H), 6.34 (d, 2 H), 5.75 (s, 1 H), 3.63 - 3.75 (m, 5 H), 1.62 (s, 3 H), 1.00 (t, 3 H).

Step 3 : To a solution of ethyl 2-((diphenylmethylene)amino)-2-(1-methyl-1H-pyrazol-3-yl)propanoate (1.6 g, 4.427 mmol) in Hexane (15 mL) was added 1N HCl (aq) (30 mL) at RT. The RM was stirred for 16 h. After completion, the RM was extracted with EtOAc (3 x 20 mL). Aqueous layer was basified with sat. $NaHCO_3$ solution (pH~0.8), extracted with 10% MeOH in DCM (3 x 30 mL). Combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford ethyl 2-amino-2-(1-methyl-1H-pyrazol-3-yl)propanoate as a brown liquid (630 mg, 72.24%). ^{1}H NMR (400 MHz, DMSO-D_6) δ ppm: 7.54 (s, 1 H), 6.18 (s, 1 H), 4.00 - 4.07 (m, 2 H), 3.99 (s, 3 H), 2.21 (s, 2 H), 1.50 (s, 3 H), 1.12 (t, 3 H).

[0224] **Synthesis of 3-amino-4-hydroxybutanamide trifluoroacetic acid (**Int-12**).**

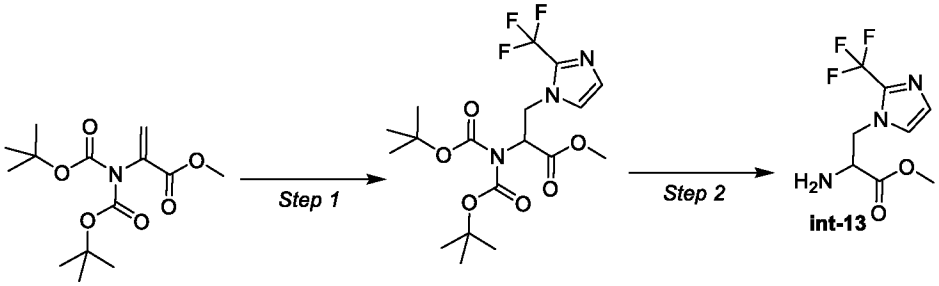


Step 1 : To a solution of (tert-butoxycarbonyl)asparagine (4.0 g, 17.22 mmol) in THF (40 mL) and MeOH (40 mL) was added (trimethylsilyl)diazomethane (2M solution in hexanes) (17 mL, 34.44 mmol) drop wise at -20 °C. The RM was stirred at 0 °C for 2 h. After completion, the RM concentrated under reduced pressure. The residue was diluted with diethyl ether (80 mL) and then distilled under high vacuum. The residue was purified by FCC on silica gel using 10% MeOH in DCM as an eluent to afford tert-butyl (4-amino-1-hydroxy-4-oxobutan-2-yl)carbamate as an off-white solid (1.4 g, 37%).

Step 2 : To a solution of methyl (tert-butoxycarbonyl)asparaginate (1.4 g, 5.68 mmol) in MeOH (28 mL) was added $NaBH_4$ (1 g, 28.4 mmol) 0 °C. The RM was stirred at RT for 2 h. After completion,, the RM was diluted with cold water (20 mL), extracted with 20% MeOH in DCM (2 × 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by FCC on silica gel using 20% MeOH in DCM as an eluent to afford tert-butyl (4-amino-1-hydroxy-4-oxobutan-2-yl)carbamate as an off-white solid (900 mg, 72%). ^{1}H NMR (400 MHz, DMSO-D_6) δ ppm: 7.19 (brs, 1 H), 6.78 (brs, 1 H), 6.45 (d, 1 H), 4.64 (t, 1 H), 3.68 – 3.73 (m, 1 H), 3.16 – 3.26 (m, 1 H), 3.31 – 3.36 (m, 1 H), 2.23 – 2.28 (m, 1 H), 2.12 – 2.18 (m, 1 H), 1.37 (s, 9 H).

Step 3 : To a solution of tert-butyl (4-amino-1-hydroxy-4-oxobutan-2-yl) carbamate (900 mg, 4.12 mmol) in DCM (10 mL) was added TFA (4.5 mL) at 0 °C. The RM mixture was stirred at RT for 2 h. The RM concentrated under high vacuum to afford 3-amino-4-hydroxybutanamide trifluoroacetic acid (Int-**12**). (1.0 g).

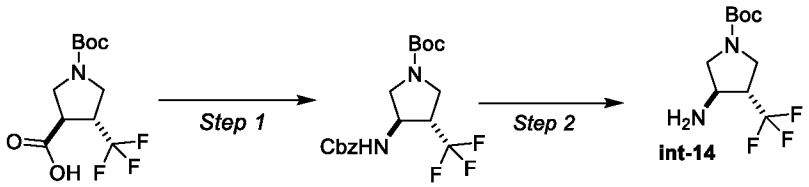
[0225] **Synthesis of methyl 2-amino-3-(2-(trifluoromethyl)-1H-imidazol-1-yl)propanoate hydrochloride (**Int-13**).**



Step 1 : To a solution of 2-(trifluoromethyl)-1H-imidazole (903 mg, 6.637 mmol) in ACN (10 mL) was added Cs_2CO_3 (6.491 g, 19.911 mmol) at 0 °C. After 5 min, methyl 2-(bis(tert-butoxycarbonyl)amino)acrylate (2 g, 6.637 mmol) was added. The RM was stirred at 70 °C for 16 h. After completion, the RM was diluted with water (50 mL) and extracted with EtOAc (2x50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by FCC on silica gel using 10% EtOAc in pet ether as an eluent to afford methyl 2-(bis(tert-butoxycarbonyl)amino)-3-(2-(trifluoromethyl)-1H-imidazol-1-yl)propanoate as a pale yellow gummy (400 mg, yield:13.78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.51 (d, 1 H), 7.10 (d, 1 H), 5.41 – 5.44 (m, 1 H), 4.71 – 4.76 (m, 1 H), 7.43 (s, 1 H), 4.54 -4.61 (m, 1 H), 3.71 (s, 3 H), 1.39 (s, 9 H).

Step 2: A solution of 4M HCl in 1,4-dioxane (4.0 mL) was added to methyl 2-(bis(tert-butoxycarbonyl)amino)-3-(2-(trifluoromethyl)-1H-imidazol-1-yl)propanoate (400 mg, 2.286 mmol) at 0 °C. The RM was stirred at RT for 3 h. After completion, the RM was concentrated under reduced pressure. The residue was basified with aq. $NaHCO_3$ solution (20 mL), extracted with EtOAc (2 x 20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by FCC on silica gel using 30% EtOAc in pet. Ether as an eluent to afford methyl 2-amino-3-(2-(trifluoromethyl)-1H-imidazol-1-yl)propanoate as a pale yellow gummy (100 mg, yield: 36.88%). ^{1}H NMR (400 MHz, DMSO-D_6) δ ppm: 7.48 (d, 1 H), 7.09 (d, 1 H), 4.31 – 4.36 (m, 1 H), 4.14 – 4.20 (m, 1H), 3.67 -3.72 (m, 1H), 3.61 (s, 3H).

[0226] **Synthesis of tert-butyl trans-3-amino-4-(trifluoromethyl)pyrrolidine-1-carboxylate (**Int-14**).**

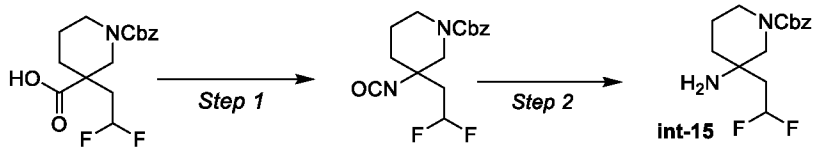


Step 1 : To a solution of Trans-1-(tert-butoxycarbonyl)-4-(trifluoromethyl)pyrrolidine-3-carboxylic acid (3 g, 10.591 mmol) in xylene (25 mL) were added TEA (1.771 mL, 12.710 mmol) and DPPA (2.505 mL ,11.651 mmol) dropwise at RT. The RM was heated to 130 °C and stirred for 1 h. After 1 h, phenyl methanol (1.211 mL, 11.651 mmol) was added into the RM and stirred at 130 °C for 3 h. After cooling to RT, the RM was quenched with 1N NaOH solution (80.0 mL), washed with EtOAc (2 x 50 mL). The aqueous layer was washed acidified

with aqueous citric acid solution (pH~5), extracted with DCM (2 x 80 mL). Organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by FCC on silica gel using 15% EtOAc in pet ether as an eluent to afford tert-butyl trans-3-(((benzyloxy)carbonyl)amino)-4-(trifluoromethyl)pyrrolidine-1-carboxylate as a yellow solid (2.2 g, 53.48 %). ^{1}H NMR (400 MHz, DMSO-D_6) δ ppm: 7.32 – 7.38 (m, 7 H), 5.10 (s, 3 H), 4.69 (d, 1 H), 4.35 - 4.40 (m, 1 H), 3.77 - 3.82 (m, 1 H), 3.49 (s, 2 H), 2.94 (s, 2 H), 1.45 (s, 9 H).

Step 2 : To a solution of tert-butyl trans-3-(((benzyloxy)carbonyl)amino)-4-(trifluoromethyl)pyrrolidine-1-carboxylate (2.4 g, 6.179 mmol) in EtOAc (20 mL) was added 10% Pd/C (1.315 g, 12.359 mmol). The RM was stirred at RT for 16 h under hydrogen balloon pressure. After completion, the RM was filtered through a celite pad, washed with EtOAc (2 x 100 mL) and the filtrate was concentrated under reduce pressure. The residue was purified by FCC on silica gel using 45% EtOAc in pet ether as an eluent to afford tert-butyl trans-3-amino-4-(trifluoromethyl)pyrrolidine-1-carboxylate as a colorless liquid (1.3 g, 82.74%). ^{1}H NMR (400 MHz, DMSO-D_6) δ ppm: 3.49 - 3.62 (m, 3 H), 3.26 - 3.31 (m, 2 H), 2.96 (s, 1 H), 2.85 (s, 1 H), 1.82 - 1.98 (m, 2 H), 1.39 (s, 9 H).

[0227] **Synthesis of benzyl 3-amino-3-(2,2-difluoroethyl)piperidine-1-carboxylate (**Int-15**).**

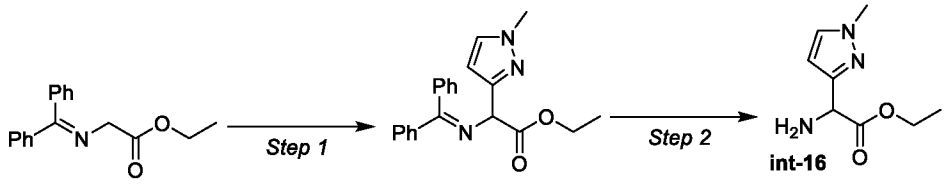


Step 1 : To a solution of 1-((benzyloxy)carbonyl)-3-(2,2-difluoroethyl)piperidine-3-carboxylic acid (2.0 g, 6.114 mmol) in toluene (20 mL) was added TEA (1.704 mL, 12.228 mmol) and DPPA (1.446 mL, 6.725 mmol) dropwise at RT. The RM was heated at 100 °C for 2 h. After cooling to RT, the RM was diluted with water, extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford benzyl 3-(2,2-difluoroethyl)-3-isocyanatopiperidine-1-carboxylate as a pale yellow liquid (1.8 g, 90.78%).

Step 2: To a solution of benzyl 3-(2,2-difluoroethyl)-3-isocyanatopiperidine-1-carboxylate (1.8 g, 5.550 mmol) in 1,4-dioxane (18 mL) was added an aqueous solution 6M HCl (18 mL). The RM was heated to 45 °C for 16 h. After completion, the RM was concentrated. The residue was diluted with water (50 mL), washed with EtOAc (100 mL). Aqueous layer was basified with 1N NaOH solution (50 mL), extracted with DCM (2 x 100 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford benzyl 3-amino-3-(2,2-difluoroethyl)piperidine-1-carboxylate (Int-15) as a pale yellow liquid (900 mg, 54.36%). ^{1}H NMR (400 MHz, DMSO d_6) δ ppm: 7.37 – 7.30 (m, 5 H), 6.37 – 6.07 (m, 1 H), 5.06 (s, 2 H), 3.56 (s, 4 H), 3.38 – 3.16 (m, 3 H), 1.90 –

1.79 (m, 2 H), 1.65 – 1.55 (m, 4 H), 1.43 – 1.38 (m, 2 H).

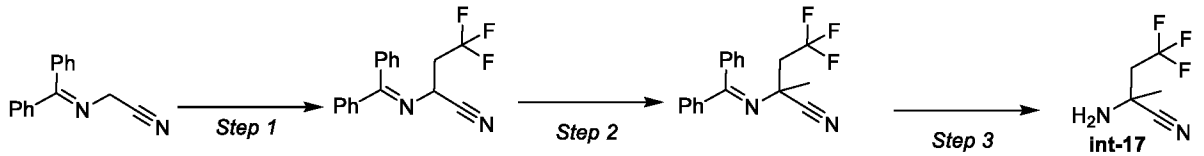
[0228] **Synthesis of ethyl 2-amino-2-(1-methyl-1H-pyrazol-3-yl)acetate (**Int-16**).**



Step 1 :To a solution of ethyl 2-((diphenylmethylene)amino)acetate (5.0 g, 18.704 mmol), 3-bromo-1-methyl-1H-pyrazole (2.850 mL, 28.056 mmol) in toluene (50 mL, taken in 100 mL sealed tube) was added K_3PO_4 (11.907 g, 56.113 mmol). The RM was degassed with argon for 20 min. Pd(t-$Bu_3P)_2$ (955.87 mg, 1.870 mmol) was added at RT. The RM was stirred at 100 °C for 16 h. After completion, the RM was diluted with cold water (100 mL), extracted with EtOAc (2 x 100 mL). Combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by FCC on silica gel using 12% EtOAc in pet ether as an eluent to afford ethyl 2-((diphenylmethylene)amino)-2-(1-methyl-1H-pyrazol-3-yl) acetate as a pale yellow gummy (2.5 g, 38.47%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.68 - 7.71 (q, 2 H), 7.42 - 7.44 (m, 3 H), 7.36 - 7.38 (m, 1 H), 7.30 - 7.33 (m, 3 H), 7.17 - 7.20 (m, 2 H), 6.45 (d, 1 H), 5.34 (s, 1 H), 4.15 - 4.19 (m, 2 H), 3.84 (s, 3 H), 1.22 (t, 3 H).

Step 2: To a solution of ethyl 2-((diphenylmethylene)amino)-2-(1-methyl-1H-pyrazol-3-yl)acetate (2.4 g, 6.908 mmol, 1.0 eq) in Hexane (10 mL) was added 1N HCl (aq) (25 mL) at RT. The RM was stirred for 16 h. After completion, the RM was extracted with EtOAc (2 x 30 mL). Aqueous layer was basified with sat. $NaHCO_3$ solution (pH~0.8), extracted with 10% MeOH in DCM (3 x 50 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford ethyl 2-amino-2-(1-methyl-1H-pyrazol-3-yl)acetate as a brown liquid (900 mg,71.11%). ^{1}H NMR (400 MHz, DMSO-D_6) δ ppm: 7.57 (d, 1 H), 6.15 (d, 1 H), 4.43 (s, 1 H), 4.11- 4.01 (m, 2 H), 3.70 (s, 3 H), 2.07 (s, 2 H), 1.14 (t, 3 H).

[0229] **Synthesis of 2-amino-4,4,4-trifluoro-2-methylbutanenitrile hydrogen chloride (**Int-17**).**



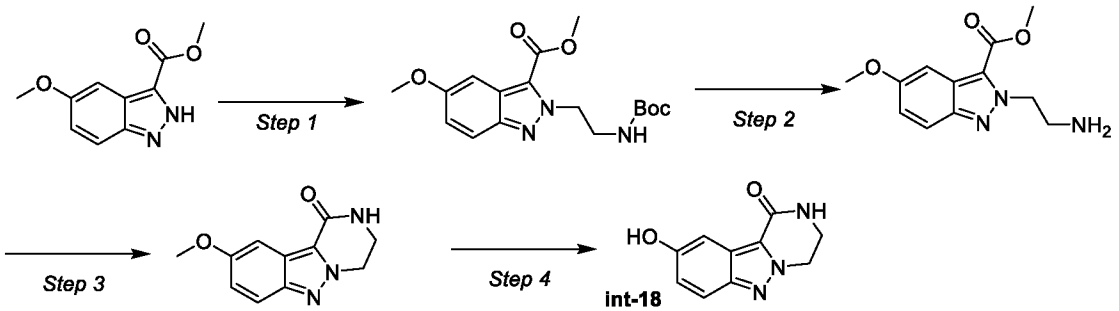
Step 1 : To a solution of 2-((diphenylmethylene)amino)acetonitrile (10 g, 45.399 mmol) in DMF (100 mL) was added potassium tert-butoxide (5.604 g, 49.939 mmol) at 0° C. The RM was stirred at 0°C for 10 min. After 10 min 1,1,1-trifluoro-2-iodoethane (4.922 mL, 49.939 mmol) was added at 0° C. The RM was stirred at 0° C for 1 h. After completion, the RM was quenched with ice water (100 mL), extracted with EtOAc (2x 100 mL). The combined organic

phases were washed with brine solution (100 mL), dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by FCC on silica gel using 1% EtOAc in pet. Ether as an eluent to afford 2-((diphenyl methylene)amino)-4,4,4-trifluorobutanenitrile as a pale yellow gummy (5 g, 36.43%).

Step 2 : To a solution of 2-((diphenylmethylene)amino)-4,4,4-trifluorobutanenitrile (5.0 g, 16.54 mmol) in THF (150 mL) was added n-BuLi (1.6 M in Hexanes) (12 mL, 19.848 mmol) at -78 °C. The RM was stirred at -78°C for 15 min. After 15 min, methyl iodide (10.22 mL, 19.84 mmol) was added at -78 °C. The RM was stirred at 0 °C for 4 h. After completion, the RM was quenched with saturated ammonium chloride solution (50 mL), extracted with EtOAc (2 x 50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by FCC on silica gel using 5% EtOAc in pet ether as an eluent to afford 2-((diphenylmethylene)amino)-4,4,4-trifluoro-2-methylbutanenitrile as a pale yellow gummy (2.0 g, 38.23%). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm: 7.59 (d, 2 H), 7.51 - 7.54 (m, 3 H), 7.40 - 7.47 (m, 2 H), 7.31 - 7.37 (m, 3 H), 2.94 (bs, 1 H), 2.92 (bs, 1 H), 1.77 (s, 3 H).

Step 3 : To a solution of 2-((diphenyl methylene)amino)-4,4-difluorobutanenitrile (2.0 g, 6.323 mmol) in THF (100 mL) and water (3.0 mL) was added 4N HCl in Dioxane (2.0 mL) at RT. The RM was stirred for 6 h. After completion, the RM was concentrated, treated with n-pentane and dried under reduced pressure to afford 2-amino-4,4,4-trifluoro-2-methylbutanenitrile hydrochloride (Int-17) as a brown solid (900 mg, 93.58%). ^{1}H NMR (400 MHz, DMSO-D_6) δ ppm: 9.64 (bs, 2 H), 3.25 - 3.33 (m, 2 H), 1.82 (s, 3 H).

[0230] **Synthesis of 9-hydroxy-3,4-dihydropyrazino[1,2-b]indazol-1(2H)-one (**Int-18**).**



Step 1 : To a solution of methyl 5-methoxy-2H-indazole-3-carboxylate (1.3 g, 6.305 mmol) in DMF (10.0 mL) were added tert-butyl (2-bromoethyl)carbamate (2.119 mg, 9.457 mmol) and cesium carbonate (6.162 mg, 18.914 mmol) at RT. The RM was stirred for 16 h. After completion, the RM was diluted with water (20 mL), extracted with EtOAc (2 x 20 mL), dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by FCC on silica gel using a gradient of 20 to 40% EtOAc in pet ether to afford methyl 2-(2-((tert-butoxycarbonyl)amino)ethyl)-5-methoxy-2H-indazole-3-carboxylate as an off white solid (desired product) (700 mg, 31.78%) .

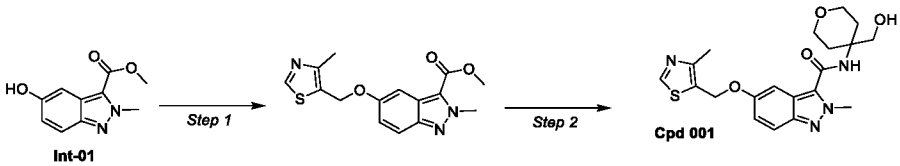
Step 2: To a solution of methyl 2-(2-((tert-butoxycarbonyl)amino)ethyl)-5-methoxy-2H-

indazole-3-carboxylate (600 mg, 1.717 mmol) in DCM (10.0 mL) was added TFA (1.3 mL, 17.173 mmol) at 0°C. The RM was stirred at RT for 4 hours. After completion, the RM was concentrated under reduced pressure. The residue was triturated n-pentane (30 mL) to afford methyl 2-(2-aminoethyl)-5-methoxy-2H-indazole-3-carboxylate as a pale yellow solid (TFA salt) (400 mg, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.60 (d, 1 H), 7.19 (d, 1 H), 7.09 - 7.12 (dd, 1 H), 5.22 (s, 2 H), 4.06 (s, 3 H), 3.97 (t, 4 H), 3.73 (s, 3 H).

Step 3: To a solution of methyl 2-(2-aminoethyl)-5-methoxy-2H-indazole-3-carboxylate (400 mg, 1.605 mmol) in MeOH (10.0 mL) was added cesium carbonate (2.091 mg, 6.419 mmol, 4 eq) at RT. The RM was stirred at RT for 16 hours. After completion, the volatiles were removed under reduced pressure. The residue was diluted with water (15 mL), extracted with EtOAc (3 x 15 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was triturated with n-pentane (15 mL) and dried to afford 9-methoxy-3,4-dihydropyrazino[1,2-b]-indazol-1(2H)-one an off white solid compound (320 mg, 91%). ^{1}H NMR (400 MHz, DMSO-D_6) δ ppm: 8.19 (s, 1 H), 7.66 (d, 1 H), 7.23 (d, 1 H), 7.00 (dd, 1 H), 4.57 (t, 2 H), 3.84 (s, 3 H), 3.66 – 3.71 (m, 2 H).

Step 4 : To a solution of 9-methoxy-3,4-dihydropyrazino[1,2-b]-indazol-1(2H)-one (350 mg, 4.803 mmol) in DCM (10.0 mL) was added BBr_3 (1M in DCM) (6.44 mL, 6.44 mmol) at 0 °C. The RM was stirred at RT for 24 h. After completion, solvent was evaporated under reduced pressure. At 0°C, the residue was quenched with saturated sodium bicarbonate (pH~9). The precipitated was collected by filtration and dried. The residue was triturated with n-pentane and dried to afford 9-hydroxy-3,4-dihydropyrazino[1,2-b]indazol-1(2H)-one (Int-18) as an off white solid (260 mg, 79.5%). ^{1}H NMR (400 MHz, DMSO-D_6) δ ppm: 9.54 (s, 1 H), 8.07 (s, 1 H), 7.59 (d, 1 H), 7.18 (d, 1 H), 6.91 - 6.94 (dd, 1 H), 4.54 (t, 2 H), 3.66-3.69 (m, 2 H).

[0231] **Synthesis (Mitsunobu) of N-[4-(hydroxymethyl)oxan-4-yl]-2-methyl-5-[(4-methyl-1,3-thiazol-5-yl)methoxy]-2H-indazole-3-carboxamide** (Cpd 001**).**



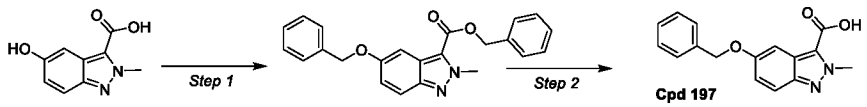
Int-01 Cpd 001

[0232] *Step 1* : To a stirred solution of methyl 5-hydroxy-2-methyl-2H-indazole-3-carboxylate (Int-01) (0.30 g, 1.45 mmol, 1.0 eq) and (4-methylthiazol-5-yl)methanol (1.25 g, 2.18 mmol, 1.5 eq) in THF (50 ml) at 0°C, was added ADDP (0.73 g, 2.90 mmol, 2.0 eq) and PBu3 (0.73 ml, 2.90 mmol, 2.0 eq) drop wise at 0 °C. Then the reaction mixture was stirred for 18 h at RT. Reaction progress was monitored by TLC. The reaction mixture was diluted with ice water and extracted with EtOAc (3 x 30 ml). Combined organic layers were washed with ice water (50 ml), brine solution (50 ml), dried over anhydrous Na_2SO_4, filtered and concentrated to get

methyl 2-methyl-5-((4-methylthiazol-5-yl)methoxy)-2H-indazole-3-carboxylate (0.33 g, crude). TLC system: 60% EtOAc/Pet ether; RF: 0.4.

[0233] *Step 2* : To a stirred solution of methyl 2-methyl-5-((4-methylthiazol-5-yl)methoxy)-2H-indazole-3-carboxylate (0.30 g, 0.94 mmol, 1.0 eq) and (4-aminotetrahydro-2H-pyran-4-yl)methanol (0.184 g, 1.13 mmol, 1.2 eq) in THF (100 ml) at RT, was added Et3N (0.27 ml, 1.88 mmol, 2.0 eq), and 1,3,4,6,7,8-hexahydro-2H-pyrimido[1,2-a]pyrimidine (0.261 g, 1.88 mmol, 2.0 eq) at RT. Then the reaction mixture was heated up to 80 °C and stirred for 18 h. Reaction progress was monitored by TLC. The reaction mixture was diluted with ice water and extracted with EtOAc (3 x 30 ml). Combined organic layers were washed with ice water (50 ml), brine solution (25 ml), dried over anhydrous Na_2SO_4, filtered and concentrated to get the crude, which was purified by prep-HPLC purification to afford N-[4-(hydroxymethyl)oxan-4-yl]-2-methyl-5-[(4-methyl-1,3-thiazol-5-yl)methoxy]-2H-indazole-3-carboxamide (**Cpd 001**). (30 mg, 1.4 %, over 3 steps). TLC system: 100% EtOAc; RF: 0.2.

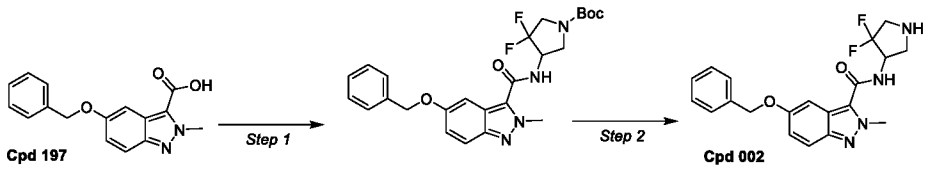
[0234] **Synthesis of 5-(benzyloxy)-2-methyl-2H-indazole-3-carboxylic acid (**Cpd 197**).**



[0235] *Step 1* : To a stirred solution of 5-hydroxy-2-methyl-2H-indazole-3-carboxylic acid (Int-03) (800 mg, 4.166 mmol, 1 eq) in DMF (20 mL), Cs2CO3 (4 g, 12.498 mmol, 3 eq) and (bromomethyl)benzene (0.98 mL, 8.333 mmol, 2 eq) were added at 0 °C. RM was stirred for 18 h at RT. Reaction progress was monitored by TLC. After completion of the reaction, RM was diluted with ice water (50 mL) and extracted with EtOAc (3 x 100 mL). Combined organic layers were washed with brine solution (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to give residue. The residue was purified by FCC using eluent 30% EtOAc-Pet ether to afford benzyl 5-(benzyloxy)-2-methyl-2H-indazole-3-carboxylate (650 mg, 43%; pale yellow solid). TLC system: 30% EtOAc-Pet ether; Rf: 0.34.

[0236] *Step 2* : To a stirred solution of afford benzyl 5-(benzyloxy)-2-methyl-2H-indazole-3-carboxylate (650 mg, 1.747 mmol, 1 eq) in MeOH-THF-H2O (1:1:1) (15 mL), NaOH (279 mg, 6.989 mmol, 4 eq) was added at RT. RM was heated to 50 °C and stirred for 1 h at 50 °C. Reaction progress was monitored by TLC. After completion of the reaction, RM was cooled to RT and solvent was evaporated. The residue was diluted with water (20 mL), acidified to PH ~1 with 1N aq. HCl (5 mL) and stirred for 5 min. The precipitated solid was filtered and washed with water (10 mL), dried to afford 5-(benzyloxy)-2-methyl-2H-indazole-3-carboxylic acid (**Cpd 197**) (450 mg, 91% pale yellow solid). TLC system: 5% MeOH-CH2Cl2; Rf: 0.24.

[0237] **Synthesis of 5-(benzyloxy)-N-(4,4-difluoropyrrolidin-3-yl)-2-methyl-2H-indazole-3-carboxamide (**Cpd 002**).**



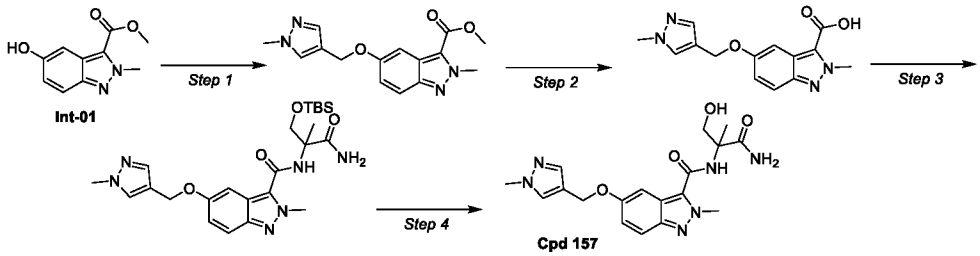
[0238] *Step 1* : To a stirred solution of 5-(benzyloxy)-2-methyl-2H-indazole-3-carboxylic acid (**Cpd 197)** (450 mg, 1.595 mmol, 1 eq) in DMF (10 mL), HATU (909 mg, 2.393 mmol, 1.5 eq), DIPEA (0.7 mL, 3.989 mmol, 2.5 eq) and tert-butyl 4-amino-3,3-difluoropyrrolidine-1-carboxylate (531 mg, 2.393 mmol, 1.5 eq) were added at RT. RM was stirred for 3 h at RT. Reaction progress was monitored by TLC. After completion of the reaction, RM was diluted with EtOAc (350 mL). Organic layer was washed with water (4 x 100 mL), brine solution (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to give residue which was triturated in n-Hexane and filtered to afford tert-butyl 4-(5-(benzyloxy)-2-methyl-2H-indazole-3-carboxamido)-3,3-difluoropyrrolidine-1-carboxylate (550 mg, crude; off-white solid. TLC system: 80% EtOAc-Pet ether; Rf: 0.46.

[0239] *Step 2* : To a stirred solution of tert-butyl 4-(5-(benzyloxy)-2-methyl-2H-indazole-3-carboxamido)-3,3-difluoropyrrolidine-1-carboxylate (550 mg, 1.131 mmol, 1 eq) in DCM (10 ml), TFA (3 mL) was added at 0 °C. RM was stirred for 2 h at RT. Reaction progress was monitored by TLC. After completion of the reaction, the reaction mixture was concentrated and diluted with EtOAc (350 mL). Organic layer was washed with sat. NaHCO3 (2 x 50 mL), water (50 mL), brine solution (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to give residue which was triturated with diethyl ether (10 mL) to afford 5-(benzyloxy)-N-(4,4-difluoropyrrolidin-3-yl)-2-methyl-2H-indazole-3-carboxamide (**Cpd 002**) (270 mg, 44% for 2 steps; off-white solid). TLC system: 5% MeOH-DCM; Rf: 0.12.

[0240] A preparative chiral SFC was performed on the racemic mixture of **Cpd 002** to afford **Cpd 002 – En1 and Cpd 002– En2.**

[0241] The following compounds were prepared in a similar manner (use of appropriate reagents (chiral or racemic) and purification methods (including chiral HPLC or chiral SFC) known to the person skilled in the art) as described for **Cpd 002 – En1 and Cpd 002 – En2** : **Cpd 003 – En1, Cpd 003 – En2, Cpd 128 – En1, Cpd 128 – En2, Cpd 132 – En1, Cpd 132 – En2, Cpd 246 – En1, Cpd 246 – En2.**

[0242] **Synthesis (Mitsunobu) of 3-hydroxy-2-methyl-2-({2-methyl-5-[(1-methyl-1H-pyrazol-4-yl)methoxy]-2H-indazol-3-yl}formamido)propanamide (**Cpd 156**).**



[0243] *Step 1* : To a stirred solution of methyl 5-hydroxy-2-methyl-2H-indazole-3-carboxylate

(**Int-01**) (400 mg, 1.939 mmol) and (1-methyl-1H-pyrazol-4-yl)methanol (0.244 ml, 2.522 mmol) in THF (20 ml) was added ADDP (978.42 mg, 3.878 mmol) at 0°C. The RM was stirred for 15 mins. Tributylphosphine (0.957 ml, 3.878 mmol) in THF (2 ml) was added at 0°C dropwise to the RM. The RM was stirred at RT for 16 h. The RM was quenched with water, extracted with EtOAc. Organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The crude was purified by FCC (using 100-200 mesh silica gel, elution with 30% EtOAc-Hexane) to afford methyl 2-methyl-5-((1-methyl-1H-pyrazol-4-yl) methoxy)-2H-indazole-3-carboxylate (450 mg, 77%) as off white solid. ^{1}H-NMR (400 MHz, DMSO-d_6) δ [ppm]: 7.81 (s, 1H), 7.68-7.66 (d, 1H), 7.52 (s, 1H), 7.34 (s, 1H), 7.03-7.01 (m, 1H), 5.01 (s, 2H), 4.37 (s, 3H), 3.97 (s, 3H), 3.78 (s, 3H), 1.98 (bs, 1H).

[0244] *Step 2* : To a stirred solution of 2-methyl-5-((1-methyl-1H-pyrazol-4-yl)methoxy)-2H-indazole-3-carboxylate (450 mg,1.498 mmol) in THF:MeOH:H2O (12 ml, 1:1:1) was added LiOH.H2O (157.33 mg, 3.746 mmol) at RT. The RM was concentrated and acidified with NaHSO4 saturated solution until PH<7. The solid was filtered and washed with ether to afford 2-methyl-5-((1-methyl-1H-pyrazol-4-yl)methoxy)-2H-indazole-3-carboxylic acid (370 mg, 64%) as off white solid.^{1}H-NMR (400 MHz, DMSO-d_6) δ [ppm]: 13.45 (s, 1H), 7.66-7.64 (d, 1H), 7.39 (s, 1H), 7.04-7.01 (m, 1H), 6.31 (s, 2H), 4.36 (s, 3H), 3.83 (s, 3H).

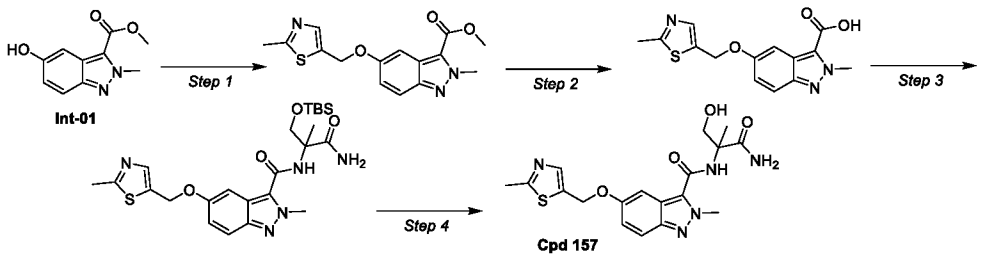
[0245] *Step 3* : To a stirred solution of 2-methyl-5-((1-methyl-1H-pyrazol-4-yl)methoxy)-2H-indazole-3-carboxylic acid (370 mg,1.292 mmol) in DMF (4 ml) was added HATU (638.65 mg, 1.680 mmol) followed by DIPEA (0.677 ml, 3.876 mmol) at RT. The RM was stirred for 15 min. 2-Amino-3-((tert-butyldimethylsilyl)oxy)-2-methylpropanamide (**Int-02**) (390.44 mg, 1.680 mmol) was added to RM at RT. RM was stirred for 16 h at RT. The RM was quenched with ice cold water, extracted with EtOAc. Organic part was dried over Na_2SO_4 and concentrated. The crude was purified by FCC (elution with 80% EtOAc-Hexane) to afford 2-methyl-5-(oxetan-3-ylmethoxy)-2H-indazole-3-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-1-carbamoyl-1-methyl-ethyl]-amide (400 mg,62%) as off white solid. ^{1}H-NMR (400 MHz, DMSO-d_6) δ [ppm]: 8.03 (s, 1H), 7.68-7.63 (m,3H), 7.53 (s, 1H), 7.40 (s, 1H), 7.04-7.02 (d, 1H), 6.35 (s, 1H), 5.03-4.95 (m, 2H), 4.30 (s, 4H), 4.04-4.01 (m, 1H), 3.77 (s, 3H), 1.57 (s, 3H), 0.875 (s, 3H), 0.77 (s, 9H), -0.012-0.06 (d, 6H).

[0246] *Step 4* : To a stirred solution of N-(1-amino-3-((tert-butyldimethylsilyl)oxy)-2-methyl-1-oxopropan-2-yl)-2-methyl-5-((1-methyl-1H-pyrazol-4-yl)methoxy)-2H-indazole-3-carboxamide (200 mg, 0.464 mmol) in DCM (3 ml) was added TFA (2 ml) at 0°C. Reaction mixture was stirred for 16 h at RT. The RM was concentrated and triturated with ether. The crude was purified by PREP SFC to afford 3-hydroxy-2-methyl-2-({2-methyl-5-[(1-methyl-1H-pyrazol-4-yl)methoxy]-2H-indazol-3-yl}formamido)propanamide (**Cpd 156**) (50 mg, 32%) as off white solid.

[0247] The following compounds were prepared in a similar manner (use of appropriate reagents (chiral or racemic) and purification methods (including chiral HPLC or chiral SFC)

known to the person skilled in the art) as described for **Cpd 156**: **Cpd 151 – En1, Cpd 151 – En2, Cpd 154 – En1, Cpd 154 – En2, Cpd 155 – En1 ,Cpd 155 – En2.**

[0248] **Synthesis of 3-hydroxy-2-methyl-2-({2-methyl-5-[(2-methyl-1,3-thiazol-5-yl)methoxy]-2H-indazol-3-yl}formamido)propanamide (**Cpd 157**).**



[0249] *Step 1* : To a stirred solution of methyl 5-hydroxy-2-methyl-2H-indazole-3-carboxylate (**Int-01**) (300 mg, 1.455 mmol) in DMF (8 ml) was added potassium carbonate (503 mg, 3.637 mmol) at RT. The RM was stirred for 15 mins at RT. 5-(bromomethyl)-2-methylthiazole (313 mg, 1.746 mmol) in DMF (2 ml) was added to the RM and stirred for 16 h at RT. The RM was quenched with ice cold water, extracted with EtOAc. Organic layer was dried over Na_2SO_4 and concentrated. The crude was purified by FCC (elution with 60% EtOAc-Hexane) to afford methyl 2-methyl-5-((2-methylthiazol-5-yl)methoxy)-2H-indazole-3-carboxylate (150 mg, 32%) as off white solid. ^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 7.75 (s, 1H), 7.71-7.69(d, 1H), 7.38 (s, 1H), 7.07-7.04 (d, 1H), 5.38 (s, 2H), 4.38 (s, 3H), 3.97 (s, 3H), 2.64 (s, 3H).

[0250] *Step* 2 : To a stirred solution of 2-methyl-5-(oxetan-3-ylmethoxy)-2H-indazole-3-carboxylic acid methyl ester (150 mg, 0.473 mmol) in THF:H2O:MeOH (12 ml, 1:1:1) was added LiOH.H_2O (50 mg, 1.182 mmol)) at RT. Reaction mixture was stirred for 16 h at RT. The RM was concentrated and quenched with saturated sodium bisulfate until pH<7. Resultant solid as filtered and washed with hexane:ether (10ml, 9:1) to afford methyl 2-methyl-5-((2-methylthiazol-5-yl)methoxy)-2H-indazole-3-carboxylic acid (150 mg) as off white solid. ^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 7.71 (s, 1H), 7.68-7.65 (d, 1H), 7.38 (s, 1H), 7.04-7.02 (d, 1H), 5.34 (s, 2H), 4.37 (s, 3H), 2.63 (s, 3H).

[0251] *Step 3* : To a stirred solution of methyl 2-methyl-5-((2-methylthiazol-5-yl) methoxy)-2H-indazole-3-carboxylic acid (150 mg, 0.495 mmol) in DMF (5 ml) was added HATU (226 mg, 0.594 mmol)) followed by DIPEA (0.246 ml, 1.485 mmol) at RT. The RM was stirred for 15 mins at RT. 2-Amino-3-(tert-butyl-dimethyl-silanyloxy)-2-methyl-propionamide (**Int-02**) (138 mg, 0.593 mmol) was added to the RM at RT. The RM was stirred for 16 h at RT. The RM was quenched with ice cold water. The solid was filtered and washed with hexane : ether (10ml, 9:1) to afford N-(1-amino-3-((tert-butyldimethylsilyl)oxy)-2-methyl-1-oxopropan-2-yl)-2-methyl-5-((2-methylthiazol-5-yl)methoxy)-2H-indazole-3-carboxamide (190 mg, 74%) as off white solid. 1H-NMR (400 MHz, DMSO-d6) δ [ppm]: 8.00 (s, 1H), 7.74 (s, 1H), 7.67-7.62 (m, 2H), 7.53 (s, 1H), 7.39 (s, 1H), 7.07-7.05(m,1H), 5.31-5.30 (m, 2H), 4.30-4.26 (m, 4H), 4.03-4.01 (m, 1H), 2.66-2.63 (m, 3H), 1.57 (s, 3H), 0.77(s, 9H), -0.006 (s, 3H), -0.0585(s, 3H).

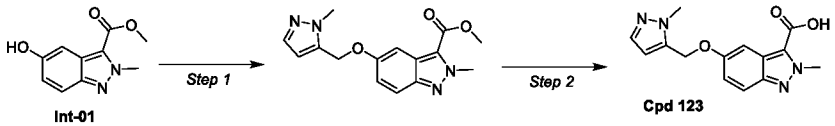
[0252] *Step* 4 :To a stirred solution of N-(1-amino-3-((tert-butyldimethylsilyl)oxy)-2-methyl-1-

oxopropan-2-yl)-2-methyl-5-((2-methylthiazol-5-yl)methoxy)-2H-indazole-3-carboxamide (190 mg, 0.367 mmol) in DCM (5 ml) was added TFA (2 ml) at 0°C. The RM was stirred for 4 h at RT. The RM was concentrated. The crude was purified by Prep HPLC (reversed phase) to afford -hydroxy-2-methyl-2-({2-methyl-5-[(2-methyl-1,3-thiazol-5-yl)methoxy]-2H-indazol-3-yl}formamido)propanamide (**Cpd 157**) (100 mg, 67 %).

[0253] A preparative chiral SFC was performed on the racemic mixture of **Cpd 157** to afford **Cpd 157 – En1 and Cpd 157– En2.**

[0254] The following compounds were prepared in a similar manner (use of appropriate reagents (chiral or racemic) and purification methods (including chiral HPLC or chiral SFC) known to the person skilled in the art) as described for **Cpd 157 – En1 and Cpd 157 – En2** : **Cpd 158 – En1, Cpd 158 – En2, Cpd 160 – En1, Cpd 160 – En2, Cpd 162 – En1, Cpd 162 – En2, Cpd 167 – En1, Cpd 167 – En2, Cpd 179 – En1, Cpd 179 – En2, Cpd 181 – En1, Cpd 181 – En2, Cpd 196.**

[0255] **Synthesis (Mitsunobu) of 2-methyl-5-[(1-methyl-1H-pyrazol-5-yl)methoxy]-2H-indazole-3-carboxylic acid (**Cpd 123**).**



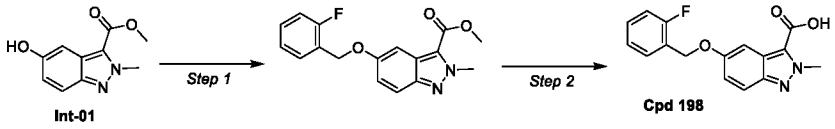
Int-01 Cpd 123

[0256] *Step 1* : To a stirred solution of methyl 5-hydroxy-2-methyl-2H-indazole-3-carboxylate (**Int-01**) (400 mg, 1.939 mmol) and (1-methyl-1H-pyrazol-5-yl)methanol (283 mg, 2.522 mmol) in THF (20 ml) was added ADDP (978.42 mg, 3.878 mmol) at 0°C. The RM was stirred for 15 min at 0°C. Tributylphosphine (0.957 ml, 3.878 mmol) in THF (2 ml) was added at 0°C dropwise. The RM was stirred for 16 h at RT. The RM was quenched with water, extracted with EtOAc. Organic part was washed with brine, dried over Na_2SO_4 and concentrated. The crude was purified by FCC (using 100-200 mesh silica gel, elution with 30% EtOAc-Hexane) to afford methyl 2-methyl-5-((1-methyl-1H-pyrazol-5-yl)methoxy)-2H-indazole-3-carboxylate (450 mg, 77%) as off white solid. ^{1}H-NMR (400 MHz, DMSO-d6) δ [ppm]: 7.72-7.69 (d, 1H), 7.41-7.39 (d, 1H), 7.10-7.08 (d, 1H), 6.41 (s, 1H), 4.38 (s, 3H), 3.98 (s, 3H), 3.85 (s, 3H), 1.62-1.64 (m, 1H), 2.42 (s, 3H).

[0257] *Step 2* : To a stirred solution of methyl 2-methyl-5-((1-methyl-1H-pyrazol-5-yl)methoxy)-2H-indazole-3-carboxylate (3) (450 mg, 1.498 mmol) in THF:H2O:MeOH (12 ml, 1:1:1) was added $LiOH.H_2O$ (158 mg, 3.746 mmol)) at RT. The RM was stirred for 16 h at RT. The RM was concentrated and quenched with saturated sodium bisulfate until pH<7. The solid as filtered and washed with hexane:ether (10ml, 9:1) to afford 2-methyl-5-[(1-methyl-1H-pyrazol-5-yl)methoxy]-2H-indazole-3-carboxylic acid (**Cpd 123**) (370 mg, 86%) as off white solid.

[0258] The following compounds were prepared in a similar manner (use of appropriate reagents (chiral or racemic) and purification methods (including chiral HPLC or chiral SFC) known to the person skilled in the art) as described for **Cpd 123** : **Cpd 122**, **Cpd 199**.

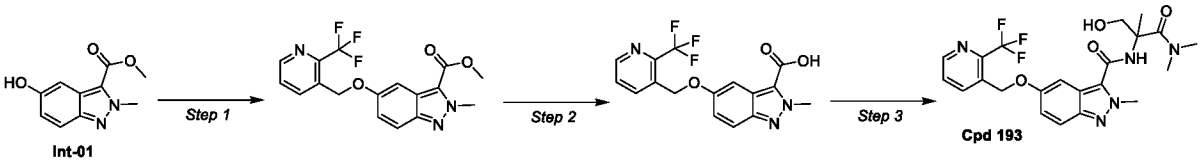
[0259] **Synthesis of 5-[(2-fluorophenyl)methoxy]-2-methyl-2H-indazole-3-carboxylic acid (**Cpd 198**).**



[0260] *Step 1* : To a stirred solution of methyl 5-hydroxy-2-methyl-2H-indazole-3-carboxylate (**Int-01**) (2.0 g, 9.708 mmol) in MeCN (40 mL) was added Cs2CO3 (12.5 g, 38.832 mmol) and followed by addition of 2-fluorobenzyl methanesulfonate (2.9 g, 14.563 mmol) at RT. The RM was heated to 80 °C and stirred for 16 h at 80 °C. Reaction progress was monitored by TLC. The reaction mixture was filtered over celite bed, and celite bed was washed with ethyl acetate (2 x 30 mL). The filtrate was concentrated under reduced pressure. The crude was purified by column chromatography over silica gel (100-200 mesh) using 15% EtOAc in pet ether as an eluent to afford methyl 5-((2-fluorobenzyl)oxy)-2-methyl-2H-indazole-3-carboxylate (2.0 g, 47%) as a pale yellow gum. TLC system: 40% Ethyl acetate in Pet ether; RF: 0.7.

[0261] *Step 2* : To a stirred solution of methyl 5-((2-fluorobenzyl)oxy)-2-methyl-2H-indazole-3-carboxylate (2.0 g, 6.369 mmol) in MeOH: THF: H2O (1:1:0.5, 75 mL) was added NaOH (1.0 g, 25.477 mmol) at RT. The reaction mixture was stirred for 3 h at 60 °C and the reaction progress was monitored by TLC. The reaction mixture was concentrated, acidified to pH ~2 with 1N HCl aq. solution, and stirred for 30 minutes. The precipitated solid was filtered, washed with water (10 mL) and dried under vacuum to afford 55-[(2-fluorophenyl)methoxy]-2-methyl-2H-indazole-3-carboxylic acid (**Cpd 198**) (1.5 g, 60%) as a pale yellow solid. TLC system: 40% Ethyl acetate in Pet ether; RF: 0.1.

[0262] **Synthesis (Mitsunobu) of 3-hydroxy-N,N,2-trimethyl-2-[(2-methyl-5-{[2-(trifluoromethyl)pyridin-3-yl]methoxy}-2H-indazol-3-yl)formamido]propanamide (**Cpd 193**).**



[0263] *Step 1* : ADDP (1.76 mg, 6.99 mmol) & TBP (1.70 mL, 6.99 mmol) were added to a stirred solution of methyl 5-hydroxy-2-methyl-2H-indazole-3-carboxylate (Int-01) (900 mg, 4.36 mmol), and (2-(trifluoromethyl)pyridin-3-yl)methanol in THF (20 mL) at 0 °C. The resulting reaction mixture was stirred at room temperature for 2 h. The reaction progress was monitored by TLC. The reaction mixture was diluted with water (20 mL) and extracted with EtOAc (2 x 80 mL). Combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford methyl 2-methyl-5-((2-(trifluoromethyl)pyridin-3-yl)methoxy)-2H-indazole-3-carboxylate (1.4 g, 88%) as colorless liquid. Crude was used in the next step without purification. TLC system: 20% Methanol in Dichloromethane, RF:0.8.

[0264] *Step 2* : An aqueous solution of 2N NaOH (3 mL) was added to a solution of methyl 2-

methyl-5-((2-(trifluoromethyl)pyridin-3-yl)methoxy)-2H-indazole-3-carboxylate (1.4 g, 3.83 mmol) in THF : EtOH (1:1, 10 mL) and stirred for 16 h at 70 °C. Reaction progress was monitored by TLC. The reaction mixture was concentrated under reduced pressure, diluted with water (30 mL), and pH was adjusted to ~2 with 1N HCl aq. solution. Solid precipitated was collected by filtration and dried under vacuum to get 2-methyl-5-((2-(trifluoromethyl)pyridin-3-yl)methoxy)-2H-indazole-3-carboxylic acid (1.2 g, crude) as a pale yellow solid. TLC system: 100% EtOAc, RF: 0.2.

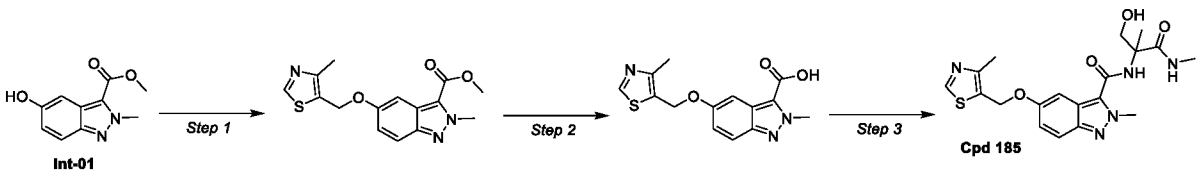
[0265] *Step 3* : 2-Amino-3-hydroxy-N,N,2-trimethylpropanamide (144.5 mg, 0.988 mmol) was added to a stirred solution of 2-methyl-5-((2-(trifluoromethyl)pyridin-3-yl)methoxy)-2H-indazole-3-carboxylic acid (200 mg, 0.6593 mmol), HATU (324.7 mg, 0.85 mmol) and DIPEA (0.29 mL, 1.70 mmol) in DMF (5 mL) at RT and the resulting reaction mixture was stirred at RT for 16 h. The reaction mixture was diluted with water (20 mL) and extracted with EtOAc (2 x 50 mL). Combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude was purified by GRACE flash column chromatography using 30% acetonitrile (ACN) and 0.1% formic acid in water as an eluent to afford 3-hydroxy-N,N,2-trimethyl-2-[(2-methyl-5-{[2-(trifluoromethyl)pyridin-3-yl]methoxy}-2H-indazol-3-yl)formamido]propanamide (**Cpd 193**) (50 mg, 18%) as a white solid. TLC system:100% EtOAc; RF: 0.1.

[0266] A preparative chiral SFC was performed on the racemic mixture of **Cpd 193** to afford **Cpd 193 – En1 and Cpd 193 – En2.**

[0267] The following compounds were prepared in a similar manner (use of appropriate reagents (chiral or racemic) and purification methods (including chiral HPLC or chiral SFC) known to the person skilled in the art) as described for **Cpd 193 – En1 and Cpd 193 – En2** : **Cpd 004, Cpd 006, Cpd 007, Cpd 008, Cpd 009, Cpd 010 – Dia1, Cpd 010 – Dia2, Cpd 011 – Dia1, Cpd 011 – Dia2, Cpd 012, Cpd 013, Cpd 014, Cpd 015, pd 016, pd 017, Cpd 019, Cpd 020, Cpd 022, Cpd 023, Cpd 025, Cpd 026, Cpd 027, Cpd 028, Cpd 029, Cpd 030, Cpd 033, Cpd 034, Cpd 035, Cpd 036, Cpd 038, Cpd 039, Cpd 040, Cpd 041, Cpd 042, Cpd 044, Cpd 045, Cpd 046, Cpd 049, Cpd 050, Cpd 051, Cpd 054, Cpd 055, Cpd 056 – Dia1, Cpd 056, Dia2, Cpd 058, Cpd 059, Cpd 060, Cpd 061, Cpd 062, Cpd 065, Cpd 066, Cpd 067, Cpd 068, Cpd 069, Cpd 071, Cpd 073, Cpd 074, Cpd 076, Cpd 077, Cpd 078, Cpd 079, Cpd 081,s Cpd 082, Cpd 083, Cpd 084, Cpd 085, Cpd 086, Cpd 087, Cpd 088, Cpd 090, Cpd 091, Cpd 092, Cpd 100, Cpd 102, Cpd 103, Cpd 104, Cpd 105, Cpd 106, Cpd 108, Cpd 111, Cpd 114, Cpd 117, Cpd 119, Cpd 120, Cpd 124, Cpd 125, Cpd 126, Cpd 127, Cpd 147, Cpd 149, Cpd 150, Cpd 152, Cpd 153, Cpd 202 – En1, Cpd 202 – En2, Cpd 204, Cpd 205, Cpd 206, Cpd 207, Cpd 208, Cpd 209, Cpd 210, Cpd 217, Cpd 218, Cpd 219, Cpd 220 – En1, Cpd 220 – En2, Cpd 221 – En1, Cpd 221 – En2, , Cpd 223 – En1, Cpd 223 – En2, Cpd 226 – En1, Cpd 226 – En2, Cpd 227 – En1, Cpd 227 – En2, Cpd 228 – En1, Cpd 228 – En2, Cpd 230 – En1, Cpd 230 – En2, Cpd 232 – En1, Cpd 232 – En2, Cpd 234, Cpd 238 – En1,**

Cpd 238 – En2, , Cpd 245 – En1, Cpd 245 – En2, Cpd 254 – En1, Cpd 254 – En2, Cpd 258 – En1, Cpd 258 – En2, Cpd 259, Cpd 262.

[0268] **Synthesis of 3-hydroxy-N,2-dimethyl-2-({2-methyl-5-[(4-methyl-1,3-thiazol-5-yl)methoxy]-2H-indazol-3-yl}formamido)propanamide (**Cpd 185**).**



[0269] *Step 1* : Cs_2CO_3 (8.86 g, 27.27 mmol) was added to a stirred solution of (4-Methylthiazol-5-yl)methyl methanesulfonate (2.61 g, 13.635 mmol) in MeCN (20 mL) and methyl 5-hydroxy-2-methyl-2H-indazole-3-carboxylate (Int-01) (2.0 g, 9.09 mmol) at RT. The RM was heated to 80 °C and stirred for 16 h. The reaction progress was monitored by TLC. The reaction mixture was filtered over celite bed and filtrate was concentrated under reduced pressure to get methyl 2-methyl-5-((4-methylthiazol-5-yl)methoxy)-2H-indazole-3-carboxylate (1.8 g, 60%) as a pale yellow solid. TLC system: 30% Ethyl acetate in Pet ether; RF: 0.8.

[0270] *Step 2* : A solution of NaOH (1.5 g, 45.1 mmol) in water (20 mL) was added to a solution of methyl 2-methyl-5-((4-methylthiazol-5-yl)methoxy)-2H-indazole-3-carboxylate (1.9 g, 5.27 mmol) in MeOH (10 mL) and THF (10 mL) at RT. The resulting reaction mixture was stirred for 16 h at RT and reaction progress was monitored by TLC. The reaction mixture was concentrated under reduced pressure, diluted with water (50 mL) and pH was adjusted to ~4 with aq. 1N HCl solution. The precipitated solid was filtered and dried under vacuum to afford 2-methyl-5-((4-methylthiazol-5-yl)methoxy)-2H-indazole-3-carboxylic acid (1.4 g, 97%) as an off-white solid. TLC system: 100% EtOAc ,RF :0.2.

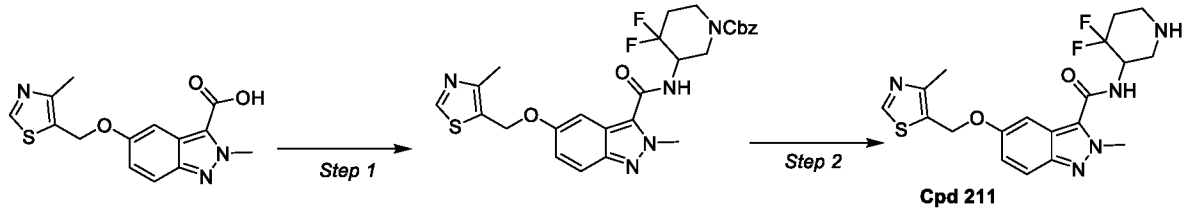
[0271] *Step* 3 : 2-Amino-3-hydroxy-N,2-dimethylpropanamide (130.68 mg, 0.9893 mmol) was added to a stirred solution of 2-methyl-5-((4-methylthiazol-5-yl)methoxy)-2H-indazole-3-carboxylic acid (200 mg, 0.6593 mmol), HATU (376.2 mg, 0.9893 mmol) and DIPEA (256.4 mg, 1.97 mmol) in DMF (5 mL) at RT and the resulting reaction mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with water (20 mL) and extracted with EtOAc (2 x 50 mL). Combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude was purified by GRACE flash column chromatography using 30% acetonitrile in 0.1% formic acid water as an eluent to afford 3-hydroxy-N,2-dimethyl-2-({2-methyl-5-[(4-methyl-1,3-thiazol-5-yl)methoxy]-2H-indazol-3-yl}formamido)propanamide (**Cpd 185**) (100 mg, 36%) as a white solid. TLC system: 20% MeOH in DCM; RF: 0.6.

[0272] A preparative chiral SFC was performed on the racemic mixture of **Cpd 185** to afford **Cpd 185 – En1 and Cpd 185– En2.**

[0273] The following compounds were prepared in a similar manner (use of appropriate

reagents (chiral or racemic) and purification methods (including chiral HPLC or chiral SFC) known to the person skilled in the art) as described for **Cpd 185 – En1 and Cpd 185 – En2** : **Cpd 005, Cpd 018, Cpd 021, Cpd 024, Cpd 031, Cpd 032, Cpd 037, Cpd 043, Cpd 047, Cpd 048, Cpd 052, Cpd 053, Cpd 057, Cpd 063, Cpd 064, Cpd 070, Cpd 072, Cpd 075, Cpd 080 – Dia1, Cpd 080 – Dia2, Cpd 089, Cpd 093, Cpd 094, Cpd 095, Cpd 096, Cpd 097, Cpd 098, Cpd 099, Cpd 101, Cpd 107 , Cpd 109, Cpd 110, Cpd 112, Cpd 113, Cpd 115, Cpd 116, Cpd 118, Cpd 121, Cpd 129, Cpd 130, Cpd 131, Cpd 133, Cpd 134, Cpd 135, Cpd 136, Cpd 137, Cpd 138, Cpd 139, Cpd 140, Cpd 141, Cpd 142, Cpd 143, Cpd 144, Cpd 145, Cpd 146, Cpd 148,Cpd 182 – En1, Cpd 182 – En2, Cpd 184 – En1, Cpd 184 – En2, Cpd 187 – En1, Cpd 187 – En2, Cpd 189, Cpd 190 – En1, Cpd 190 – En2, Cpd 191 – En1, Cpd 191 – En2, Cpd 192 – En1, Cpd 192 – En2, Cpd 194 – En1, Cpd 194 – En2, Cpd 203 – En1, Cpd 203 – En2.**

[0274] **Synthesis of N-(4,4-difluoropiperidin-3-yl)-2-methyl-5-[(4-methyl-1,3-thiazol-5-yl)methoxy]-2H-indazole-3-carboxamide (**Cpd 211**).**



[0275] *Step 1* : To a solution of 2-methyl-5-((4-methylthiazol-5-yl)methoxy)-2H-indazole-3-carboxylic acid (400 mg, 1.319 mmol) in DMF (15 mL) were added HATU (750 mg, 1.978 mmol), DIPEA (1.15 mL, 6.593 mmol) and tert-butyl 3-amino-4,4-difluoropiperidine-1-carboxylate(445 mg, 1.648 mmol) at 0 °C . The RM was stirred at RT for 16 h. After completion, the RM was poured into ice cold water (50 mL), extracted with DCM (2 x 50 mL). The combined organic layers were washed with sat. solution of $NaHCO_3$ (50 mL), water (50 mL), brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to get crude compound and which was triturated with n-pentane (30 mL) and dried to afford benzyl 4,4-difluoro-3-(2-methyl-5-((4-methylthiazol-5-yl) methoxide)-2H-indazole-3-carboxamido) piperidine-1-carboxylate as off-white solid (550 mg, 75.07%). ^{1}H NMR (400 MHz, DMSO-D6) δ ppm: 8.99 (s, 1 H), 8.86 (d, 1 H), 7.64 (d, 1 H), 7.38 - 7.34 (m, 5 H), 7.18 (brs, 1 H), 7.07 - 7.05 (m, 1 H), 5.32 (d, 2 H), 5.13 - 5.10 (m, 2 H), 4.56 (brs, 1 H), 4.21 (s, 3 H), 3.86 (d, 1 H), 3.72 (s, 1 H), 3.58 - 3.36 (m, 2 H), 2.41 (s, 3 H), 2.36 - 2.32 (m, 1 H), 2.32 - 2.13 (m, 1 H).

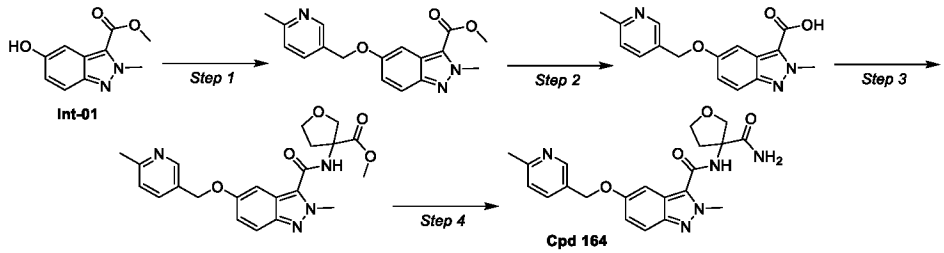
[0276] *Step 2 :* A solution of benzyl 4,4-difluoro-3-(2-methyl-5-((4-methylthiazol-5-yl)methoxy)-2H-indazole-3-carboxamido) piperidine-1-carboxylate (450 mg, 0.810 mmol) in TFA (15 mL) was heated to 60 °C and stirred for 4 h. After completion, the RM was concentrated under reduced pressure. To the residue was added a sat. solution of $NaHCO_3$ (50 mL). The aqueous layer was extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with

water (30 mL), brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The compound was purified by Prep. HPLC. [Prep. HPLC conditions: Mobile phase: 10mM ABC in Water, Mobile phase B: ACN, Column: X-Select CSH C18 (250 x 19 mm) 5µm, FLOW: 14 ml/min, Method: (T in min./ % of B): 0/15,2/15,10/50,13/50,13.20/98,17/98,17.10/15,20/15, Solubility: ACN+Water+THF, Temperature: RT.] The desired fractions were evaporated and lyophilized to afford -(4,4-difluoropiperidin-3-yl)-2-methyl-5-[(4-methyl-1,3-thiazol-5-yl)methoxy]-2H-indazole-3-carboxamide (Cpd 211) (190 mg, 55.66%).

[0277] A preparative chiral SFC was performed on the racemic mixture of **Cpd 211** to afford **Cpd 211 – En1 and Cpd 211– En2.**

[0278] The following compounds were prepared in a similar manner (use of appropriate reagents (chiral or racemic) and purification methods (including chiral HPLC or chiral SFC) known to the person skilled in the art) as described for **Cpd 211 – En1 and Cpd 211 – En2** : **Cpd 248 – En1, Cpd 248 – En2.**

[0279] **Synthesis of N-(3-carbamoyloxolan-3-yl)-2-methyl-5-[(6-methylpyridin-3-yl)methoxy]-2H-indazole-3-carboxamide (**Cpd 164**).**



[0280] *Step 1* :To a stirred solution of methyl 5-hydroxy-2-methyl-2H-indazole-3-carboxylate (Int-01) (1.5 g, 7.28 mmol) in MeCN (100 mL) was added Cs_2CO_3 (8.0 g, 24.75 mmol) and followed by addition of (6-Methylpyridin-3-yl)methyl methanesulfonate (2.92 g, 14.563 mmol) at RT. The RM was heated to 100 °C, stirred for 16 h at 100 °C and the reaction progress was monitored by TLC. The reaction mixture was filtered over celite bed, and celite bed was washed with EtOAc (2 x 30 mL). The filtrate was concentrated under reduced pressure. The crude was purified by FCC (100-200 mesh) using 15% EtOAc in pet ether as an eluent to afford methyl 2-methyl-5-((6-methylpyridin-3-yl)methoxy)-2H-indazole-3-carboxylate (800 mg, 31% for 2 steps) as a brown residue. TLC system: 50% Ethyl acetate in pet ether; RF: 0.2.

[0281] *Step 2* : To a stirred solution of methyl 2-methyl-5-((6-methylpyridin-3-yl) methoxy)-2H-indazole-3-carboxylate (1.5 g, 4.82 mmol) in MeOH: THF: H2O (1:1:0.5, 50 mL) was added NaOH (1.92 g, 48.23 mmol) at RT. The reaction mixture was stirred for 4 h at 50 °C and the reaction progress was monitored by TLC. The reaction mixture was concentrated, acidified to pH ~2 with 1N aq. HCl solution, and stirred for 30 minutes. The solid precipitated was filtered, washed with water (10 mL) and dried under vacuum to afford 2-Methyl-5-((6-methylpyridin-3-yl)methoxy)-2H-indazole-3-carboxylic acid (1.0 g) as off-white solid. TLC system: 100% Ethyl

acetate; RF: 0.1.

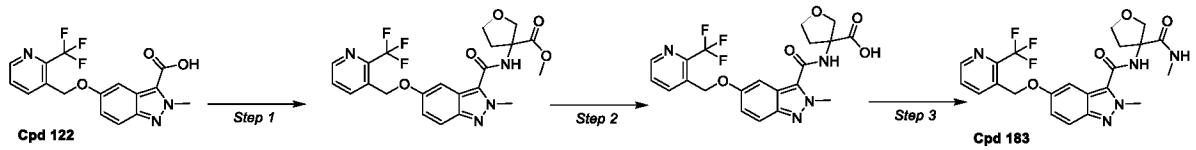
[0282] *Step 3* : To a stirred solution of 2-methyl-5-((6-methylpyridin-3-yl)methoxy)-2H-indazole-3-carboxylic acid (800 mg, 2.69 mmol) in DMF (20.0 mL) was added DIPEA (1.9 mL, 10.76 mmol), HATU (1.53 g, 4.04 mmol) at 0 °C, followed by addition of methyl 3-aminotetrahydrofuran-3-carboxylate (585 mg, 4.04 mmol). The RM was stirred for 16 h at RT and reaction progress was monitored by TLC. The RM was diluted with water (50 mL) and extracted with EtOAc (2 x 50 mL). Combined extracts were washed with brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude was purified by FCC with 65% ethyl acetate in pet ether as an eluent to afford methyl-3-(2-methyl-5-((6-methylpyridin-3-yl)methoxy)-2H-indazole-3-carboxamido)tetrahydrofuran-3-carboxylate (400 mg, 56 %) as an off-white solid. TLC system: 100% ethyl acetate ; RF: 0.34.

[0283] *Step 4* : To a stirred solution of methyl-3-(2-methyl-5-((6-methylpyridin-3-yl)methoxy)-2H-indazole-3-carboxamido)tetrahydrofuran-3-carboxylate (400 mg, 0.94 mmol) in MeOH (5 mL) was added NH3 in MeOH (7M, 20 mL) at 0 °C. The reaction mixture was stirred for 16 h at 100 °C and reaction progress was monitored by TLC. The reaction mixture was concentrated. Crude was purified by FCC using 0.1% formic acid in acetonitrile as an eluent to afford N-(3-carbamoyloxolan-3-yl)-2-methyl-5-[(6-methylpyridin-3-yl)methoxy]-2H-indazole-3-carboxamide (**Cpd 164**) (200 mg, 51 %) as an off-white solid. TLC system: 100% ethyl acetate; RF: 0.2.

[0284] A preparative chiral SFC was performed on the racemic mixture of **Cpd 164** to afford **Cpd 164 – En1 and Cpd 164– En2.**

[0285] The following compounds were prepared in a similar manner (use of appropriate reagents (chiral or racemic) and purification methods (including chiral HPLC or chiral SFC) known to the person skilled in the art) as described for **Cpd 164 – En1 and Cpd 164 – En2** : **Cpd 165 – En1, Cpd 165 – En2, Cpd 166 – En1, Cpd 166 – En2, Cpd 168 – En1, Cpd 168 – En2, Cpd 170 – En1, Cpd 170 – En2, Cpd 172 – En1, Cpd 172 – En2, Cpd 173 – En1, Cpd 173 – En2, Cpd 174 – En1, Cpd 174 – En2, Cpd 175 – En1, Cpd 175 – En2, Cpd 178 – En1, Cpd 178 – En2.**

[0286] **Synthesis of 2-methyl-N-[3-(methylcarbamoyl)oxolan-3-yl]-5-{[2-(trifluoromethyl)pyridin-3-yl]methoxy}-2H-indazole-3-carboxamide** (Cpd 183)**.**



[0287] *Step 1* : To a stirred solution of 2-methyl-5-((2-(trifluoromethyl)pyridin-3-yl)methoxy)-2H-indazole-3-carboxylic acid (Cpd 122) (750 mg, 2.136 mmol) in DMF (10 mL) was added DIPEA (1.48 mL, 8.54 mmol), HATU (1.6 g, 4.27 mmol) at 0 °C, after 15 min methyl 3-aminotetrahydrofuran-3-carboxylate hydrochloride (464 mg, 3.205 mmol) was added. The reaction mixture was stirred for 2 h at RT and reaction progress was monitored by TLC. The

reaction mixture was diluted with water (50 mL) and extracted with ethyl acetate (3 x 100 mL). Combined organic layers were washed with water (100 mL), brine (100 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford methyl 3-(2-methyl-5-((2-(trifluoromethyl)pyridin-3-yl)methoxy)-2H-indazole-3-carboxamido)tetrahydrofuran-3-carboxylate (800 mg, 78%) as an off-white solid. TLC system: 100% Ethyl acetate; Rf: 0.71.

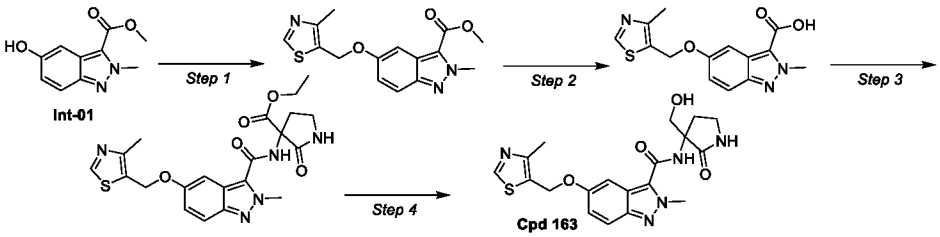
[0288] *Step 2* : To a stirred solution of methyl 3-(2-methyl-5-((2-(trifluoromethyl)pyridin-3-yl)methoxy)-2H-indazole-3-carboxamido)tetrahydrofuran-3-carboxylate (1.0 g, 2.09 mmol) in MeOH:THF (1:1; 14 mL) was added NaOH (167 mg, 4.184 mmol) in H2O (7 mL) at 0 °C. The reaction mixture was stirred for 2 h at RT and reaction progress was monitored by TLC. The reaction mixture was diluted with water (50 mL) and washed with diethyl ether (2 x 50 mL). The aqueous layer was acidified to pH ~1 with 1N aq. HCl solution and extracted with ethyl acetate (3 x 100 mL). Combined organic layers were washed with water (100 mL), brine (100 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford 3-(2-methyl-5-((2-(trifluoromethyl)pyridin-3-yl)methoxy)-2H-indazole-3-carboxamido)tetrahydrofuran-3-carboxylic acid (900 mg, 92%) as an off-white solid. TLC system: 100% EtOAc; Rf: 0.21.

[0289] *Step 3* : To a stirred solution of 3-(2-methyl-5-((2-(trifluoromethyl)pyridin-3-yl)methoxy)-2H-indazole-3-carboxamido)tetrahydrofuran-3-carboxylic acid (2391-6) (500 mg, 1.07 mmol) in DMF (10 mL) was added DIPEA (0.75 mL, 4.30 mmol), HATU (818 mg, 2.155 mmol) at 0 °C, after 15 min methanamine hydrochloride (145 mg, 2.155 mmol) was added. The reaction mixture was stirred for 2 h at RT and reaction progress was monitored by TLC. The reaction mixture was diluted with water (50 mL) and extracted with ethyl acetate (3 x 80 mL). Combined organic layers were washed with water (80 mL), brine (80 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to get crude. Crude was triturated with diethyl ether (20 mL) and dried under reduced pressure to afford 2-methyl-N-[3-(methylcarbamoyl)oxolan-3-yl]-5-{[2-(trifluoromethyl)pyridin-3-yl]methoxy}-2H-indazole-3-carboxamide (**Cpd 183**) (400 mg, 77%) as an off-white solid. TLC system: 10% Methanol in Dichloromethane; Rf: 0.51.

[0290] A preparative chiral SFC was performed on the racemic mixture of **Cpd 183** to afford **Cpd 183 – En1 and Cpd 183– En2.**

[0291] The following compounds were prepared in a similar manner (use of appropriate reagents (chiral or racemic) and purification methods (including chiral HPLC or chiral SFC) known to the person skilled in the art) as described for **Cpd 183 – En1 and Cpd 183 – En2** : **Cpd 186 – En1, Cpd 186 – En2**

[0292] **Synthesis of N-[3-(hydroxymethyl)-2-oxopyrrolidin-3-yl]-2-methyl-5-[(4-methyl-1,3-thiazol-5-yl)methoxy]-2H-indazole-3-carboxamide (**Cpd 163**).**



[0293] *Step 1* : To a stirred solution of methyl 5-hydroxy-2-methyl-2H-indazole-3-carboxylate (Int-01) (800 mg, 3.883 mmol) in MeCN (15 mL) was added Cs2CO3 (5.0 g, 15.532 mmol) and followed by addition of (4-methylthiazol-5-yl)methyl methanesulfonate (4) (1.1 g, 5.825 mmol) at RT. The RM was stirred for 16 h at RT and 2 h at 80 °C. The reaction progress was monitored by TLC. The reaction mixture was diluted with water (30 mL), and extracted with EtOAc (2 x 30 mL). Combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford methyl 2-methyl-5-((4-methylthiazol-5-yl)methoxy)-2H-indazole-3-carboxylate (400 mg, crude) as a brown gum. Proceeded to next step without further purification .TLC system: 40% ethyl acetate in pet ether; Rf: 0.4.

[0294] *Step 2* : To a stirred solution of methyl 2-methyl-5-((4-methylthiazol-5-yl)methoxy)-2H-indazole-3-carboxylate (400 mg, 1.208 mmol) in MeOH: THF (1:1, 32 mL) was added a solution of NaOH (193.4 mg, 4.834 mmol) in water (8 mL) at RT. The reaction mixture was stirred for 3 h at 60 °C and the reaction progress was monitored by TLC. The reaction mixture was concentrated, acidified to pH ~2 with 1N aq. HCl; precipitated solid was filtered, washed with water (10 mL) and dried under vacuum to afford 2-methyl-5-((4-methylthiazol-5-yl)methoxy)-2H-indazole-3-carboxylic acid (300 mg, crude) as an off-white semi solid. TLC system: 40% ethyl acetate in pet-ether; RF: 0.1.

[0295] *Step 3* : To a stirred solution of 2-methyl-5-((4-methylthiazol-5-yl)methoxy)-2H-indazole-3-carboxylic acid (300 mg, 0.943 mmol) in DMF (10.0 mL) was added HATU (537.7 mg, 1.415 mmol), DIPEA (0.5 mL, 2.829 mmol) at 0 °C and followed by addition of ethyl 3-amino-2-oxopyrrolidine-3-carboxylate (220.8 mg, 1.415 mmol). The reaction mixture was stirred for 2 h at RT and reaction progress was monitored by TLC. The reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (2 x 30 mL). Combined extracts were washed with water (2 x 20 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to get crude. Crude was purified by column chromatography using silica gel (100-200 mesh size) and 15% ethyl acetate in pet ether as an eluent to afford ethyl 3-(2-methyl-5-((4-methylthiazol-5-yl)methoxy)-2H-indazole-3-carboxamido)-2-oxopyrrolidine-3-carboxylate (200 mg, crude) as an off-white solid. TLC system: 5% methanol in dichloromethane; RF: 0.4.

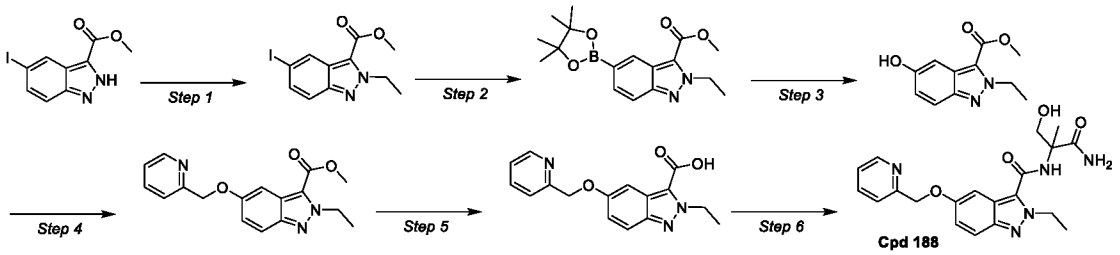
[0296] *Step 4* : To a stirred solution of ethyl 3-(2-methyl-5-((4-methylthiazol-5-yl)methoxy)-2H-indazole-3-carboxamido)-2-oxopyrrolidine-3-carboxylate (200 mg, 0.436 mmol) in Methanol (10 mL) was added NaBH4 (139.4 mg, 3.493 mmol) at 0 °C. The reaction mixture was stirred for 16 h at room temperature. Reaction progress was monitored by TLC. The reaction mixture

was concentrated, diluted with water (10 mL), and extracted with ethyl acetate (2 x 20 mL). Combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum to get crude. Crude was purified by Grace flash chromatography using 0.1% formic acid in acetonitrile as an eluent to afford (60 mg, 4% over 4 steps) of N-[3-(hydroxymethyl)-2-oxopyrrolidin-3-yl]-2-methyl-5-[(4-methyl-1,3-thiazol-5-yl)methoxy]-2H-indazole-3-carboxamide (**Cpd 163**). as an off-white solid. TLC system: 5% methanol in dichloromethane; RF: 0.4.

[0297] A preparative chiral SFC was performed on the racemic mixture of **Cpd 163** to afford **Cpd 163 – En1 and Cpd 163– En2.**

[0298] The following compounds were prepared in a similar manner (use of appropriate reagents (chiral or racemic) and purification methods (including chiral HPLC or chiral SFC) known to the person skilled in the art) as described for **Cpd 163 – En1 and Cpd 163 – En2** : **Cpd 159 – En1, Cpd 159 – En2, Cpd 161 – En1, Cpd 161 – En2, Cpd 171 – En1, Cpd 171 – En2, Cpd 175 – En1, Cpd 175 – En2, Cpd 176 – En1, Cpd 176 – En2, Cpd 177 – En1, Cpd 177 – En2, Cpd 180 – En1, Cpd 180 – En2, Cpd 253 – En1, Cpd 253 – En2.**

[0299] **Synthesis of 2-({2-ethyl-5-[(pyridin-2-yl)methoxy]-2H-indazol-3-yl}formamido)-3-hydroxy-2-methylpropanamide (**Cpd 188**).**



[0300] *Step 1*: To a stirred solution of methyl 5-iodo-1H-indazole-3-carboxylate (5.0 g, 16.55 mmol) in EtOAc (150 mL) was added triethyloxonium tetrafluoroborate (7.6 g, 41.39 mmol) at RT. The RM was stirred at RT for 4 h. The reaction progress was monitored by TLC. The reaction mixture was diluted with water (150 mL) and extracted with EtOAc (2 x 150 mL). Combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude was purified by silica gel (100-200 mesh) chromatography using 10% ethyl acetate in pet ether as an eluent to afford methyl 2-ethyl-5-iodo-2H-indazole-3-carboxylate (2.0 g,36%) as an off-white solid. TLC system: 40% Ethyl acetate in Pet ether; RF: 0.7.

[0301] *Step 2* : To a stirred solution of methyl 2-ethyl-5-iodo-2H-indazole-3-carboxylate (1.5 g, 4.54 mmol) in 1,4-Dioxane (30 mL) was added Bis-Pinacolate diborane (1.3 g, 4.99 mmol) and followed by addition of potassium acetate (1.34 g, 13.63 mmol) at RT and degassed with argon for 10 minutes, pd(dppf)cl2.CH2Cl2 was added at RT. The reaction mixture was heated to 110 °C and stirred for 16 h. The reaction progress was monitored by TLC. Reaction mixture was filtered over celite pad, celite bed was washed with EtOAc (2 x 20 mL). Combined filtrate was concentrated under reduced pressure to afford methyl 2-ethyl-5-(4,4,5,5-tetramethyl-1,3,2-

dioxaborolan-2-yl)-2H-indazole-3-carboxylate (3.1 g) as brown solid. Proceeded to next step without any purification. TLC system: 20% Ethyl acetate in Pet ether; Rf: 0.3.

[0302] *Step 3* : To a stirred solution of methyl 2-ethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2H-indazole-3-carboxylate (4.0 g, 12.121 mmol) in acetone (80 mL) was added oxone (7.4 g, 12.12 mmol) in water (80 mL) at 0 °C. The RM was stirred for 2 h at RT and the reaction progress was monitored by TLC. The RM was diluted with EtOAc (200 mL) and aqueous layer was extracted with EtOAc (2 x 200 mL). Combined organic layers were washed with water (100 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude was purified by column chromatography using silica gel (100-200) with 25% EtOAc in pet ether as an eluent to afford methyl 2-ethyl-5-hydroxy-2H-indazole-3-carboxylate (1.0 g, 50% over 2 steps) as a pale yellow solid. TLC system: 40% Ethyl acetate in Pet ether; Rf: 0.3.

[0303] *Step 4* : To a stirred solution of methyl 2-ethyl-5-hydroxy-2H-indazole-3-carboxylate (400 mg, 1.818 mmol) in MeCN (50 mL) was added Cs_2CO_3 (1.7 g, 5.45 mmol) and followed by addition of pyridin-2-ylmethyl methanesulfonate (610 mg, 5.45 mmol) at RT. The reaction mixture was heated to 80 °C for 16 h. Reaction progress was monitored by TLC. The reaction mixture was filtered through celite bed, and celite bed was washed with ethyl acetate (2 x 30 mL). The filtrate was concentrated under reduced pressure. The crude was purified by column chromatography over silica gel (100-200 mesh) using 15% ethyl acetate in pet ether as an eluent to afford methyl 2-ethyl-5-(pyridin-2-ylmethoxy)-2H-indazole-3-carboxylate (150 mg, 26%) as a brown residue, TLC system: 40% Ethyl acetate in Pet ether; RF: 0.2.

[0304] *Step 5* : To a stirred solution of methyl 2-ethyl-5-(pyridin-2-ylmethoxy)-2H-indazole-3-carboxylate (150 mg, 0.482 mmol) in MeOH: THF: H2O (1:1:0.5, 20 mL) was added NaOH (192 mg, 4.823 mmol) at RT. The reaction mixture was stirred for 16 h at RT and the reaction progress was monitored by TLC. The reaction mixture was concentrated, acidified to pH ~2 with 1N HCl, and stirred for 30 minutes. The precipitated solid was filtered, washed with water (5 mL) and dried under vacuum to afford 2-ethyl-5-(pyridin-2-ylmethoxy)-2H-indazole-3-carboxylic acid (100 mg) as an off-white solid. TLC system: 10% MeOH in DCM; RF: 0.1.

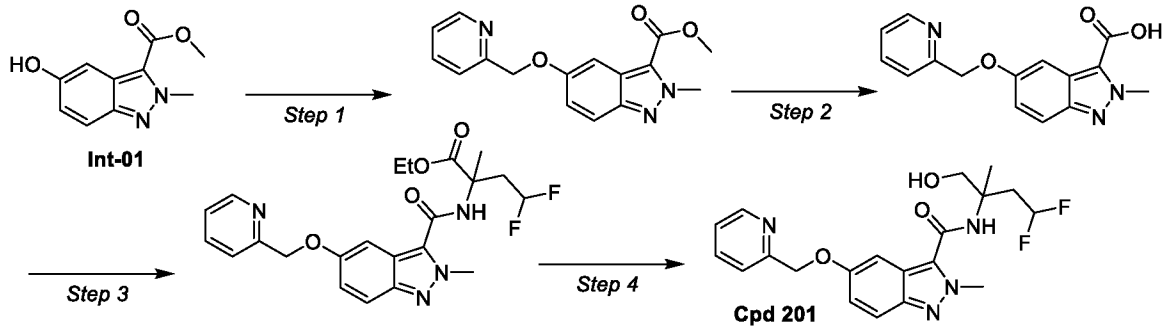
[0305] *Step 6* : To a stirred solution of 2-ethyl-5-(pyridin-2-ylmethoxy)-2H-indazole-3-carboxylic acid (100 mg, 0.336 mmol) in DMF (10 mL) was added HATU (191 mg, 0.505 mmol), DIPEA (0.3 mL, 1.34 mmol) at 0 °C and followed by addition of 2-amino-3-hydroxy-2-methylpropanamide (397 mg, 3.36 mmol). The reaction mixture was stirred for 16 h at RT. The reaction progress was monitored by TLC. The reaction mixture was diluted with water (50 mL) and extracted with ethyl acetate (2 x 50 mL). Combined organic layers were washed with water (2 x 50 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude was purified by reverse phase column chromatography using 0.01% formic acid in water and MeCN as an eluent to afford 2-({2-ethyl-5-[(pyridin-2-yl)methoxy]-2H-indazol-3-yl}formamido)-3-hydroxy-2-methylpropanamide (**Cpd 188**) (70 mg,52%) as an off-white solid.

TLC system: 10% MeOH in DCM; RF: 0.2.

[0306] A preparative chiral SFC was performed on the racemic mixture of **Cpd 188** to afford **Cpd 188 – En1 and Cpd 188– En2.**

[0307] The following compounds were prepared in a similar manner (use of appropriate reagents (chiral or racemic) and purification methods (including chiral HPLC or chiral SFC) known to the person skilled in the art) as described for **Cpd 188 – En1 and Cpd 188 – En2** : **Cpd 195 – En1, Cpd 195 – En2.**

[0308] **Synthesis of N-(4,4-difluoro-1-hydroxy-2-methylbutan-2-yl)-2-methyl-5-[(pyridin-2-yl)methoxy]-2H-indazole-3-carboxamide** (Cpd 201**).**



[0309] *Step 1*: To a solution of methyl 5-hydroxy-2-methyl-2H-indazole-3-carboxylate (Int-01) (3 g, 14.54 mmol) in THF (75 mL) were added ADDP (7.34 g, 29.09 mmol), tributylphosphine (5.8 g, 29.09 mmol) and then 181yridine-2-ylmethanol (1.60 g, 14.69 mmol) at 0 °C. The RM was stirred at RT for 16 h. After completion, the RM was diluted with water (100 mL), extracted with EtOAc (3 x 30 mL). Combined organic layer was washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by FCC on silica gel using 10% EtOAc in pet ether as an eluent to afford methyl 2-methyl-5-(pyridin-2-ylmethoxy)-2H-indazole-3-carboxylate as an off-white solid (3.10 g, 71.67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.62 (d, 1 H), 7.74 (dt, 1 H), 7.68 (d, 1 H), 7.60 (d, 1 H), 7.34 (d, 1 H), 7.25-7.23 (m, 1 H), 7.17 (dd, 1 H), 5.29 (s, 2 H), 4.46 (s, 3 H), 4.00 (s, 3 H). *Step 2* : To a solution of methyl 2-methyl-5-(pyridin-2-ylmethoxy)-2H-indazole-3-carboxylate (4 g, 13.45 mmol) in MeOH:THF:H_2O (2:2:1, 75 mL) was added NaOH (5.32 g, 134.5 mmol) . The RM was stirred for 4 h at RT. After completion, the RM was concentrated and diluted with water (50 mL), acidified with AcOH (pH ~6) and stirred for 30 minutes. The precipitated solid was filtered, washed with water (50 mL) and dried under vacuum to afford crude compound as an off-white solid (3.0 g) and which was triturated with n-pentane (30 mL) and dried to afford 2-methyl-5-(pyridin-2-ylmethoxy)-2H-indazole-3-carboxylic acid as an off-white solid (2.650 g yield: 69%). ^{1}H NMR (400 MHz, DMSO-D_6) δ ppm: 8.59 (d, 1 H), 7.84 (dt, 1 H), 7.67 (d, 1 H), 7.55 (d, 1 H), 7.36-7.33 (m, 2 H), 7.12 (dd, 1 H), 5.21 (s, 2 H), 4.36 (s, 3 H).

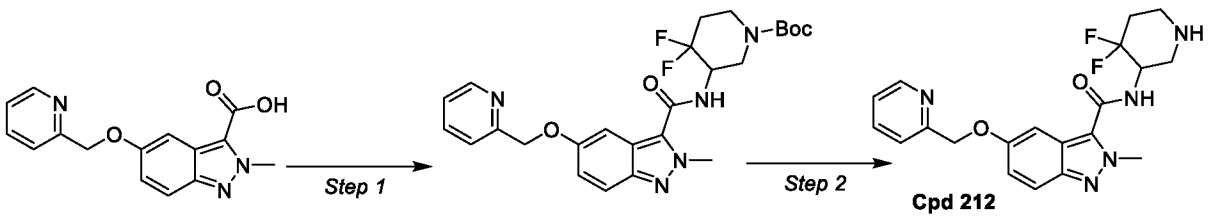
[0310] *Step 3* : To a solution of 2-methyl-5-(pyridin-2-ylmethoxy)-2H-indazole-3-carboxylic acid (600 mg, 2.11 mmol) in DMF (10 mL) were added HATU (1.208 g, 3.17 mmol), DIPEA

(1.174 mg, 6.35 mmol) and ethyl 2-amino-4,4-difluoro-2-methylbutanoate (575 mg, 3.17 mmol) at RT. The RM was stirred at RT for 1 h. The RM was diluted with water (50 mL), extracted with EtOAc (3 X 30 mL). Combined organic layer was washed with brine (40 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by FCC on silica gel using 20% EtOAc in pet ether as an eluent to afford ethyl 4,4-difluoro-2-methyl-2-(2-methyl-5-(pyridin-2-ylmethoxy)-2H-indazole-3-carboxamido)butanoate an pale yellow gum (700 mg, 74.03%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.60 - 8.61 (m, 1H), 7.69 - 7.75 (m, 2H), 7.55 (d, 1H), 7.22 - 7.27 (m, 2H), 7.15 - 7.18 (m, 2H), 6.00 - 6.02 (m, 1H), 5.29 (s, 2H), 4.40 (s, 3H), 4.31 - 4.37 (m, 2H), 3.13 - 3.23 (m, 1H), 2.62 - 2.68 (m, 1H), 1.79 (s, 3H), 1.39 (t, 3 H).

[0311] *Step 4* : To a solution of ethyl 4,4-difluoro-2-methyl-2-(2-methyl-5-(pyridin-2-ylmethoxy)-2H-indazole-3-carboxamido)butanoate (870 mg, 1.94 mmol) in EtOH (15 mL) was added Sodium borohydride (221 mg, 5.84 mmol) at 0 °C. Then the RM was stirred at RT for 7 h. The RM was quenched with water, extracted with EtOAc (3 x 20 mL). Combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by FCC on silica gel using 30% EtOAc in pet ether as an eluent. The compound was purified by Prep. HPLC. [Prep. HPLC conditions: Mobile phase: 0.1%Formic acid in water, Mobile phase B: ACN, Column: Sunfire C18 (19 x 250mm) 5µm, FLOW: 17 ml/min, Method: (T in min./ % of B): 0/20,2/20,8/60,11/60,11.01/100,15/100,15.1/20,18/20, Solubility: ACN+Water+THF, Temperature: RT.] The desired fractions were evaporated and lyophilized to N-(4,4-difluoro-1-hydroxy-2-methylbutan-2-yl)-2-methyl-5-[(pyridin-2-yl)methoxy]-2H-indazole-3-carboxamide (Cpd **201**) (350 mg, 44.41%).

[0312] A preparative chiral SFC was performed on the racemic mixture of **Cpd 201** to afford **Cpd 201 – En1 and Cpd 201 – En2.**

[0313] **Synthesis of N-(4,4-difluoropiperidin-3-yl)-2-methyl-5-[(pyridin-2-yl)methoxy]-2H-indazole-3-carboxamide (**Cpd 212**).**



[0314] *Step 1*: To a solution of 2-methyl-5-(pyridin-2-ylmethoxy)-2H-indazole-3-carboxylic acid (225 mg, 0.794 mmol) in DMF (8 mL) were added HATU (450 mg, 1.191 mmol), DIPEA (0.4 mL, 2.383 mmol) and tert-butyl 3-amino-4,4-difluoropiperidine-1-carboxylate (300 mg, 1.191 mmol) in DMF (2 mL) at 0 °C . The RM was stirred at RT for 4 h. After completion, the RM was diluted with cold water (25 mL), extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with sat. sodium bicarbonate solution (50 mL), brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford tert-butyl 4,4-difluoro-3-(2-methyl-5-(pyridin-2-ylmethoxy)-2H-indazole-3-carboxamido) piperidine-1-carboxylate as

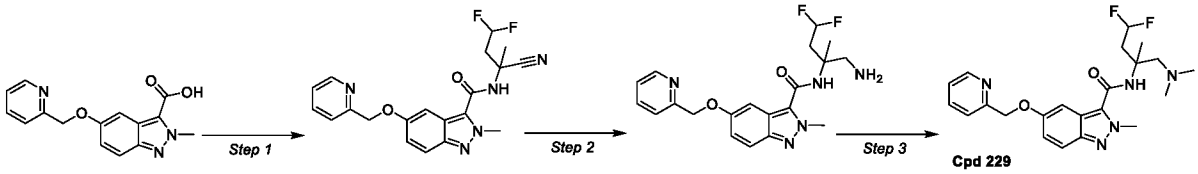
off-white solid (350 mg, 87%). ^{1}H NMR (400 MHz, DMSO-D_6) δ ppm: 8.74 (d, 1 H), 8.59 - 8.57 (m, 1 H), 7.87 - 7.82 (m, 1 H), 7.65 (d, 1 H), 7.57 (d, 1 H), 7.37 - 7.34 (m, 1 H), 7.14 - 7.12 (m, 2 H), 5.19 (s, 2 H), 4.50 - 4.37 (m, 1 H), 4.24 (s, 3 H), 4.00 - 3.70 (m, 2 H), 3.2 - 3.14 (m, 1 H), 2.89 (m, 1 H), 2.32 - 1.98 (m, 2 H), 1.41 (s, 9 H).

[0315] *Step 2* : To a solution of tert-butyl 4,4-difluoro-3-(2-methyl-5-(pyridin-2-ylmethoxy)-2H-indazole-3-carboxamido) piperidine-1-carboxylate (400 mg, 0.798 mmol) in DCM (10 mL) was added 4N HCl in dioxane (2 mL) at 0 °C. The RM was stirred at RT for 3 h. After completion, the reaction mixture was concentrated under reduced pressure the resulting solid was triturated with n-pentane (20 mL) to afford crude compound as an off white solid (HCl salt) and which was dissolved in water (25 mL), basified with sat. sodium bicarbonate solution (pH~10), extracted with EtOAc (2 x 25 mL). Combined organic layers were washed with water (30 mL), brine (30 mL), dried over Na_2SO_4,and concentrated under reduced pressure to afford N-(4,4-difluoropiperidin-3-yl)-2-methyl-5-[(pyridin-2-yl)methoxy]-2H-indazole-3-carboxamide (Cpd **212**) (300 mg, 93%).

[0316] A preparative chiral SFC was performed on the racemic mixture of **Cpd 212** to afford **Cpd 212 – En1 and Cpd 212 – En2.**

[0317] The following compounds were prepared in a similar manner (use of appropriate reagents (chiral or racemic) and purification methods (including chiral HPLC or chiral SFC) known to the person skilled in the art) as described for **Cpd 212 – En1 and Cpd 212 – En2** : **Cpd 213 – En1, Cpd 213 – En2, Cpd 214 – En1, Cpd 214 – En2, Cpd 215 – En1, Cpd 215 – En2, Cpd 216 – En1, Cpd 216 – En2.**

[0318] **Synthesis of N-[1-(dimethylamino)-4,4-difluoro-2-methylbutan-2-yl]-2-methyl-5-[(pyridin-2-yl)methoxy]-2H-indazole-3-carboxamide (**Cpd 229**).**



Step 1: To a solution of 2-methyl-5-(pyridin-2-ylmethoxy)-2H-indazole-3-carboxylic acid (500 mg, 1.767 mmol) in ACN (10 mL) were added phosphorus trichloride (0.5 mL) and amino-4,4-difluoro-2-methylbutanenitrile (600 mg, 3.534 mmol) at RT. The RM was stirred at 100 °C for 16 h in a sealed tube. After cooling to RT, the RM was basified with saturated $NaHCO_3$ (20 mL), extracted with EtOAc (2 x 20 mL). Combined organic layers were washed with sodium bicarbonate solution (20 mL), brine (20 mL), dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by FCC on silica gel using 70% EtOAc in pet. Ether as an eluent to afford N-(2-cyano-4,4-difluorobutan-2-yl)-2-methyl-5-(pyridin-2-ylmethoxy)-2H-indazole-3-carboxamide as a pale yellow gummy (250 mg, yield: 87.45%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.60 - 8.58 (m, 1 H), 7.75 - 7.70 (m, 2 H), 7.55 (d, 1 H), 7.27 - 7.24 (m, 1 H), 7.16 - 7.13 (m, 1 H), 6.90 (d, 1 H), 6.35 - 6.05 (m, 2 H), 5.28 (s, 2

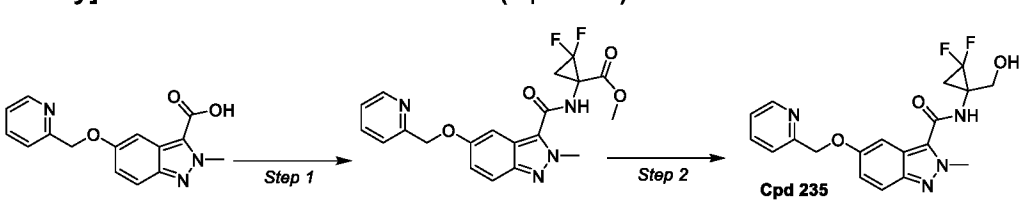
H), 4.42 (s, 3 H), 2.80 - 2.71 (m, 2 H), 1.78 (s, 3 H).

Step 2 : To a solution of N-(2-cyano-4,4-difluorobutan-2-yl)-2-methyl-5-(pyridin-2-ylmethoxy)-2H-indazole-3-carboxamide (250 mg, 0.626 mmol) in MeOH (25 mL) were added sodium borohydride (162.117 mg, 4.382 mmol) and nickel chloride hexahydrate (48.635 mg, 0.376 mmol) at RT. The RM was stirred at RT for 2 h. After completion, MeOH was removed under reduced pressure. The residue was diluted with ice cold water (20 mL), extracted with EtOAc (2 x 20 mL). The combined organic phases were washed with brine solution (20 mL), dried over Na_2SO_4, filtered and evaporated under reduced pressure to afford N-(1-amino-4,4-difluoro-2-methylbutan-2-yl)-2-methyl-5-(pyridin-2-ylmethoxy)-2H-indazole-3-carboxamide as a pale brown solid (260 mg). ^{1}H NMR (400 MHz, DMSO-D_6) δ ppm: 8.59 (d, 1 H), 7.72 - 7.67 (m, 2 H), 7.52 (d, 1 H), 7.14 (s, 1 H), 7.26 - 7.20 (m, 2 H), 7.15 (d, 1 H), 6.12 - 5.83 (m, 1 H), 5.29 (s, 2 H), 4.43 (t, 3 H), 4.13 - 4.09 (m, 1 H), 3.04 - 2.76 (m, 1 H), 2.73 - 2.63 (m, 1 H), 2.62 - 2.56 (m, 1 H), 2.53 - 2.32 (m, 1 H), 2.28 (s, 2 H), 1.27 (s, 3 H).

Step 3 : To a solution of N-(1-amino-4,4-difluoro-2-methylbutan-2-yl)-2-methyl-5-(pyridin-2-ylmethoxy)-2H-indazole-3-carboxamide (260 mg, 0.645 mmol) in THF/MeOH (1:1) (6.0 mL) were added paraformaldehyde (193 mg, 6.452 mmol), AcOH (0.074 mL, 1.290 mmol) and sodium cyanoborohydride (100 mg,1.613 mmol) at RT. The RM was stirred at RT for 16 h. After completion, the volatiles were removed under reduced pressure. The residue was diluted with ice cold water (20 mL), extracted with EtOAc (2 x 20 mL). The combined organic phases were washed with sodium bicarbonate solution (20 mL), brine (20 mL), dried over Na_2SO_4, filtered and evaporated under reduced pressure. The compound was purified by Prep. HPLC. [Prep. HPLC conditions: Mobile phase: 10mM ABC in Water, Mobile phase B: ACN, Column: LUNA C18 (250 x 21.2) mm, 5 µm, FLOW: 18 ml/min, Method: (T in min./ % of B 0/30,2/30,10/60,17/60,17.20/98,23/98,23.20/30,26/30, Solubility: ACN+Water+THF, Temperature: RT.] The desired fractions were evaporated and lyophilized to afford N-[1-(dimethylamino)-4,4-difluoro-2-methylbutan-2-yl]-2-methyl-5-[(pyridin-2-yl)methoxy]-2H-indazole-3-carboxamide (Cpd **229**) (70 mg).

[0319] A preparative chiral SFC was performed on the racemic mixture of **Cpd 229** to afford **Cpd 229 – En1 and Cpd 229 – En2.**

[0320] **Synthesis of N-[2,2-difluoro-1-(hydroxymethyl)cyclopropyl]-2-methyl-5-[(pyridin-2-yl)methoxy]-2H-indazole-3-carboxamide** (Cpd 235**).**



Step 1: To a solution of 2-methyl-5-(pyridin-2-ylmethoxy)-2H-indazole-3-carboxylic acid (500 mg, 1.765 mmol) in DMF (5.0 mL) were added HATU (1.342 g, 3.530 mmol), DIPEA (2.154 mL, 12.355 mmol) at RT and stirred for 10 min. After 10 min, methyl 1-amino-2,2-

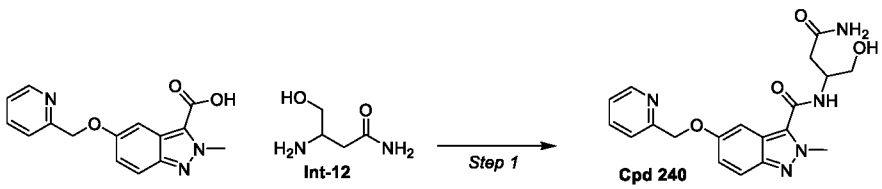
difluorocyclopropane-1-carboxylate hydrobromide (**Int-08**) (696.18 mg, 3.000 mmol) was added. The RM was stirred at RT for 24 h. After completion, the RM was diluted with ice-cold water (20 mL), extracted with EtOAc (2 x 30 mL). Combined organic layers were washed with saturated $NaHCO_3$ (20 mL), brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by FCC on silica gel using 3% MeOH in DCM as an eluent to afford methyl 2,2-difluoro-1-(2-methyl-5-(pyridin-2-ylmethoxy)-2H-indazole-3-carboxamido)cyclopropane-1-carboxylate as pale yellow solid (300 mg, 40.82%).

Step 2 : To a solution of methyl 2,2-difluoro-1-(2-methyl-5-(pyridin-2-ylmethoxy)-2H-indazole-3-carboxamido)cyclopropane-1-carboxylate (300 mg, 0.720 mmol) in ethanol (5.0 mL) was added $NaBH_4$ (81.70 mg, 2.161 mmol) portion wise at 0 °C. The RM was stirred at RT for 16 h. After completion, the RM was concentrated under reduced pressure and the obtained residue was diluted with water (30 mL) and extracted with DCM (2 x 30 mL). Organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure . The compound was purified by Prep. HPLC. [Prep. HPLC conditions: Mobile phase: 10mM ABC in Water, Mobile phase B: ACN, Column: YMC TRIART C18 (150X 25 mm), 10µm, FLOW: 20 ml/min, Method: (T in min./ % of B): 0/20, 2/20,10/40, 14.60/40,14.61/98, 18/98, 18.10/20, 21/20, Solubility: ACN+Water+THF, Temperature: RT.] The desired fractions were evaporated and lyophilized to afford N-[2,2-difluoro-1-(hydroxymethyl)cyclopropyl]-2-methyl-5-[(pyridin-2-yl)methoxy]-2H-indazole-3-carboxamide (Cpd 235) (140 mg, 50.03%).

[0321] A preparative chiral SFC was performed on the racemic mixture of **Cpd 235** to afford **Cpd 235 – En1 and Cpd 235 – En2**

The following compounds were prepared in a similar manner (use of appropriate reagents (chiral or racemic) and purification methods (including chiral HPLC or chiral SFC) known to the person skilled in the art) as described for **Cpd 235 – En1 and Cpd 235 – En2** : **Cpd 237 – En1, Cpd 237 – En2, Cpd 239 – En1, Cpd 239 – En2, Cpd 241 – En1, Cpd 241 – En2, Cpd 242, Cpd 243 – En1, Cpd 243 – En2, Cpd 251 – En1, Cpd 251 – En2, Cpd 252 – En1, Cpd 252 – En2**

[0322] **Synthesis of 4-hydroxy-3-({2-methyl-5-[(pyridin-2-yl)methoxy]-2H-indazol-3-yl}formamido)butanamide (**Cpd 240**).**

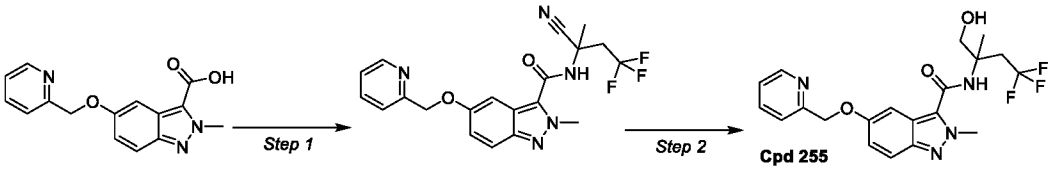


Step 1: To a solution of 2-methyl-5-(pyridin-2-ylmethoxy)-2H-indazole-3-carboxylic acid (0.35 g, 1.23 mmol) and 3-amino-4-hydroxybutanamide trifluoroacetic acid (Int-12) (0.657 g, 5.56 mmol) in DMF (14 mL) were added HATU (0.94 g, 2.47 mmol) and DIPEA (1.1 mL, 6.17 mmol) at 0 °C. The RM mixture was stirred at RT for 16 h under Nitrogen atmosphere.

After completion,, the RM was diluted with cold water (50 mL), extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with sat. sodium bicarbonate solution (20 mL), dried over Na_2SO_4, filtered and was concentrated under reduced pressure to afford the 2-methyl-N-(5-oxotetrahydrofuran-3-yl)-5-(pyridin-2-ylmethoxy)-2H-indazole-3-carboxamide. A solution of 2-methyl-N-(5-oxotetrahydrofuran-3-yl)-5-(pyridin-2-ylmethoxy)-2H-indazole-3-carboxamide (700 mg, 1.91 mmol) in Aqueous ammonia 25% (15 mL) was stirred at RT for 16 h. After completion, the RM was concentrated under reduced pressure. The compound was purified by Prep. HPLC. [Prep. HPLC conditions: Mobile phase: 10mM ABC in Water, Mobile phase B: ACN, Column: YMC Triant C18 (25X150):5µm, FLOW: 20 ml/min, Method: (T in min./ % of B): 0/30,2/30,8/45,17/45,17.10. /98,18/98,18.10/30,21/30, Solubility: ACN+Water+THF, Temperature: RT.] The desired fractions were evaporated and lyophilized to afford 4-hydroxy-3-({2-methyl-5-[(pyridin-2-yl)methoxy]-2H-indazol-3-yl}formamido)butanamide (Cpd 240) (120 mg, 16%).

[0323] A preparative chiral SFC was performed on the racemic mixture of **Cpd 240** to afford **Cpd 240 – En1 and Cpd 240 – En2**

[0324] **Synthesis of 2-methyl-5-[(pyridin-2-yl)methoxy]-N-(4,4,4-trifluoro-1-hydroxy-2-methylbutan-2-yl)-2H-indazole-3-carboxamide (**Cpd 255**).**



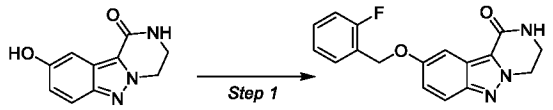
Step 1: To a solution of 2-methyl-5-(pyridin-2-ylmethoxy)-2H-indazole-3-carboxylic acid (200 mg, 0.706 mmol) in ACN (25 mL) was added 2-amino-4,4,4-trifluoro-2-methylbutanenitrile hydrochloride (Int-17) (265.4 mg, 1.412 mmol) and phosphorous trichloride (0.2 mL) at RT. The RM was stirred at 100 °C for 16 h in a sealed tube. After completion, the RM was diluted with ice cold water (15 mL), extracted with EtOAc (2 x 25 mL). The combined organic phases were washed with sat. sodium bicarbonate solution (25 mL), dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by FCC on silica gel using 25% EtOAc in pet ether as an eluent to afford N-(2-cyano-4,4,4-trifluorobutan-2-yl)-2-methyl-5-(pyridin-2-ylmethoxy)-2H-indazole-3-carboxamide (100 mg, 33.93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.59 (d, 1 H), 7.71 - 7.75 (m, 2 H), 7.53 (d, 1 H), 7.27 (t, 1 H), 7.16 (dd, 1 H), 6.88 (d, 1 H), 6.12 (s, 1H), 5.31 (s, 2 H), 4.43 (s, 3 H), 3.26 - 3.33 (m, 1 H), 3.04 - 3.10 (m, 1 H), 2.03 (s, 3 H).

Step 2 : To a solution of N-(2-cyano-4,4,4-trifluorobutan-2-yl)-2-methyl-5-(pyridin-2-ylmethoxy)-2H-indazole-3-carboxamide (300 mg, 0.719 mmol) in Toluene (20 mL), water (20 mL) were added paraformaldehyde (215.917 mg, 7.194 mmol) and [Ru(*p*-cymene)Cl_2]$_2$ (44.05 mg, 0.072 mmol) at RT . The RM was stirred at 90 °C for 16 h. After completion, the RM was cooled to RT and filtered on celite bed, washed with EtOAc (15 mL), extracted with EtOAc

(2 x 25 mL). The combined organic phases were washed with brine solution (25 mL), dried over Na_2SO_4, filtered and evaporated under reduced pressure. The compound was purified by Prep. HPLC. [Prep. HPLC conditions: Mobile phase: 10mM ABC in Water, Mobile phase B: ACN, Column: YMC TRIART C18 (150X 25 mm), 10µm, FLOW: 20 ml/min, Method: (T in min./ % of B): 0/60,2/60,10/60,13/60,13.2/100.18/100,18.10/40,22/40, Solubility: ACN+Water+THF, Temperature: RT.] The desired fractions were evaporated and lyophilized to afford 2-methyl-5-[(pyridin-2-yl)methoxy]-N-(4,4,4-trifluoro-1-hydroxy-2-methylbutan-2-yl)-2H-indazole-3-carboxamide (Cpd **255**) (150 mg, 49.36%).

[0325] A preparative chiral SFC was performed on the racemic mixture of **Cpd 255** to afford **Cpd 255 – En1 and Cpd 255 – En2**

[0326] **Synthesis of 9-[(2-fluorophenyl)methoxy]-1H,2H,3H,4H-pyrazino[1,2-b]indazol-1-one (**Cpd 256**).**

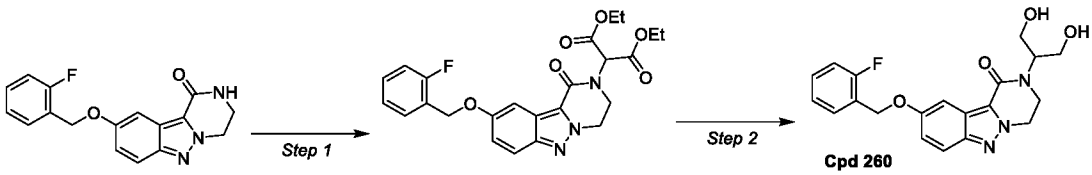


Int-18 Cpd 256

Step 1: To a solution of 9-hydroxy-3,4-dihydropyrazino[1,2-b]indazol-1(2H)-one (Int-18) (150 mg, 0.738 mmol) in DMF (10.0 mL) were added 1-(bromomethyl)-2-fluorobenzene (153.49 mg, 0.812 mmol) and potassium carbonate (306.075 mg, 2.215 mmol) at RT. The RM stirred at RT for 16 h. After completion, the RM was quenched with cold water (10 mL), extracted with 10% MeOH in DCM (3 x 10 mL), dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by FCC on silica gel using a gradient of 70 to 80% EtOAc in pet ether to afford 9-[(2-fluorophenyl)methoxy]-1H,2H,3H,4H-pyrazino[1,2-b]indazol-1-one (Cpd **256**) (115 mg, 50%).

The **Cpd 257** was prepared in a similar manner (use of appropriate reagents and purification methods known to the person skilled in the art) as described for **Cpd 256.**

[0327] **Synthesis of 2-(1,3-dihydroxypropan-2-yl)-9-[(2-fluorophenyl)methoxy]-1H,2H,3H,4H-pyrazino[1,2-b]indazol-1-one (**Cpd 260**).**



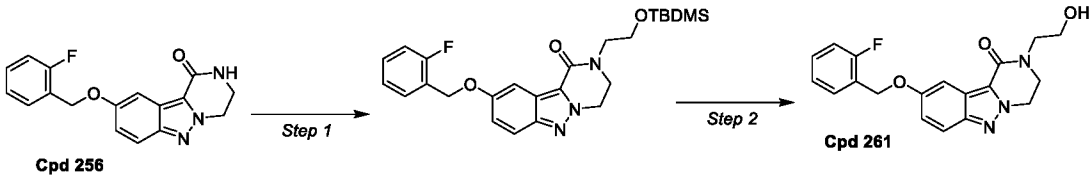
Cpd 256 Cpd 260

Step 1: To a solution of 9-[(2-fluorophenyl)methoxy]-1H,2H,3H,4H-pyrazino[1,2-b]indazol-1-one (Cpd **256**) (200 mg, 0.642 mmol) in DMF (5.0 mL) was added NaH (46.25 mg, 1.927 mmol) at 0 °C. The RM was stirred for 15 min at 0°C. Then diethyl 2-bromomalonate (230.375 mg, 0.964 mmol) in DMF (2 mL) was added at 0°C. The RM stirred at 60 °C for 16 h. After completion, the RM was quenched with cold water (10 mL), extracted with EtOAc (3 x 10 mL), dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by FCC on silica gel using a gradient of 70 to 80% EtOAc in pet ether to afford

diethyl 2-(9-((2-fluorobenzyl)oxy)-1-oxo-3,4-dihydropyrazino[1,2-b]indazol-2(1H)-yl)malonate as a solid (150 mg, 96%). ^{1}H NMR (400 MHz, DMSO-D_6) δ ppm: 7.67 (d, 1 H), 7.52 - 7.57 (m, 2 H), 7.30 - 7.34 (m, 1 H), 7.08 - 7.19 (m, 3 H), 6.22 (s, 1 H), 5.19 (s, 2 H), 4.69 - 4.72 (m, 2 H), 4.28 - 4.35 (m, 4 H), 4.12 - 4.15 (m, 2 H), 1.34 (t, 6 H).

Step 2 : To a solution of diethyl 2-(9-((2-fluorobenzyl)oxy)-1-oxo-3,4-dihydropyrazino[1,2-b]indazol-2(1H)-yl)malonate (150 mg, 0.320 mmol) in ethanol (20.0 mL) was added $NaBH_4$ (75.52 mg, 1.917 mmol) at 0 °C. The RM was stirred at RT for 20 h. After completion, the RM was quenched with cold water (3 mL), concentrated under reduced pressure. The residue was purified by FCC on silica gel using a gradient of 70 to 80% EtOAc in petroleum ether to afford 2-(1,3-dihydroxypropan-2-yl)-9-[(2-fluorophenyl)methoxy]-1H,2H,3H,4H-pyrazino[1,2-b]indazol-1-one (Cpd **260**) as an off white solid (83 mg, 55%).

[0328] **Synthesis of 9-[(2-fluorophenyl)methoxy]-2-(2-hydroxyethyl)-1H,2H,3H,4H-pyrazino[1,2-b]indazol-1-one (**Cpd 261**).**



Step 1: To a stirred solution of 9-[(2-fluorophenyl)methoxy]-1H,2H,3H,4H-pyrazino[1,2-b]indazol-1-one (Cpd **256**) (100 mg, 0.321 mmol) in DMF (6 mL) was added NaH (60 % dispersion in mineral oil, 15.4 mg, 0.642 mmol) at 0 °C. The RM wad stirred for 15 min at 0°C. Then, a solution of (2-bromoethoxy)(tert-butyl)dimethylsilane (115.2 mg, 0.482 mmol) in DMF (2 mL) was added at 0 °C. The RM was heated at 70 °C for 16 h. After completion, the RM was quenched with ice cold water (10 mL) and the obtained solid was filtered, washed with cold water (10 mL), n-pentane (10 mL) and dried under high vacuum to afford 2-(2-((tert-butyldimethylsilyl)oxy) ethyl)-9-((2-fluorobenzyl)oxy)-3,4-dihydropyrazino[1,2-b]indazol-1(2H)-one (90 mg, 60%) as an off white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.67 (d, 1 H), 7.56–-7.54 (m, 2 H), 7.33–7.31 (m, 1 H), 7.20-7.17 (m, 1 H), 7.16–7.07 (m, 2 H), 5.19 (s, 2 H), 4.62 (d, 2 H), 4.05-4.01 (m, 2 H), 3.91 (t, 2 H), 3.75 (t, 2 H), 0.88 (s, 9 H), 0.07 (s, 6 H).

Step 2 : To a stirred solution of Hydrogen fluoride-pyridine (65-70%, 0.298 mL, 1.703 mmol) in THF (3 mL) was added pyridine (0.386 mL, 1.703 mmol) at 0 °C. The RM was stirred for 10 min. Then, a solution of 2-(2-((tert-butyldimethylsilyl)oxy)ethyl)-9-((2-fluorobenzyl)oxy)-3,4-dihydropyrazino[1,2-b]indazol-1(2H)-one (80 mg, 0.170 mmol) in THF (1 mL) was added at 0 °C. The RM was stirred at RT for 16 h. After completion, the RM was concentrated under reduce pressure. The residue was diluted with water (1 mL), neutralized with saturated $NaHCO_3$ solution (pH ~7). The solid was filtered, washed with cold water (10 mL) followed by n-pentane, and then dried under high vacuum. The compound was purified by Prep. HPLC. The desired fractions were evaporated and lyophilized to afford 9-[(2-fluorophenyl)methoxy]-2-(2-hydroxyethyl)-1H,2H,3H,4H-pyrazino[1,2-b]indazol-1-one (Cpd **261**) (30 mg, 49%) as an off white solid.

[0329] *Analytical data*

Cpd Code	[M+H]+ (m/z) :	^{1}H NMR (δ ppm)
Cpd 001	417.2	(400MHz, DMSO) δ = 1.61-1.68 (m, 2H), 2.25 (d, J=14.4 Hz, 2H), 2.41 (s, 3H), 3.64 - 3.76 (m, 6H), 4.22 (s, 3H), 4.95 (s, 1H), 5.30 (s, 2H), 7.04 (dd, J=2.4.-9.6 Hz, 1H), 7.26 (d, J=2.0 Hz, 1H), 7.61 (d, J=9.2, 1H), 7.87 (s, 1H), 9.00 (s, 1H).
Cpd 002 - En1	387.2	(400 MHz, DMSO-d6) δ = 2.91 - 3.06 (m, 3H), 3.23 - 3.32 (m, 2H), 4.24 (s, 3H), 4.58 - 4.68 (m, 1H), 5.10 – 5.16 (m, 2H), 7.08 (dd, J = 2.4 Hz, J=2.4 Hz, 1H), 7.15-7.16 (m, 1H), 7.33-7.36 (m, 1H), 7.38 – 7.42 (m, 2H), 7.46 – 7.49 (m, 2H), 7.63 (d, J = 9.2 Hz, 1H), 8.62 (d, J = 8.4 Hz, 1H).
Cpd 002 - En2	387.2	(400 MHz, DMSO-d6) δ =2.91 – 3.06 (m, 3H), 3.27-3.32 (m, 2H), 4.24 (s, 3H), 4.60 - 4.68 (m, 1H), 5.10 – 5.16 (m, 2H), 7.09 – 7.10 (m, 1H), 7.15-7.16 (m, 1H), 7.33 – 7.36 (m, 1H), 7.38-7.39 (m, 2H), 7.46 – 7.49 (m, 2H), 7.63 (d, J = 9.2 Hz, 1H), 8.63 (d, J = 8.8 Hz, 1H).
Cpd 003 - En1	470.1	: (400 MHz, DMSO-d6) δ = 1.73 - 1.80 (m, 2H), 2.49 - 2.50 (m, 1H), 2.62 - 2.67 (m, 1H), 2.80-2.94 (m, 2H), 3.08-3.15 (m, 1H), 4.23 (s, 3H), 4.46-4.53 (m, 1H), 5.27-5.35 (m, 2H), 7.10-7.15 (m, 2H), 7.66 (d, J = 9.2 Hz, 1H), 7.77-7.80 (m, 1H), 8.27 (d, J = 8 Hz, 1H), 8.73-8.75 (m, 2H).
Cpd 003 - En2	470.1	(400 MHz, DMSO-d6) : δ = 1.73 - 1.83 (m, 2H), 2.49 - 2.51 (m, 1H), 2.59 - 2.67 (m, 1H), 2.80-2.94 (m, 2H), 3.07-3.15 (m, 1H), 4.23 (s, 3H), 4.45-4.55 (m, 1H), 5.27-5.35 (m, 2H), 7.10-7.15 (m, 2H), 7.66 (d, J = 9.2 Hz, 1H), 7.77-7.80 (m, 1H), 8.27 (d, J = 8 Hz, 1H), 8.73-8.75 (m, 2H).
Cpd 104	-	1H NMR (600 MHz, DMSO) d 8.588 (ddd, 1H), 8.536 (s, 1H), 7.843 (td, 1H), 7.581 (dd, 2H), 7.356 (ddd, 1H), 7.161 (d, 1H), 7.085 (dd, 1H), 5.237 (s, 2H), 4.798 (t, 1H), 4.224 (s, 3H), 3.594 (d, 2H), 0.815 (dt, 4H).
Cpd 120	-	1H NMR (600 MHz, DMSO) d 8.353 (d, 1H), 7.711 (s, 1H), 7.606 (dd, 1H), 7.139 (d, 1H), 7.025 (dd, 1H), 5.346 (s, 2H), 4.236 (s, 3H), 4.114 – 4.014 (m, 1H), 3.907 (ddd, 2H), 3.433 (td, 2H), 2.642 (s, 3H), 1.873 (ddt, 2H), 1.678 (dtd, 2H).
Cpd 122	-	(400 MHz, DMSO-d6) δ [ppm]: 13.5 (Br S, 1H),8.73 (d, 1H), 8.26 (d, 1H). 7.80-7.70 (m, 2H), 7.34 (d, 1H), 7.11 (d, 1H), 5.32 (s, 2H), 4.37 (s, 3H).
Cpd 123	287.2	(400 MHz, DMSO-d6) δ [ppm]: 13.11 (bs, 1H), 7.68-7.66 (d, 1H), 7.42-7.38 (d, 2H), 7.07-7.05 (d, 1H), 6.387 (s, 1H), 5.22 (s, 2H), 4.38 (s, 3H), 3.85 (s, 3H).

Cpd 124	-	1H NMR (600 MHz, DMSO) d 7.827 (s, 1H), 7.705 (s, 1H), 7.594 (d, 1H), 7.234 (d, 1H), 7.014 (dd, 1H), 5.313 (s, 2H), 4.934 (td, 1H), 4.213 (s, 3H), 3.761 – 3.706 (m, 2H), 3.691 (d, 2H), 3.660 (dd, 2H), 2.635 (s, 3H), 2.240 (d, 2H), 1.655 (ddd, 2H).
Cpd 125	-	1H NMR (600 MHz, DMSO) d 8.611 – 8.565 (m, 1H), 8.044 (d, 1H), 7.857 (td, 1H), 7.633 (dd, 2H), 7.512 (s, 1H), 7.436 (d, 1H), 7.363 (ddd, 1H), 7.218 (s, 1H), 7.122 (dd, 1H), 5.205 (s, 2H), 4.523 (dt, 1H), 4.278 (s, 3H), 3.813 (d, 2H).
Cpd 126	-	1H NMR (600 MHz, DMSO) d 8.066 (d, 1H), 7.757 (s, 1H), 7.618 (d, 1H), 7.585 (s, 1H), 7.427 (s, 1H), 7.229 (s, 1H), 7.020 (d, 1H), 5.334 (s, 2H), 4.539 (s, 1H), 4.271 (s, 3H), 3.820 (d, 2H), 2.628 (s, 3H).
Cpd 127	-	1H NMR (600 MHz, DMSO) d 8.587 (d, 1H), 7.850 (td, 1H), 7.623 (d, 1H), 7.587 (d, 1H), 7.394 – 7.334 (m, 2H), 7.232 (d, 1H), 7.099 (dd, 1H), 5.182 (s, 2H), 4.942 (t, 2H), 4.237 (s, 3H), 3.679 (dd, 2H), 3.606 (dd, 2H), 1.351 (s, 3H).
Cpd 128 - En1	-	1H NMR (600 MHz, DMSO) d 8.628 (d, 1H), 8.580 (ddd, 1H), 7.845 (td, 1H), 7.638 (d, 1H), 7.567 (dd, 1H), 7.354 (ddd, 1H), 7.188 – 7.085 (m, 2H), 5.181 (q, 2H), 4.515 (s, 1H), 4.229 (s, 3H), 3.152 (d, 1H), 2.952 (d, 1H), 2.876 (dd, 1H), 2.704 – 2.584 (m, 1H), 1.791 (ddd, 2H).
Cpd 128 - En2	-	1H NMR (600 MHz, DMSO) d 8.624 (d, 1H), 8.580 (ddd, 1H), 7.844 (td, 1H), 7.638 (d, 1H), 7.568 (d, 1H), 7.353 (ddd, 1H), 7.189 – 7.084 (m, 2H), 5.181 (q, 2H), 4.554 – 4.458 (m, 1H), 4.229 (s, 3H), 3.201 – 3.092 (m, 1H), 2.944 (d, 1H), 2.859 (dd, 1H), 2.634 (t, 1H), 1.877 – 1.714 (m, 2H).
Cpd 129	-	1H NMR (600 MHz, DMSO) d 7.597 – 7.547 (m, 1H), 7.350 (s, 1H), 7.120 (d, 1H), 6.976 (dd, 1H), 4.959 (td, 2H), 4.237 (s, 3H), 3.958 (d, 2H), 3.679 (dd, 2H), 3.596 (dd, 2H), 2.761 (h, 1H), 2.136 – 2.050 (m, 2H), 1.982 – 1.802 (m, 4H), 1.360 (s, 3H).
Cpd 130	-	1H NMR (600 MHz, DMSO) d 7.967 (d, 1H), 7.621 – 7.572 (m, 1H), 7.513 (s, 1H), 7.271 (d, 1H), 7.208 (s, 1H), 7.004 (dd, 1H), 5.037 (t, 1H), 4.513 (d, 1H), 4.266 (s, 3H), 4.033 – 3.953 (m, 2H), 3.800 (t, 2H), 2.854 – 2.699 (m, 1H), 2.139 – 2.050 (m, 2H), 1.982 – 1.799 (m, 4H).
Cpd 131	-	1H NMR (600 MHz, DMSO) d 7.607 (d, 1H), 7.411 (s, 1H), 7.267 (d, 1H), 7.208 (s, 1H), 7.015 (dd, 1H), 5.106 (s, 2H), 4.969 (tt, 2H), 4.244 (d, 3H), 3.696 (dd, 2H), 3.614 (dd, 2H), 2.419 (s, 3H), 1.372 (s, 3H).
Cpd 132 - En1	-	1H NMR (600 MHz, DMSO) d 9.001 (s, 1H), 8.837 (d, 1H), 7.651 (d, 1H), 7.169 (d, 1H), 7.082 (dd, 1H), 5.359 – 5.251 (m, 2H), 4.249 (s, 3H), 3.775 (s, 2H), 3.317 (s, 1H), 3.168 (s, 2H), 2.539 (s, 1H), 2.424 (s, 3H), 2.161 – 2.000 (m, 2H).

Cpd 132 - En2	-	1H NMR (600 MHz, DMSO) d 9.001 (s, 1H), 8.828 (d, 1H), 7.650 (d, 1H), 7.169 (d, 1H), 7.081 (dd, 1H), 5.359 – 5.241 (m, 2H), 4.833 (s, 1H), 4.248 (s, 3H), 3.786 (d, 1H), 3.459 – 3.266 (m, 2H), 2.424 (s, 3H), 2.176 – 1.963 (m, 4H).
Cpd 141	-	1H NMR (600 MHz, DMSO) d 8.020 (d, 1H), 7.630 (d, 1H), 7.541 (s, 1H), 7.437 (d, 1H), 7.254 (s, 1H), 7.247 – 7.203 (m, 1H), 7.037 (dd, 1H), 5.141 (s, 2H), 5.094 – 5.041 (m, 1H), 4.618 – 4.484 (m, 1H), 4.274 (d, 3H), 3.816 (t, 2H), 2.414 (d, 3H).
Cpd 142	-	1H NMR (600 MHz, DMSO) d 7.744 (d, 1H), 7.648 (d, 1H), 7.534 (s, 1H), 7.491 (d, 1H), 7.258 (s, 1H), 7.219 (s, 1H), 7.048 (dd, 1H), 5.132 (s, 2H), 4.434 (dd, 1H), 4.278 (s, 3H), 4.194 (qd, 1H), 2.409 (s, 3H), 1.187 (d, 3H).
Cpd 143	-	1H NMR (600 MHz, DMSO) d 7.963 (d, 1H), 7.596 (dd, 1H), 7.506 (s, 1H), 7.265 (d, 1H), 7.202 (s, 1H), 7.000 (dd, 1H), 5.024 (t, 1H), 4.508 (dt, 1H), 4.265 (s, 3H), 3.939 – 3.859 (m, 2H), 3.794 (t, 2H), 2.360 (dt, 1H), 1.800 (dq, 2H), 1.619 (tdd, 2H), 1.588 – 1.489 (m, 2H), 1.347 (ddd, 2H).
Cpd 144	-	1H NMR (600 MHz, DMSO) d 7.572 (d, 1H), 7.347 (s, 1H), 7.115 (d, 1H), 6.974 (dd, 1H), 4.236 (s, 3H), 3.861 (d, 2H), 3.673 (d, 2H), 3.591 (d, 2H), 2.354 (p, 1H), 1.842 – 1.747 (m, 2H), 1.655 – 1.581 (m, 2H), 1.609 – 1.512 (m, 2H), 1.398 – 1.308 (m, 2H), 1.356 (s, 3H).
Cpd 145	-	1H NMR (600 MHz, DMSO) d 8.168 (s, 1H), 7.598 (d, 1H), 7.407 (s, 1H), 7.199 – 7.143 (m, 2H), 7.001 (dd, 1H), 4.268 (s, 2H), 3.918 (d, 2H), 2.366 (p, 1H), 1.799 (ddd, 3H), 1.598 (s, 6H), 1.675 – 1.489 (m, 4H), 1.357 (dq, 2H).
Cpd 146	-	1H NMR (600 MHz, DMSO) d 7.644 – 7.598 (m, 1H), 7.381 (s, 1H), 7.125 (d, 1H), 7.059 (dd, 1H), 4.932 (t, 2H), 4.246 (s, 3H), 4.028 (s, 2H), 3.683 (dd, 2H), 3.595 (dd, 2H), 1.422 – 1.373 (m, 2H), 1.360 (s, 3H), 1.225 – 1.175 (m, 2H).
Cpd 147	-	1H NMR (600 MHz, DMSO) d 7.740 (s, 1H), 7.616 (d, 1H), 7.296 (d, 1H), 7.274 (s, 1H), 7.011 (dd, 1H), 5.286 (s, 2H), 4.890 (t, 1H), 4.259 (s, 3H), 3.769 (d, 6H), 2.635 (s, 3H).
Cpd 148	-	1H NMR (600 MHz, DMSO) d 8.024 (d, 1H), 7.643 (d, 1H), 7.508 (s, 1H), 7.273 (d, 1H), 7.202 (s, 1H), 7.082 (dd, 1H), 5.040 (d, 1H), 4.509 (dt, 1H), 4.272 (s, 3H), 4.066 (s, 2H), 3.798 (t, 2H), 1.448 – 1.354 (m, 2H), 1.219 – 1.165 (m, 2H).
Cpd 149	-	1H NMR (600 MHz, DMSO) d 7.765 (s, 1H), 7.721 (d, 1H), 7.645 (d, 1H), 7.524 (s, 1H), 7.486 (d, 1H), 7.219 (s, 1H), 7.041 (dd, 1H), 5.328 (s, 2H), 5.124 (d, 1H), 4.427 (dd, 1H), 4.277 (s, 3H), 4.196 (td, 1H), 2.626 (s, 3H), 1.186 (d, 3H).
Cpd 150	-	1H NMR (600 MHz, DMSO) d 8.610 (t, 1H), 7.722 (s, 1H), 7.638 (d, 1H), 7.263 (d, 1H), 7.046 (dd, 1H), 6.232 (tt, 1H), 5.344 (s, 2H), 4.275 (s, 3H), 3.789 (tdd, 2H), 2.642 (s, 3H).

Cpd 151 - En1	404.3	(400 MHz, DMSO-d6) δ [ppm]: 9.00 (s, 3H), 7.94 (s, 1H), 7.65-7.63 (d, 1H), 7.51 (s, 1H), 7.42 (s, 1H), 7.34 (s, 1H), 7.06-7.04 (d, 1H), 5.32 (s, 2H), 5.18-5.17 (t, 1H), 4.29 (s, 3H), 3.98-3.77 (m, 4H), 2.32 (s, 3H), 1.56 (m, 3H).
Cpd 151 - En2	404.3	(400 MHz, DMSO-d6) δ [ppm]: 9.00 (s, 3H), 7.94 (s, 1H), 7.65-7.63 (d, 1H), 7.51 (s, 1H), 7.42 (s, 1H), 7.34 (s, 1H), 7.06-7.04 (d, 1H), 5.32 (s, 2H), 5.18-5.17 (t, 1H), 4.29 (s, 3H), 3.98-3.77 (m, 4H), 2.32 (s, 3H), 1.56 (m, 3H).
Cpd 152	-	1H NMR (600 MHz, DMSO) d 8.612 – 8.545 (m, 2H), 7.855 (td, 1H), 7.636 (d, 1H), 7.598 (dt, 1H), 7.360 (ddd, 1H), 7.324 (d, 1H), 7.119 (dd, 1H), 5.220 (s, 2H), 4.770 – 4.678 (m, 2H), 4.269 (s, 3H), 3.543 (q, 2H), 3.503 – 3.398 (m, 3H), 3.193 (dt, 1H), 2.438 – 2.355 (m, 1H), 2.086 – 1.984 (m, 1H).
Cpd 153	-	1H NMR (600 MHz, DMSO) d 8.616 – 8.542 (m, 2H), 7.855 (td, 1H), 7.636 (d, 1H), 7.598 (dd, 1H), 7.392 – 7.302 (m, 2H), 7.119 (dd, 1H), 5.220 (s, 2H), 4.773 – 4.673 (m, 2H), 4.269 (s, 3H), 3.543 (q, 2H), 3.502 – 3.391 (m, 3H), 3.193 (dt, 1H), 2.441 – 2.351 (m, 1H), 2.035 (dq, 1H).
Cpd 154 - En1	387.2	(400 MHz, DMSO-d6) δ [ppm]: 7.96 (s, 1H), 7.66-7.64 (d, 1H), 7.54 (s, 1H), 7.46 (s, 1H), 7.37 (s, 2H), 7.08-7.06 (d, 2H), 5.31-5.17 (m, 3H), 4.29 (s, 3H), 4.02-3.98 (m, 1H), 3.82 (s, 3H), 3.78 (m, 1H), 1.57 (m, 3H).
Cpd 154 - En2	387.2	(400 MHz, DMSO-d6) δ [ppm]: 7.96 (s, 1H), 7.66-7.64 (d, 1H), 7.54 (s, 1H), 7.46 (s, 1H), 7.37 (s, 2H), 7.08-7.06 (d, 2H), 5.31-5.17 (m, 3H), 4.29 (s, 3H), 4.02-3.98 (m, 1H), 3.82 (s, 3H), 3.78 (m, 1H), 1.57 (m, 3H).
Cpd 155 - En1	387.2	(400 MHz, DMSO-d6) δ [ppm]: 7.95 (s, 1H), 7.67-7.65 (d, 1H), 7.63-7.61 (d, 1H), 7.42 (s, 1H), 7.03-7.00 (d, 1H), 6.37 (s, 1H), 5.17-5.16 (t, 1H), 5.01 (s, 2H), 4.29 (s, 3H), 3.98-3.97 (m, 1H), 3.83-3.79 (m, 4H), 1.57 (s, 3H).
Cpd 155 - En2	387.4	(400 MHz, DMSO-d6) δ [ppm]: 7.95 (s, 1H), 7.67-7.64 (d, 1H), 7.63-7.61 (d, 1H), 7.52 (s, 1H), 7.36 (s, 1H), 7.03-7.00 (d, 1H), 6.37 (s, 1H), 5.17-5.16 (t, 1H), 5.01 (s, 2H), 4.29 (s, 3H), 3.98-3.97 (m, 1H), 3.83-3.79 (m, 4H), 1.57 (s, 3H).
Cpd 156	387.3	(400 MHz, DMSO-d6) δ [ppm]: 7.97 (s, 1H), 7.85 (s, 1H), 7.62-7.53 (m, 3H), 7.39 (s, 1H), 6.99-6.96 (m, 1H), 5.22 (m, 1H), 4.99 (s, 2H), 4.28 (s, 3H), 4.05-4.01 (m, 1H), 3.81 (s, 3H), 1.57 (s, 3H).
Cpd 157 - En1	404.1	(400 MHz, DMSO-d6) δ [ppm]: 7.94 (s,1H), 7.76 (s, 1H), 7.65-7.62 (d, 1H),7.54(bs, 1H), 7.42-7.38 (m, 2H), 7.04-7.02 (d, 1H), 5.33 (s, 2H), 5.20 (s, 1H), 4.29 (s, 3H), 4.00-3.98 (d, 1H), 3.81-3.78 (d, 1H), 2.63 (s, 3H), 1.56 (s, 3H).
Cpd 157 - En2	404.1	(400 MHz, DMSO-d6) δ [ppm]: 7.94 (s,1H), 7.76 (s, 1H), 7.65-7.62 (d, 1H), 7.54 (bs, 1H), 7.42-7.38 (m, 2H), 7.04-7.02 (d, 1H), 5.33 (s, 2H), 5.19 (s, 1H), 4.29 (s, 3H), 4.00-3.98 (d, 1H), 3.81-3.78 (d, 1H), 2.63 (s, 3H), 1.56 (s, 3H).

Cpd 158 - En1	391	(400 MHz, DMSO-d6) δ [ppm]: 7.91 (s, 1H), 7.63-7.60 (m, 1H), 7.51 (s, 1H), 7.34 (s, 1H), 7.26 (s, 1H), 7.02-7.00 (d, 1H), 5.14 (t, 1H), 4.28 (s, 3H), 3.99-3.96 (m, 1H), 3.89-3.88 (m, 4H), 3.79-3.76 (m, 2H), 2.07 (m, 1H), 1.71-1.68 (d, 2H), 1.55 (s, 3H), 1.39-1.31 (m, 2H).
Cpd 158 - En2	391	(400 MHz, DMSO-d6) δ [ppm]: 7.91 (s, 1H), 7.63-7.60 (m, 1H), 7.51 (s, 1H), 7.34 (s, 1H), 7.26 (s, 1H), 7.02-7.00 (d, 1H), 5.14 (t, 1H), 4.28 (s, 3H), 3.99-3.96 (m, 1H), 3.89-3.88 (m, 4H), 3.79-3.76 (m, 2H), 2.06 (m, 1H), 1.71-1.68 (d, 2H), 1.55 (s, 3H), 1.39-1.31 (m, 2H).
Cpd 159 - En1	373.2	(400 MHz, DMSO-d6): δ 7.95 (s, 1H), 7.85 (s, 1H), 7.59 (d, 1H), 7.04 (d, 1H), 7.01 - 6.97 (dd, 1H), 5.29 (bs, 1H), 4.22 (s, 3H), 3.97 (d, 2H), 3.68 - 3.60 (m, 2H), 3.30 (s, 1H), 3.26 - 3.18 (m, 1H), 2.80 - 2.75 (m, 1H), 2.46 - 2.39 (m, 2H), 2.13 - 2.06 (m, 2H), 1.94 - 1.86 (m, 4H).
Cpd 159 - En2	373.2	(400 MHz, DMSO-d6): δ 8.50 (s, 1H), 7.99 (s, 1H), 7.84 (s, 1H), 7.59 (d, 1H), 7.04 (d, 1H), 7.00 (dd, 1H), 5.36 (bs, 1H), 4.22 (s, 3H), 3.97 (d, 2H), 3.68 - 3.61 (m, 2H), 3.31 (s, 1H), 3.25 - 3.20 (m, 1H), 2.81 - 2.66 (m, 1H), 2.46 - 2.38 (m, 2H), 2.12 - 2.06 (m, 2H), 1.96 - 1.88 (m, 4H).
Cpd 160 - En1	404.1	(400 MHz, DMSO-d6) δ [ppm]: 7.96 (s, 1H), 7.62-7.52 (m, 3H), 7.40-7.37 (d, 2H), 7.04-7.02 (d, 1H), 5.18-5.10 (m, 3H), 4.26 (s, 3H), 3.98-3.77 (m, 2H), 2.64 (s, 3H), 1.54 (s, 3H).
Cpd 160 - En2	404.2	(400 MHz, DMSO-d6) δ [ppm]: 7.93 (s, 1H), 7.64-7.55 (m, 3H), 7.42-7.40 (m, 2H), 7.07-7.05 (d, 1H), 5.19-5.17 (m, 3H), 4.29 (s, 3H), 4.01-3.77 (m, 2H), 2.66 (s, 3H), 1.57 (s, 3H).
Cpd 161 - En1	359.2	(500 MHz, DMSO-d6): δ 7.95 (s, 1H), 7.83 (s, 1H), 7.60-7.58 (m, 1H), 7.02-7.00 (m, 2H), 5.38 (bs, 1H), 4.22 (s, 3H), 3.84 (d, 2H), 3.67-3.59 (m, 2H), 3.31 (s, 1H), 3.25-3.19 (m, 2H), 1.29-1.23 (m, 1H), 0.61-0.53 (m, 2H), 0.37-0.35 (m, 2H).
Cpd 161 - En2	359.2	(400 MHz, DMSO-d6): δ 7.91- 7.83 (m, 2H), 7.61-7.57 (m, 1H), 7.02-7.00 (m, 2H), 5.27 (bs, 1H), 4.22 (s, 3H), 3.84 (d, 2H), 3.67-3.59 (m, 2H), 3.31 -3.18 (m, 2H), 2.50-2.32 (m, 2H), 1.29-1.24 (m, 1H), 0.62-052 (m, 2H),0.35 (d, 2H).
Cpd 162 - En1	384.2	(400 MHz, DMSO-d6) δ [ppm]: 8.59-8.58(d, 1H), 7.94(s, 1H), 7.87-7.84 (m, 1H), 7.67-7.62 (d, 2H), 7.51-(s, 2H), 7.40-7.37 (m, 3H), 7.14-7.11 (d, 1H), 5.19-5.17 (m, 3H), 4.28 (m, 3H), 4.04-3.96 (m, 1H), 3.81-3.77 (m, 1H), 1.55 (s, 3H).
Cpd 162 - En2	384.2	(400 MHz, DMSO-d6) δ [ppm]: 8.59-8.58(d, 1H), 7.94(s, 1H), 7.87-7.84 (m, 1H), 7.67-7.62 (d, 2H), 7.51-(s, 1H), 7.40-7.36 (m, 3H), 7.13-7.11 (d, 1H), 5.19-5.17 (m, 3H), 4.28 (m, 3H), 4.04-3.96 (m, 1H), 3.81-3.77 (m, 1H), 1.55 (s, 3H).

Cpd 163 - En1	414.1	(400 MHz, DMSO-d6): δ 9.0 (s, 1H), 8.02 (s, 1H), 7.83 (s, 1H), 7.62 (d, 1H), 7.19 (d, 1H), 7.05 (dd, 1H), 5.32 (s, 2H), 5.27 (s, 1H), 4.23 (s, 3H), 3.70 - 3.62 (m, 2H), 3.35 - 3.32 (m, 1H), 3.26 - 3.20 (m, 1H), 2.51 - 2.43 (m, 5H)
Cpd 163 - En2	414.1	(400 MHz, DMSO-d6): δ 9.01 (s, 1H), 8.04 (s, 1H), 7.83 (s, 1H), 7.63 (d, 1H), 7.20 (d, 1H), 7.06 (dd, 1H), 5.33 (s, 3H), 4.23 (s, 3H), 3.70 - 3.62 (m, 2H), 3.32 (s, 1H), 3.25 - 3.21 (m, 1H), 2.46 - 2.42 (m, 5H).
Cpd 164 - En1	410.2	(400 MHz, DMSO-d6): δ 8.67 (s, 1H), 8.56 (d, 1H), 7.78 (dd, 1H), 7.62 (d, 1H), 7.30 - 7.14 (m, 4H), 7.07 (dd, 1H), 5.15 (s, 2H), 4.24 (s, 3H), 4.17 (d, 1H), 4.02 (d, 1H), 3.90 (t, 2H), 2.47 (s, 3H), 2.43 - 2.38 (m, 2H).
Cpd 164 - En2	410.2	(400 MHz, DMSO-d6): δ 8.68 (s, 1H), 8.56 (d, 1H), 7.78 (dd, 1H), 7.62 (d, 1H), 7.30 - 7.26 (m, 2H), 7.21 (d, 1H), 7.14 (bs, 1H),7.07 (dd, 1H), 5.15 (s, 2H), 4.24 (s, 3H), 4.17 (d, 1H), 4.02 (d, 1H), 3.90 (t, 2H), 2.47 (s, 3H), 2.41 - 2.38 (m, 2H).
Cpd 165 - En1	359.2	(400 MHz, DMSO-d6): δ 8.69 (s, 1H), 7.59 (d, 1H), 7.29 (bs, 1H), 7.13 (bs, 1H), 7.06 (d, 1H), 7.01 (dd, 1H), 4.23 (s, 3H), 4.15 (d, 1H), 4.00 (d, 1H), 3.92 - 3.84 (m, 4H), 2.45 - 2.32 (m, 2H), 1.32 - 1.25 (m, 1H), 0.63 - 0.56 (m, 2H),0.36 - 0.33 (m, 2H).
Cpd 165 - En2	359.2	(400 MHz, DMSO-d6): δ 8.72 (s, 1H), 7.59 (d, 1H), 7.31 (bs, 1H), 7.13 (s, 1H), 7.06 - 7.00 (m, 2H), 4.23 (s, 3H), 4.15 (d, 1H), 4.01 (d, 1H), 3.93 - 3.82 (m, 4H), 2.46 - 2.32 (m, 2H), 1.33 - 1.22 (m, 1H), 0.62 - 0.56 (m, 2H), 0.37 - 0.31(m, 2H)
Cpd 166 - En1	413.2	(400 MHz, DMSO-d6): δ 8.72 (s, 1H), 7.64 - 7.56 (m, 2H), 7.46 - 7.40 (m, 1H), 7.30 - 7.23 (m, 4H), 7.14 (bs, 1H), 7.06 (dd, 1H), 5.20 (s, 2H), 4.24 (s, 3H), 4.18 (d, 1H), 4.01 (d, 1H), 3.92 - 3.86 (m, 2H), 2.44-2.35 (m, 2H).
Cpd 166 - En2	413.2	(400 MHz, DMSO-d6): δ 8.72 (s, 1H), 7.64 - 7.56 (m, 2H), 7.47 - 7.40 (m, 1H), 7.30 - 7.23 (m, 4H), 7.14 (bs, 1H), 7.06 (dd, 1H), 5.20 (s, 2H), 4.24 (s, 3H), 4.18 (d, 1H), 4.01 (d, 1H), 3.92 - 3.86 (m, 2H), 2.44-2.35 (m, 2H)
Cpd 167 - En1	363.1	1H-NMR (400 MHz, DMSO-d6) δ [ppm]: 7.93 (s, 1H), 7.64-7.62 (d, 1H), 7.52 (s, 1H), 7.35 (s, 1H), 7.32-7.31 (s, 1H), 7.04-7.01 (d, 1H), 5.19 (s, 1H), 4.75-4.72 (m, 2H), 4.46-4.43 (t, 2H), 4.29 (s, 3H), 4.25-4.23 (d, 2H), 3.98-3.96 (d, 1H), 3.80-3.77 (d, 1H), 3.47-3.42 (m, 1H), 1.56 (s, 3H).
Cpd 167 - En2	363.1	1H-NMR (400 MHz, DMSO-d6) δ [ppm]: 7.94 (s, 1H), 7.64-7.62 (d, 1H), 7.51 (s, 1H), 7.34-7.31 (m, 2H), 7.04-7.01 (d, 1H), 5.21 (s, 1H), 4.75-4.72 (m, 2H), 4.46-4.43 (t, 2H), 4.29 (s, 3H), 4.25-4.23 (d, 2H), 3.99-3.96 (d, 1H), 3.80-3.77 (d, 1H), 3.47-3.44 (m, 1H), 1.56 (s, 3H).
Cpd 168 - En1	396.2	(400 MHz, DMSO-d6): δ 8.69 (d, 2H), 8.56 (d, 1H), 7.91 (d, 1H), 7.63 (d, 1H), 7.46 - 7.42 (m, 1H), 7.27 - 7.22 (m, 2H), 7.15 - 7.07 (m, 2H) 5.21 (s, 2H), 4.24 (s, 3H), 4.17 (d, 1H), 4.02 (d, 1H), 3.90 (t, 2H), 2.42 - 2.37 (m,2H)

Cpd 168 - En2	396.2	(400 MHz, DMSO-d6): δ 8.70 (s, 2H), 8.56 (d, 1H), 7.91 (d, 1H), 7.63 (d, 1H), 7.46 - 7.42 (m, 1H), 7.29 - 7.22 (m, 2H), 7.15 - 7.07 (m, 2H), 5.21 (s, 2H), 4.24 (s, 3H), 4.17 (d, 1H), 4.02 (d, 1H), 3.90 (t, 2H), 2.42 - 2.37 (m,2H).
Cpd 169 - En1	410.2	(400 MHz, DMSO-d6): δ 8.56 (d, 1H), 7.97 (bs, 1H), 7.84 (bs, 1H), 7.80 (dd, 1H), 7.62 (d, 1H), 7.29 (d, 1H), 7.18 (d, 1H), 7.06 (dd, 1H), 5.28 (bs, 1H), 5.12 (s, 2H), 4.23 (s, 3H), 3.67 - 3.65 (m, 2H), 3.36 (s, 1H), 3.31 - 3.24 (m, 1H), 2.47 - 2.43 (m, 5H).
Cpd 169 - En2	410.2	(400 MHz, DMSO-d6): δ 8.56 (d, 1H), 7.97 (bs, 1H), 7.84 (bs, 1H), 7.80 (dd, 1H), 7.62 (d, 1H), 7.29 (d, 1H), 7.18 (d, 1H), 7.06 (dd, 1H), 5.28 (bs, 1H), 5.12 (s, 2H), 4.23 (s, 3H), 3.70 - 3.61 (m, 2H), 3.35 (s, 1H), 3.26 - 3.19 (m, 1H), 2.46 - 2.38 (m, 5H).
Cpd 170 - En1	416.2	1HNMR (400 MHz, DMSO-d6): δ 9.01 (s, 1H), 8.71 (s, 1H), 7.63 (d, 1H), 7.30 - 7.24 (m, 2H), 7.14 (bs, 1H), 7.05 (dd, 1H), 5.35 (s, 2H), 4.24 (s, 3H), 4.19 (d, 1H), 4.02 (d, 1H), 3.93 - 3.87 (m, 2H), 2.44 - 2.36 (m, 5H).
Cpd 170 - En2	416.2	(400 MHz, DMSO-d6): δ 9.01 (s, 1H), 8.73 (s, 1H), 7.62 (d, 1H), 7.29 - 7.25 (m, 2H), 7.14 (bs, 1H), 7.05 (dd, 1H), 5.35 (s, 2H), 4.24 (s, 3H), 4.19 (d, 1H), 4.02 (d, 1H), 3.93 - 3.88 (m, 2H), 2.44 - 2.37 (m, 5H),
Cpd 171 - En1	413.2	(400 MHz, DMSO-d6): δ 8.00 (s, 1H), 7.83 (s, 1H), 7.64 - 7.60 (m, 2H), 7.47 - 7.40 (m, 1H), 7.30 - 7.22 (m, 2H), 7.21 (d, 1H), 7.06 (dd, 1H), 5.24 (t, 1H), 5.16 (s, 2H), 4.23 (s, 3H), 3.71 - 3.61 (m, 2H), 3.37 - 3.35 (m, 1H), 3.27 - 3.20 (m, 1H), 2.47 - 2.40 (m, 2H).
Cpd 171 - En2	413.2	(400 MHz, DMSO-d6): δ 8.02 (s, 1H), 7.83 (s, 1H), 7.64 - 7.60 (m, 2H), 7.47 - 7.40 (m, 1H), 7.30 - 7.22 (m, 2H), 7.21 (d, 1H), 7.06 (dd, 1H), 5.24 (t, 1H), 5.16 (s, 2H), 4.23 (s, 3H), 3.71 - 3.61 (m, 2H), 3.37 - 3.35 (m, 1H), 3.27 - 3.20 (m, 1H), 2.47 - 2.40 (m, 2H).
Cpd 172 - En1	307.2	(400 MHz, DMSO-d6): δ 7.95 (bs, 2H), 7.62 (d, 1H), 7.53 (bs, 1H), 7.35 (bs, 1H), 7.29 (d, 1H), 7.01 (dd, 1H), 5.16 (bs, 1H), 4.29 (s, 3H), 3.99 (d, 1H), 3.82 (s, 4H), 1.56 (s, 3H)
Cpd 172 - En2	307.2	(400 MHz, DMSO-d6): δ 7.95 (bs, 2H), 7.62 (d, 1H), 7.53 (bs, 1H), 7.35 (bs, 1H), 7.28 (d, 1H), 7.01 (dd, 1H), 5.17 (bs, 1H), 4.29 (s, 3H), 3.99 (d, 1H), 3.82 (s, 4H), 1.56 (s, 3H).
Cpd 173 - En1	361.3	(400 MHz, DMSO-d6): δ 7.91 (s, 1H), 7.61 (d, 1H), 7.51 (bs, 1H), 7.35 (bs, 1H), 7.26 (d, 1H), 7.00 (dd, 1H), 5.15 (t, 1H), 4.28 (s,3H), 4.01 - 3.95 (m, 3H), 3.85 - 3.74 (m, 1H), 2.81 - 2.73 (m, 1H), 2.13 - 2.05 (m, 2H), 1.95 - 1.82 (m, 4H), 1.56 (s,3H),1.23 (s, 1H).
Cpd 173 - En2	361.3	(400 MHz, DMSO-d6): δ 7.91 (s, 1H), 7.61 (d, 1H), 7.51 (bs, 1H), 7.34 (s, 1H),7.26 (d, 1H), 7.00 (dd,1H), 5.16 (t, 1H), 4.28 (s,3H), 3.98 (d, 3H), 3.82 - 3.75 (m, 1H), 2.81 - 2.75 (m, 1H), 2.13 - 2.05 (m, 2H), 1.96 -1.82 (m, 4H), 1.56 (s,3H),1.23 (s, 1H).

Cpd 174 - En1	398.2	(400 MHz, DMSO-d6): δ 8.56 (d, 1H), 7.94 (s, 1H), 7.80 (dd, 1H), 7.64 (d, 1H), 7.53 (bs, 1H), 7.43 - 7.36 (m, 2H), 7.28 (d, 1H), 7.06 (dd, 1H), 5.21 - 5.12 (m, 3H), 4.29 (s, 3H), 4.02 - 3.96 (m, 1H), 3.83 - 3.77 (m, 1H), 2.47 (s, 3H), 1.56 (s, 3H).
Cpd 174 - En2	398.2	(400 MHz, DMSO-d6): δ 8.56 (d, 1H), 7.94 (s, 1H), 7.80 (dd, 1H), 7.64 (d, 1H), 7.53 (bs, 1H), 7.43 - 7.36 (m, 2H), 7.28 (d, 1H), 7.06 (dd, 1H), 5.18 (t, 1H), 5.13 (s, 2H), 4.29 (s, 3H), 4.02 - 3.96 (m, 1H), 3.83 - 3.77 (m, 1H), 2.47 (s, 3H), 1.56 (s, 3H).
Cpd 175 - En1	445.2	(400 MHz, DMSO-d6): δ 8.72 (bs, 1H), 7.69 - 7.50 (m, 5H), 7.39 - 7.07 (m, 5H), 5.33 (s, 2H), 4.24 (s, 3H), 4.18 (d, 1H), 4.01 (d, 1H), 3.89 - 3.85 (m, 2H), 2.41 - 2.37 (m, 2H).
Cpd 175 - En2	445.2	(400 MHz, DMSO-d6): δ 8.73 (bs, 1H), 7.69 - 7.50 (m, 5H), 7.39 - 7.07 (m, 5H), 5.33 (s, 2H), 4.24 (s, 3H), 4.18 (d, 1H), 4.01 (d, 1H), 3.91 - 3.85 (m, 2H), 2.41 - 2.37 (m, 2H).
Cpd 176 - En1	445.2	(400 MHz, DMSO-d6): δ 8.02 (bs, 1H), 7.83 (bs, 1H), 7.70 - 7.64 (m, 2H), 7.62 - 7.60 (m, 1H), 7.59 - 7.54 (m, 1H), 7.52 - 7.51 (m, 1H), 7.40 - 7.13 (m, 2H), 7.07 (dd, 1H), 5.30 (s, 3H), 4.23 (s, 3H),3.66 - 3.64 (m, 2H), 3.31 (s, 1H), 3.24 - 3.22 (m, 1H), 2.46 - 2.42 (m, 2H).
Cpd 176 - En2	445.2	(400 MHz, DMSO-d6): δ 8.00 (bs, 1H), 7.83 (bs, 1H), 7.70 - 7.51 (m, 5H), 7.40 - 7.11 (m, 2H), 7.07 (dd, 1H), 5.30 (s, 3H), 5.26 - 5.23 (m, 1H), 4.23 (s, 3H), 3.67- 3.64 (m, 2H), 3.31 (s, 1H),3.24 - 3.22 (m, 1H), 2.46 - 2.42 (m, 2H).
Cpd 177 - En1	464.2	(400 MHz, DMSO-d6): δ 8.74 (d, 1H), 8.29 (d, 1H), 8.06 (s, 1H), 7.84 - 7.82 (m, 2H), 7.65 (d, 1H), 7.16 (d, 1H), 7.14 - 7.05 (m, 1H), 5.33 (s, 3H), 5.21 (m, 1H), 4.23 (s, 3H), 3.64 (d, 2H), 3.34 (s, 1H), 3.22 - 3.20 (m, 1H), 2.54 - 2.40 (m, 2H).
Cpd 177 - En2	464.2	(400 MHz, DMSO-d6): δ 8.74 (d, 1H), 8.29 (d, 1H), 8.05 (s, 1H), 7.84 - 7.76 (m, 2H), 7.65 (d, 1H), 7.16 (d, 1H), 7.14 - 7.05 (m, 1H), 5.33 (s, 3H), 5.19 (m, 1H), 4.23 (s, 3H), 3.64 (d, 2H), 3.31(s, 1H), 3.21 (m, 1H), 2.50 (m,2H).
Cpd 178 - En1	464.2	(400 MHz, DMSO-d6): δ 8.79 - 8.70 (m, 2H), 8.28 (d, 1H), 7.84 - 7.86 (m, 1H), 7.66 (d, 1H), 7.28 (s, 1H), 7.20 (d, 1H), 7.16 - 7.08 (m, 2H), 5.36 (s, 2H), 4.25 (s, 3H), 4.17 (d, 1H), 4.0 (d, 1H), 3.92 - 3.80 (m, 2H), 2.45 - 2.30 (m, 2H).
Cpd 178 - En2	464.2	(400 MHz, DMSO-d6): δ 8.75- 8.70 (m, 2H), 8.28 (d, 1H), 7.85 - 7.80 (m, 1H), 7.66 (d, 1H), 7.27 (s, 1H), 7.20 (d, 1H), 7.14 - 7.08 (m, 2H), 5.36 (s, 2H), 4.30 (s,3H), 4.28 - 4.14 (m, 1H), 4.0 (d, 1H), 3.93 - 3.80 (m, 2H), 2.58 - 2.30 (m, 2H)
Cpd 179 - En1	388.1	(400 MHz, DMSO-d6) δ [ppm]: 7.95 (s, 1H), 7.66-7.64 (d, 1H), 7.54 (s, 1H), 7.41-7.37 (m, 2H), 7.24 (s, 1H), 7.05-7.03 (d, 1H), 5.19-5.13 (m, 3H), 4.29 (s, 3H), 4.02-3.78 (m, 2H), 3.41 (s, 3H), 1.57 (s, 3H).

Cpd 179 - En2	388.2	(400 MHz, DMSO-d6) δ [ppm]: 7.95 (s, 1H), 7.66-7.64 (d, 1H), 7.54 (s, 1H), 7.41-7.37 (m, 2H), 7.24 (s, 1H), 7.05-7.03 (d, 1H), 5.19-5.13 (m, 3H), 4.29 (s, 3H), 4.02-3.78 (m, 2H), 3.41 (s, 3H), 1.57 (s, 3H).
Cpd 180 - En1	396.2	(400 MHz, DMSO-d6): δ 8.72 (d, 1H), 8.56 (dd, 1H), 8.02 (bs, 1H), 7.95 - 7.90 (m, 1H), 7.84 (bs, 1H), 7.63 (d, 1H), 7.46 - 7.41 (m, 1H), 7.19 (d, 1H), 7.08 (dd, 1H), 5.34 (bs, 1H), 5.18 (s, 2H), 4.23 (s, 3H), 3.71 - 3.61 (m, 2H), 3.26 - 3.22 (m, 2H), 2.52 – 2.48 (m, 1H).
Cpd 180 - En2	396.2	(400 MHz, DMSO-d6): δ 8.72 (d, 1H), 8.56 (dd, 1H), 8.04 (bs, 1H), 7.95 - 7.91 (m, 1H), 7.84 (bs, 1H), 7.63 (d, 1H), 7.46 - 7.41 (m, 1H), 7.18 (d, 1H), 7.08 (dd, 1H), 5.34 (bs, 1H), 5.18 (s, 2H), 4.23 (s, 3H), 3.71 - 3.61 (m, 2H), 3.26 - 3.22 (m, 2H), 2.46 – 2.42 (m, 1H).
Cpd 181 - En1	398.2	(400 MHz, DMSO-d6) δ [ppm]: 8.42 (s, 1H), 7.95 (s, 1H), 7.67-7.64 (d, 2H), 7.51-7.49 (d, 2H), 7.40-7.37 (d, 2H), 7.11-7.08 (d, 3H), 5.14 (m, 3H), 4.28 (s, 3H), 3.99-3.78 (m, 2H), 3.156 (s, 1H), 2.312 (s, 3H), 1.55 (s, 3H).
Cpd 181 - En2	398.2	(400 MHz, DMSO-d6) δ [ppm]: 8.42 (s, 1H), 7.95 (s, 1H), 7.67-7.64 (d, 2H), 7.51-7.49 (d, 2H), 7.40-7.37 (d, 2H), 7.11-7.08 (d, 3H), 5.14 (m, 3H), 4.28 (s, 3H), 3.99-3.78 (m, 2H), 3.156 (s, 1H), 2.312 (s, 3H), 1.55 (s, 3H).
Cpd 182 - En1	425.2	(400 MHz, DMSO-d6): δ 9.00 (s, 1H), 7.86 (s, 1H), 7.60 (d, 1H), 7.21 (d, 1H), 7.02 (dd, 1H), 6.28 (tt, 1H), 5.30 - 5.25 (m, 3H), 4.22 (s, 3H), 3.71 - 3.58 (m, 2H), 2.62 - 2.54 (m, 1H), 2.44 - 2.32 (m, 4H), 1.44 (s, 3H).
Cpd 182 - En2	425.2	(400 MHz, DMSO-d6): δ 9.00 (s, 1H), 7.86 (s, 1H), 7.60 (d, 1H), 7.21 (d, 1H), 7.02 (dd, 1H), 6.28 (tt, 1H), 5.30 (s, 2H), 5.24 (t, 1H), 4.22 (s, 3H), 3.71 - 3.58 (m, 2H), 2.63 - 2.57 (m, 1H), 2.43 - 2.30 (m, 4H), 1.44 (s, 3H),
Cpd 183 - En1	478.2	(400 MHz, DMSO-d6): δ 8.74 (s, 2H), 8.28 (d, 1H), 7.82 - 7.73 (m, 2H), 7.66 (d, 1H), 7.19 (d, 1H), 7.11 (dd, 1H), 5.37 (s, 2H), 4.24 (s, 3H), 4.14 (d, 1H), 4.02 (d, 1H), 3.94 - 3.81 (m, 2H), 2.62 (d, 3H), 2.45 - 2.30 (m, 2H).
Cpd 183 - En2	478.2	(400 MHz, DMSO-d6): δ 8.74 (d, 2H), 8.28 (d, 1H), 7.82 - 7.77 (m, 1H), 7.76 - 7.73 (m, 1H), 7.66 (d, 1H), 7.19 (d, 1H), 7.12 (dd, 1H), 5.37 (s, 2H), 4.24 (s, 3H), 4.13 (d, 1H), 4.02 (d, 1H), 3.96 - 3.82 (m, 2H), 2.64 (s, 3H), 2.42 - 2.33 (m, 2H).
Cpd 184 - En1	430.1	(400 MHz, DMSO-d6): δ 9.00 (s, 1H), 8.55 (s, 1H), 7.62 (d, 1H), 7.29 (s, 1H), 7.04 (dd, 1H), 5.31 (s, 2H), 5.06 (t, 1H), 4.23 (s, 3H), 3.91 - 3.87 (m, 1H), 3.73 - 3.69 (m, 1H), 2.96 (bs, 6H), 2.43 (s, 3H), 1.50 (s, 3H)
Cpd 184 - En2	430.1	(400 MHz, DMSO-d6): δ 9.00 (s, 1H), 8.54 (s, 1H), 7.62 (d, 1H), 7.29 (s, 1H), 7.04 (dd, 1H), 5.31 (s, 2H), 5.05 (s, 1H), 4.23 (s, 3H), 3.90 (d, 1H), 3.71 (d, 1H), 2.96 (s, 6H), 2.43 (s, 3H), 1.50 (s, 3H).
Cpd 185 - En1	418.2	(400 MHz, DMSO-d6): δ 9.00 (s, 1H), 7.90 - 7.86 (m, 2H), 7.65 (d, 1H), 7.39 (d, 1H), 7.06 (dd, 1H), 5.34 (s, 2H), 5.22 (t, 1H), 4.28 (s, 3H), 3.90 - 3.86 (m, 1H), 3.79 - 3.74 (m, 1H), 2.65 (d, 3H), 2.43 (s, 3H), 1.56 (s, 3H),

Cpd 185 - En2	418.2	(400 MHz, DMSO-d6): δ 9.00 (s, 1H), 7.91 - 7.86 (m, 2H), 7.65 (d, 1H), 7.39 (d, 1H), 7.06 (dd, 1H), 5.34 (s, 2H), 5.23 (t, 1H), 4.28 (s, 3H), 3.90 - 3.86 (m, 1H), 3.79 - 3.74 (m, 1H), 2.65 (d, 3H), 2.43 (s, 3H), 1.56 (s, 3H),
Cpd 186 - En1	492.2	(400 MHz, DMSO-d6): δ 9.15 (s, 1H), 8.74 (d, 1H), 8.26 (d, 1H), 7.82 - 7.77 (m, 1H), 7.68 (d, 1H), 7.14 (dd, 1H), 7.07 (s, 1H), 5.36 (s, 2H), 4.32 (d, 1H), 4.20 (s, 3H), 3.96 (d, 1H), 3.92 - 3.82 (m, 2H), 2.96 - 2.83 (brm, 6H), 2.44-2.37 (m, 2H).
Cpd 186 - En2	492.2	(400 MHz, DMSO-d6): δ 9.15 (s, 1H), 8.73 (d, 1H), 8.26 (d, 1H), 7.81 - 7.78 (m, 1H), 7.68 (d, 1H), 7.12 (dd, 1H), 7.07 (s, 1H), 5.36 (s, 2H), 4.32 (d, 1H), 4.20 (s, 3H), 3.95 (d, 1H), 3.91 - 3.84 (m, 2H), 2.95 - 2.84 (brm, 6H), 2.44 - 2.38 (m, 2H)
Cpd 187 - En1	357.2	(400 MHz, DMSO-d6): δ 7.94 (s, 1H),7.67 (d, 1H), 7.51 (bs, 1H), 7.35 - 7.32 (m, 2H), 7.08 (dd, 1H), 6.61 - 6.32 (m, 1H), 5.14 (t, 1H), 4.37 - 4.29 (m, 5H), 3.99 - 3.95 (m, 1H), 3.82 - 3.77 (m, 1H), 1.56 (s, 3H).
Cpd 187 - En2	357.2	(400 MHz, DMSO-d6): δ 7.94 (s, 1H), 7.67 (d, 1H), 7.51 (bs, 1H), 7.35 - 7.33 (m, 2H), 7.08 (dd, 1H), 6.60 - 6.33 (m, 1H), 5.14 (t, 1H), 4.36 - 4.29 (m, 5H), 3.99 - 3.95 (m, 1H), 3.82 - 3.77 (m, 1H), 1.56 (s, 3H).
Cpd 188 - En1	398.2	(400 MHz, DMSO-d6): δ 8.58 (d, 1H), 7.94 (bs, 1H), 7.89 - 7.82 (m, 1H), 7.67 (d, 1H), 7.61 (d, 1H), 7.47 (bs, 1H), 7.40 - 7.33 (m, 3H), 7.12 (dd, 1H), 5.18 (s, 3H), 4.71 - 4.65 (m, 2H), 3.99 - 3.95 (m, 1H), 3.81 - 3.77 (m, 1H), 1.55 (s, 3H), 1.44 (t, 3H)
Cpd 188 - En2	398.2	(400 MHz, DMSO-d6): δ 8.58 (d, 1H), 8.48 (bs, 1H), 7.95 (bs, 1H), 7.89 - 7.83 (m, 1H), 7.67 (d, 1H), 7.61 (d, 1H), 7.47 (bs, 1H), 7.40 - 7.33 (m, 3H), 7.12 (dd, 1H), 5.19 (s, 3H), 4.71 - 4.65 (m, 2H), 3.96 (d, 1H), 3.79 (d, 1H), 1.55 (s, 3H), 1.44 (t, 3H).
Cpd 189	398.2	(500 MHz, DMSO-d6): δ 8.58 - 8.56 (m, 1H), 8.52 (bs, 1H), 7.87 - 7.82 (m, 2H), 7.69 - 7.67 (m, 2H), 7.61 - 7.58 (m, 2H), 7.43 (d, 1H), 7.37 - 7.34 (m, 1H), 7.14 (dd, 1H), 5.21 – 5.15 (m, 2H), 5.05 (bs, 1H), 4.30 (s, 3H), 4.20 – 4.17 (m, 1H), 3.81 – 3.78 (m, 2H), 2.36 - 2.32 (m, 1H), 1.80 - 1.76 (m, 1H).
Cpd 190 - En1	384.2	(400 MHz, DMSO-d6): δ 8.71 (d, 1H), 8.55 (dd, 1H), 7.94 - 7.91 (m, 2H), 7.65 (d, 1H), 7.52 (bs, 1H), 7.46 - 7.41 (m, 2H), 7.36 (bs, 1H), 7.08 (dd, 1H), 5.18 (s, 3H), 4.29 (s, 3H), 3.98 (d, 1H),3.80 (d, 1H), 1.56 (s, 3H)
Cpd 190 - En2	384.2	(400 MHz, DMSO-d6): δ 8.71 (d, 1H), 8.56 (dd, 1H), 7.96 - 7.91 (m, 2H), 7.65 (d, 1H), 7.53 - 7.36 (m, 4H), 7.08 (dd, 1H), 5.18 (s, 3H), 4.29 (s, 3H), 3.98 (d, 1H), 3.80 (d, 1H), 1.56 (s, 3H).
Cpd 191 - En1	433.2	(400 MHz, DMSO-d6): δ 7.95 (bs, 1H), 7.68 - 7.64 (m, 3H), 7.60 - 7.50 (m, 3H), 7.42 - 7.06 (m, 4H), 5.30 (s, 2H), 5.19 (bs, 1H), 4.29 (s, 3H), 3.97 (d, 1H), 3.79 (d, 1H),1.56 (s, 3H)
Cpd 191 - En2	433.2	(400 MHz, DMSO-d6): δ 7.96 (bs, 1H), 7.68 - 7.62 (m, 3H), 7.60 - 7.50 (m, 3H), 7.42 - 7.06 (m, 4H), 5.30 (s, 2H), 5.20 (bs, 1H), 4.29 (s, 3H), 3.97 (d, 1H), 3.79 (d, 1H), 1.56 (s, 3H).

Cpd 192 - En1	452.2	(400 MHz, DMSO-d6): δ 8.76 - 8.73 (m, 1H), 8.30 (d, 1H), 7.96 (s, 1H), 7.81 - 7.76 (m, 1H), 7.67 (d, 1H), 7.48 (bs, 1H), 7.38 (d,1H), 7.30 (bs, 1H), 7.08 (dd,1H), 5.32 (s, 2H), 5.14 (t, 1H), 4.29 (s, 3H), 3.99 - 3.93 (m, 1H), 3.82 - 3.76 (m, 1H), 1.55 (s,3H).
Cpd 192 - En2	452.2	(400 MHz, DMSO-d6): δ 8.74 (d, 1H), 8.30 (d, 1H), 7.95 (s, 1H), 7.80 - 7.76 (m, 1H), 7.67 (d, 1H), 7.48 (bs, 1H), 7.38 (d,1H), 7.30 (bs, 1H), 7.08 (dd,1H), 5.32 (s, 2H), 5.13 (t, 1H), 4.29 (s, 3H), 3.98 - 3.94 (m, 1H), 3.83 - 3.76 (m, 1H),1.55 (s,3H).
Cpd 193 - En1	478.2	(400 MHz, DMSO-d6): δ 8.74 (d, 1H), 8.60 (s, 1H), 8.24 (d, 1H), 7.80 - 7.75 (dd, 1H), 7.65 (d, 1H), 7.21 (d, 1H), 7.10 (dd, 1H), 5.35 (s, 2H), 4.98 (m, 1H), 4.22 (s, 3H), 3.89 - 3.85 (m, 1H), 3.72 - 3.67 (m, 1H), 2.91 (s, 6H), 1.47 (s, 3H).
Cpd 193 - En2	478.2	(400 MHz, DMSO-d6): δ 8.74 (d, 1H), 8.59 (s, 1H), 8.24 (d, 1H), 7.78 (dd, 1H), 7.65 (d, 1H), 7.21 (d, 1H), 7.10 (dd, 1H), 5.35 (s, 2H), 4.96 (s, 1H), 4.22 (s, 3H), 3.90 - 3.84 (m, 1H), 3.73 - 3.67 (m, 1H), 2.91 (s, 6H), 1.47 (s, 3H).
Cpd 194 - En1	401.1	(400 MHz, DMSO-d6): δ 7.97 (s, 1H), 7.66 - 7.60 (m, 2H), 7.51 (bs, 1H), 7.48 - 7.41 (m, 2H), 7.35 (bs, 1H), 7.30 - 7.22 (m, 2H), 7.06 (dd, 1H), 5.16 (s, 3H), 4.29 (s, 3H), 4.01 - 3.95 (m, 1H), 3.83 - 3.77 (m, 1H), 1.56 (s, 3H)
Cpd 194 - En2	401.1	(400 MHz, DMSO-d6): δ 7.97 (s, 1H), 7.66 - 7.60 (m, 2H), 7.51 (bs, 1H), 7.48 - 7.41 (m, 2H), 7.35 (bs, 1H), 7.30 - 7.22 (m, 2H), 7.05 (dd, 1H), 5.16 (s, 3H), 4.29 (s, 3H), 4.01 - 3.96 (m, 1H), 3.82 - 3.77 (m, 1H), 1.56 (s, 3H)
Cpd 195 - En1	432.3	(400 MHz, DMSO-d6): δ 7.95 (s, 1H), 7.75 (s, 1H), 7.67 (d, 1H), 7.49 (bs, 1H), 7.41 (d, 1H), 7.34 (bs, 1H), 7.01 (dd, 1H), 5.59 - 5.50 (m, 1H), 5.32 (s, 2H), 5.22 (s, 1H), 3.97 (d, 1H), 3.80 (d, 1H), 2.63 (s, 3H), 1.57 (s, 3H), 1.52 - 1.47 (m, 6H).
Cpd 195 - En2	432.3	(400 MHz, DMSO-d6): δ 7.96 (s, 1H), 7.75 (s, 1H), 7.66 (d, 1H), 7.49 (bs, 1H), 7.40 (d, 1H), 7.34 (bs, 1H), 7.01 (dd, 1H), 7.59 - 7.50 (m, 1H), 5.32 (s, 2H), 5.24 (s, 1H), 3.97 (d, 1H), 3.80 (d, 1H), 2.63 (s, 3H), 1.57 (s, 3H), 1.52 - 1.47 (m, 6H).
Cpd 196	375.2	(400 MHz, DMSO-d6) δ [ppm]: 7.90 (s, 1H), 7.62-7.59 (d, 1H), 7.51 (s, 1H), 7.34 (s, 1H), 7.27-7.23 (d, 1H), 7.01-6.99 (d, 1H), 5.15 (s, 1H), 4.29 (s, 3H), 4.03-3.91 (m, 3H), 2.74 (m, 1H), 2.56 (m, 1H), 2.29-2.20 (m, 2H), 2.02-1.98 (m, 1H), 1.77-1.75 (m, 1H), 1.55 (s, 3H), 1.45-1.40 (m, 1H), 1.12-1.03 (dd, 3H).
Cpd 197	-	(400 MHz, DMSO-d6) δ [ppm]: 13.6 (Br S, 1H), 7.69 (d 1H), 7.49 (d, 2H), 7.41 (t, 2H),7.36-7.33 (m, 2H), 7.11 (dd, 1H), 5.15 (s, 2H), 4.37 (s, 3H).
Cpd 198	301.2	(400 MHz, DMSO-d6): δ 7.66 (d, 1H), 7.60 (t, 1H), 7.47 - 7.40 (m, 2H), 7.29 - 7.21 (m, 2H), 7.06 (dd, 1H), 5.18 (s, 2H), 4.37 (s, 3H).

Cpd 199	-	(400 MHz, DMSO-d6) δ [ppm]: 13.52 (bs, 1H), 8.99 (s, 1H), 7.68-7.66 (d, 1H), 7.37 (s, 1H), 7.05-7.03 (d, 1H), 5.35 (s, 2H), 4.37 (s, 3H), 2.32 (s, 3H).
Cpd 201 - En1	405.36	(400 MHz, DMSO-D6) δ ppm: 8.59 (d, 1H), 7.83 -7.86 (m, 2 H),7.56 - 7.63 (m, 2 H), 7.34 - 7.37 (m, 1 H), 7.08 - 7.14 (m, 2 H), 6.09 - 6.34 (m, 1 H), 5.20 - 5.23 (m, 3 H), 4.21 (s, 3 H), 3.59 - 3.68 (m, 2 H), 2.49 - 2.57 (m, 1 H), 2.32 - 2.41 (m, 1 H), 1.23 (s, 3 H);
Cpd 201 - En2	405.36	(400 MHz, DMSO-D6) δ ppm: 8.57 - 8.58 (m, 1 H), 7.82 - 7.86 (m, 2 H),7.56 (d, 1 H), 7.62 (dd, 1 H), 7.34 - 7.37 (m, 1 H), 7.08 - 7.15 (m, 2 H), 6.09 - 6.40 (m, 1 H), 5.20 - 5.23 (m, 3 H), 4.21 (s, 3 H), 3.59-3.68 (m, 2 H), 2.52 - 2.67 (m, 1 H), 2.28 - 2.49 (m, 1 H), 1.42 (s, 3 H)
Cpd 202 - En1	473.23	(400 MHz, DMSO-D6) δ ppm: 8.73 (d, 1H), 8.26 (d, 1H), 7.91 (S, 1H), 7.74-7.80 (m, 1H),7.64 (d, 1H), 7.13 (d, 1H), 7.07- 7.10 (m, 1H), 6.08-6.38 (m, 1H), 5.32 (s, 2H), 5.16 (t, 1H), 4.21 (s, 3H), 3.58-3.67 (m, 2H), 2.50-2.58 (m, 1H), 2.29-2.39 (m, 1H), 1.41 (s, 3H)
Cpd 202 - En2	473.23	(400 MHz, DMSO-D6) δ ppm: 8.73 (d, 1H), 8.26 (d, 1H), 7.91 (S, 1H), 7.77-7.80 (m, 1H),7.64 (d, 1H), 7.13 (d, 1H), 7.07- 7.10 (m, 1H), 6.08-6.38 (m, 1H), 5.32 (s, 2H), 5.16 (t, 1H), 4.21 (s, 3H), 3.58-3.67 (m, 2H), 2.49-2.67 (m, 1H), 2.30-2.34 (m, 1H), 1.41 (s, 3H)
Cpd 203 - En1	422.26	(400 MHz, DMSO-D6) δ ppm: 7.87 (S, 1 H), 7.57 - 7.61 (M, 2 H), 7.41 - 7.46 (m, 1 H), 7.19 - 7.28 (m, 3 H),7.04 (dd, 1 H), 6.11 - 6.41 (m, 1 H), 5.22 (t, 1 H), 5.19 (s, 2 H), 4.21 (s, 3 H), 3.59 - 3.69 (m, 2 H), 2.57 - 2.66 (m, 1 H), 2.33 - 2.37 (m, 1 H), 1.43 (s, 3 H);
Cpd 203 - En2	422.3	(400 MHz, DMSO-D6) δ ppm: 7.87 (S, 1 H), 7.57 - 7.61 (M, 2 H), 7.41 - 7.47 (m, 1 H), 7.19 - 7.28 (m, 3 H),7.04 (dd, 1 H), 6.11 - 6.40 (m, 1 H), 5.22 (s, 1 H), 5.15 (s, 2 H), 4.21 (s, 3 H), 3.60 - 3.68 (m, 2 H), 2.50 - 2.67 (m, 1 H), 2.07 - 2.12 (m, 1 H), 1.43 (s, 3 H);
Cpd 204	365.29	(400 MHz, DMSO-D6) δ ppm: 8.95 (t, 1 H), 8.59 (d, 1 H), 7.83 - 7.87 (m, 1 H), 7.67 (d, 1 H), 7.57 (d, 1 H), 7.34 - 7.37 (m, 1 H), 7.20 (d, 1 H), 7.13 - 7.16 (dd, 1 H), 5.23 (s, 2 H), 4.27 (s, 3 H), 4.13 - 4.22 (m, 2 H).
Cpd 205	327.33	(400 MHz, DMSO-D6) δ ppm: 8.58 – 8.60 (m, 1 H), 8.27 (t, 1 H), 7.86 (dt, 1 H), 7.58 – 7.63 (m, 2 H), 7.35 – 7.38 (m, 1 H), 7.27 (d, 1 H), 7.10 (dd, 1 H), 5.23 (s, 2 H), 4.82 (t, 1 H), 4.25 (s, 3 H), 3.59 (q, 2 H), 3.43 (q, 2 H).
Cpd 206	363.2	1H NMR (400 MHz, DMSO-D6) δ ppm: 11.88 (s, 1 H), 8.73 (t, 1 H), 8.59 (d, 1 H), 7.86 (dt, 1 H), 7.59 – 7.65 (m, 1 H), 7.51 (d, 1 H), 7.35 – 7.38 (m, 1 H), 7.12 (dd, 1 H), 7.06 (s, 1 H), 6.87 (s, 1 H), 5.24 (s, 2 H), 4.60 (d, 2 H), 4.29 (s, 3 H).
Cpd 207	396.28	(400 MHz, DMSO-D6) δ ppm: 8.57 - 8.58 (m, 1 H), 8.44 (t, 1 H), 7.83 (dt, 1 H), 7.65 (dd, 1 H), 7.52 (d, 1 H), 7.33 - 7.35 (m, 1 H), 7.12 - 7.15 (t, 2 H), 5.22 (s, 2 H) 4.24 (s, 3 H), 3.25 (s, 2 H), 2.49 (s, 6 H), 2.23 (s, 2 H) ,0.90 (s, 6 H).
Cpd 208	423.19	(400 MHz, DMSO-D6) δ ppm: 8.83 (t, 1 H), 8.60 - 8.62 (m, 1 H), 7.85 - 7.90 (m, 1 H), 7.58 - 7.67 (m, 4 H), 7.49 - 7.52 (m, 3 H), 7.36 - 7.39 (m, 1 H), 7.10- 7.13 (dd, 1 H), 7.06 (d, 1 H), 5.15 (s, 2 H), 4.09 - 4.16 (m, 5 H).
Cpd 209	459.34	(400 MHz, DMSO-D6) δ ppm: 8.88 (s, 1 H), 8.58 - 8.59 (m, 1 H), 7.81 - 7.85 (m, 1 H), 7.60 - 7.64 (m, 4 H), 7.52 (d, 1 H), 7.34 - 7.37 (m, 1 H), 7.08 (dt, 2 H), 5.11 (s, 2 H), 4.70 (d, 2 H), 4.22 (s, 3 H)
Cpd 210	439.2	(400 MHz, DMSO-D6) δ ppm: 8.90 (t, 1 H), 8.57 (d, 1 H), 7.84 (dt, 1 H), 7.66 (d, 1 H), 7.57 (d, 1 H), 7.11 – 7.43 (m, 8 H), 5.22 (s, 2 H), 4.59 (d, 2 H), 4.27 (s, 3 H)

Cpd 211 - En1	422.3	(400 MHz, DMSO-D6) δ ppm: 9.0 (s ,1 H), 8.55 (d, 1 H), 7.63 (d, 1 H), 7.17 (s, 1 H), 7.05 (dd, 1 H), 5.30 (s, 2 H), 4.43 - 4.36 (m, 1 H), 4.23 (s, 3 H), 3.02 - 2.99 (m, 2 H), 2.94 - 2.90 (m, 1 H), 2.76 (t, 1 H), 2.59 (t, 1 H), 2.42 (s, 3 H), 2.13 - 2.07 (m, 1H), 1.97 - 1.91 (m, 1 H).
Cpd 211 - En2	422.3	(400 MHz, DMSO-D6) δ ppm: 9.0 (s ,1 H), 8.55 (d, 1 H), 7.63 (d, 1 H), 7.17 (s, 1 H), 7.05 (dd, 1 H), 5.30 (s, 2 H), 4.43 - 4.36 (m, 1 H), 4.23 (s, 3 H), 3.02 - 2.90 (m, 2 H), 2.75 (t, 1 H), 2.66 (t, 1 H), 2.42 (s, 3 H), 2.17 - 2.07 (m, 1H), 1.96 - 1.90 (m, 1H).
Cpd 212 - En1	402.3	(400 MHz, DMSO-D6) δ ppm: 8.59 (d, 1 H), 8.53 (d, 1 H), 7.86 (t, 1 H), 7.66 - 7.63 (m, 1 H), 7.56 (d, 1 H), 7.36 (t, 1H), 7.13 - 7.12 (m, 2 H), 5.19 (q, 2 H), 4.40 - 4.35 (m, 1 H), 4.23 (s, 3 H), 3.00 - 2.89 (m, 2 H), 2.77 - 2.67 (m, 2 H), 2.5 (m, 1 H), 2.12 - 2.07 (m, 1 H), 1.95 - 1.88 (m, 1 H).
Cpd 212 - En2	402.3	(400 MHz, DMSO-D6) δ ppm: 8.59 (d, 1 H), 8.53 (d, 1 H), 7.86 - 7.82 (m, 1 H), 7.66 - 7.63 (m, 1H), 7.56 (d, 1H), 7.37 - 7.34 (m, 1 H), 7.14 - 7.11 (m, 1 H), 7.18 (d, 2 H), 4.41 - 4.34 (m, 1 H), 4.23 (s, 3 H), 3.0 - 2.92 (m, 2 H), 2.89 - 2.64 (m, 2 H), 2.64 (m, 1 H), 2.12 - 2.06 (m, 1 H), 1.98 - 1.87 (m, 1 H)
Cpd 213 - En1	422.3	(400.32 MHz, DMSO-D6) δ ppm: 9.01 (s, 1 H), 8.32 (d, 1 H), 7.62 (d, 1 H), 7.19 (d, 1 H), 7.02-7.05 (dd, 1 H), 5.33 (s, 2 H), 4.24 (s, 3 H), 4.17 (t, 1H), 3.02 (t, 2H), 2.83 (d, 2 H), 2.58 (t, 1 H), 2.43 (s, 4 H), 2.05-2.19 (m, 1 H).
Cpd 213 - En2	422.3	(400.32 MHz, DMSO-D6) δ ppm: 9.01 (s, 1 H), 8.32 (d, 1 H), 7.62 (d, 1 H), 7.19 (d, 1 H), 7.02-7.05 (dd, 1 H), 5.33 (s, 2 H), 4.24 (s, 3 H), 4.17 (t, 1H), 3.02 (t, 2H), 2.83 (d, 2 H), 2.58 (t, 1 H), 2.43 (s, 4 H), 2.05-2.19 (m, 1 H).
Cpd 214 - En1	402.2	1H NMR (400 MHz, DMSO-D6) δ ppm: 8.57 (d, 1 H), 8.32 (d, 1 H), 7.84 - 7.87 (t, 1 H), 7.63 (d, 1 H), 7.56 (d, 1 H), 7.34 - 7.37 (m, 1 H), 7.13 (s, 1 H),7.10 (s, 1H), 5.23 (s, 2 H), 4.23 (s, 3 H), 4.14 (bs, 1H), 3.01 (d, 2 H), 2.7 (bs, 2 H), 2.49 - 2.55 (m, 1 H), 2.38 (t, 1 H), 2.05 - 2.12 (m, 1 H).
Cpd 214 - En2	402.2	1H NMR (400 MHz, DMSO-D6) δ ppm: 8.57 (d, 1 H), 8.32 (d, 1 H), 7.84 - 7.87 (t, 1 H), 7.63 (d, 1 H), 7.56 (d, 1 H), 7.34 - 7.37 (m, 1 H), 7.13 (s, 1 H),7.10 (s, 1H), 5.23 (s, 2 H), 4.23 (s, 3 H), 4.14 (bs, 1H), 3.01 (d, 2 H), 2.7 (bs, 2 H), 2.49 - 2.55 (m, 1 H), 2.38 (t, 1 H), 2.05 - 2.12 (m, 1 H).
Cpd 215 - En1	372.4	1H NMR (400 MHz, DMSO-D6) δ ppm: 9.00 (d, 1 H), 8.43 (d, 1 H), 7.60 (d, 1 H), 7.13 (t, 1 H), 7.01-7.04 (dd, 1 H), 5.13 (d, 2 H), 4.37 (t, 1 H), 4.23 (s, 3 H), 3.32 (s, 1 H), 2.91-3.02 (m, 3 H), 2.77-2.79 (m, 2 H), 2.43 (s, 3 H), 2.78 (d, 1 H).
Cpd 215 - En2	372.2	(400 MHz, DMSO-D6) δ ppm: 9.00 (d, 1 H), 8.43 (d, 1 H), 7.60 (d, 1 H), 7.13 (t, 1 H), 7.01-7.04 (dd, 1 H), 5.13 (d, 2 H), 4.37 (t, 1 H), 4.23 (s, 3 H), 3.32 (s, 1 H), 2.91-3.02 (m, 3 H), 2.77-2.79 (m, 2 H), 2.43 (s, 3 H), 2.78 (d, 1 H)
Cpd 216 - En1	352.3	1H NMR (400 MHz, DMSO-D6) δ ppm: 8.58 (d, 1 H), 8.39 (d, 1 H), 7.82 - 7.86 (m, 1 H), 7.61 (d, 1 H), 7.55 (d, 1 H), 7.34 - 7.37 (m, 1 H), 7.08 - 7.11 (m, 2 H), 5.23 (s, 2 H), 4.35 - 4.36 (m, 1 H), 4.22 (s, 3 H), 2.91 -2.98 (m, 2 H), 2.72 - 2.78 (m, 2 H), 1.98 - 2.03 (m, 1 H), 1.70 - 1.72 (m, 1 H)
Cpd 216 - En2	352.4	1H NMR (400 MHz, DMSO-D6) δ ppm: 8.60 (dd, 1 H), 8.39 (d, 1 H), 7.82 - 7.86 (m, 1 H), 7.61 (d, 1 H), 7.55 (d, 1 H), 7.34 - 7.37 (m, 1 H), 7.07 - 7.12 (m, 2 H), 5.24 (s, 2 H), 4.35 - 4.39 (m, 1 H), 4.22 (s, 3 H), 2.92 - 2.99 (m, 2 H), 2.74 - 2.79 (m, 2 H), 1.96 - 2.03 (m, 1 H), 1.68 - 1.75 (m, 1 H);

Cpd 217	403	1H NMR (400 MHz, DMSO-D6) δ ppm: 8.68 (S, 1 H), 8.59 (d, 1 H), 7.83 – 7.87 (m, 1 H), 7.63 (d, 1 H), 7.58 (d, 1 H), 7.37 – 7.34 (m, 1 H), 7.22 (d, 1H), 7.11 (dd, 1 H) 5.27 (t, 1 H), 5.20 (s, 2 H), 4.23 (s, 3 H), 3.67 (d, 2 H), 2.90 (t, 4 H).
Cpd 218	444.3	1H NMR (400 MHz, DMSO-D6) δ ppm: 12.85 (s, 1 H), 9.50 (s, 1 H), 8.59 (d, 1 H), 8.44 (d, 1 H), 7.89 - 7.83 (m, 2 H), 7.77 (d, 1 H), 7.65 (d, 1 H), 7.54 (d, 1 H), 7.38 - 7.36 (m, 1 H), 7.21 (d, 1 H), 5.25 (s, 2 H), 4.39 (s, 3 H).
Cpd 219	427.25	1H NMR (400 MHz, DMSO-D6) δ ppm: 8.57 – 8.59 (m, 1 H), 7.83 – 7.87 (m, 2 H), 7.63 (d, 1 H), 7.58 (d, 1 H), 7.34 – 7.38 (m, 1 H), 7.28 (d, 1 H), 7.12 (dd, 1 H), 5.19 (s, 2 H), 5.03 (brs, 1 H), 4.23 – 4.26 (m, 2 H), 4.24 (s, 3 H), 3.91 – 3.94 (m, 2 H), 3.79 (s, 2 H), 1.43 (s, 3 H), 1.37 (s, 3 H).
Cpd 220 - En1	421.3	1H NMR (400 MHz, DMSO-D6) δ ppm: 8.76 (d, 1 H), 8.58 - 8.60 (m, 1 H), 7.83 - 7.87 (dt, 1 H), 7.64 (d, 1 H), 7.57 (d, 1 H), 7.47 - 7.50 (m, 2 H), 7.35 - 7.38 (m, 1 H), 7.28 (d, 1 H), 7.10 - 7.20 (m, 3 H), 5.22 (s, 2 H), 5.07 - 5.12 (q, 2 H), 4.20 (s, 3 H), 3.73 (br s, 2 H),
Cpd 220 - En2	421.3	1H NMR (400 MHz, DMSO-D6) δ ppm: 8.77 (d, 1 H), 8.58-8.60 (m, 1 H), 7.83-7.87 (dt, 1 H), 7.64 (d, 1 H), 7.57 (d, 1 H), 7.47-7.50 (m, 2 H), 7.35-7.38 (m, 1 H), 7.28 (d, 1 H), 7.10–7.20 (m, 3 H), 5.22 (s, 2 H), 5.07-5.12 (q, 2 H), 4.20 (s, 3 H), 3.68-3.76 (m, 2 H).
Cpd 221 - En1	404.2	1H NMR (400 MHz, DMSO-D6) δ ppm: 8.64 (d, 1 H), 8.60 (d, 2 H), 7.77 (m, 2 H), 7.66 (d, 1 H), 7.60 (d, 1 H), 7.50 (d 1 H), 7.44 (s 1 H), 7.38 – 7.35 (m, 1 H), 7.33 – 7.30 (m, 1 H), 7.14 (dd, 1 H), 5.28 – 5.19 (m, 3 H), 5.05 (t, 1 H), 4.26 (s, 3 H), 3.89 -3.81 (m, 2 H)
Cpd 221 - En2	404.2	1H NMR (400 MHz, DMSO-D6) δ ppm: 8.64 (d, 1 H), 8.60 (d, 2 H), 7.77 (m, 2 H), 7.66 (d, 1 H), 7.60 (d, 1 H), 7.50 (d 1 H), 7.44 (s 1H), 7.35 – 7.38 (m, 1 H), 7.30 – 7.33 (m, 1 H), 7.14 (dd, 1 H), 5.19 - 5.28 (m, 3 H), 5.05 (t, 1 H), 4.26 (s, 3 H), 3.81 - 3.89 (m, 2 H).
Cpd 223 - En1	435.3	1H NMR (400 MHz, DMSO-D6) δ ppm: 8.87 (d, 1 H), 8.60 - 8.59 (m, 1 H), 7.87 - 7.83 (m, 1 H) 7.64 (d, 1 H), 7.56 (d, 1 H), 7.48 - 7.44 (m, 2 H), 7.38 - 7.35 (m, 1 H), 7.19 - 7.10 (m, 4 H), 5.24 - 5.18 (m, 3 H), 4.76 (t, 1 H), 4.18 (s, 3 H), 3.53 - 3.43 (m, 2 H), 2.10 - 2.03 (m, 1 H), 1.98 - 1.91 (m, 1 H).
Cpd 223 - En2	435.2	1H NMR (400 MHz, DMSO-D6) δ ppm: 8.87 (d, 1 H), 8.60 - 8.59 (m, 1 H), 7.87 - 7.83 (m, 1 H) 7.64 (d, 1 H), 7.56 (d, 1 H), 7.48 - 7.44 (m, 2 H), 7.38 - 7.35 (m, 1 H), 7.19 - 7.10 (m, 4 H), 5.24 - 5.18 (m, 3 H), 4.76 (t, 1 H), 4.18 (s, 3 H), 3.53 - 3.43 (m, 2 H), 2.10 - 2.03 (m, 1 H), 1.98 - 1.91 (m, 1 H).
Cpd 226-En1	409.3	1H NMR (400 MHz, DMSO-D6) δ ppm: 8.59 - 8.57 (m, 1 H), 8.37 (d, 1 H), 7.87 - 7.82 (m, 1 H), 7.65 (d, 1 H), 7.57 (d, 1 H), 7.37 - 7.34 (m, 1 H), 7.18 (d, 1 H), 7.13 - 7.10 (m, 1 H), 5.24 - 5.13 (m, 3 H), 4.38 - 4.34 (m, 1 H), 4.24 (s, 3 H), 3.60 - 3.55 (m, 1 H), 3.48 - 3.42 (m, 1 H), 2.70 -2.60 (m, 2 H).
Cpd 226-En2	409.3	1H NMR (400 MHz, DMSO-D6) δ ppm: 8.59 - 8.58 (m, 1 H), 8.37 (d, 1 H), 7.87 - 7.82 (m, 1 H), 7.65 (d, 1 H), 7.57 (d, 1 H), 7.37 - 7.34 (m, 1 H), 7.18 (d, 1 H), 7.13 - 7.10 (m, 1 H), 5.24 -5.14 (m, 3 H), 4.37 - 4.34 (m, 1 H), 4.22 (s, 3 H), 3.59 - 3.56 (m, 1 H), 3.46 - 3.45 (m, 1 H), 2.67 -2.60 (m, 2 H).
Cpd 227 - En1	477.2	1H NMR (400 MHz, DMSO-D6) δ ppm: 8.57 (d, 2H), 7.84 (t, 1 H),7.65 (d, 1 H), 7.55 (d, 1 H), 7.034 (m, 1 H), 7.11 – 7.15 (m, 2 H), 5.28 (t, 1 H), 5.10-5.19 (m, 2 H), 4.90 (d, 1 H), 4.27 (s, 4 H), 3.67 (d, 2 H);

Cpd 227 - En2	477.2	1H NMR (400 MHz, DMSO-D6) δ ppm: 8.57 (d, 2H), 7.84 (t, 1 H),7.65 (d, 1 H), 7.55 (d, 1 H), 7.034 (m, 1 H), 7.11 – 7.15 (m, 2 H), 5.28 (t, 1 H), 5.10-5.19 (m, 2 H), 4.90 (d, 1 H), 4.27 (s, 4 H), 3.67 (d, 2 H)
Cpd 228 - En1	391.4	1H NMR (400 MHz, DMSO-D6) δ ppm: 8.59 - 8.57 (m, 1 H), 8.27 (d, 1 H), 7.87 - 7.83 (m, 1 H), 7.63 (d, 1 H), 7.57 (d, 1 H), 7.38 - 7.34 (m, 1 H), 7.20 (d, 1 H), 7.12 - 7.09 (m, 1 H), 6.36 - 6.05 (m, 1 H), 5.21 (s, 2 H), 5.05 (t, 1 H), 4.23 (s, 4 H), 3.59 – 3.47 (m, 2 H), 2.25 - 2.16 (m, 2 H).
Cpd 228 - En2	391.3	1H NMR (400 MHz, DMSO-D6) δ ppm: 8.59 - 8.57 (m, 1 H), 8.27 (d, 1 H), 7.87 - 7.83 (m, 1 H), 7.63 (d, 1 H), 7.57 (d, 1 H), 7.38 - 7.34 (m, 1 H), 7.20 (d, 1 H), 7.12 - 7.09 (m, 1 H), 6.36 - 6.05 (m, 1 H), 5.21 (s, 2 H), 5.05 (t, 1 H), 4.23 (s, 4 H), 3.60 - 3.46 (m, 2 H), 2.25 - 2.12 (m, 2H).
Cpd 229 - En1	432.3	(400 MHz, DMSO-D6) δ ppm: 8.59 (d, 1 H), 7.96 (s, 1 H), 7.86 - 7.81 (m, 1 H), 7.64 (d, 1 H), 7.55 (d, 1 H), 7.37 - 7.34 (m, 1 H), 7.10 (t, 3 H), 6.36 - 6.06 (m, 1 H), 5.21 (s, 2 H), 4.20 (s, 3 H), 2.78 (d, 1 H), 2.70 - 2.62 (m, 2 H), 2.32 - 2.18 (m, 7 H), 1.42 (s, 3 H).
Cpd 229 - En2	432.3	(400 MHz, DMSO-D6) δ ppm: 8.59 - 8.57 (m, 1 H), 7.96 (s, 1 H), 7.84 (t, 1 H) 7.82 (d, 1 H), 7.36 - 7.34 (m, 1 H), 7.10 (t, 2 H), 6.36 - 6.06 (m, 1 H), 5.21 (s, 2 H), 4.20 (s, 3 H), 2.78 - 2.70 (m, 1 H), 2.68 - 2.61 (m, 2 H), 2.33 - 2.16 (m, 7 H), 2.15 (s, 3 H).
Cpd 230 - En1	419.2	(400 MHz, DMSO-D6) δ ppm: 8.57 - 8.59 (m, 1 H), 8.02 (s, 1 H), 7.82 - 7.86(m, 1H), 7.61 - 7.64 (m, 1 H), 7.56 (d, 1 H), 7.34 - 7.37 (m, 1 H), 7.09 - 7.12 (m, 2 H), 6.08 - 6.39 (m, 1 H), 5.21 (s, 2 H), 4.21 (s, 3 H), 3.62 (d, 1 H), 3.53 - 3.56 (d, 1 H), 3.27 - 3.39 (m, 3 H), 2.67 (s, 1 H), 2.31 - 2.61 (m, 1 H), 1.31 (s, 3 H)
Cpd 230 - En2	419.3	(400 MHz, DMSO-D6) δ ppm: 8.57 - 8.59 (m, 1 H), 8.02 (s, 1 H), 7.82 - 7.86(m, 1H), 7.61 - 7.64 (m, 1 H), 7.56 (d, 1 H), 7.34 - 7.37 (m, 1 H), 7.09 - 7.12 (m, 2 H), 6.08 - 6.39 (m, 1 H), 5.21 (s, 2 H), 4.21 (s, 3 H), 3.62 (d, 1 H), 3.53 - 3.56 (d, 1 H), 3.27 - 3.39 (m, 3 H), 2.67 (s, 1 H), 2.31 - 2.61 (m, 1 H), 1.31 (s, 3 H)
Cpd 232 - En1	383.4	1H NMR (400 MHz, DMSO-D6) δ ppm: 8.58 (d, 1 H), 8.46 (s, 1 H), 7.84 (dt, 1 H), 7.65 (d, 1 H), 7.57 (d, 1 H), 7.34 - 7.37 (m, 1 H), 7.23 (d, 1 H), 7.12 - 7.14 (dd, 1H), 5.23 (s, 2 H), 5.16 (t, 1 H), 4.23 (s, 3 H), 3.76 (d, 2 H), 2.14 (s, 3 H), 1.42 (s, 3 H)
Cpd 232 - En2	383.4	1H NMR (400 MHz, DMSO-D6) δ ppm: 8.58 (d, 1 H), 8.46 (s, 1 H), 7.82 - 7.86 (dt, 1 H), 7.65 (d, 1 H), 7.57 (d, 1 H), 7.34 - 7.37 (m, 1 H), 7.23 (d, 1 H), 7.12 - 7.14 (dd, 1H), 5.23 (s, 2 H), 5.16 (t, 1 H), 4.23 (s, 3 H), 3.76 (d, 2 H), 2.14 (s, 3 H), 1.42 (s, 3 H)
Cpd 234	416.2	(400 MHz, DMSO-D6) δ ppm: 8.58 (d, 1 H), 7.95 (s, 1 H), 7.87 - 7.83 (dt, 1 H), 7.70-7.67 (m, 2 H), 7.62 - 7.58 (m, 2 H), 7.42 (d, 1 H), 7.38 - 7.35 (m, 1 H), 7.15 - 7.12 (dd, 1 H), 5.20 - 5.17 (m, 3 H), 4.57 - 4.18 (m, 2 H), 4.29 (s, 3 H), 4.17 - 4.13 (q, 1 H), 3.84 - 3.79 (q, 1 H), 2.74 - 2.63 (m, 1 H), 2.39 - 2.32 (m, 1H).
Cpd 235 - En1	389.2	(400 MHz, DMSO-D6) δ ppm: 8.89 (s, 1 H), 8.59 (d, 1 H), 7.83 - 7.87 (dt, 1 H), 7.63 (d, 1 H), 7.57 (d, 1 H), 7.34 – 7.37 (dt, 1 H), 7.21 (d, 1 H), 7.09 – 7.12 (dd, 1 H), 5.22 (s, 2 H), 5.15 (t, 1 H), 4.25 (s, 3 H), 3.85 – 3.89 (m, 1 H), 3.64 – 3.69 (m, 1 H), 1.89 – 1.96 (m, 1 H), 1.73 – 1.80 (m, 1 H).
Cpd 235 - En2	389.2	(400 MHz, DMSO-D6) δ ppm: 8.89 (s, 1 H), 8.59 (d, 1 H), 7.83 - 7.87 (dt, 1 H), 7.63 (d, 1 H), 7.57 (d, 1 H), 7.34 – 7.37 (dt, 1 H), 7.21 (d, 1 H), 7.09 – 7.12 (dd, 1 H), 5.22 (s, 2 H), 5.15 (t, 1 H), 4.25 (s, 3 H), 3.85 – 3.89 (m, 1 H), 3.64 – 3.69 (m, 1 H), 1.73 - 1.96 (m, 2 H).

Cpd 237 - En1	403.3	1H NMR (400 MHz, DMSO-D6) δ ppm: 8.75 (s, 1H), 8.59 - 8.58 (m, 1 H), 7.87 - 7.83 (dt, 1 H), 7.61 - 7.57 (q, 2 H), 7.37 - 7.34 (dt, 1 H), 7.18 (q, 1 H), 7.10- 7.07 (dd, 1 H), 6.16 - 5.87 (dt, 1 H), 5.24 (s, 2 H), 5.07 (t, 1 H), 4.22 (s, 3 H), 3.85 - 3.81 (dd, 1 H), 3.77 - 3.73 (dd, 1 H), 1.81 - 1.75 (m, 1 H), 1.26 (d, 2 H).
Cpd 237 - En2	403.3	1H NMR (400 MHz, DMSO-D6) δ ppm: 8.75 (s, 1H), 8.59 - 8.58 (m, 1 H), 7.87 - 7.83 (dt, 1 H), 7.61 - 7.57 (q, 2 H), 7.37 - 7.34 (dt, 1 H), 7.18 (q, 1 H), 7.10 - 7.07 (dd, 1 H), 6.16 - 5.87 (dt, 1 H), 5.24 (s, 2 H), 5.07 (t, 1 H), 4.22 (s, 3 H), 3.85 - 3.81 (dd, 1 H), 3.77 - 3.73 (dd, 1 H), 1.79 - 1.75 (m, 1 H), 1.25 (d, 2 H).
Cpd 238 - En1	433.3	1H NMR (400 MHz, DMSO-D6) δ ppm: 8.63 (d, 1 H), 8.59 (t, 1 H), 7.87 - 7.83 (m, 1 H), 7.63 - 7.58 (m, 2 H), 7.45 (d, 1 H), 7.38 - 7.34 (m, 1 H), 7.12 - 7.08 (m, 2 H), 6.84 (d, 1 H), 5.55 (q, 1 H), 5.22 (q, 2 H), 5.04 (t, 2 H), 4.24 (s, 3 H), 3.91 - 3.87 (m, 2 H), 3.47 - 3.44 (m, 1 H), 1.06 - 0.98 (m, 4 H).
Cpd 238 - En2	433.3	1H NMR (400 MHz, DMSO-D6) δ ppm: 8.64 (d, 1 H), 8.60 (d, 1 H), 7.87 - 7.83 (m, 1 H), 7.61 (t, 2 H), 7.45 (d, 1 H), 7.38 - 7.35 (m, 1 H), 7.12 - 7.08 (m, 2 H), 6.84 (d, 1 H), 5.55 (q, 1 H), 5.22 (q, 2 H), 5.04 (t, 2 H), 4.24 (s, 3 H), 3.89 (t, 2 H), 3.49 - 3.43 (m, 1 H), 1.06 - 0.97 (m, 4 H).
Cpd 239 - En1	421.3	1H NMR (400 MHz, DMSO-D6) δ ppm: 8.58 - 8.56 (m, 1 H), 7.97 (s, 1 H), 7.87 - 7.83 (dt, 1 H), 7.66 (d, 1 H), 7.61 - 7.58 (m, 2 H), 7.39 - 7.34 (m, 2 H), 7.15 - 7.12 (dd, 1 H), 6.17 (d, 1 H), 5.23 (s, 2 H), 5.06 (bs, 1 H), 4.25 (s, 3 H), 3.80 (s, 5 H), 1.72 (s, 3 H).
Cpd 239 - En2	421.3	1H NMR (400 MHz, DMSO-D6) δ ppm: 8.58 - 8.56 (m, 1 H), 7.97 (s, 1 H), 7.87 - 7.83 (dt, 1 H), 7.66 (d, 1 H), 7.61 - 7.58 (m, 2 H), 7.39 - 7.34 (m, 2 H), 7.15 - 7.12 (dd, 1 H), 6.17 (d, 1 H), 5.23 (s, 2 H), 5.06 (bs, 1 H), 4.25 (s, 3 H), 3.80 (s, 5 H), 1.72 (s, 3 H).
Cpd 240 - En1	384.2	1H NMR (400 MHz, DMSO-D6) δ ppm: 8.59 (d, 1 H), 8.22 (d, 1 H), 7.86 - 7.84 (m, 1 H), 7.61 (t, 2 H), 7.46 (br s, 1H), 7.38 - 7.33 (m, 2 H), 7.08 (dd, 1 H), 6.96 (br s, 1 H), 5.21 (s, 2 H), 4.90 (t, 1 H), 4.34 - 4.32 (m, 1 H), 4.25 (s, 3 H), 3.56 - 3.54 (m, 1 H), 3.48 - 3.46 (m, 1 H), 2.49 - 2.46 (m, 2 H);
Cpd 240 - En2	384.2	1H NMR (400 MHz, DMSO-D6) δ ppm: 8.59 (d, 1 H), 8.21 (d, 1 H), 7.86 - 7.84 (m, 1 H), 7.61 (t, 2 H), 7.46 (br s, 1H), 7.38 - 7.34 (m, 2 H), 7.08 (dd, 1 H), 6.94 (br s, 1 H), 5.21 (s, 2 H), 4.90 (t, 1 H), 4.36 - 4.32 (m, 1 H), 4.25 (s, 3 H), 3.57 - 3.44 (m, 2 H), 2.48 - 2.44 (m, 2 H)
Cpd 241 - En1	411.3	1H NMR (400 MHz, DMSO-D6) δ ppm: 8.61 (dd, 1 H), 8.54 - 8.59 (m, 1 H), 8.08 (d, 1 H), 7.82 - 7.86 (m, 1 H), 7.62 (d, 1 H), 7.56 (d, 1 H), 7.34 - 7.37 (m, 1 H), 7.22 (d, 1 H), 7.09 - 7.12 (m, 1H), 5.16 - 5.23 (t, 2 H), 4.76 (d, 1 H), 4.22 (s, 3 H), 3.86 - 3.93 (m, 3 H), 3.59 - 3.63 (m, 2 H), 3.16 - 3.17 (m, 2 H), 1.86 - 1.94 (m, 1 H), 1.62 - 1.65 (m, 2 H), 1.38 - 1.41 (m, 2 H)
Cpd 241 - En2	411.4	1H NMR (400 MHz, DMSO-D6) δ ppm: 8.58 (dd, 1 H), 8.08 (d, 1 H), 7.82 - 7.86 (m, 1 H), 7.62 (d, 1 H), 7.56 (d, 1 H), 7.34 - 7.37 (m, 1 H), 7.22 (d, 1 H), 7.09 - 7.12 (m, 1H), 5.16 - 5.23 (t, 2 H), 4.76 (d, 1 H), 4.22 (s, 3 H), 3.86 - 3.93 (m, 3 H), 3.59 - 3.63 (m, 2 H), 3.16 - 3.17 (m, 2 H), 1.86 - 1.94 (m, 1 H), 1.62 - 1.65 (m, 2 H), 1.38 - 1.41 (m, 2 H).
Cpd 242	475.3	(400 MHz, DMSO-D6) δ ppm: 8.60 (d, 1 H), 8.36 (d, 1 H), 7.85 – 7.89 (dt, 1 H), 7.59 - 7.64 (m, 2 H), 7.43 (s, 1 H), 7.36 -7.39 (m, 1 H), 7.10 – 7.13 (m, 1 H), 7.07 (s, 1 H), 5.22 – 5.26 (m, 3 H), 4.42 – 4.51 (m, 2 H), 4.22 – 4.27 (m, 1 H), 4.09 (s, 3 H), 3.61 – 3.69 (m, 2 H).

Cpd 243 - En1	419.2	1H NMR (400 MHz, DMSO-D6) δ ppm: 8.73 (d, 2 H), 8.61 - 8.59 (m, 1 H), 8.25 (d, 1 H), 7.90 - 7.85 (m, 1 H), 7.61 (t, 2 H), 7.39 - 7.36 (m, 1 H), 7.32 (t, 1 H), 7.18 (d, 1 H), 7.10 - 7.07 (dd, 1 H), 5.23 - 5.14 (m, 2 H), 4.95 (t, 1 H), 4.63 - 4.57 (m, 1 H), 4.14 (s, 3 H), 3.66 - 3.61 (m, 1 H), 3.56 - 3.50 (m, 1 H), 3.35 - 3.29 (m, 1 H), 3.15 - 3.09 (m, 1 H).
Cpd 243 - En2	419.2	1H NMR (400 MHz, DMSO-D6) δ ppm: 8.73 (d, 2 H), 8.61 - 8.59 (m, 1 H), 8.25 (d, 1 H), 7.90 - 7.85 (m, 1 H), 7.61 (t, 2 H), 7.39 - 7.36 (m, 1 H), 7.32 (t, 1 H), 7.18 (d, 1 H), 7.10 - 7.07 (dd, 1 H), 5.23 - 5.14 (m, 2 H), 4.95 (t, 1 H), 4.63 - 4.57 (m, 1 H), 4.14 (s, 3 H), 3.66 - 3.61 (m, 1 H), 3.56 - 3.50 (m, 1 H), 3.35 - 3.29 (m, 1 H), 3.15 - 3.09 (m, 1 H).
Cpd 245 - En1	409.3	1H NMR (400 MHz, DMSO-D6) δ ppm: 8.59 (d, 1 H), 8.38 (t, 1 H), 7.86 (dt, 1 H), 7.59 - 7.64 (m, 2 H),7.35 - 7.38 (m, 1 H), 7.28 (d, 1 H), 7.11 (dd, 1 H), 5.40 (br s, 1 H), 5.21 (s, 2 H), 4.26 (s, 3 H), 4.06 - 4.07 (m, 1 H), 3.35 - 3.45 (m, 2 H), 2.49 - 2.57 (m, 1 H), 2.33 - 2.38 (m, 1 H)
Cpd 245 - En2	409.3	1H NMR (400 MHz, DMSO-D6) δ ppm: 8.59 (d, 1 H), 8.38 (t, 1 H), 7.86 (dt, 1 H), 7.59 - 7.64 (m, 2 H),7.35 - 7.38 (m, 1 H), 7.28 (d, 1 H), 7.11 (dd, 1 H), 5.41 (br s, 1 H), 5.21 (s, 2 H), 4.26 (s, 3 H), 4.06 - 4.07 (m, 1 H), 3.36 - 3.45 (m, 2 H), 2.54 - 2.55 (m, 1 H), 2.36 - 2.50 (m, 1 H);
Cpd 246 - En1	420.4	1H NMR (400 MHz, DMSO-D6) δ 8.65 (d, 1 H), 8.58 – 8.56 (m, 1 H), 7.86 – 7.82 (m, 1H), 7.65 (d, 1 H), 7.56 (d, 1 H), 7.37 – 7.34 (m, 1 H), 7.14 – 7.11 (m, 2 H), 5.28 (s, 2 H), 4.56 – 4.52(m, 1H), 4.23 (s, 3 H), 3.31 – 3.23 (m, 1 H), 3.15 – 3.06 (m, 2 H), 2.91 – 2.87 (m, 1 H), 2.80 – 2.67 (m, 2 H);
Cpd 246 - En2	420.4	1H NMR (400 MHz, DMSO-D6) δ ppm: 8.65 (d, 1 H), 8.58 – 8.56 (m, 1 H), 7.86 – 7.82 (m, 1H), 7.65 (d, 1 H), 7.56 (d, 1 H), 7.37 – 7.34 (m, 1 H), 7.14 – 7.11 (m, 2 H), 5.28 (s, 2 H), 4.56– 4.52 (m, 1H), 4.23 (s, 3 H), 3.29 – 3.23 (m, 1 H), 3.16 – 3.06 (m, 2 H), 2.91 – 2.87 (m, 1 H) 2.80 – 2.67 (m, 2 H);
Cpd 248 - En1	430.4	1H NMR (400 MHz, CDCl3) δ ppm: 8.58 (d, 1 H), 7.86 – 7.81 (m, 1 H), 7.68 – 7.64 (m, 2 H), 7.55 (d, 1 H), 7.46 (s, 1 H), 7.36 – 7.33 (m, 1 H), 7.12 (dd, 1 H), 6.34 – 6.04 (m, 1 H), 5.26 – 5.17 (m, 2 H), 4.24 (s, 3 H), 3.14 (d, 1 H), 2.90 (d, 1 H), 2.67 – 2.54 (m, 3 H), 2.39 – 2.23 (m, 2 H), 1.59 – 1.54 (m, 1 H), 1.46 – 1.39 (m, 2 H)
Cpd 248 - En2	430.4	1H NMR (400 MHz, DMSO-D6) δ ppm: 8.58 (d, 1 H), 7.86 – 7.81 (m, 1 H), 7.68 – 7.64 (m, 2 H), 7.55 (d, 1 H), 7.46 (s, 1 H), 7.36 – 7.33 (m, 1 H), 7.12 (dd, 1 H), 6.34 – 6.03 (m, 1 H), 5.26 – 5.17 (m, 2 H), 4.24 (s, 3 H), 3.13 (d, 1 H), 2.90 (d, 1 H), 2.71 – 2.61 (m, 3 H), 2.39 – 2.32 (m, 1 H), 2.28 – 2.23 (m, 1 H), 1.59 -1.54 (m, 3 H);
Cpd 251 - En1	407.2	1H NMR (400 MHz, DMSO-D6) δ ppm: 8.59 (d, 1 H), 8.49 (d, 1 H), 7.85 (dt, 1 H), 7.64 - 7.57 (m, 3 H), 7.38 - 7.34 (m, 2 H), 7.13 - 7.10 (dd, 1 H), 6.24 (d, 1 H), 5.21 - 5.20 (m, 3 H), 4.92 (t, 1 H), 4.24 (s, 3 H), 3.81 - 3.73 (m, 5 H).
Cpd 251 - En2	407.3	1H NMR (400 MHz, DMSO-D6) δ ppm: 8.59 (d, 1 H), 8.49 (d, 1 H), 7.85 (dt, 1 H), 7.64 - 7.57 (m, 3 H), 7.38 - 7.35 (m, 2 H), 7.12 - 7.10 (dd, 1 H), 6.24 (d, 1 H), 5.21 - 5.18 (m, 3 H), 4.92 (bs, 1 H), 4.24 (s, 3 H), 3.81 - 3.76 (m, 5 H).
Cpd 252 - En1	418.3	1H NMR (400 MHz, DMSO-D6) δ ppm: 8.60 (d, 1 H), 8.49 (d, 1 H), 8.24 (d, 1 H), 7.85 - 7.90 (m, 1 H), 7.68 - 7.73 (m, 1 H), 7.58 - 7.62 (m, 2 H), 7.33 - 7.39 (m, 2 H), 7.17 - 7.20 (m, 1 H), 7.08 – 7.10 (m, 2 H), 5.12 - 5.22 (m, 2 H), 4.96 (brs, 1 H), 4.47 – 4.52 (m, 1 H), 4.13 (s, 3 H), 3.53 - 3.63 (m, 1 H), 3.49 - 3.51 (m, 1H), 3.14 - 3.18 (m, 1 H), 2.98 - 3.04 (m, 1 H).

Cpd 252 - En2	418.3	1H NMR (400 MHz, DMSO-D6) δ ppm: 8.60 (d, 1 H), 8.49 (d, 1 H), 8.24 (d, 1 H), 7.85 - 7.90 (m, 1 H), 7.68 - 7.73 (m, 1 H), 7.58 - 7.62 (m, 2 H), 7.33 - 7.39 (m, 2 H), 7.17 - 7.20 (m, 1 H), 7.08 – 7.10 (m, 2 H), 5.12 - 5.22 (m, 2 H), 4.96 (brs, 1 H), 4.47 – 4.52 (m, 1 H), 4.13 (s, 3 H), 3.53 - 3.63 (m, 1 H), 3.49 - 3.51 (m, 1H), 3.14 - 3.18 (m, 1 H), 2.98 - 3.04 (m, 1 H).
Cpd 253 - En1	396.3	(400 MHz, DMSO) δ ppm: 8.59 (d, 1 H), 7.96 (s, 1 H), 7.87- 7.83 (m, 2 H), 7.65 - 7.59 (m, 2 H), 7.38 – 7.35 (m, 1 H), 7.17 (s, 1 H), 7.13 – 7.10 (m, 1 H), 5.24 (s, 1 H), 5.20 (s, 2 H), 4.22 (s, 3 H), 3.69 – 3.62 (m, 2 H), 3.34 (s, 1 H), 3.25 – 3.19 (m, 1 H), 2.49 – 2.41 (m, 2 H)
Cpd 253 - En2	396.2	(400 MHz, DMSO) δ ppm: 8.59 (d, 1 H), 7.96 (s, 1 H), 7.87- 7.83 (m, 2 H), 7.65 - 7.59 (m, 2 H), 7.38 – 7.35 (m, 1 H), 7.17 (s, 1 H), 7.13 – 7.10 (m, 1 H), 5.24 (s, 1 H), 5.20 (s, 2 H), 4.22 (s, 3 H), 3.69 – 3.62 (m, 2 H), 3.34 (s, 1 H), 3.25 – 3.19 (m, 1 H), 2.49 – 2.41 (m, 2 H)
Cpd 254 - En1	395.1	(400 MHz, DMSO-D6) δ ppm: 8.79 (d, 1 H), 8.58 (d, 1 H), 7.82 - 7.86 (m, 1 H), 7.66 (d, 1 H), 7.34 – 7.37 (m, 1 H), 7.12 – 7.17 (m, 2 H), 5.27 (t, 1 H), 5.20 (s, 2H), 4.79 - 4.85 (m, 1 H), 4.24 (s, 3 H), 3.83 – 3.87 (m, 1 H), 3.12 – 3.81 (m, 1H).
Cpd 254 - En2	395.1	(400 MHz, DMSO-D6) δ ppm: 8.79 (d, 1 H), 8.57 – 8.58 (m, 1 H), 7.82 - 7.86 (m, 1 H), 7.66 (d, 1 H), 7.34 – 7.37 (m, 1 H), 7.12 – 7.17 (m, 2 H), 5.27 (t, 1 H), 5.18 (s, 2H), 4.79 - 4.85 (m, 1 H), 4.25 (m, 3 H), 3.83 – 3.87 (m, 1 H), 3.76 – 3.81 (m, 1H).
Cpd 255 - En1	423.4	(400 MHz, DMSO-D6) δ ppm: 8.64 (d, 1 H), 8.07 (s, 1 H), 7.97 (t, 1 H), 7.62 - 7.68 (m, 2 H), 7.48 (t, 1 H), 7.09 - 7.13 (m, 2 H), 5.24 (s, 2 H), 4.19 (s, 3 H), 3.62 - 3.69 (m, 2 H), 3.09 - 3.19 (m, 1 H), 2.66 - 2.74 (m, 3 H), 1.44 (s, 3 H).
Cpd 255 - En2	423.5	(400 MHz, DMSO-D6) δ ppm: 8.57 (d, 1 H), 8.05 (s, 1 H), 7.84 (dt, 1 H), 7.61 (d, 2 H), 7.55 (t, 1 H), 7.34 – 7.37 (m, 2 H), 7.09 – 7.12 (m, 2 H), 5.20 – 5.23 (m, 1 H), 5.18 (s, 2 H), 4.19 (s, 3 H), 3.64 - 3.66 (m, 2 H), 3.12 - 3.19 (m, 1 H), 2.68 - 2.74 (m, 1 H), 1.45 (s, 3 H).
Cpd 256	312.3	(400 MHz, DMSO-D6) δ ppm: 8.20 (s, 1 H), 7.79 (d, 1 H), 7.57 - 7.61 (dt, 1 H), 7.39 - 7.45 (m, 2 H), 7.23 - 7.29 (m, 2 H), 7.07 - 7.09 (dd, 1 H), 5.18 (s, 2 H), 4.58 (t, 2 H), 3.69 - 3.72 (m, 2 H)
Cpd 257	294.1	(400 MHz, DMSO-D6) δ ppm: 8.19 (s, 1 H), 7.68 (d, 1 H), 7.49 (d, 2 H), 7.32 - 7.42 (m, 4 H), 7.10 (dd, 1 H), 5.14 (s, 2 H), 4.57 (t, 2 H), 3.68 - 3.72 (m, 2 H)
Cpd 258 - En1	385.4	(400 MHz, DMSO-D6) δ ppm: 8.59 (d, 1 H), 7.85 (t, 1 H), 7.55 - 7.64 (m, 3 H), 7.36 (t, 1 H), 7.18 (s, 1 H), 7.11 (dd, 1 H), 5.19 (s, 2 H), 4.99 (s, 1 H), 4.22 (s, 3 H), 3.54 - 3.68 (m, 4 H), 3.31 (s, 3 H), 1.37 (s, 3 H).
Cpd 258 - En2	385.3	(400 MHz, DMSO-D6) δ ppm: 8.59 (d, 1 H), 7.85 (t, 1 H),7.55 - 7.64 (m, 3 H), 7.36 (t, 1 H), 7.18 (s, 1 H), 7.11 (dd, 1 H), 5.19 (s, 2H), 4.99 (s, 1 H), 4.22 (s, 3 H), 3.54 - 3.68 (m, 4 H), 3.31 (s, 3 H), 1.37 (s, 3 H).
Cpd 259	357.2	(400 MHz, DMSO-D6) δ ppm: 8.58 – 8.59 (d, 1 H), 792 – 7.94 (d, 1 H), 7.83 – 7.87 (t, 1 H), 7.58 – 7.63 (t, 2 H), 7.35 - 7.38 (t, 1 H), 7.25 (s, 1 H), 7.08 – 7.11 (dd, 1 H), 5.19 (s, 2 H), 4.76 – 4.79 (t, 2 H), 4.24 (s, 3 H), 4.01 – 4.06 (m, 1 H), 3.57 – 3.60 (t, 4 H)
Cpd 260	386.2	(400 MHz, DMSO-D6) δ ppm: 7.66 (d, 1 H), 7.61 - 7.57 (m, 1 H), 7.40 - 7.44 (m, 2 H), 7.23 - 7.29 (m, 2 H), 7.07 - 7.10 (dd, 1 H), 5.19 (s, 2 H), 4.77 (t, 2 H), 4.55 - 4.63 (m, 3 H), 3.86 (t, 2 H), 3.61 - 3.64 (m, 4 H)

Cpd 261	356.2	(400 MHz, DMSO-d6) δ ppm: 7.69 (d, 1 H), 7.59 (dt, 1 H), 7.44–7.41 (m, 2 H), 7.29–7.22 (m, 2 H), 7.07 (dd, 1 H), 5.18 (s, 2 H), 4.82 (brs, 1 H), 4.64 (t, 2 H), 3.94 (t, 2 H), 3.63–3.57 (m, 4 H)
Cpd 262	374.2	(400 MHz, DMSO-d6) δ ppm: 7.98 (d, 1 H), 7.62–7.59 (m, 2 H), 7.47–7.42 (m, 1 H), 7.29–7.23 (m, 3 H), 7.04 (dd, 1 H), 5.15 (s, 2 H), 4.77 (t, 2 H), 4.25 (s, 3 H), 4.08–4.00 (m, 1 H), 3.61–3.58 (m, 4 H).

[0330] *Chiral analytical data*

Chiral SFC						
Cpd Code	Column Name	co-solvent	co-solvent %	Flow [g/min]	RT [min]	*Purity [%]*
Cpd 002 - En1	(8)	MeOH	40	3	1.13	99.7
Cpd 002 - En2	(8)	MeOH	40	3	3.1	97.7
Cpd 003 - En1	(9)	MeOH	15	3	5.29	99.3
Cpd 003 - En2	(9)	MeOH	15	3	6.53	96.4
Cpd 151 - En1	(11)	0.3% IPAmine in MeOH	50	2	3.4	99.7
Cpd 151 - En2	(11)	0.3% IPAmine in MeOH	50	2	3.82	99.9
Cpd 154 - En1	(11)	0.3%IPAmine in MeOH	60	2	2.62	>99.9
Cpd 154 - En2	(11)	0.3%IPAmine in MeOH	60	2	3.09	99.8
Cpd 155 - En1	(11)	0.3%IPAmine in MeOH	60	2	5.08	>99.9
Cpd 155 - En2	(11)	0.3%IPAmine in MeOH	60	2	6.14	99.7
Cpd 157 - En1	(11)	0.3%IPAmine in MeOH	70	2	3.12	>99.9
Cpd 157 - En2	(11)	0.3%IPAmine in MeOH	70	2	3.88	99.8
Cpd 159 - En1	(1)	MeOH	30	3	2.91	98.8
Cpd 159 - En2	(1)	MeOH	30	3	3.52	95.9
Cpd 160 - En1	(11)	0.3%IPAmine in MeOH	60	2	3.89	>99.9
Cpd 160 - En2	(11)	0.3%IPAmine in MeOH	60	2	4.73	98.1
Cpd 161 - En1	(6)	MeOH	70	3	2.8	99.8
Cpd 161 - En2	(6)	MeOH	70	3	3.54	99.5
Cpd 162 - En1	(11)	0.3%IPAmine in MeOH	70	2	10.57	>99
Cpd 162 - En2	(11)	0.3%IPAmine in MeOH	70	2	12.87	>99

Cpd 163 - En1	(4)	MeOH	40	4	6.99	99
Cpd 163 - En2	(4)	MeOH	40	4	9.13	95.5
Cpd 164 - En1	(1)	MeOH	40	3	2.53	99.9
Cpd 164 - En2	(1)	MeOH	40	3	4.76	99.8
Cpd 165 - En1	(9)	EtOH	25	3	6.49	99.8
Cpd 165 - En2	(9)	EtOH	25	3	7.62	99.6
Cpd 166 - En1	(7)	MeOH	50	4	3.99	99.9
Cpd 166 - En2	(7)	MeOH	50	4	5.45	99.7
Cpd 167 - En1	(7)	0.3% IPAmine in MeOH	50	2	4.58	99.5
Cpd 167 - En2	(7)	0.3% IPAmine in MeOH	50	2	5.11	99.3
Cpd 168 - En1	(1)	MeOH	40	3	2.41	99.5
Cpd 168 - En2	(1)	MeOH	40	3	3.64	96
Cpd 169 - En1	(10)	0.5%DEA in MeOH	40	3	2.68	99.9
Cpd 169 - En2	(10)	0.5%DEA in MeOH	40	3	3.56	99.8
Cpd 170 - En1	(5)	MeOH	35	3	3.41	99.9
Cpd 170 - En2	(5)	MeOH	35	3	4.29	99.2
Cpd 171 - En1	(5)	0.5%DEA in MeOH	30	3	3.58	99.9
Cpd 171 - En2	(5)	0.5%DEA in MeOH	30	3	4.15	99.1
Cpd 172 - En1	(2)	MeOH	40	3	2.9	99.5
Cpd 172 - En2	(2)	MeOH	40	3	6.8	99.8
Cpd 173 - En1	(2)	IPA	30	3	2.62	99.7
Cpd 173 - En2	(2)	IPA	30	3	3.87	97.9
Cpd 174 - En1	(1)	MeOH	40	3	2.04	98.9
Cpd 174 - En2	(1)	MeOH	40	3	2.91	88.4
Cpd 175 - En1	(10)	MeOH	40	3	2.25	99.9
Cpd 175 - En2	(10)	MeOH	40	3	3.01	99.7
Cpd 177 - En1	(5)	0.5%DEA in MeOH	30	3	3.03	99.8

Cpd 177 - En2	(5)	0.5%DEA in MeOH	30	3	3.68	99.2
Cpd 178 - En1	(9)	MeOH	30	3	4.3	99.9
Cpd 178 - En2	(9)	MeOH	30	3	4.87	97.7
Cpd 179 - En1	(11)	0.5%IPAmine in MeOH	25	2	10.2	>99.9
Cpd 179 - En2	(11)	0.5%IPAmine in MeOH	25	2	11.56	97.6
Cpd 180 - En1	(3)	MeOH	40	3	4.42	99.8
Cpd 180 - En2	(3)	MeOH	40	3	5.44	99.3
Cpd 181 - En1	(11)	0.1%NH3 in MeOH	70	2	5.91	92.3
Cpd 181 - En2	(11)	0.1%NH3 in MeOH	70	2	7.07	96.8
Cpd 183 - En1	(7)	MeOH	30	3	2.57	99.9
Cpd 183 - En2	(7)	MeOH	30	3	3.46	99.5
Cpd 185 - En1	(1)	MeOH	35	3	1.56	99.5
Cpd 185 - En2	(1)	MeOH	35	3	2.4	99.3
Cpd 186 - En1	(3)	0.5%DEA in MeOH	30	3	4.1	99.9
Cpd 186 - En2	(3)	0.5%DEA in MeOH	30	3	7.18	99.8
Cpd 188 - En1	(10)	MeOH	40	3	1.88	99.7
Cpd 188 - En2	(10)	MeOH	40	3	2.29	99.3
Cpd 190 - En1	(1)	MeOH	35	3	2.45	99.3
Cpd 190 - En2	(1)	MeOH	35	3	3.21	97.4
Cpd 192 - En1	(1)	IPA	20	3	4.2	99.5
Cpd 192 - En2	(1)	IPA	20	3	5.63	95.2
Cpd 193 - En1	(1)	0.5%DEA in MeOH	20	3	2.47	99.2
Cpd 193 - En2	(1)	0.5%DEA in MeOH	20	3	3.29	95.1
Cpd 194 - En1	(1)	MeOH	40	3	1.82	99
Cpd 194 - En2	(1)	MeOH	40	3	2.52	97.5
Cpd 195 - En1	(7)	MeOH	40	3	5.13	99.9
Cpd 195 - En2	(7)	MeOH	40	3	7.25	98.8

Cpd 201 - En1	(13)	MeOH	25	3	2.33	99.9
Cpd 201 - En2	(13)	MeOH	25	3	3.35	99.7
Cpd 203 - En1	(16)	0.5%IPAmine in IPA	15	3	4.32	99.9
Cpd 203 - En2	(16)	0.5%IPAmine in IPA	15	3	5.22	96.5
Cpd 211 - En1	(15)	0.5%IPAmine in IPA	40	3	1.97	99.9
Cpd 211 - En2	(15)	0.5%IPAmine in IPA	40	3	3.29	99.8
Cpd 212 - En1	(2)	0.5%IPAmine in IPA	30	3	2.21	99.7
Cpd 212 - En2	(2)	0.5%IPAmine in IPA	30	3	3.71	99.2
Cpd 213 - En1	(2)	0.5%IPAmine in IPA	25	3	4.16	99.2
Cpd 213 - En2	(2)	0.5%IPAmine in IPA	25	3	6.7	99.4
Cpd 214 - En1	(2)	0.5%DEA in MeOH	40	3	1.64	99.9
Cpd 214 - En2	(2)	0.5%DEA in MeOH	40	3	3.59	99.9
Cpd 215 - En1	(3)	0.5%IPAmine in IPA	35	3	7.08	99.9
Cpd 215 - En2	(3)	0.5%IPAmine in IPA	35	3	10.68	99.6
Cpd 216 - En1	(2)	0.5%DEA in MeOH	30	3	4.64	99.5
Cpd 216 - En2	(2)	0.5%DEA in MeOH	30	3	6.57	98.6
Cpd 220 - En1	(7)	0.5%IPAmine in IPA	40	3	1.85	99.7
Cpd 220 - En2	(7)	0.5%IPAmine in IPA	40	3	6.96	99.9
Cpd 221 - En1	(2)	MeOH	50	3	4.76	99.7
Cpd 221 - En2	(2)	MeOH	50	3	9.25	97
Cpd 223 - En1	(7)	MeOH	40	4	3.81	99.8
Cpd 223 - En2	(7)	MeOH	40	4	5.7	98.6
Cpd 226- En1	(7)	MeOH	20	3	4.97	99.7
Cpd 226- En2	(7)	MeOH	20	3	8.22	99.1
Cpd 227 - En1	(7)	MeOH	15	3	1.8	99.9
Cpd 227 - En2	(7)	MeOH	15	3	2.84	99.5
Cpd 228 - En1	(7)	MeOH	30	3	4.92	98.4

Cpd 228 - En2	(7)	MeOH	30	3	7.26	99.9
Cpd 229 - En1	(7)	MeOH	30	3	2.36	99.9
Cpd 229 - En2	(7)	MeOH	30	3	6.9	99.9
Cpd 230 - En1	(7)	0.5%DEA in MeOH	40	3	2.8	99.7
Cpd 230 - En2	(7)	0.5%DEA in MeOH	40	3	5.02	99.1
Cpd 232 - En1	(17)	0.5%DEA in EtOH	20	3	6.5	99.9
Cpd 232 - En2	(17)	0.5%DEA in EtOH	20	3	7.6	99.4
Cpd 235 - En1	(2)	MeOH	30	3	1.68	99.9
Cpd 235 - En2	(2)	MeOH	30	3	3.8	99.9
Cpd 237 - En1	(3)	0.5%IPAmine in IPA	25	3	2.24	99.9
Cpd 237 - En2	(3)	0.5%IPAmine in IPA	25	3	4.06	99.4
Cpd 238 - En1	(7)	0.5%IPAmine in IPA	40	4	2.29	99.8
Cpd 238 - En2	(7)	0.5%IPAmine in IPA	40	4	3.94	98.5
Cpd 239 - En1	(7)	MeOH	30	3	12.16	99.9
Cpd 239 - En2	(7)	MeOH	30	3	15.79	99.8
Cpd 240 - En1	(3)	0.5%DEA in MeOH	40	3	4.14	99.4
Cpd 240 - En2	(3)	0.5%DEA in MeOH	40	3	4.85	95.1
Cpd 241 - En1	(5)	MeOH	25	3	2.11	99.1
Cpd 241 - En2	(5)	MeOH	25	3	2.56	94
Cpd 243 - En1	(7)	0.5%IPAmine in IPA	40	3	9.36	99.9
Cpd 243 - En2	(7)	0.5%IPAmine in IPA	40	3	12.19	99.4
Cpd 245 - En1	(14)	MeOH	10	3	1.82	99.8
Cpd 245 - En2	(14)	MeOH	10	3	2.37	98.5
Cpd 246 - En1	(2)	0.5%DEA in MeOH	30	3	1.69	99.9
Cpd 246 - En2	(2)	0.5%DEA in MeOH	30	3	3.31	97.1
Cpd 248 - En1	(7)	EtOH	35	3	3.58	99.7
Cpd 248 - En2	(7)	EtOH	35	3	4.47	99.8

Cpd 251 - En1	(17)	MeOH	40	3	3.65	99.8
Cpd 251 - En2	(17)	MeOH	40	3	4.79	99.4
Cpd 252 - En1	(4)	0.5%DEA in MeOH	40	3	6.43	97.7
Cpd 252 - En2	(4)	0.5%DEA in MeOH	40	3	7.84	99.9
Cpd 253 - En1	(12)	0.5%DEA in MeOH	30	3	2.83	99.9
Cpd 253 - En2	(12)	0.5%DEA in MeOH	30	3	3.21	99.9
Cpd 254 - En1	(7)	MeOH	15	3	4.41	99.9
Cpd 254 - En2	(7)	MeOH	15	3	5.71	99.8
Cpd 258 - En1	(3)	MeOH	30	3	3.32	99.9
Cpd 258 - En2	(3)	MeOH	30	3	4.01	99.5

[0331] *Chiralpak AD-3(4.6*150mm)3.5μm = (1); Chiralpak AD-H(4.6*250 mm)5 μm = (2); Chiralpak IC (4.6*250mm)5μm = (3); Chiralpak IE-3(4.6*150mm)3μm = (4); Chiralpak IF-3(4.6*150mm)3μm = (5); Chiralpak IF (4.6*250mm)5μm = (6); Chiralpak IG-3(4.6*150 mm)3μm = (7); ChiralCel OD-3(4.6*150mm)3μm = (8); ChiralCel OH-3(4.6*150mm)3μm = (9); ChiralCel OZ-3(4.6*150mm)3μm = (10); C-AMYLOSE A = (11) ; (R,R) WHELK-01 (4.6*150mm)3.5μm = (12) CHIRALART Amylose-C-Neo (4.6*250mm)5μm = (13); CHIRALCE OJ-H (4.6*150mm)5μm = (14); CHIRALCEL OD-H (4.6*250mm) 5μm = (15); LUX CELLULOSE-2 (4.6*150mm)3μm = (16); LUX CELLULOSE-4 (4.6*250mm) 5μm = (17).*

Chiral HPLC						
Cpd Code	Column	Phase A/B	Ratio A/B	Flow [mL/min]	RT [min]	*Purity [%]*
Cpd 158 - En1	(2)	Hex/EtOAc/ EtOH/IPAmine	70/15/15/0.1	1	5.96	>99
Cpd 158 - En2	(2)	Hex/EtOAc/ EtOH/IPAmine	70/15/15/0.1	1	6.87	98.1
Cpd 176 - En1	(3)	n-Hex / IPA	50 / 50	1	7.95	99.9
Cpd 176 - En2	(3)	n-Hex / IPA	50 / 50	1	15.98	99.9
Cpd 182 - En1	(1)	n-Hex / EtOH	90 /10	1	19.71	99.8
Cpd 182 - En2	(1)	n-Hex / EtOH	90 /10	1	25.94	99.8
Cpd 187 - En1	(5)	nHex / EtOH	80 / 20	1	12.61	99.6
Cpd 187 - En2	(5)	nHex / EtOH	80 / 20	1	16.15	97.6
Cpd 191 - En1	(4)	nHex / EtOH	90 / 10	1	14.25	98.7

Cpd 191 - En2	(4)	nHex / EtOH	90 / 10	1	16.89	99.1
Cpd 202 - En1	(6)	nHex / EtOH:IPA (1:1)	90/10	1	18.44	99.6
Cpd 202 - En2	(6)	nHex / EtOH:IPA (1:1)	90/10	1	20.33	95
Cpd 255 - En1	(7)	MeOH.NH3 / ACN	0.2 / 99.8	0.5	12.4	99.8
Cpd 255 - En2	(7)	MeOH.NH3 / ACN	0.2 / 99.8	0.5	14.35	99.6

[0332] Chiralcel ODH (250x4.6 mm) 5 µm = (1) ; Chiralpak IA (4.6x250 mm) 5 µm = (2); Chiralpak IG (250x4.6 mm) 5 µm = (3); Lux Amylose-2 (250x4.6mm) 5 µm = (4); Lux Cellulose-2 (250x4.6mm) 5 µm = (5) ; Chiralcel OX-H (250 x 4.6mm)5µm = (6); Chiralpak IC (4.6 x 250 mm)5µm = (7).

[0333] **Part B**

[0334] **Monitoring the TRPM3 ion channel driven Ca2+ uptake.**

[0335] In order to monitor the inhibition of the mouse TRPM3α2 (mTRPM3) ion channel by the compounds of the invention, a cellular system making use of an mTRPM3alpha2 or hTRPM3 overexpressing cell line (flip-in HEK293) was used. The TRPM3 channel was stimulated/opened with Pregnenolone sulfate (PS) (50µM) which results in Ca^{2+} influx.

[0336] For mTRPM3, the intracellular Ca^{2+} was measured with a Calcium responsive dye, Fluor-4 AM ester (Invitrogen). Cells were cultured until a confluence of 80-90%, washed with Versene (Invitrogen) and detached from the surface by a short incubation with 0.05% Trypsin (Invitrogen). The trypsination process was stopped by the addition of complete cell culture medium (DMEM, glutamax,10%FCS,NEAA,Pen-Strep). Cells were collected and resuspended in Krebs buffer without Calcium at RT.

[0337] Prior the cell seeding (±2000 cells/well into a black, 384 well plate (Greiner)) the diluted compound was added in the assay plate, together with the PS dissolved in Krebs buffer containing Calcium. This resulted in a 2.4mM Ca^{2+} assay solution. Directly after cell addition the plates were read on an Envision fluorescence reader (Perkin Elmer) by an Excitation of 485nM and emission at 535nM.

[0338] Channel inhibition was calculated compared to a non-PS stimulated control versus a condition stimulated with PS (50µM) with vehicle. The ability of the compounds of the invention to inhibit this activity was determined as: Percentage inhibition = [1-((RFU determined for sample with test compound present – RFU determined for sample with positive control inhibitor) divided by (RFU determined in the presence of vehicle – RFU determined for sample with positive control inhibitor))] * 100.

[0339] The activities of the Example compounds **cpd 001-262** tested are depicted in the table below. All tested compounds show an activity in the Fluo-4 AM assay. The activity ranges A, B and C refer to IC50 values in the Fluo-4 AM assay as follows: “A”: IC_{50} <1 µM; “B” : 1 µM ≤ IC_{50} ≤20 µM and “C” : IC_{50} > 20 µM.

[0340]

Cpd Code	IC50
Cpd 001	B
Cpd 002 - En1	C
Cpd 002 - En2	B
Cpd 003 - En1	A
Cpd 003 - En2	B
Cpd 004	B
Cpd 005	B
Cpd 006	C
Cpd 007	A
Cpd 008	B
Cpd 009	B
Cpd 010 - Dia1	B
Cpd 010 - Dia2	B
Cpd 011 - Dia1	B
Cpd 011 - Dia2	B
Cpd 012	B
Cpd 013	B
Cpd 014	B
Cpd 015	B
Cpd 016	A
Cpd 017	B
Cpd 018	B
Cpd 019	C
Cpd 020	B
Cpd 021	A
Cpd 022	B
Cpd 023	B
Cpd 024	B
Cpd 025	A
Cpd 026	A
Cpd 027	B
Cpd 028	B
Cpd 029	B
Cpd 030	C
Cpd 031	B
Cpd 032	B
Cpd 033	B
Cpd 034	B
Cpd 035	B
Cpd 036	B
Cpd 037	C
Cpd 038	B

Cpd Code	IC50
Cpd 100	B
Cpd 101	B
Cpd 102	C
Cpd 103	B
Cpd 104	C
Cpd 105	B
Cpd 106	B
Cpd 107	B
Cpd 108	B
Cpd 109	B
Cpd 110	B
Cpd 111	C
Cpd 112	C
Cpd 113	B
Cpd 114	C
Cpd 115	B
Cpd 116	A
Cpd 117	C
Cpd 118	B
Cpd 119	B
Cpd 120	C
Cpd 121	A
Cpd 122	B
Cpd 123	C
Cpd 124	C
Cpd 125	B
Cpd 126	B
Cpd 127	A
Cpd 128 - En1	B
Cpd 128 - En2	C
Cpd 129	B
Cpd 130	A
Cpd 131	B
Cpd 132 - En1	B
Cpd 132 - En2	B
Cpd 133	C
Cpd 134	B
Cpd 135	B
Cpd 136	B
Cpd 137	A
Cpd 138	B
Cpd 139	B

Cpd Code	IC50
Cpd 178 - En2	A
Cpd 179 - En1	B
Cpd 179 - En2	A
Cpd 180 - En1	A
Cpd 180 - En2	B
Cpd 181 - En1	C
Cpd 181 - En2	B
Cpd 182 - En1	A
Cpd 182 - En2	A
Cpd 183 - En1	A
Cpd 183 - En2	B
Cpd 184 - En1	B
Cpd 184 - En2	B
Cpd 185 - En1	B
Cpd 185 - En2	A
Cpd 186 - En1	B
Cpd 186 - En2	B
Cpd 187 - En1	C
Cpd 187 - En2	B
Cpd 188 - En1	B
Cpd 188 - En2	A
Cpd 189	A
Cpd 190 - En1	B
Cpd 190 - En2	A
Cpd 191 - En1	A
Cpd 191 - En2	A
Cpd 192 - En1	A
Cpd 192 - En2	A
Cpd 193 - En1	B
Cpd 193 - En2	C
Cpd 194 - En1	A
Cpd 194 - En2	A
Cpd 195 - En1	C
Cpd 195 - En2	A
Cpd 196	B
Cpd 197	B
Cpd 198	B
Cpd 199	C

Cpd 039	C	Cpd 140	C		
Cpd 040	B	Cpd 141	A		
Cpd 041	B	Cpd 142	B		
Cpd 042	B	Cpd 143	A		
Cpd 043	B	Cpd 144	C		
Cpd 044	B	Cpd 145	B		
Cpd 045	C	Cpd 146	C		
Cpd 046	B	Cpd 147	B		
Cpd 047	B	Cpd 148	B		
Cpd 048	B	Cpd 149	A		
Cpd 049	C	Cpd 150	B		
Cpd 050	B	Cpd 151 - En1	A		
Cpd 051	B	Cpd 151 - En2	B		
Cpd 052	B	Cpd 152	B		
Cpd 053	C	Cpd 153	C		
Cpd 054	B	Cpd 154 - En1	C		
Cpd 055	B	Cpd 154 - En2	A		
Cpd 056 - Dia1	B	Cpd 155 - En1	C		
Cpd 056 - Dia2	C	Cpd 155 - En2	B		
Cpd 057	B	Cpd 156	B		
Cpd 058	C	Cpd 157 - En1	B		
Cpd 059	C	Cpd 157 - En2	A		
Cpd 060	B	Cpd 158 - En1	B		
Cpd 061	B	Cpd 158 - En2	C		
Cpd 062	C	Cpd 159 - En1	B		
Cpd 063	B	Cpd 159 - En2	A		
Cpd 064	B	Cpd 160 - En1	B		
Cpd 065	B	Cpd 160 - En2	A		
Cpd 066	C	Cpd 161 - En1	A		
Cpd 067	C	Cpd 161 - En2	C		
Cpd 068	B	Cpd 162 - En1	B		
Cpd 069	C	Cpd 162 - En2	A		
Cpd 070	A	Cpd 163 - En1	A		
Cpd 071	B	Cpd 163 - En2	B		
Cpd 072	B	Cpd 164 - En1	B		
Cpd 073	B	Cpd 164 - En2	B		
Cpd 074	B	Cpd 165 - En1	B		
Cpd 075	B	Cpd 165 - En2	C		
Cpd 076	B	Cpd 166 - En1	B		
Cpd 077	B	Cpd 166 - En2	A		
Cpd 078	B	Cpd 167 - En1	C		
Cpd 079	C	Cpd 167 - En2	C		
Cpd 080 - Dia1	B	Cpd 168 - En1	B		
Cpd 080 - Dia2	C	Cpd 168 - En2	A		
Cpd 081	B	Cpd 169 - En1	C		

Cpd 082	B	Cpd 169 - En2	A		
Cpd 083	B	Cpd 170 -En1	B		
Cpd 084	B	Cpd 170 -En2	B		
Cpd 085	B	Cpd 171 -En1	A		
Cpd 086	B	Cpd 171 -En2	B		
Cpd 087	B	Cpd 172 - En1	C		
Cpd 088	C	Cpd 172 - En2	B		
Cpd 089	A	Cpd 173 - En1	A		
Cpd 090	B	Cpd 173 - En2	B		
Cpd 091	B	Cpd 174 - En1	B		
Cpd 092	B	Cpd 174 - En2	A		
Cpd 093	B	Cpd 175 - En1	A		
Cpd 094	B	Cpd 175 - En2	B		
Cpd 095	B	Cpd 176 - En1	A		
Cpd 096	B	Cpd 176 - En2	B		
Cpd 097	A	Cpd 177 - En1	A		
Cpd 098	B	Cpd 177 - En2	B		
Cpd 099	A	Cpd 178 - En1	A		

Cpd Code	IC50
Cpd 201 - En1	A
Cpd 201 - En2	A
Cpd 202 - En1	A
Cpd 202 - En2	A
Cpd 203 - En1	A
Cpd 203 - En2	A
Cpd 204	C
Cpd 205	C
Cpd 206	B
Cpd 207	C
Cpd 208	C
Cpd 209	C
Cpd 210	C
Cpd 211 - En1	B
Cpd 211 - En2	A
Cpd 212 - En1	B
Cpd 212 - En2	C
Cpd 213 - En1	B
Cpd 213 - En2	C
Cpd 214 - En1	C
Cpd 214 - En2	B
Cpd 215 - En1	C
Cpd 215 - En2	B
Cpd 216 - En1	C

Cpd Code	IC50
Cpd 221 - En1	B
Cpd 221 - En2	B
Cpd 223 - En1	C
Cpd 223 - En2	C
Cpd 226- En1	A
Cpd 226- En2	C
Cpd 227 - En1	A
Cpd 227 - En2	C
Cpd 228 - En1	A
Cpd 228 - En2	C
Cpd 229 - En1	B
Cpd 229 - En2	C
Cpd 230 - En1	C
Cpd 230 - En2	B
Cpd 232 - En1	B
Cpd 232 - En2	A
Cpd 234	A
Cpd 235 - En1	C
Cpd 235 - En2	B
Cpd 237 - En1	B
Cpd 237 - En2	C
Cpd 238 - En1	B
Cpd 238 - En2	B
Cpd 239 - En1	C

Cpd Code	IC50
Cpd 242	C
Cpd 243 - En1	C
Cpd 243 - En2	C
Cpd 245 - En1	C
Cpd 245 - En2	C
Cpd 246 - En1	C
Cpd 246 - En2	A
Cpd 248 - En1	C
Cpd 248 - En2	B
Cpd 251 - En1	C
Cpd 251 - En2	C
Cpd 252 - En1	C
Cpd 252 - En2	C
Cpd 253 - En1	A
Cpd 253 - En2	B
Cpd 254 - En1	B
Cpd 254 - En2	C
Cpd 255 - En1	B
Cpd 255 - En2	B
Cpd 256	C
Cpd 257	C
Cpd 258 - En1	B
Cpd 258 - En2	B
Cpd 259	B

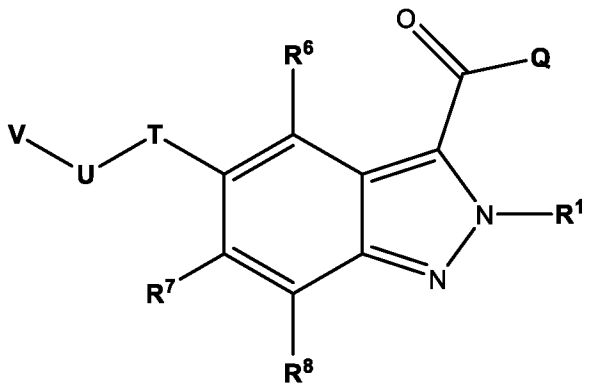
Cpd 216 - En2	B
Cpd 217	B
Cpd 218	C
Cpd 219	C
Cpd 220 - En1	C
Cpd 220 - En2	C

Cpd 239 - En2	C
Cpd 240 - En1	C
Cpd 240 - En2	C
Cpd 241 - En1	B
Cpd 241 - En2	C

Cpd 260	A
Cpd 261	B
Cpd 262	B

CLAIMS

1. A compound of formula (I), a stereo-isomeric form, a physiologically acceptable salt, solvate and/or polymorph thereof



(I)

wherein

$\mathbf{R^1}$ represents -F, -Cl, -Br, -I, -CN, -$\mathbf{R^W}$, -O$\mathbf{R^W}$, -OC(=O)$\mathbf{R^W}$, -N$\mathbf{R^W R^X}$, -N$\mathbf{R^W}$C(=O)$\mathbf{R^X}$, -S$\mathbf{R^W}$, -S(=O)$\mathbf{R^W}$, -S(=O)$_2\mathbf{R^W}$, -C(=O)$\mathbf{R^W}$, -C(=O)O$\mathbf{R^W}$, or -C(=O)N$\mathbf{R^W R^X}$;

Q represents -O$\mathbf{R^2}$ or -N$\mathbf{R^3 R^4}$;

$\mathbf{R^2}$ represents -$\mathbf{R^Y}$;

$\mathbf{R^3}$ represents -OH or -$\mathbf{R^Y}$;

$\mathbf{R^4}$ represents -$\mathbf{R^Y}$ or -S(=O)$_2\mathbf{R^Y}$;

or $\mathbf{R^3}$ and $\mathbf{R^4}$ together form a 4, 5, 6, 7 or 8 membered heterocycle containing 1 to 3 heteroatoms selected from N, O and S, saturated or unsaturated, unsubstituted or mono- or polysubstituted;

T represents -O- and **U** represents -C$\mathbf{R^5 R^{5'}}$-; or **T** represents -C$\mathbf{R^5 R^{5'}}$- and **U** represents -O-;

$\mathbf{R^5}$ and $\mathbf{R^{5'}}$ independently of one another represent -$\mathbf{R^Y}$;

$\mathbf{R^6}$, $\mathbf{R^7}$ and $\mathbf{R^8}$ independently of one another represent -F, -Cl, -Br, -I, -CN, -NO_2, -SF_5, -$\mathbf{R^W}$, -O$\mathbf{R^W}$, -OC(=O)$\mathbf{R^W}$, -N$\mathbf{R^W R^X}$, -N$\mathbf{R^W}$C(=O)$\mathbf{R^X}$, -S$\mathbf{R^W}$, -S(=O)$\mathbf{R^W}$, -S(=O)$_2\mathbf{R^W}$, -C(=O)$\mathbf{R^W}$, -C(=O)O$\mathbf{R^W}$, or -C(=O)N$\mathbf{R^W R^X}$;

V represents 3-14-membered heterocycloalkyl, saturated or unsaturated; 3-14-membered cycloalkyl, saturated or unsaturated; 5-14-membered aryl; C_1-C_6 alkyl or 5-14-membered heteroaryl; in each case unsubstituted, mono- or polysubstituted with substituents independently of one another selected from -F, -Cl, -Br, -I, -CF_3, -CF_2H, C_1-C_6 alkyl, -CN, -NO, -NO_2, =O, =S, -SF_5, -$\mathbf{R^Y}$, -O$\mathbf{R^Y}$, -OC(=O)$\mathbf{R^Y}$, -N$\mathbf{R^Y R^Z}$, -N$\mathbf{R^Y}$C(=O)$\mathbf{R^Z}$, -S$\mathbf{R^Y}$, -S(=O)$\mathbf{R^Y}$, -S(=O)$_2\mathbf{R^Y}$, -C(=O)$\mathbf{R^Y}$, -C(=O)O$\mathbf{R^Y}$, or -C(=O)N$\mathbf{R^Y R^Z}$;

wherein

R^W and R^X independently of one another and in each case independently represent
-H;
-C_1-C_6-alkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted;
-C_1-C_6-heteroalkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted;
3-14-membered cycloalkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted; wherein said 3-14-membered cycloalkyl is optionally connected through -C_1-C_6-alkylene- or -C_1-C_6-heteroalkylene-, in each case saturated or unsaturated, unsubstituted, mono- or polysubstituted; or
3-14-membered heterocycloalkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted; wherein said 3-14-membered heterocycloalkyl is optionally connected through -C_1-C_6-alkylene- or -C_1-C_6-heteroalkylene-, in each case saturated or unsaturated, unsubstituted, mono- or polysubstituted;

R^Y and R^Z independently of one another and in each case independently represent
-H;
-C_1-C_6-alkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted;
-C_1-C_6-heteroalkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted;
3-14-membered cycloalkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted; wherein said 3-14-membered cycloalkyl is optionally connected through -C_1-C_6-alkylene- or -C_1-C_6-heteroalkylene-, in each case saturated or unsaturated, unsubstituted, mono- or polysubstituted;
3-14-membered heterocycloalkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted; wherein said 3-14-membered heterocycloalkyl is optionally connected through -C_1-C_6-alkylene- or -C_1-C_6-heteroalkylene-, in each case saturated or unsaturated, unsubstituted, mono- or polysubstituted;
6-14-membered aryl, unsubstituted, mono- or polysubstituted; wherein said 6-14-membered aryl is optionally connected through -C_1-C_6-alkylene- or -C_1-C_6-heteroalkylene-, in each case saturated or unsaturated, unsubstituted, mono- or polysubstituted; or
5-14-membered heteroaryl, unsubstituted, mono- or polysubstituted; wherein said 5-14-membered heteroaryl is optionally connected through -C_1-C_6-alkylene- or -C_1-C_6-heteroalkylene-, in each case saturated or unsaturated, unsubstituted, mono- or polysubstituted;

or R^Y and R^Z together form a 4, 5, 6, 7 or 8 membered heterocycle containing 1 to 3 heteroatoms selected from N, O and S, saturated or unsaturated, unsubstituted or mono- or polysubstituted;

and wherein "mono- or polysubstituted" in each case independently means substituted with one or more substituents independently of one another selected from -F, -Cl, -Br, -I, -CN, -C_{1-6}-alkyl, -CF_3, -CF_2H, -CFH_2, -CF_2Cl, -$CFCl_2$, -C_{1-6}-alkylene-CF_3, -C_{1-6}-alkylene-CF_2H, -C_{1-6}-alkylene-CFH_2, -C_{1-6}-alkylene-O-CF_3, -C_{1-6}-alkylene-O-CF_2H, -C_{1-6}-alkylene-O-CFH_2, -C_{1-6}-alkylene-NH-C_{1-6}-alkylene-CF_3, -C_{1-6}-alkylene-N(C_{1-6}-alkyl)-C_{1-6}-alkylene-CF_3, -C(=O)-C_{1-6}-alkyl, -C_{1-6}-alkylene-C(=O)-C_{1-6}-alkyl, -C(=O)OH, -C_{1-6}-alkylene-C(=O)-OH, -C(=O)-OC_{1-6}-alkyl, -C_{1-6}-alkylene-C(=O)-OC_{1-6}-alkyl, -C(=O)O-C_{1-6}-alkylene-CF_3, -C(=O)-NH_2, -C_{1-6}-alkylene-C(=O)-NH_2, -C(=O)-NH(C_{1-6}-alkyl), -C_{1-6}-alkylene-C(=O)-NH(C_{1-6}-alkyl), -C(=O)-N(C_{1-6}-alkyl)$_2$, -C_{1-6}-alkylene-C(=O)-N(C_{1-6}-alkyl)$_2$, -C(=O)-NH(OH), -C_{1-6}-alkylene-C(=O)-NH(OH), -OH, -C_{1-6}-alkylene-OH, =O, -OCF_3, -OCF_2H, -$OCFH_2$, -OCF_2Cl, -$OCFCl_2$, -O-C_{1-6}-alkyl, -C_{1-6}-alkylene-O-C_{1-6}-alkyl, -O-C_{1-6}-alkylene-O-C_{1-6}-alkyl, -O-C_{1-6}-alkylene-NH_2, -O-C_{1-6}-alkylene-NH-C_{1-6}-alkyl, -O-C_{1-6}-alkylene-N(C_{1-6}-alkyl)$_2$, -O-C(=O)-C_{1-6}-alkyl, -C_{1-6}-alkylene-O-C(=O)-C_{1-6}-alkyl, -O-C(=O)-O-C_{1-6}-alkyl, -C_{1-6}-alkylene-O-C(=O)-O-C_{1-6}-alkyl, -O-C(=O)-NH(C_{1-6}-alkyl), -C_{1-6}-alkylene-O-C(=O)-NH(C_{1-6}-alkyl), -O-C(=O)-N(C_{1-6}-alkyl)$_2$, -C_{1-6}-alkylene-O-C(=O)-N(C_{1-6}-alkyl)$_2$, -O-S(=O)$_2$-NH_2, -C_{1-6}-alkylene-O-S(=O)$_2$-NH_2, -O-S(=O)$_2$-NH(C_{1-6}-alkyl), -C_{1-6}-alkylene-O-S(=O)$_2$-NH(C_{1-6}-alkyl), -O-S(=O)$_2$-N(C_{1-6}-alkyl)$_2$, -C_{1-6}-alkylene-O-S(=O)$_2$-N(C_{1-6}-alkyl)$_2$, -NH_2, -NO, -NO_2, -C_{1-6}-alkylene-NH_2, -NH(C_{1-6}-alkyl), -N(3-14-membered cycloalkyl)(C_{1-6}-alkyl), -N(C_{1-6}-alkyl)-C_{1-6}-alkylene-OH, -N(H)-C_{1-6}-alkylene-OH, -C_{1-6}-alkylene-NH(C_{1-6}-alkyl), -N(C_{1-6}-alkyl)$_2$, -C_{1-6}-alkylene-N(C_{1-6}-alkyl)$_2$, -NH-C(=O)-C_{1-6}-alkyl, -C_{1-6}-alkylene-NH-C(=O)-C_{1-6}-alkyl, -NH-C(=O)-O-C_{1-6}-alkyl, -C_{1-6}-alkylene-NH-C(=O)-O-C_{1-6}-alkyl, -NH-C(=O)-NH_2, -C_{1-6}-alkylene-NH-C(=O)-NH_2, -NH-C(=O)-NH(C_{1-6}-alkyl), -C_{1-6}-alkylene-NH-C(=O)-NH(C_{1-6}-alkyl), -NH-C(=O)-N(C_{1-6}-alkyl)$_2$, -C_{1-6}-alkylene-NH-C(=O)-N(C_{1-6}-alkyl)$_2$, -N(C_{1-6}-alkyl)-C(=O)-C_{1-6}-alkyl, -C_{1-6}-alkylene-N(C_{1-6}-alkyl)-C(=O)-C_{1-6}-alkyl, -N(C_{1-6}-alkyl)-C(=O)-O-C_{1-6}-alkyl, -C_{1-6}-alkylene-N(C_{1-6}-alkyl)-C(=O)-O-C_{1-6}-alkyl, -N(C_{1-6}-alkyl)-C(=O)-NH_2, -C_{1-6}-alkylene-N(C_{1-6}-alkyl)-C(=O)-NH_2, -N(C_{1-6}-alkyl)-C(=O)-NH(C_{1-6}-alkyl), -C_{1-6}-alkylene-N(C_{1-6}-alkyl)-C(=O)-NH(C_{1-6}-alkyl), -N(C_{1-6}-alkyl)-C(=O)-N(C_{1-6}-alkyl)$_2$, -C_{1-6}-alkylene-N(C_{1-6}-alkyl)-C(=O)-N(C_{1-6}-alkyl)$_2$, -NH-S(=O)$_2$OH, -C_{1-6}-alkylene-NH-S(=O)$_2$OH, -NH-S(=O)$_2$-C_{1-6}-alkyl, -C_{1-6}-alkylene-NH-S(=O)$_2$-C_{1-6}-alkyl, -NH-S(=O)$_2$-O-C_{1-6}-alkyl, -C_{1-6}-alkylene-NH-S(=O)$_2$-O-C_{1-6}-alkyl, -NH-S(=O)$_2$-NH_2, -C_{1-6}-alkylene-NH-S(=O)$_2$-NH_2, -NH-S(=O)$_2$-NH(C_{1-6}-alkyl), -C_{1-6}-alkylene-NH-S(=O)$_2$-NH(C_{1-6}-alkyl), -NH-S(=O)$_2$N(C_{1-6}-alkyl)$_2$, -C_{1-6}-alkylene-NH-S(=O)$_2$N(C_{1-6}-alkyl)$_2$, -N(C_{1-6}-alkyl)-S(=O)$_2$-OH, -C_{1-6}-alkylene-N(C_{1-6}-alkyl)-S(=O)$_2$-OH, -N(C_{1-6}-alkyl)-S(=O)$_2$-C_{1-6}-alkyl, -C_{1-6}-alkylene-N(C_{1-6}-alkyl)-S(=O)$_2$-C_{1-6}-alkyl, -N(C_{1-6}-alkyl)-S(=O)$_2$-O-C_{1-6}-alkyl, -C_{1-6}-alkylene-N(C_{1-6}-alkyl)-S(=O)$_2$-O-C_{1-6}-alkyl, -N(C_{1-6}-alkyl)-S(=O)$_2$-NH_2, -C_{1-6}-alkylene-N(C_{1-6}-alkyl)-S(=O)$_2$-NH_2, -N(C_{1-6}-alkyl)-S(=O)$_2$-NH(C_{1-6}-alkyl), -C_{1-6}-alkylene-N(C_{1-6}-

alkyl)-S(=O)$_2$-NH(C_{1-6}-alkyl), -N(C_{1-6}-alkyl)-S(=O)$_2$-N(C_{1-6}-alkyl)$_2$, -C_{1-6}-alkylene-N(C_{1-6}-alkyl)-S(=O)$_2$-N(C_{1-6}-alkyl)$_2$, -SH, =S, -SF_5, -SCF_3, -SCF_2H, -$SCFH_2$, -S-C_{1-6}-alkyl, -C_{1-6}-alkylene-S-C_{1-6}-alkyl, -S(=O)-C_{1-6}-alkyl, -C_{1-6}-alkylene-S(=O)-C_{1-6}-alkyl, -S(=O)$_2$-C_{1-6}-alkyl, -C_{1-6}-alkylene-S(=O)$_2$-C_{1-6}-alkyl, -S(=O)$_2$-OH, -C_{1-6}-alkylene-S(=O)$_2$-OH, -S(=O)$_2$-O-C_{1-6}-alkyl, -C_{1-6}-alkylene-S(=O)$_2$-O-C_{1-6}-alkyl, -S(=O)$_2$-NH_2, -C_{1-6}-alkylene-S(=O)$_2$-NH_2, -S(=O)$_2$-NH(C_{1-6}-alkyl), -C_{1-6}-alkylene-S(=O)$_2$-NH(C_{1-6}-alkyl), -S(=O)$_2$-N(C_{1-6}-alkyl)$_2$, -C_{1-6}-alkylene-S(=O)$_2$-N(C_{1-6}-alkyl)$_2$, 3-14-membered cycloalkyl, -C_{1-6}-alkylene-(3-14-membered cycloalkyl), 3 to 14-membered heterocycloalkyl, -C_{1-6}-alkylene-(3 to 14-membered heterocycloalkyl), -phenyl, -C_{1-6}-alkylene-phenyl, 5 to 14-membered heteroaryl, -C_{1-6}-alkylene-(5 to 14-membered heteroaryl), -O-(3-14-membered cycloalkyl), -O-(3 to 14-membered heterocycloalkyl), -O-phenyl, -O-(5 to 14-membered heteroaryl), -C(=O)-(3-14-membered cycloalkyl), -C(=O)-(3 to 14-membered heterocycloalkyl), -C(=O)-phenyl, -C(=O)-(5 to 14-membered heteroaryl), -S(=O)$_2$-(3-14-membered cycloalkyl), -S(=O)$_2$-(3 to 14-membered heterocycloalkyl), -S(=O)$_2$-phenyl, -S(=O)$_2$-(5 to 14-membered heteroaryl).

2. The compound of claim 1, wherein $\mathbf{R^3}$ represents -H.

3. The compound of claim 2, wherein $\mathbf{R^4}$ represents a residue other than -H.

4. The compound of any one of claims 1 to 3, wherein $\mathbf{R^1}$ represents -methyl or ethyl.

5. The compound of any one of claims 1 to 3, wherein **T** represents -O- and **U** represents -C$\mathbf{R^5R^{5'}}$-.

6. The compound of any one of claims 1 to 5, wherein the $\mathbf{R^Y}$ representing each of $\mathbf{R^5}$ and $\mathbf{R^{5'}}$ is H.

7. The compound of one of claims 1 to 6, wherein **V** represents (i) 5-14-membered heteroaryl selected from benzimidazole, benzisoxazole, benzoazole, benzodioxole, benzofuran, benzothiadiazole, benzothiazole, benzothiophene, carbazole, cinnoline, dibenzofuran, furane, furazane, imidazole, imidazopyridine, indazole, indole, indolizine, isobenzofuran, isoindole, isoquinoline, isothiazole, isoxazole, naphthyridine, oxadiazole, oxazole, oxindole, phthalazine, purine, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, pyrrole, quinazoline, quinoline, quinoxaline, tetrazole, thiadiazole, thiazole, thiophene, triazine, triazole, and [1,2,4]triazolo[4,3-a]pyrimidine; in each case unsubstituted, mono- or polysubstituted with substituents independently of one another

selected from -F, -Cl, -CN, -OH, =O, -C_{1-6}-alkyl, -CHF_2, -CF_3, -C_{1-6}-alkylene-NH_2, -C_{1-6}-alkylene-NHC(=O)O-C_{1-6}-alkyl, -C_{1-6}-alkylene-OH, -C_{1-6}-alkylene-CHF_2, -C_{1-6}-alkylene-CF_3, -C_{1-6}-alkylene-cyclopropyl, -cyclopropyl, -O-cyclopropyl, -C_{1-6}-alkylene-NHC(=O)-O-C_{1-6}-alkyl, -C(=O)O-C_{1-6}-alkyl, -N(C_{1-6}-alkyl)$_2$, -OC_{1-6}-alkyl, -OCF_3, -O-C_{1-6}-alkylene-N(C_{1-6}-alkyl)$_2$, -S(=O)$_2$-C_{1-6}-alkyl, -azetidine, -C_{1-6}-alkylene-O-tetrahydropyran, or -piperazine substituted with -C_{1-6}-alkyl; particularly in each case unsubstituted, mono- or polysubstituted with substituents independently of one another selected from -F, -Cl, -CN, -OH, =O, -C_{1-6}-alkyl, -CHF_2, -CF_3, -C_{1-6}-alkylene-NH_2, -C_{1-6}-alkylene-NHC(=O)O-C_{1-6}-alkyl, -C_{1-6}-alkylene-OH, -C_{1-6}-alkylene-NHC(=O)-O-C_{1-6}-alkyl, -C(=O)O-C_{1-6}-alkyl, -N(C_{1-6}-alkyl)$_2$, -OC_{1-6}-alkyl, -OCF_3, -O-C_{1-6}-alkylene-N(C_{1-6}-alkyl)$_2$, -S(=O)$_2$-C_{1-6}-alkyl, -azetidine, -C_{1-6}-alkylene-O-tetrahydropyran, or -piperazine substituted with -C_{1-6}-alkyl; or represents (ii) -oxetanyl, unsubstituted, mono- or polysubstituted.

8. The compound of any one of claims 1 to 6, wherein the 3-14-membered cycloalkyl, saturated or unsaturated within the definition of **V** is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, or cyclodecyl including unfused or unbridged, fused, or bridged cycloalkyls; in each case unsubstituted, mono- or polysubstituted with substituents independently of one another selected from -F, -Cl, -Br, -I, , CF_3, -CF_2H, C_1-C_6 alkyl, -CN, -NO, -NO_2, =O, =S, -SF_5, -$\mathbf{R^Y}$, -O$\mathbf{R^Y}$, -OC(=O)$\mathbf{R^Y}$, -N$\mathbf{R^Y}$$\mathbf{R^Z}$, -N$\mathbf{R^Y}$C(=O)$\mathbf{R^Z}$, -S$\mathbf{R^Y}$, -S(=O)$\mathbf{R^Y}$, -S(=O)$_2$$\mathbf{R^Y}$, -C(=O)$\mathbf{R^Y}$, -C(=O)O$\mathbf{R^Y}$, or -C(=O)N$\mathbf{R^Y}$$\mathbf{R^Z}$.

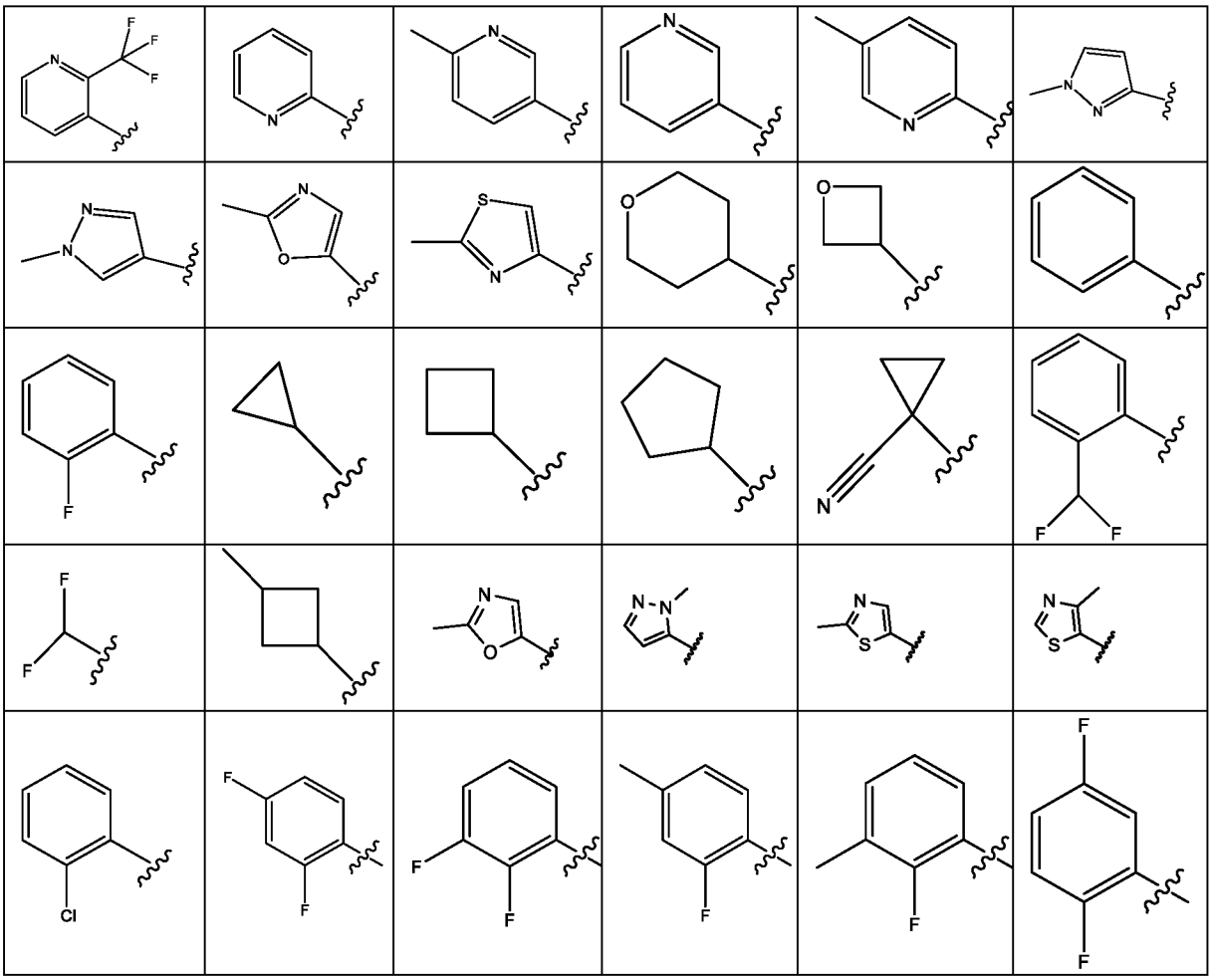
9. The compound of any one of claims 1 to 6 wherein the 5-14-membered aryl within the definition of **V** is phenyl or another 5-14-membered aryl, unsubstituted, mono- or polysubstituted with substituents independently of one another selected from -F, -Cl, -Br, -I, CF_3, -CF_2H, C_1-C_6 alkyl, -CN, -NO, -NO_2, =O, =S, -SF_5, -$\mathbf{R^Y}$, -O$\mathbf{R^Y}$, -OC(=O)$\mathbf{R^Y}$, -N$\mathbf{R^Y}$$\mathbf{R^Z}$, -N$\mathbf{R^Y}$C(=O)$\mathbf{R^Z}$, -S$\mathbf{R^Y}$, -S(=O)$\mathbf{R^Y}$, -S(=O)$_2$$\mathbf{R^Y}$, -C(=O)$\mathbf{R^Y}$, -C(=O)O$\mathbf{R^Y}$, or -C(=O)N$\mathbf{R^Y}$$\mathbf{R^Z}$.

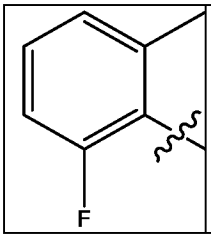
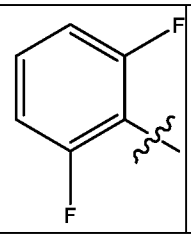
10. The compound of any one of claims 1 to 6 wherein the 3-14-membered heterocycloalkyl within the definition of **V** is selected from azepane, 1,4-oxazepane, azetane, azetidine, aziridine, azocane, diazepane, dioxane, dioxolane, dithiane, dithiolane, imidazolidine, isothiazolidine, isoxalidine, morpholine, oxazolidine, oxane, oxepane, oxetane, oxirane, piperazine, piperidine, pyrazolidine, pyrrolidine, quinuclidine, tetrahydrofurane, tetrahydropyrane, tetrahydrothiopyrane, thiazolidine, thietane, thiirane, thiolane, thiomorpholine, indoline, dihydrobenzofuran, dihydrobenzo-thiophene, 1,1-dioxothia-cyclohexane, 2-azaspiro[3.3]heptane, 2-oxaspiro[3.3]heptane, 7-azaspiro[3.5]nonane,

8-azabicyclo[3.2.1]octane, 9-azabicyclo[3.3.1]nonane, hexahydro-1H-pyrrolizine, hexahydro-cyclopenta[c]pyrrole, octahydro-cyclopenta[c]pyrrole, and octahydro-pyrrolo[1,2-a]pyrazine; in each case unsubstituted, mono- or polysubstituted with substituents independently of one another selected from -F, -Cl, -Br, -I, CF_3, $-CF_2H$, C_1-C_6 alkyl, -CN, -NO, $-NO_2$, =O, =S, $-SF_5$, $-\mathbf{R}^{Y}$, $-O\mathbf{R}^{Y}$, $-OC(=O)\mathbf{R}^{Y}$, $-N\mathbf{R}^{Y}\mathbf{R}^{Z}$, $-N\mathbf{R}^{Y}C(=O)\mathbf{R}^{Z}$, $-S\mathbf{R}^{Y}$, $-S(=O)\mathbf{R}^{Y}$, $-S(=O)_2\mathbf{R}^{Y}$, $-C(=O)\mathbf{R}^{Y}$, $-C(=O)O\mathbf{R}^{Y}$, or $-C(=O)N\mathbf{R}^{Y}\mathbf{R}^{Z}$.

11. The compound of any one of claims 1 to 6 wherein **V** represents C_1-C_6 alkyl or C_1-C_6 heteroalkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted with substituents independently of one another selected from -F, -Cl, -Br, -I, CF_3, $-CF_2H$, C_1-C_6 alkyl, -CN, -NO, $-NO_2$, =O, =S, $-SF_5$, $-\mathbf{R}^{Y}$, $-O\mathbf{R}^{Y}$, $-OC(=O)\mathbf{R}^{Y}$, $-N\mathbf{R}^{Y}\mathbf{R}^{Z}$, $-N\mathbf{R}^{Y}C(=O)\mathbf{R}^{Z}$, $-S\mathbf{R}^{Y}$, $-S(=O)\mathbf{R}^{Y}$, $-S(=O)_2\mathbf{R}^{Y}$, $-C(=O)\mathbf{R}^{Y}$, $-C(=O)O\mathbf{R}^{Y}$, or $-C(=O)N\mathbf{R}^{Y}\mathbf{R}^{Z}$.

12. The compound of any one of claims 1 to 6 wherein **V** is a residue selected from the group consisting of:



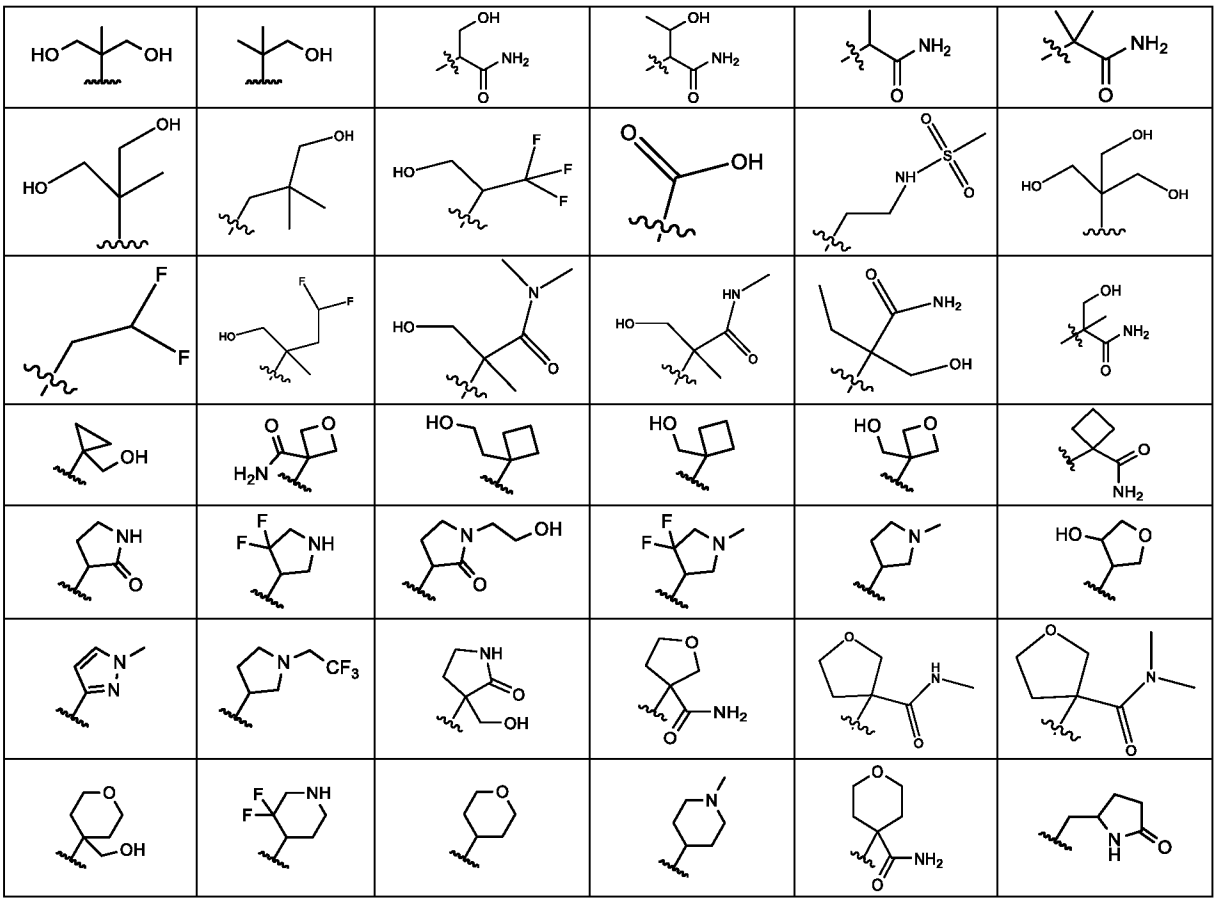
13. The compound according to claim 1 , wherein R^1 represents -H, -F, -Cl, -Br, -I, -C_{1-6}-alkyl, -O-C_{1-6}-alkyl, -C_{1-6}-alkylene-O-C_{1-6}-alkyl, -C_{1-6}-alkylene-NH(C_{1-6}-alkyl), -C_{1-6}-alkylene-N(C_{1-6}-alkyl)$_2$, -CF_3, -CF_2H, -CFH_2, -CF_2Cl, -$CFCl_2$, -C_{1-6}-alkylene-CF_3, -C_{1-6}-alkylene-CF_2H, -C_{1-6}-alkylene-CFH_2, -C_{1-6}-alkylene-NH-C_{1-6}-alkylene-CF_3, -C_{1-6}-alkylene-N(C_{1-6}-alkyl)-C_{1-6}-alkylene-CF_3, -C(=O)C_{1-6}-alkyl, -C(=O)OC_{1-6}-alkyl, -C(=O)NH_2, -C(=O)NHC_{1-6}-alkyl, -C(=O)N(C_{1-6}-alkyl)$_2$, -S(=O)-C_{1-6}-alkyl, -S(=O)$_2$-C_{1-6}-alkyl, -O-C_{1-6}-alkyl, -cyclopropyl unsubstituted, cyclobutyl unsubstituted, cyclopentyl unsubstituted or cyclohexyl unsubstituted.

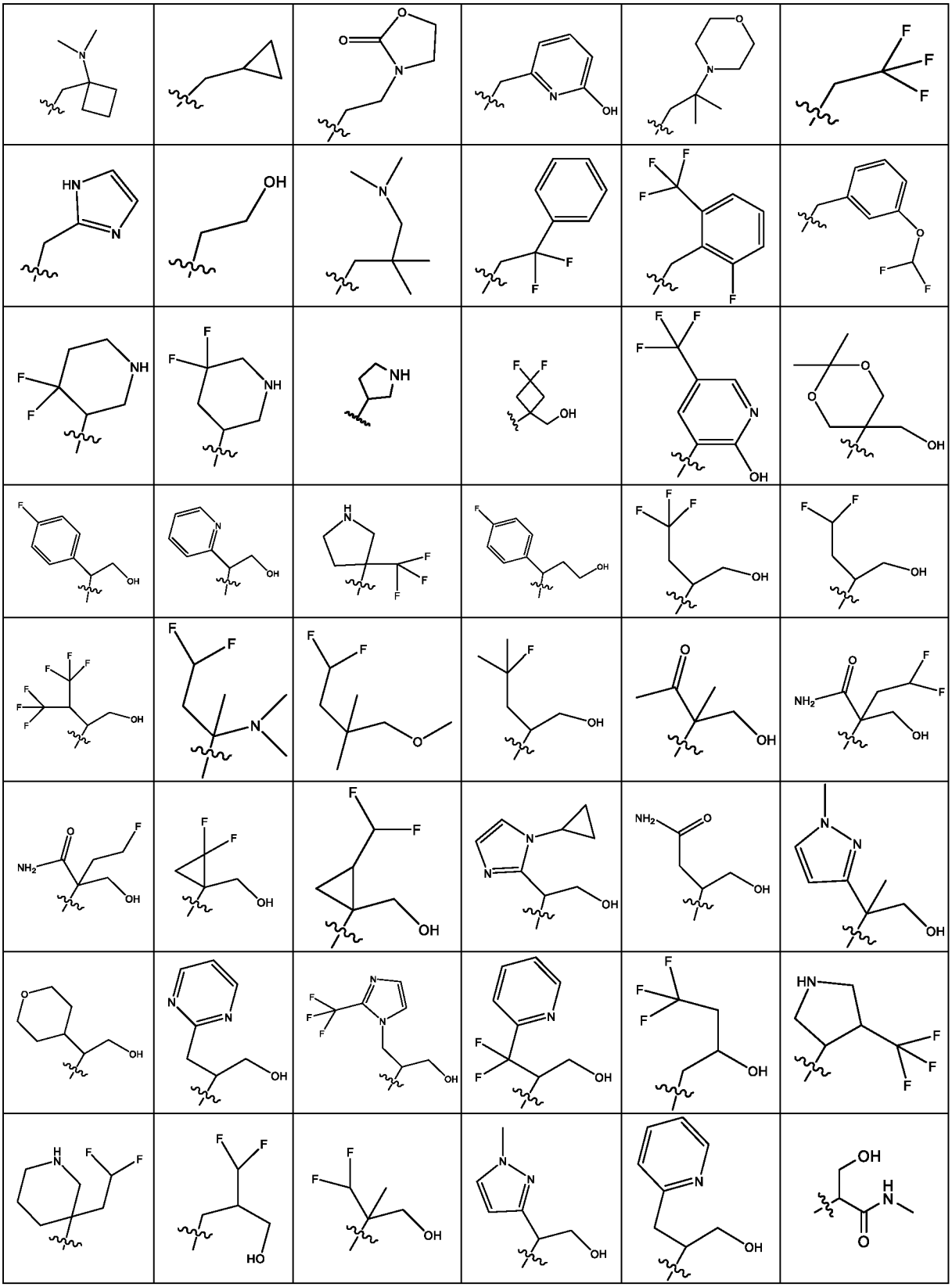
14. The compound according to claim 1 , wherein R^3 represents -H, -OH, -C_{1-6}-alkyl, -C_{1-6}-alkylene-OH, -C_{1-6}-alkylene-O-C_{1-6}-alkyl, -C_{1-6}-alkylene-NH_2, -C_{1-6}-alkylene-NH(C_{1-6}-alkyl), -C_{1-6}-alkylene-N(C_{1-6}-alkyl)$_2$, -CF_3, -CF_2H, -CFH_2, -CF_2Cl, -$CFCl_2$, -C_{1-6}-alkylene-CF_3, -C_{1-6}-alkylene-CF_2H, -C_{1-6}-alkylene-CFH_2, -C_{1-6}-alkylene-NH-C_{1-6}-alkylene-CF_3, or -C_{1-6}-alkylene-N(C_{1-6}-alkyl)-C_{1-6}-alkylene-CF_3.

15. The compound according to any one of claims 1 to 14, wherein R^4 represents
-H;
-S(=O)$_2$$C_{1-6}$-alkyl, saturated, unsubstituted, monosubstituted or polysubstituted with -F;
-S(=O)$_2$(3-14-membered cycloalkyl), saturated, unsubstituted;
-C_{1-6}-alkyl, saturated, unsubstituted mono- or polysubstituted ;
3-14-membered cycloalkyl or -C_{1-6}-alkylene-(3-14-membered cycloalkyl), each unsubstituted, mono- or polysubstituted;
3-14-membered heterocycloalkyl or -C_{1-6}-alkylene-(3-14-membered heterocycloalkyl), unsubstituted, mono- or polysubstituted;
-phenyl, or -C_{1-6}-alkylene-phenyl, each unsubstituted, mono- or polysubstituted; or
5-14-membered heteroaryl or -C_{1-6}-alkylene-(5-14-membered heteroaryl), each unsubstituted, mono- or polysubstituted.

16. The compound according to any one of claims 1 to 14 wherein R^4 represents a 3-14-membered cycloalkyl (preferably a 3, 4, 5 or 6-membered cycloalkyl), saturated or unsaturated, unsubstituted, mono- or polysubstituted; wherein said 3-14-membered cycloalkyl is connected through -C_1-C_6-alkylene-, saturated or unsaturated, unsubstituted, mono- or polysubstituted; or a 3-14-membered heterocycloalkyl (preferably a 4, 5 or 6-membered heterocycloalkyl), saturated or unsaturated, unsubstituted, mono- or polysubstituted; wherein said 3-14-membered heterocycloalkyl is connected through -C_1-C_6-alkylene-, saturated or unsaturated, unsubstituted, mono- or polysubstituted; or a 6-14-membered aryl (preferably a 6-membered aryl), unsubstituted, mono- or polysubstituted; wherein said 6-14-membered aryl is connected through -C_1-C_6-alkylene-, saturated or unsaturated, unsubstituted, mono- or polysubstituted; or a 5-14-membered heteroaryl (preferably a 5 or 6-membered heteroaryl), unsubstituted, mono- or polysubstituted; wherein said 5-14-membered heteroaryl is connected through -C_1-C_6-alkylene-, saturated or unsaturated, unsubstituted, mono- or polysubstituted.

17. The compound according to any one of claims 1 to 16 wherein R^3 is H and R^4 is a residue selected from the group consisting of:





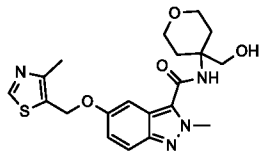
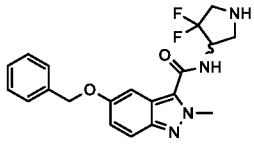
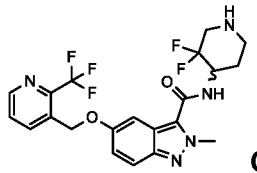
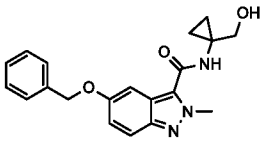
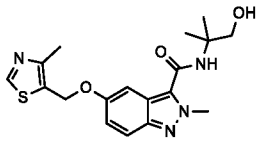
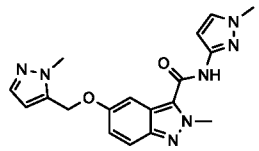
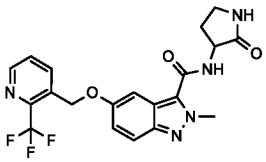
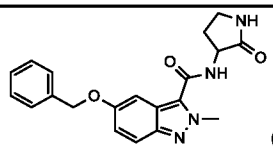
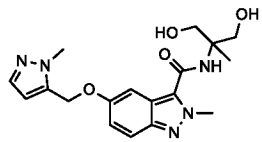
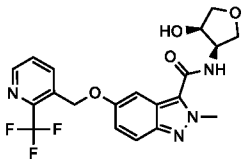
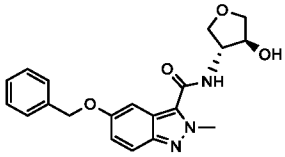
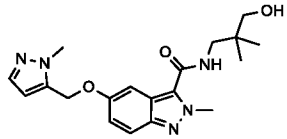
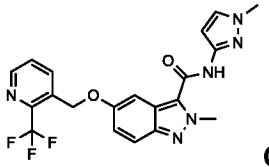
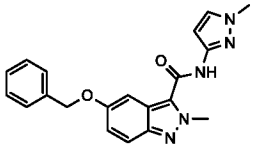
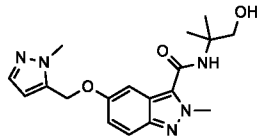
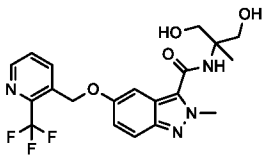
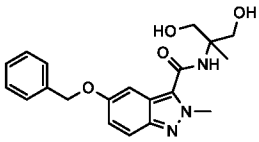
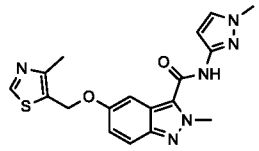
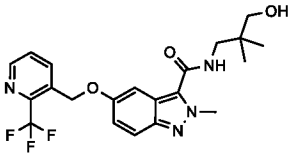
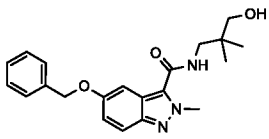
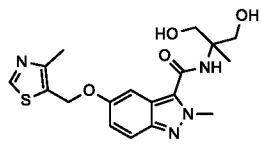
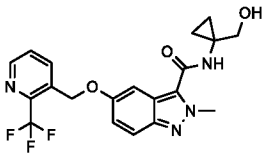
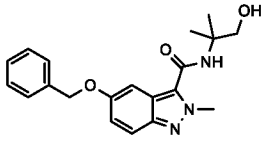
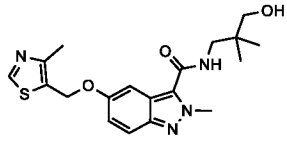
18. The compound of claim 1 wherein R^3 and R^4 together form a heterocycle selected from the group consisting of pyrrolidine, piperidine, morpholine, and piperazine, in each case

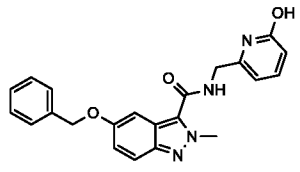
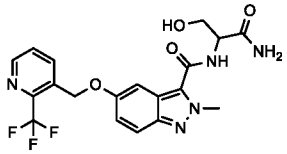
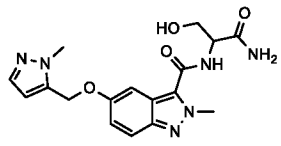
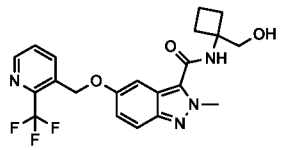
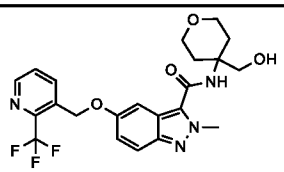
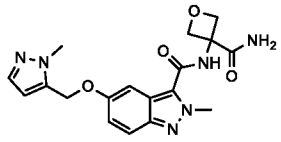
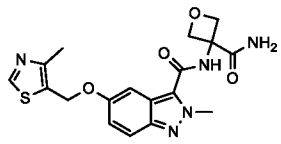
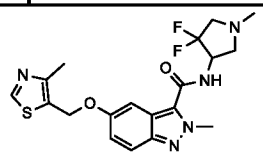
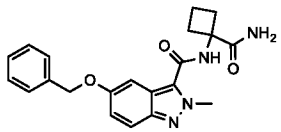
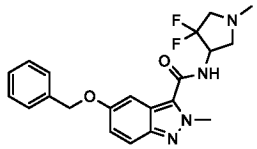
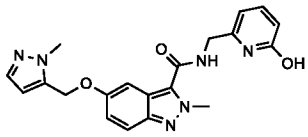
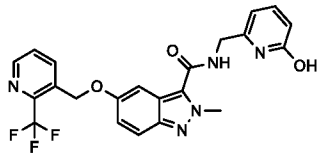
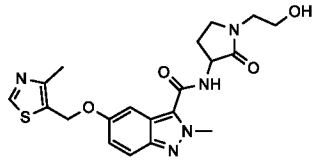
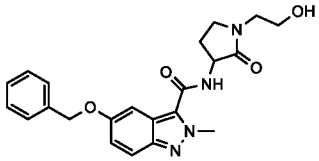
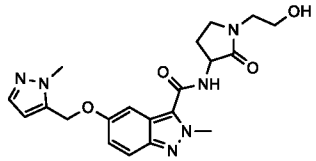
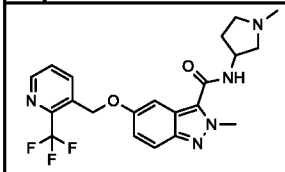
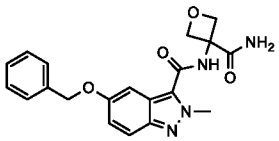
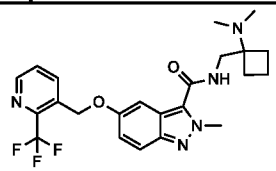
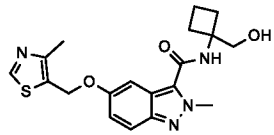
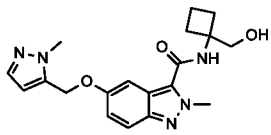
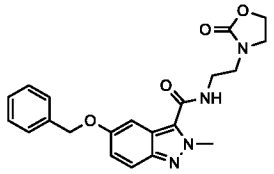
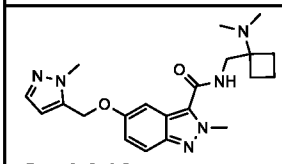
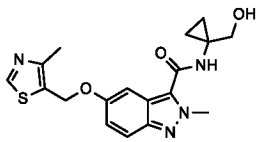
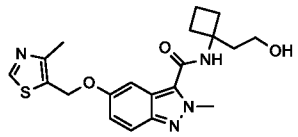
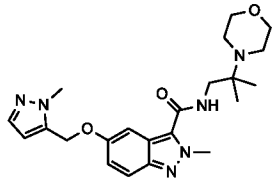
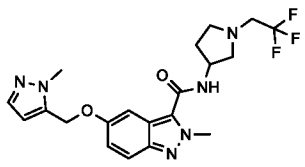
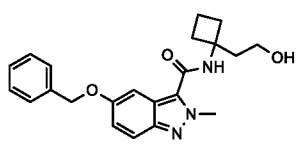
unsubstituted, mono- or polysubstituted with substituents independently of one another selected from the group consisting of -F, -C_{1-6}-alkyl, -NH_2, -$NHCH_3$, -$N(CH_3)_2$, -C(=O)NH-C_{1-6}-alkyl, -C(=O)N(C_{1-6}-alkyl)$_2$, -C(=O)O-C_{1-6}-alkyl, -NHC(=O)O-C_{1-6}-alkyl, -pyridyl unsubstituted, and 1,2,4-oxadiazole unsubstituted or monosubstituted with -C_{1-6}-alkyl.

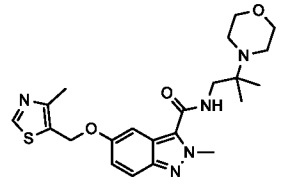
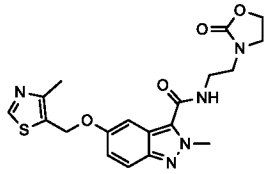
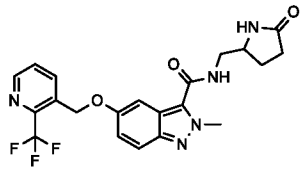
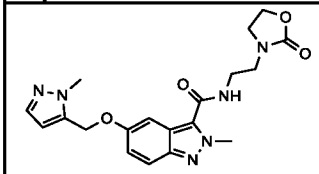
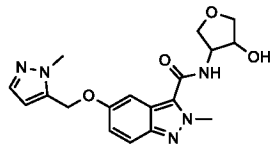
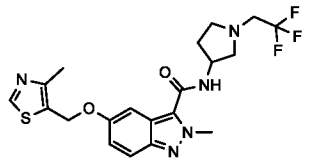
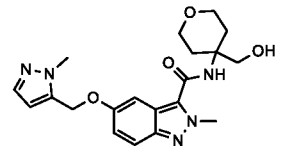
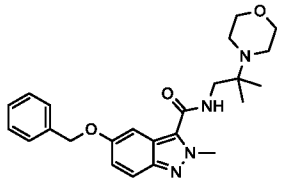
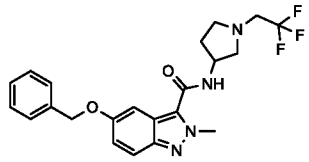
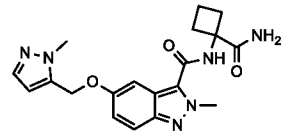
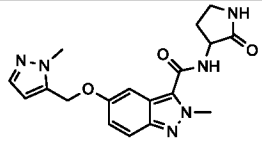
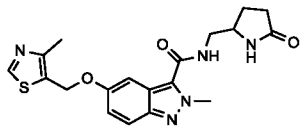
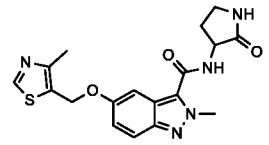
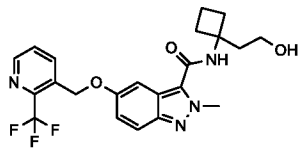
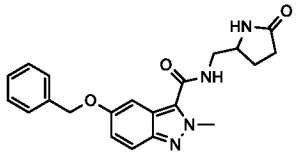
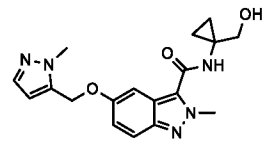
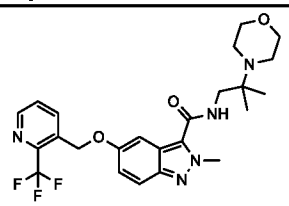
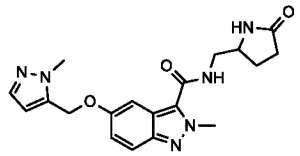
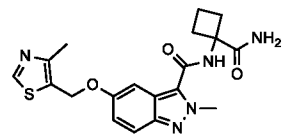
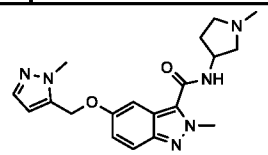
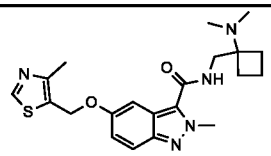
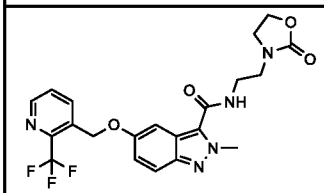
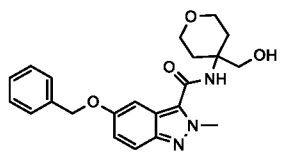
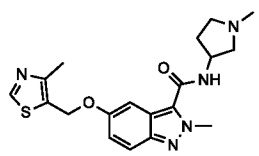
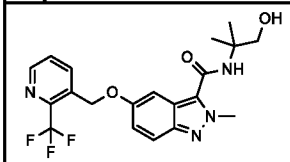
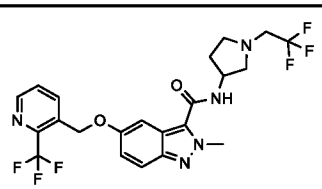
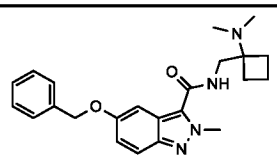
19. The compound of claim 1, wherein **R^5** and **$R^{5'}$** independently of one another represent
-H;
-C_1-C_6-alkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted;
-C_1-C_6-heteroalkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted;
3-14-membered cycloalkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted; wherein said 3-14-membered cycloalkyl is optionally connected through -C_1-C_6-alkylene- or -C_1-C_6-heteroalkylene-, in each case saturated or unsaturated, unsubstituted, mono- or polysubstituted.

20. The compound according to any one of claims 1 to 19, wherein **R^6**, **R^7** and **R^8** independently of one another represent
-H, -F, -Cl, -Br, -I, -OH, -SH, -SF_5, -CN, -NO_2, -C(=O)OH, -NH_2,
-C_{1-6}-alkyl, -CF_3, -CHF_2, -CH_2F,
-O-C_{1-6}-alkyl, -OCF_3, -$OCHF_2$, -OCH_2F,
-NHC_{1-6}-alkyl unsubstituted or substituted with one or more substituents independently of one another selected from -OH, =O, -F, -Cl, -Br, -I, -SH, =S, -CN, -CF_3, -CHF_2, -CH_2F, -OCF_3, -$OCHF_2$, -OCH_2F, SF_5, -NO_2, -C(=O)OH, -NH_2, and -C(=O)NH_2;
-N(C_{1-6}-alkyl)$_2$ unsubstituted or substituted with one or more substituents independently of one another selected from -OH, =O, -F, -Cl, -Br, -I, -SH, =S, -CN, -CF_3, -CHF_2, -CH_2F, -OCF_3, -$OCHF_2$, -OCH_2F, SF_5, -NO_2, -C(=O)OH, -NH_2, and -C(=O)NH_2;
-C(=O)OC_{1-6}-alkyl unsubstituted or substituted with one or more substituents independently of one another selected from -OH, =O, -F, -Cl, -Br, -I, -SH, =S, -CN, -CF_3, -CHF_2, -CH_2F, -OCF_3, -$OCHF_2$, -OCH_2F, SF_5, -NO_2, -C(=O)OH, -NH_2, and -C(=O)NH_2;
-OC(=O)C_{1-6}-alkyl unsubstituted or substituted with one or more substituents independently of one another selected from -OH, =O, -F, -Cl, -Br, -I, -SH, =S, -CN, -CF_3, -CHF_2, -CH_2F, -OCF_3, -$OCHF_2$, -OCH_2F, SF_5, -NO_2, -C(=O)OH, -NH_2, and -C(=O)NH_2;
or
-C_{1-6}-heteroalkyl unsubstituted or substituted with one or more substituents independently of one another selected from -OH, =O, -F, -Cl, -Br, -I, -SH, =S, -CN, -CF_3, -CHF_2, -CH_2F, -OCF_3, -$OCHF_2$, -OCH_2F, SF_5, -NO_2, -C(=O)OH, -NH_2, and -C(=O)NH_2.

21. The compound of claim 1, which is selected from the group consisting of compounds 001 – 199 as shown in the table below:

Structure and **Compound CODE**	Structure and **Compound CODE**	Structure and **Compound CODE**
 **Cpd 001**	 **Cpd 002**	 **Cpd 003**
 **Cpd 004**	 **Cpd 005**	 **Cpd 006**
 **Cpd 007**	 **Cpd 008**	 **Cpd 009**
 **Cpd 010**	 **Cpd 011**	 **Cpd 012**
 **Cpd 013**	 **Cpd 014**	 **Cpd 015**
 **Cpd 016**	 **Cpd 017**	 **Cpd 018**
 **Cpd 019**	 **Cpd 020**	 **Cpd 021**
 **Cpd 022**	 **Cpd 023**	 **Cpd 024**

 Cpd 025	 Cpd 026	 Cpd 027
 Cpd 028	 Cpd 029	 Cpd 030
 Cpd 031	 Cpd 032	 Cpd 033
 Cpd 034	 Cpd 035	 Cpd 036
 Cpd 037	 Cpd 038	 Cpd 039
 Cpd 040	 Cpd 041	 Cpd 042
 Cpd 043	 Cpd 044	 Cpd 045
 Cpd 046	 Cpd 047	 Cpd 048
 Cpd 049	 Cpd 050	 Cpd 051

 Cpd 052	 Cpd 053	 Cpd 054
 Cpd 055	 Cpd 056	 Cpd 057
 Cpd 058	 Cpd 059	 Cpd 060
 Cpd 061	 Cpd 062	 Cpd 063
 Cpd 064	 Cpd 065	 Cpd 066
 Cpd 067	 Cpd 068	 Cpd 069
 Cpd 070	 Cpd 071	 Cpd 072
 Cpd 073	 Cpd 074	 Cpd 075
 Cpd 076		 Cpd 078

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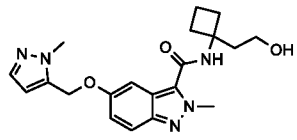
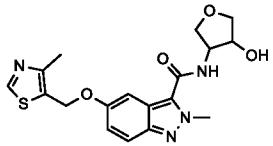
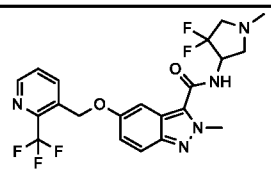
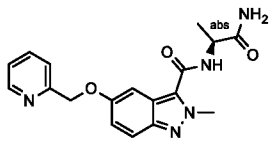
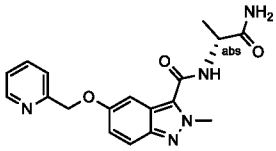
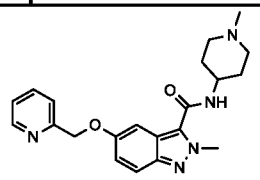
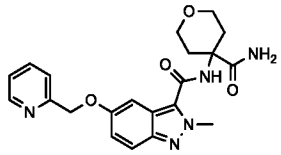
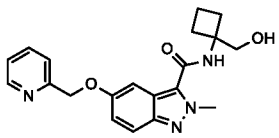
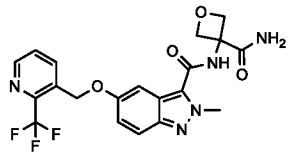
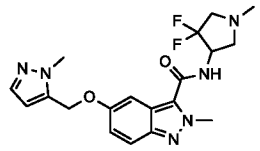
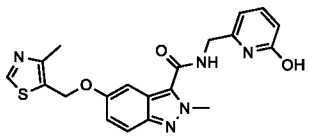
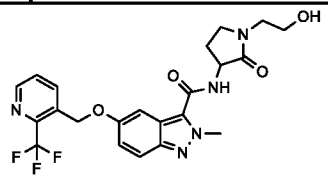
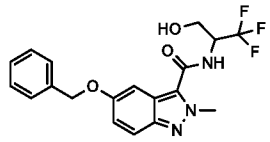
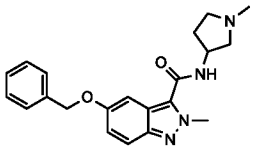
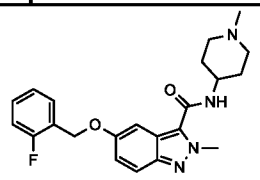
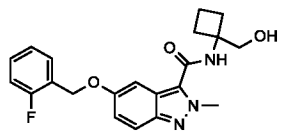
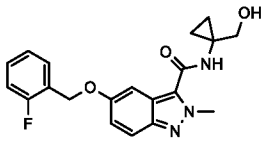
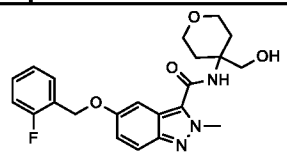
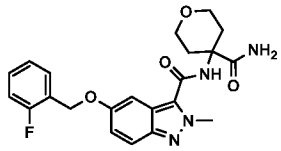
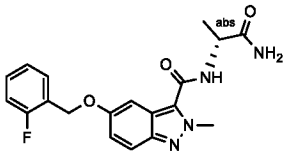
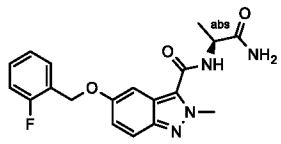
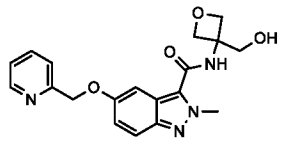
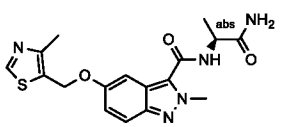
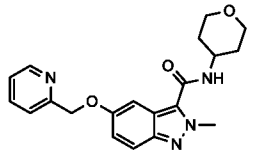
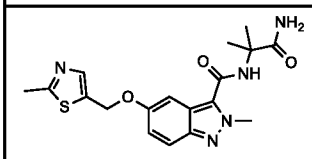
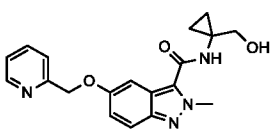
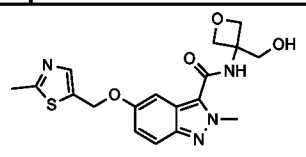
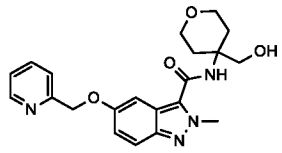
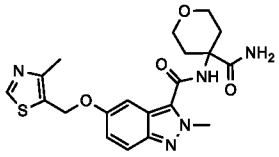
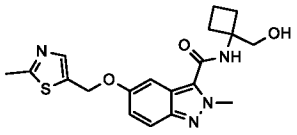
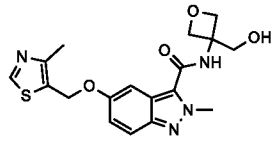
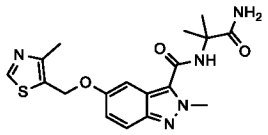
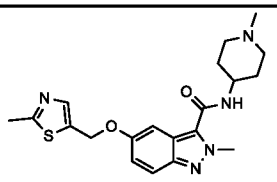
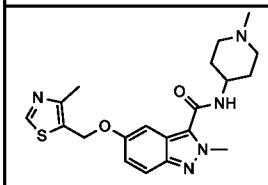
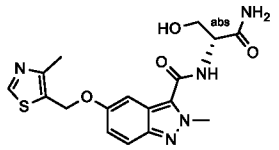
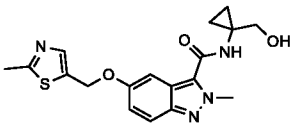
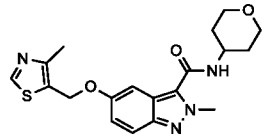
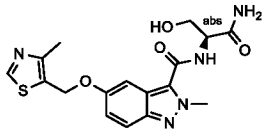
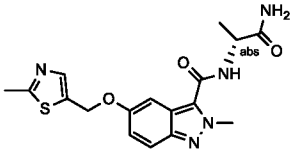
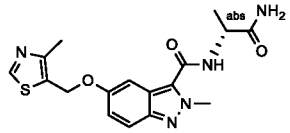
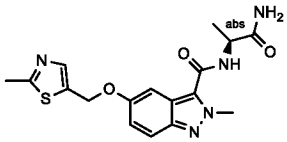
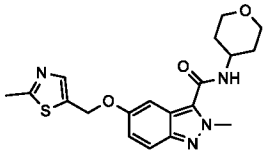
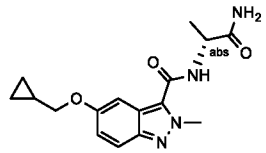
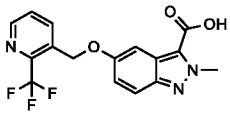
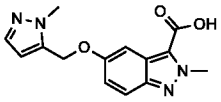
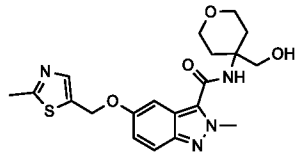
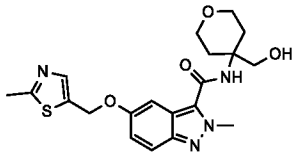
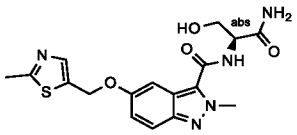
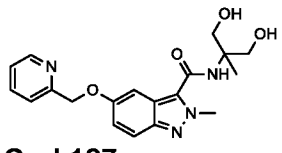
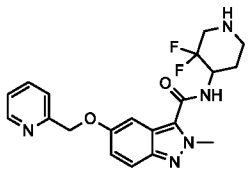
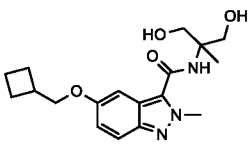
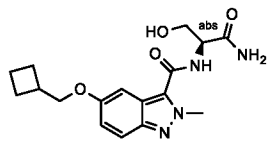
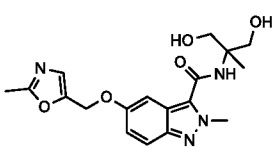
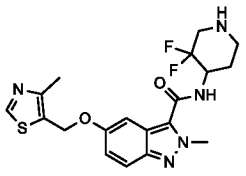
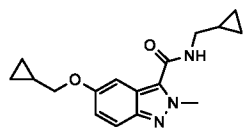
 Cpd 079	 Cpd 080	 Cpd 081
 Cpd 082	 Cpd 083	 Cpd 084
 Cpd 085	 Cpd 086	 Cpd 087
 Cpd 088	 Cpd 089	 Cpd 090
 Cpd 091	 Cpd 092	 Cpd 093
 Cpd 094	 Cpd 095	 Cpd 096
 Cpd 097	 Cpd 098	 Cpd 099
 Cpd 100	 Cpd 101	 Cpd 102
 Cpd 103	 Cpd 104	 Cpd 105

 Cpd 106	 Cpd 107	 Cpd 108
 Cpd 109	 Cpd 110	 Cpd 111
 Cpd 112	 Cpd 113	 Cpd 114
 Cpd 115	 Cpd 116	 Cpd 117
 Cpd 118	 Cpd 119	 Cpd 120
 Cpd 121	 Cpd 122	 Cpd 123
 Cpd 124	 Cpd 125	 Cpd 126
 Cpd 127	 Cpd 128	 Cpd 129
 Cpd 130	 Cpd 131	 Cpd 132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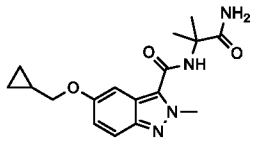
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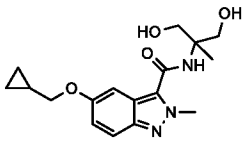
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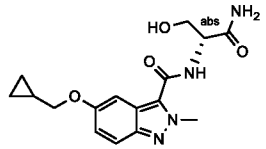
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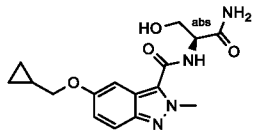
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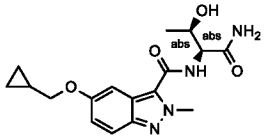
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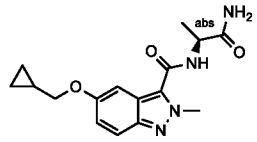
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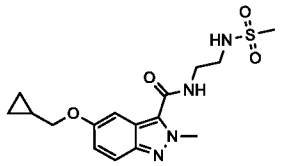
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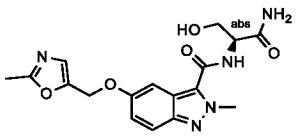
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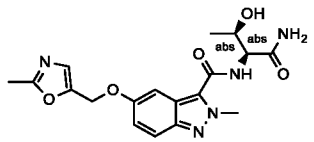
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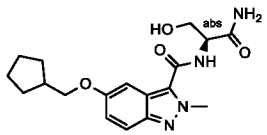
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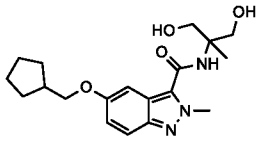
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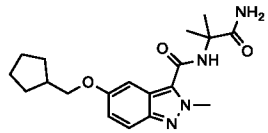
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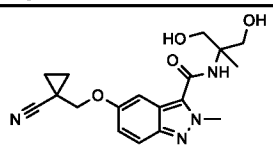
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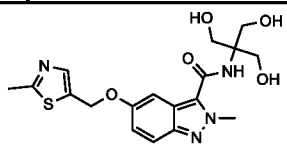
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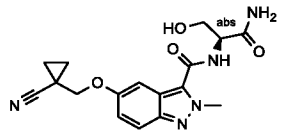
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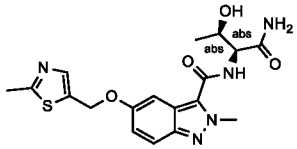
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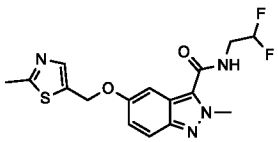
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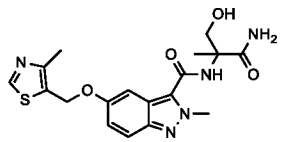
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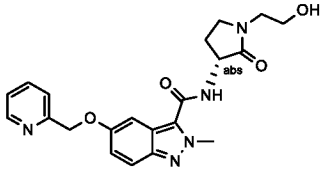
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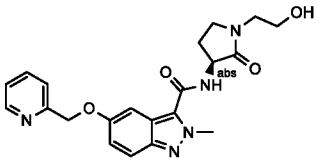
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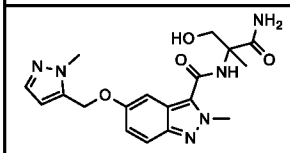
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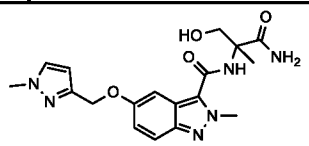
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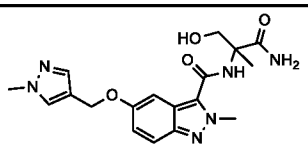
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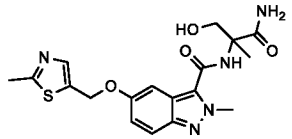
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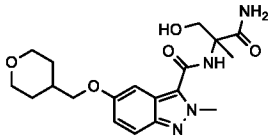
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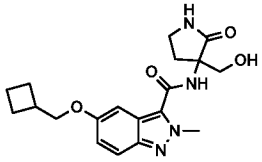
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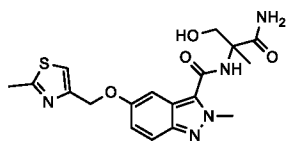
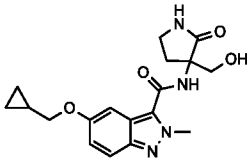
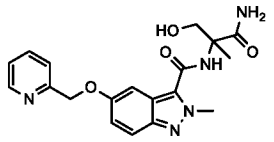
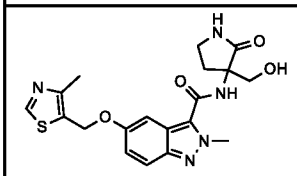
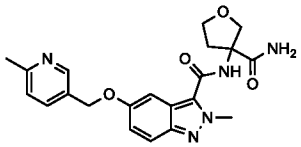
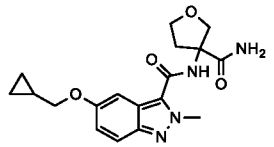
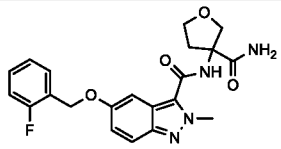
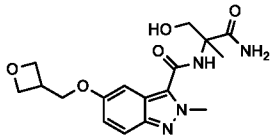
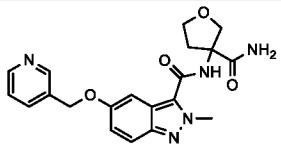
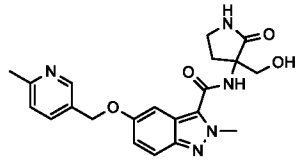
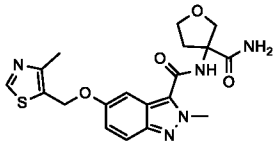
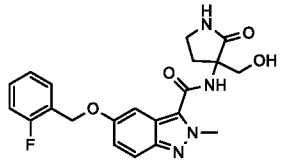
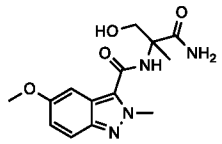
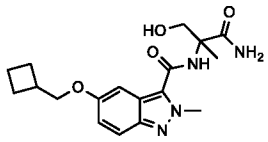
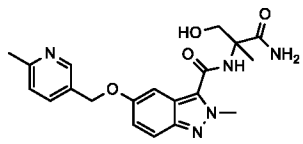
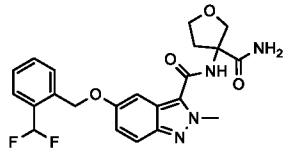
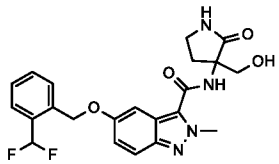
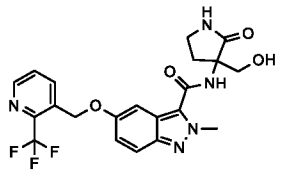
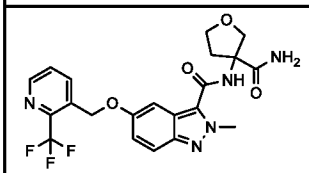
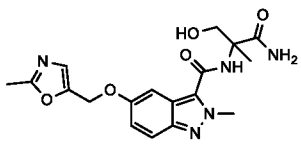
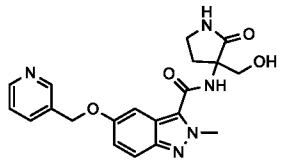
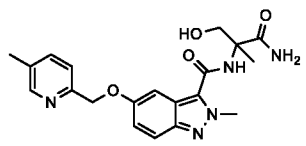
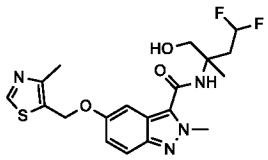
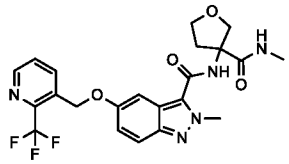
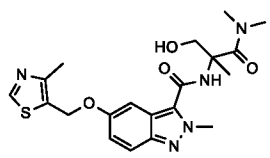
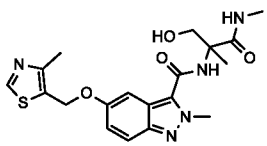
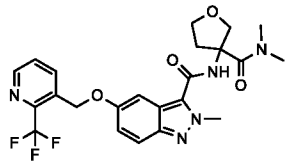
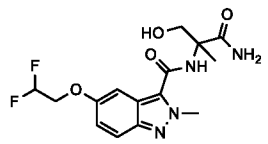
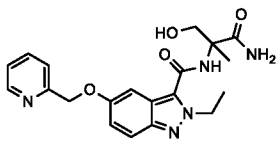
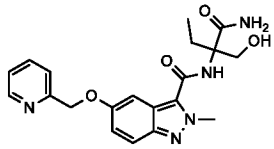
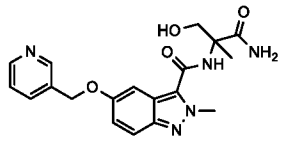
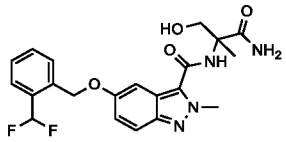
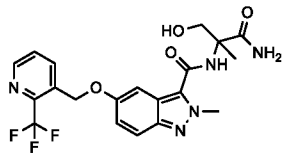
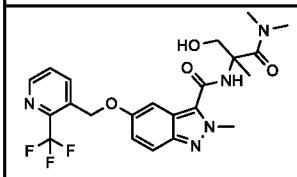
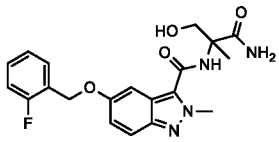
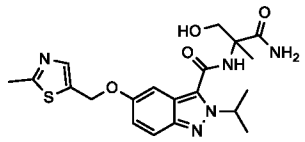
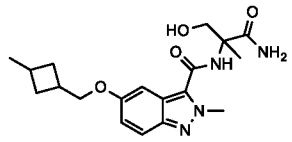
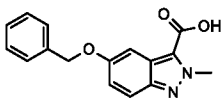
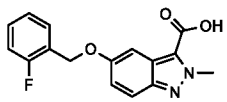
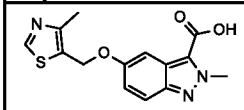
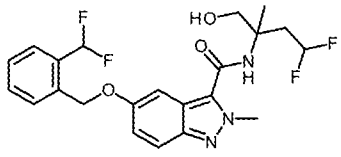
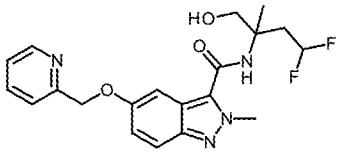
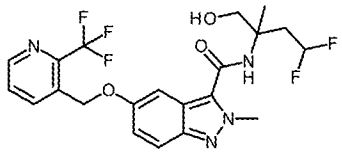
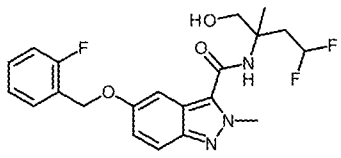
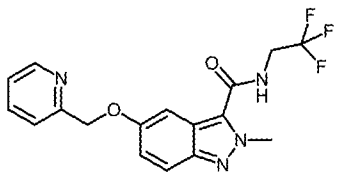
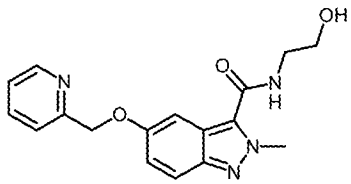
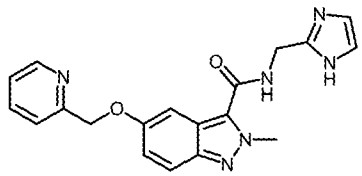
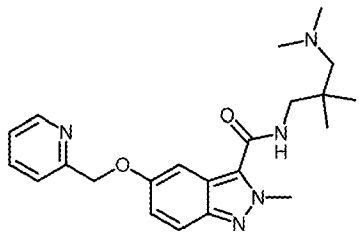
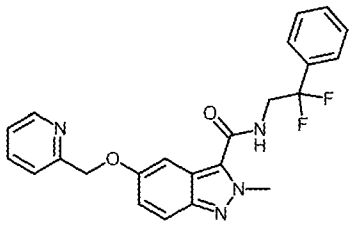
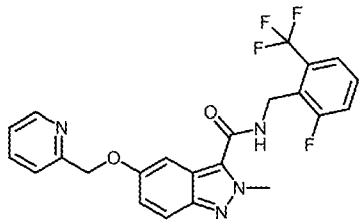
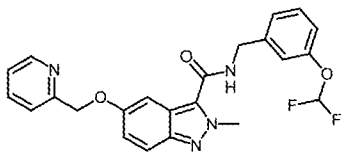
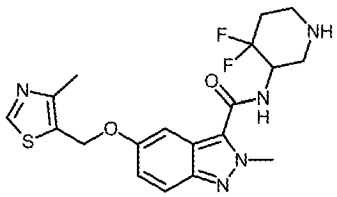
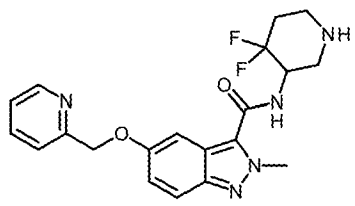
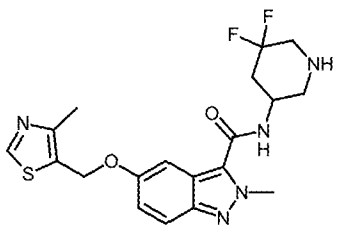
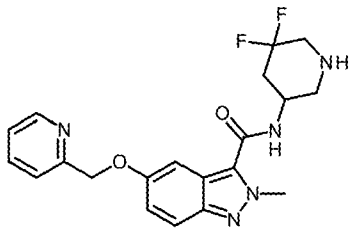
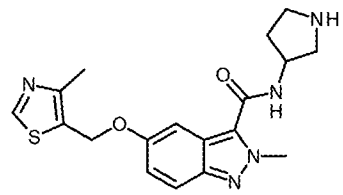
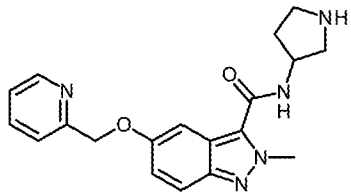
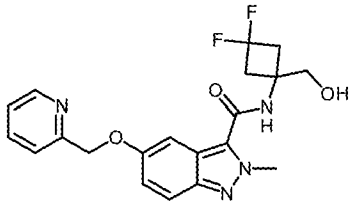
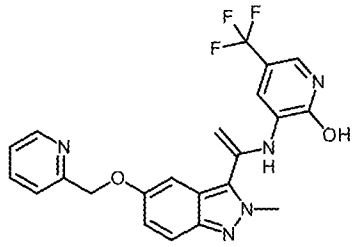
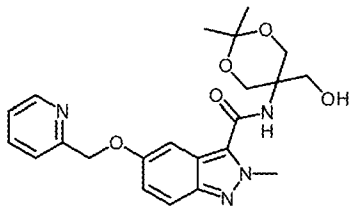
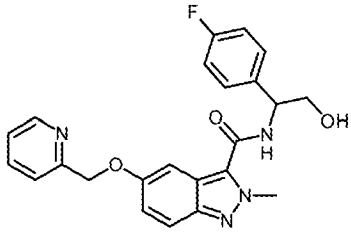
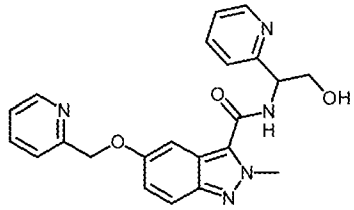
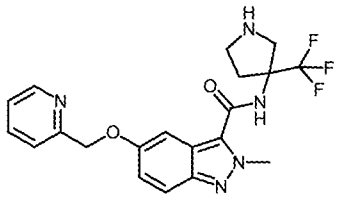
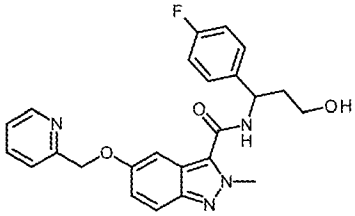
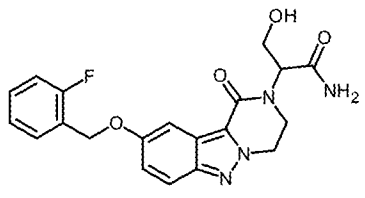
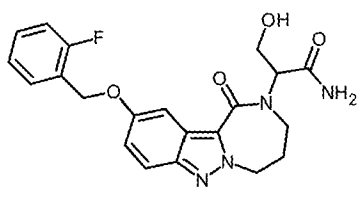
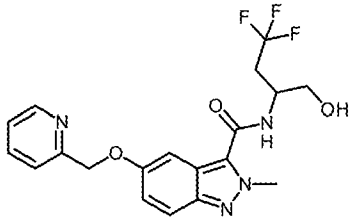
 Cpd 160	 Cpd 161	 Cpd 162
 Cpd 163	 Cpd 164	 Cpd 165
 Cpd 166	 Cpd 167	 Cpd 168
 Cpd 169	 Cpd 170	 Cpd 171
 Cpd 172	 Cpd 173	 Cpd 174
 Cpd 175	 Cpd 176	 Cpd 177
 Cpd 178	 Cpd 179	 Cpd 180
 Cpd 181	 Cpd 182	 Cpd 183
 Cpd 184	 Cpd 185	 Cpd 186

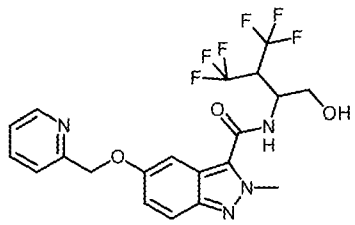
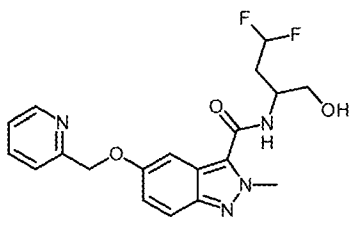
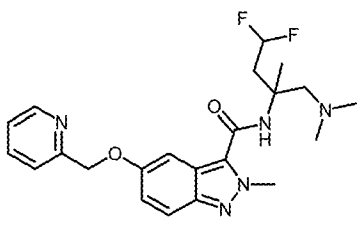
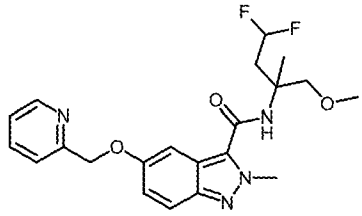
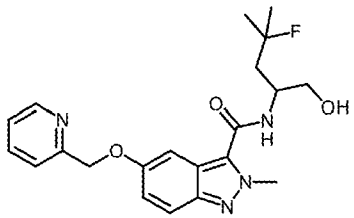
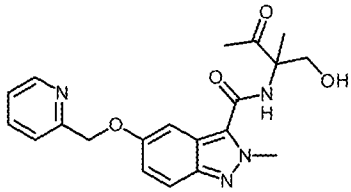
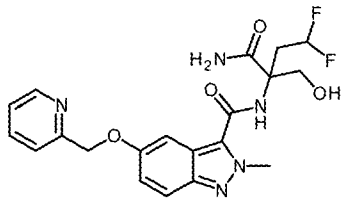
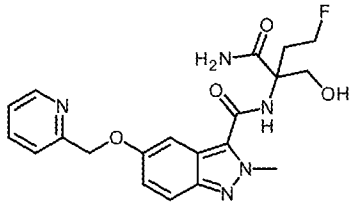
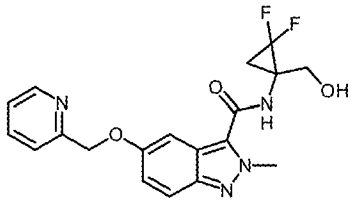
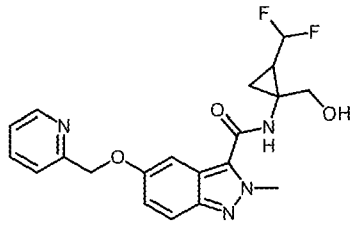
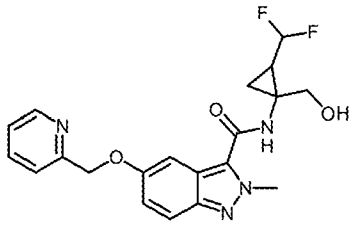
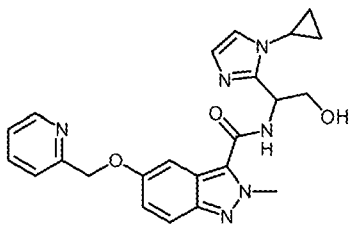
 **Cpd 187**	 **Cpd 188**	 **Cpd 189**
 **Cpd 190**	 **Cpd 191**	 **Cpd 192**
 **Cpd 193**	 **Cpd 194**	 **Cpd 195**
 **Cpd 196**	 **Cpd 197**	 **Cpd 198**
 **Cpd 199**		

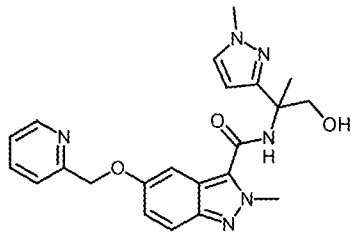
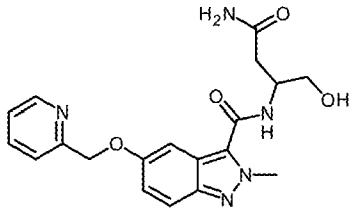
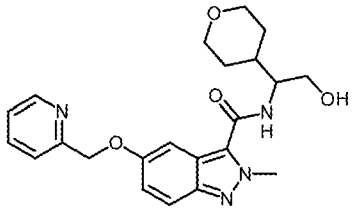
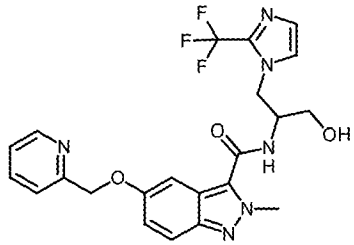
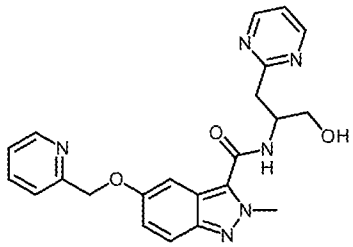
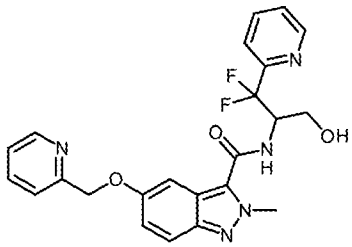
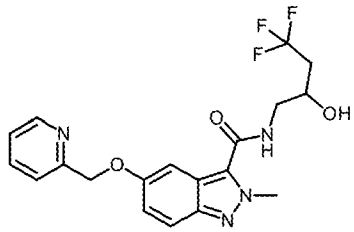
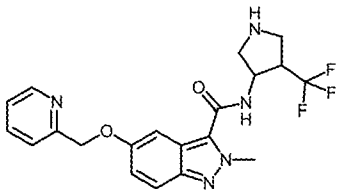
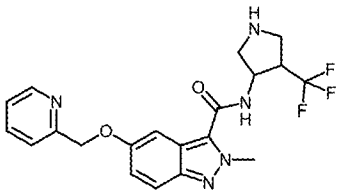
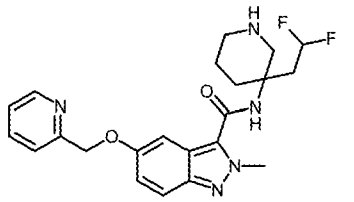
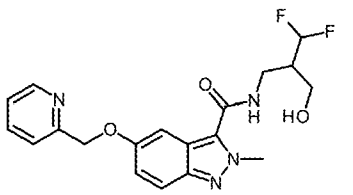
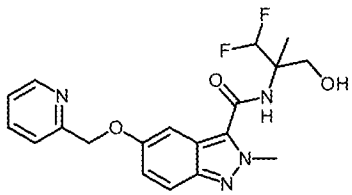
22. The compound of claim 1, which is selected from the group consisting of compounds 200 – 262 as shown in the table below:

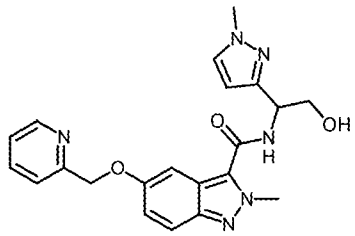
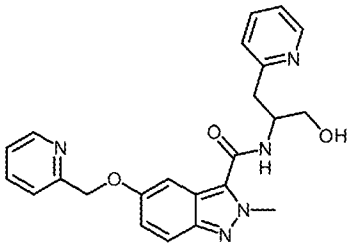
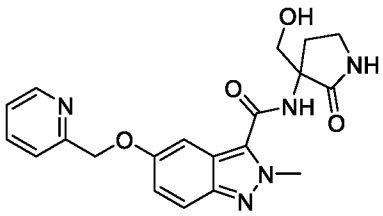
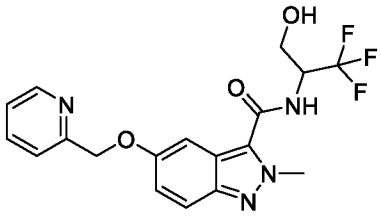
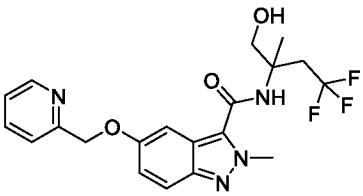
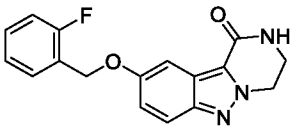
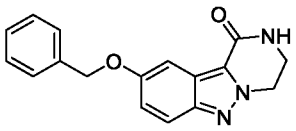
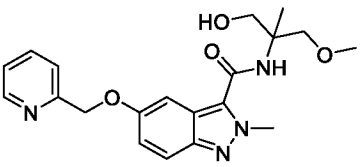
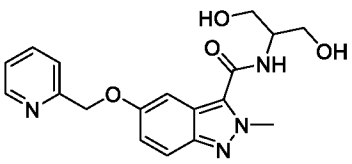
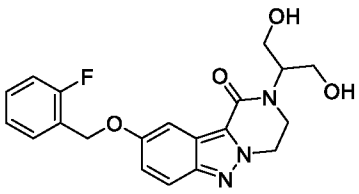
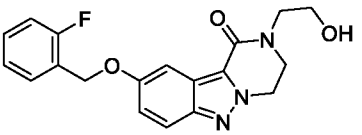
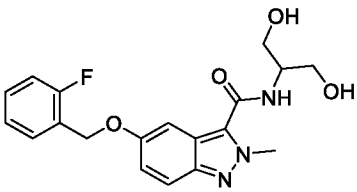
Structure and **Compound CODE**	Structure and **Compound CODE**	Structure and **Compound CODE**
 **Cmd 200**	 **Cpd 201**	 **Cpd 202**

 Cpd 203	 Cpd 204	 Cpd 205
 Cpd 206	 Cpd 207	 Cpd 208
 Cpd 209	 Cpd 210	 Cpd 211
 Cpd 212	 Cpd 213	 Cpd 214

 Cpd 215	 Cpd 216	 Cpd 217
 Cpd 218	 Cpd 219	 Cpd 220
 Cpd 221	 Cpd 222	 Cpd 223
 Cpd 224	 Cpd 225	 Cpd 226

 Cpd 227	 Cpd 228	 Cpd 229
 Cpd 230	 Cpd 231	 Cpd 232
 Cpd 233	 Cpd 234	 Cpd 235
 Cpd 236 (trans isomer)	 Cpd 237 (cis isomer)	 Cpd 238

 Cpd 239	 Cpd 240	 Cpd 241
 Cpd 242	 Cpd 243	 Cpd 244
 Cpd 245	 Cpd 246 (trans isomer)	 Cpd 247 (cis isomer)
 Cpd 248	 Cpd 249	 Cpd 250

 Cpd 251	 Cpd 252	 Cpd 253
 Cpd 254	 Cpd 255	 Cpd 256
 Cpd 257	 Cpd 258	 Cpd 259
 Cpd 260	 Cpd 261	 Cpd 262

23. A pharmaceutical composition comprising a compound according to any one of claims 1 to 22.

24. The compound according to any one of claims 1 to 22 or the pharmaceutical composition according to claim 23, for use in the treatment of pain.

25. The compound or the pharmaceutical composition for use in the treatment of pain according to claim 24, wherein the pain is selected from nociceptive pain, inflammatory pain, and neuropathic pain; preferably post-operative pain.

26. A method of treating of pain comprising administering a compound according to any one of claims 1 – 22, or a pharmaceutical composition according to any one of claims 23 to 25, to a subject in need thereof.

27. The method of claim 26 wherein the pain is selected from nociceptive pain, inflammatory pain, and neuropathic pain; preferably post-operative pain.

28. The compound according to any one of claims 1 to 22 or the pharmaceutical composition according to claim 23, for use in the treatment of epilepsy.

29. A method of treating of epilepsy comprising administering a compound according to any one of claims 1 – 22, or a pharmaceutical composition according to claim 23, to a subject in need thereof.