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(54) Title: INDOLIZINE 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.

WO 2023/230543 A1

INDOLIZINE 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 indolizine derivatives and pharmaceutical compositions comprising such indolizine derivatives. The invention also provides indolizine 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 indolizine 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 indolizine 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;

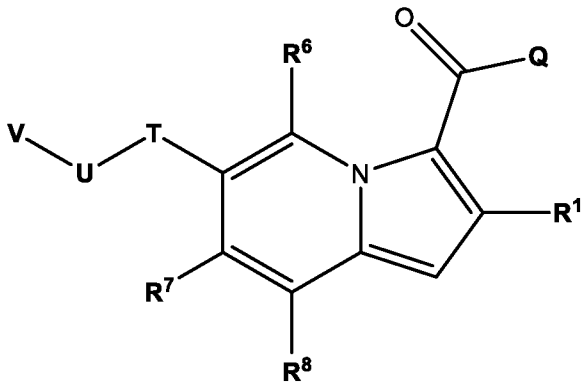
and/or for counteracting pain and/or inflammatory hypersensitivity and/or epilepsy.

[0011] The invention further provides a method for the preparation of the indolizine 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

$\mathbf{R^1}$ 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, -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 indolizine 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

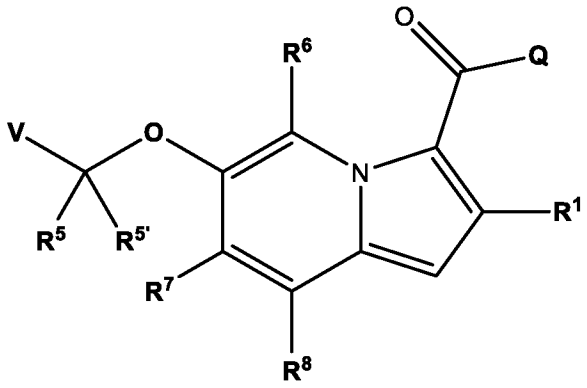
(b-1)

(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 indolizine derivatives according to the invention **T** represents -O- and **U** represents -C**R^{5}R$^{5'}$**-. According to this embodiment, the indolizine 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 indolizine derivatives according to Formula I, **T** represents -C**R**^{5}**R**$^{5'}$- and **U** represents -O-.

[0017] In an embodiment of the indolizine 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 indolizine derivatives according to the invention **Q** represents -N**R**^{3}**R**^{4}.

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

[0020] In some embodiments of the indolizine 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, imdidazole, 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 indolizine 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 indolizine 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 indolizine 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 indolizine derivative according to the invention **V** is

(i) unsubstituted;

(ii) monosubstituted;

(iii) disubstituted;

(iv) trisubstituted; or

(v) tetrasubstituted.

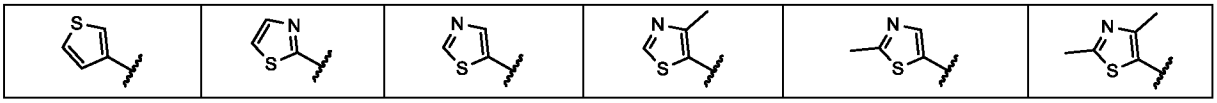
[0036] In a some embodiments of the indolizine derivatives according to the invention **V** is

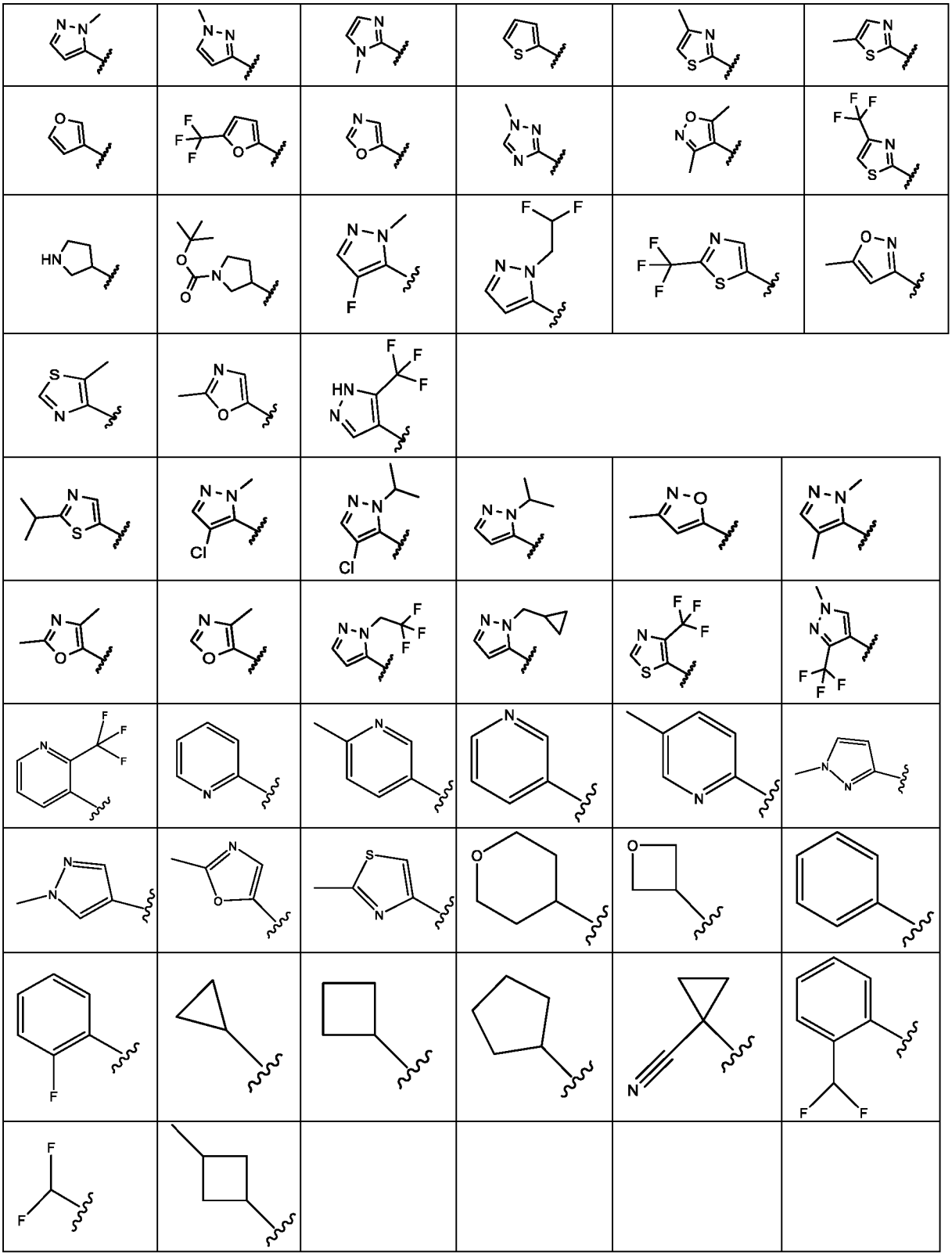
(i) unsubstituted;

(ii) monosubstituted; or

(iii) disubstituted.

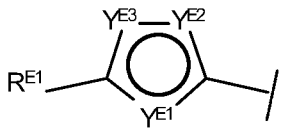
[0037] In some embodiments, **V** represents a 3-14-membered heterocycloalkyl (preferably 3-5-membered heterocycloalkyl), saturated or unsaturated; 5-14-membered heteroaryl (preferably 5-6-membered heteroaryl); 3-14-membered cycloalkyl, saturated or unsaturated; 5-14-membered aryl; or C_1-C_6 alkyl; 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)

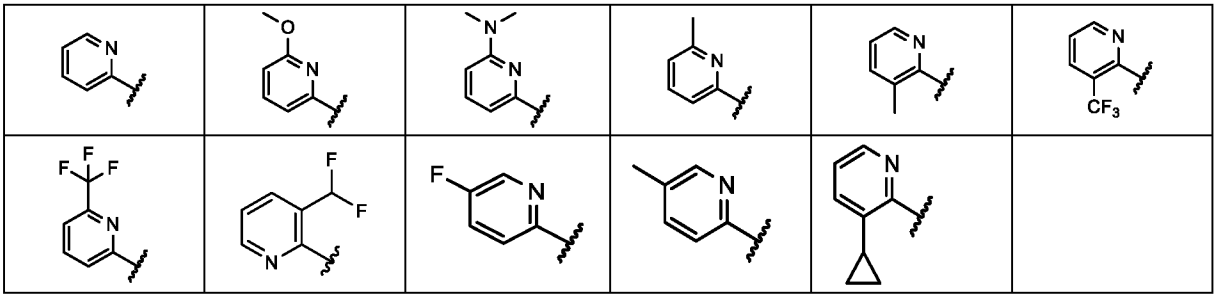
wherein

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)

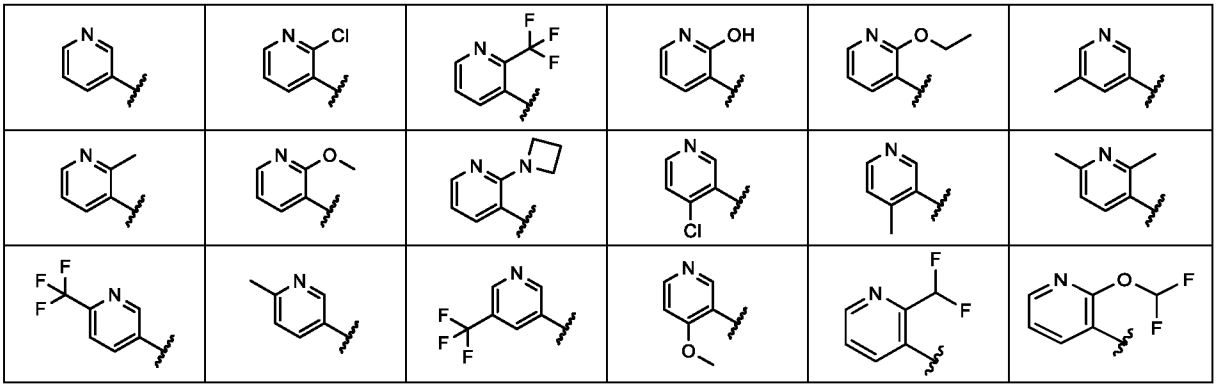
wherein YE1 represents -N=, -NRE2-, S, or -CRE3=; YE2 represents -N=, -NRE3-, S, or -CRE4=; and YE3 represent -N=, -NRE4-, S, or -CRE5=; with the proviso that at least one of YE1, YE2, and YE3 is not -CRE3=, -CRE4=, and -CRE5=, respectively.

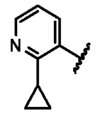
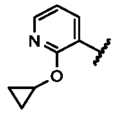
R^{E1}, R^{E2}, R^{E3}, and R^{E4} independently of one another represent -H, -CH_3,-CH_2-cyclopropyl, -CH_2CF_3, -CH_2CHF_2 or -CF_3; more in particular R^{E1}, R^{E2}, R^{E3}, and R^{E4} independently of one another represent -H, -CH_3, or -CF_3; preferably with the proviso that only one of R^{E1}, 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:

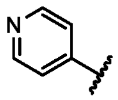


[0041] In some embodiments, **V** represents 3-pyridine, unsubstituted, mono- or polysubstituted. In preferred embodiments, **V** represents a residue selected from the group consisting of:

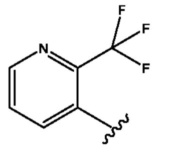
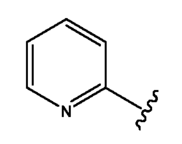
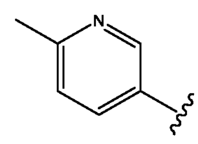
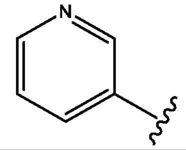
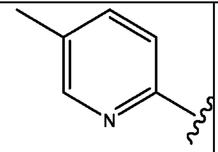
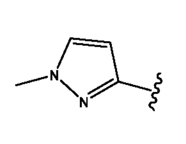
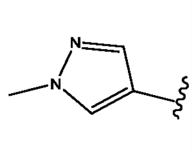
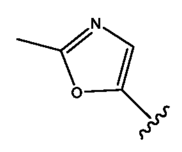
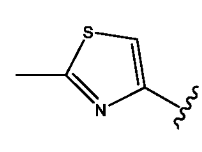
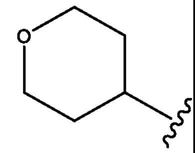
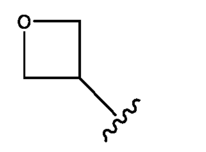
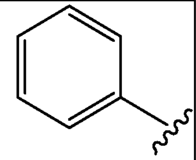
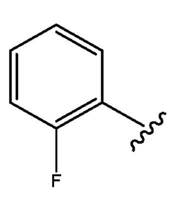
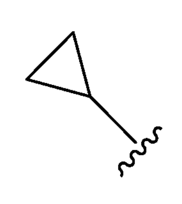
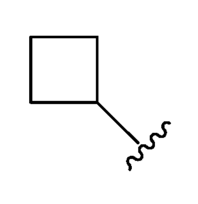
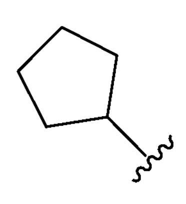
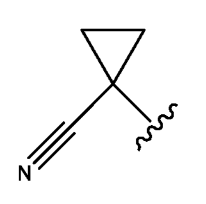
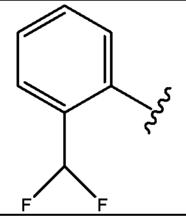
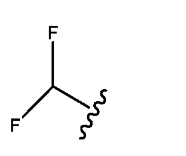
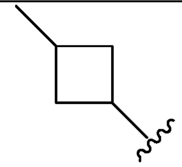
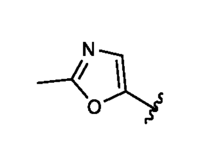
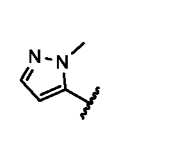
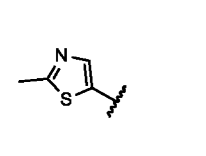
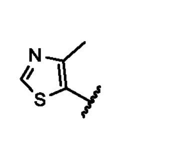
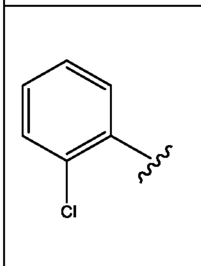
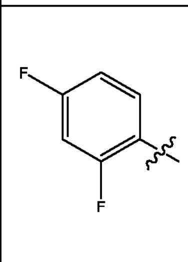
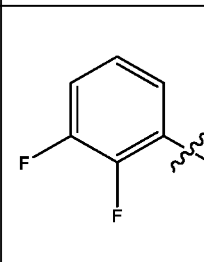
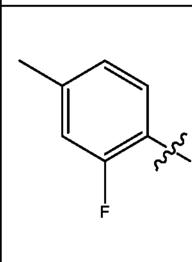
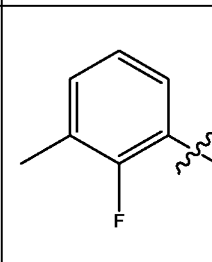
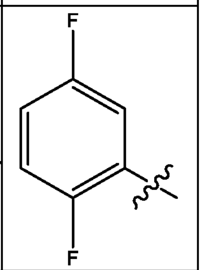
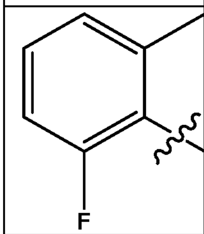
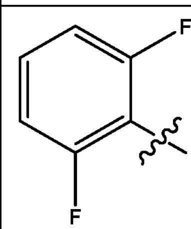


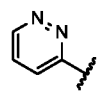
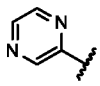
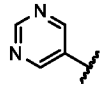
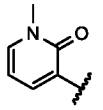
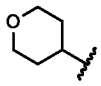
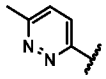
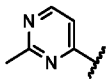
[0042] In some embodiments, **V** represents 4-pyridine, unsubstituted, mono- or polysubstituted. In preferred embodiments, **V** represents a residue selected from the group consisting of:


.

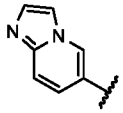
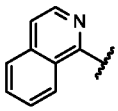
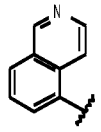
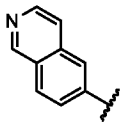
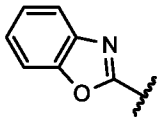
[0043] In some embodiments, optionally where **U** – CH_2, **V** represents a residue selected from the group consisting of:

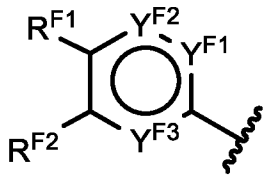
[0044] In alternative embodiments, **V** represents a residue selected from the group consisting of:

[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')



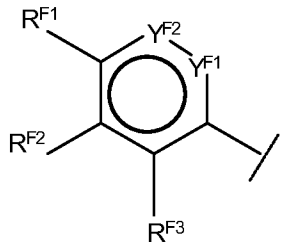
(F')

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)



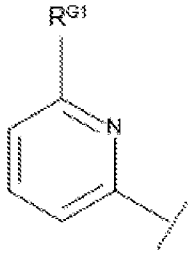
(F)

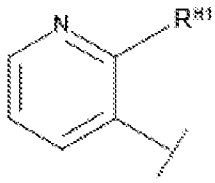
wherein

$\mathbf{Y^{F1}}$ 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)

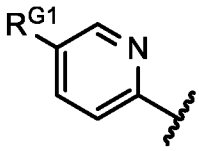


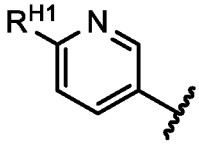


(G) (H)

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 indolizine 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 indolizine 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 indolizine 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 indolizine 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 indolizine derivative according to the invention $\mathbf{R^3}$ 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.

[0064] In some embodiments, $\mathbf{R^3}$ 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 -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 a embodiment, $\mathbf{R^3}$ and $\mathbf{R^4}$ together do not form morpholine unsubstituted, mono- or polysubstituted.

[0065] In some embodiments, $\mathbf{R^3}$ and $\mathbf{R^4}$ together form a

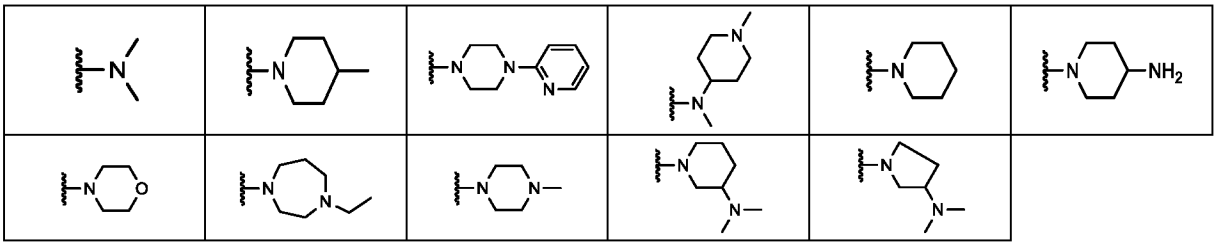
pyrrolidine ring, unsubstituted or monosubstituted with $-N(CH_3)_2$;

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.

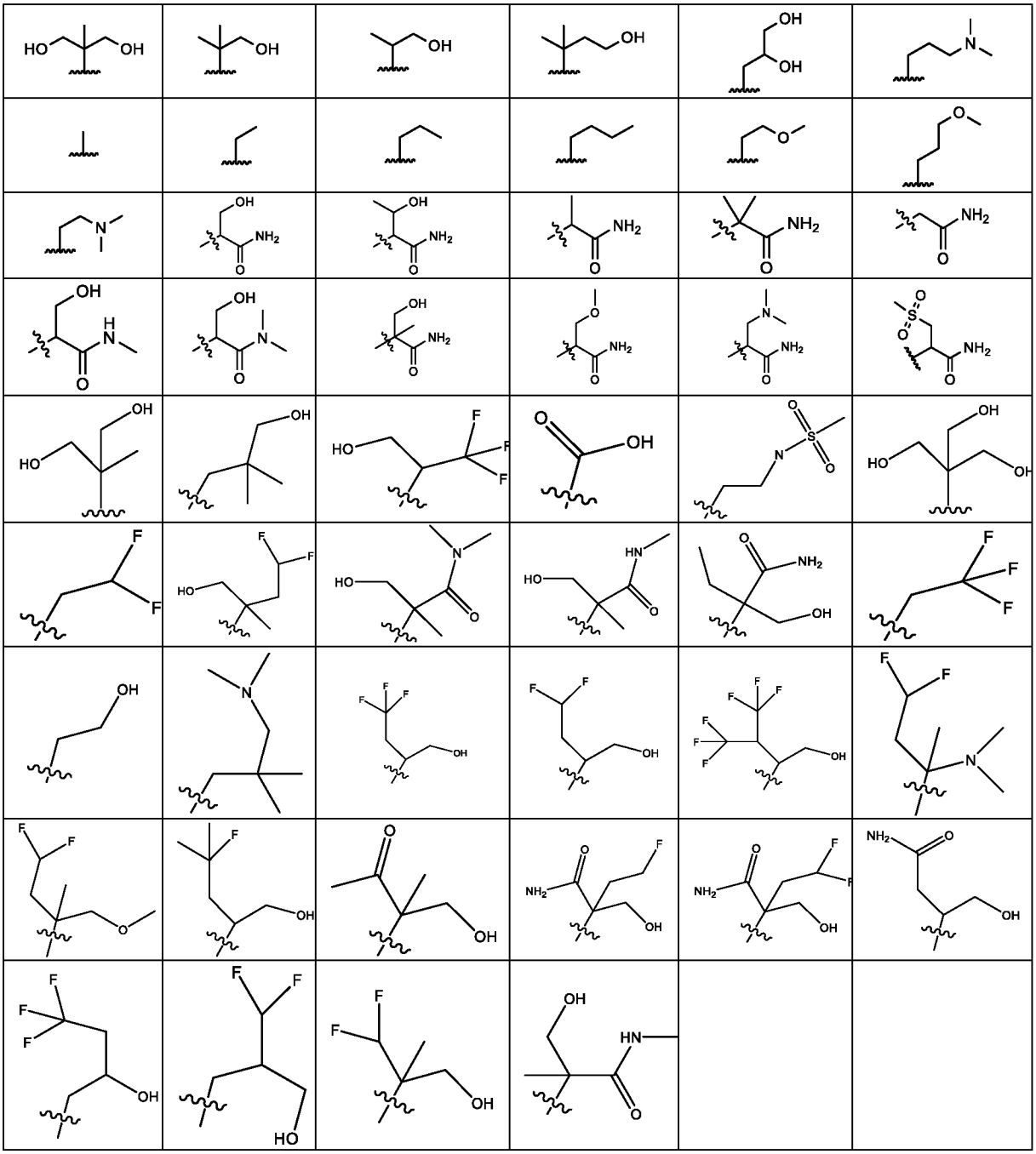
[0066] In some embodiments, $\mathbf{R^3}$ and $\mathbf{R^4}$ both do not represent -H. In some embodiments, $\mathbf{R^3}$ and $\mathbf{R^4}$ together with the nitrogen atom to which they are attached form a residue selected from the group consisting of:



[0067] In other embodiments, $\mathbf{R^3}$ represents -H and $\mathbf{R^4}$ does not represent -H.

[0068] In some embodiments, $\mathbf{R^3}$ represents -H and $\mathbf{R^4}$ 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:

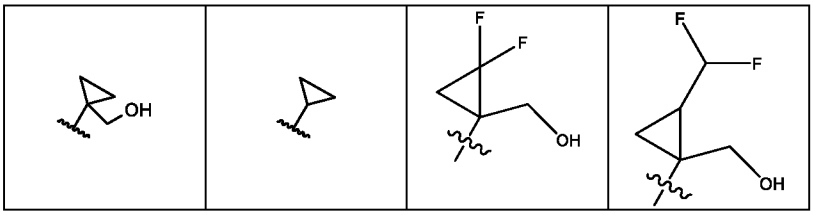


[0069] In further embodiments, **R**^{3} represents -H and **R**^{4} represents a residue -C**R'R"**-$(CH_2)_m$-OH, wherein **m** is an integer of from 1 to 6, preferably from 1 to 3; and wherein **R'** and **R"** independently of one another represent -H, -C_{1-3}-alkyl, -CF_3, -CF_2H, -CFH_2, -C_{1-3}-alkylene-CF_3, -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.

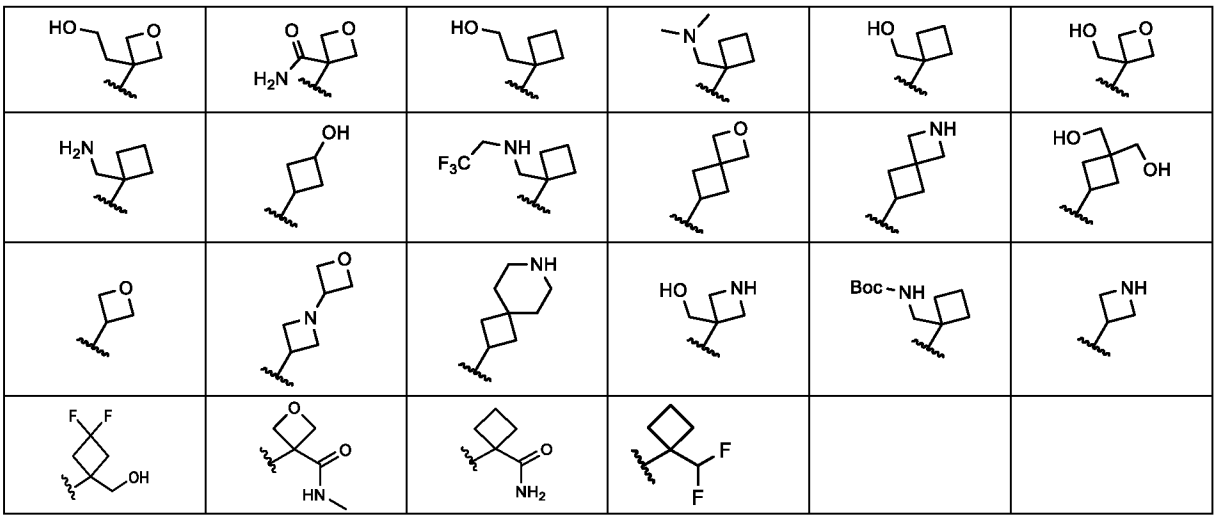
[0070] In further embodiments, **R**^{3} represents -H and **R**^{4} represents a 3-14-membered

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

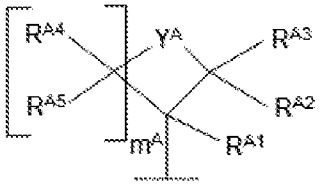
[0071] In further embodiments, **R**^{3} represents -H and **R**^{4} represents a 3-membered cycloalkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted; or a 3-membered heterocycloalkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted. In some embodiments, **R**^{3}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



[0072] In some embodiments, **R**^{3} represents -H and **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, **R**^{3} represents -H and **R**^{4} represents a residue selected from the group consisting of:



[0073] In some embodiments, **R**^{3} represents -H and **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.

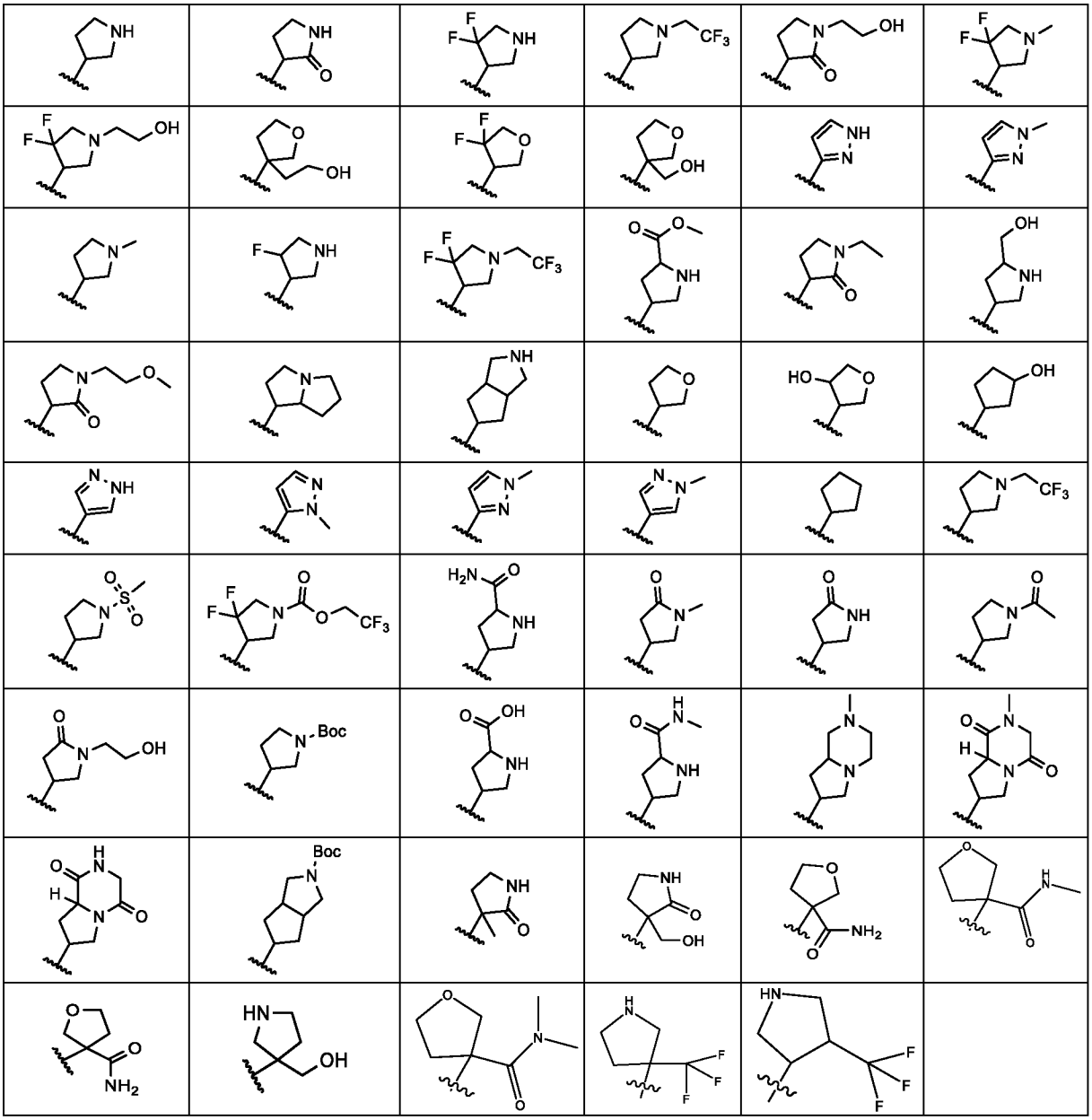
[0075] In some embodiments, R^3 represents -H and R^4 represents a residue according to general formula (A) as defined above, wherein

m^A is 0 or 1;

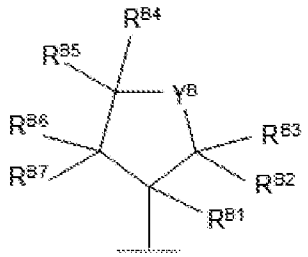
Y^A is selected from -O- and -$CR^{A7}R^{A8}$-; and

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 -

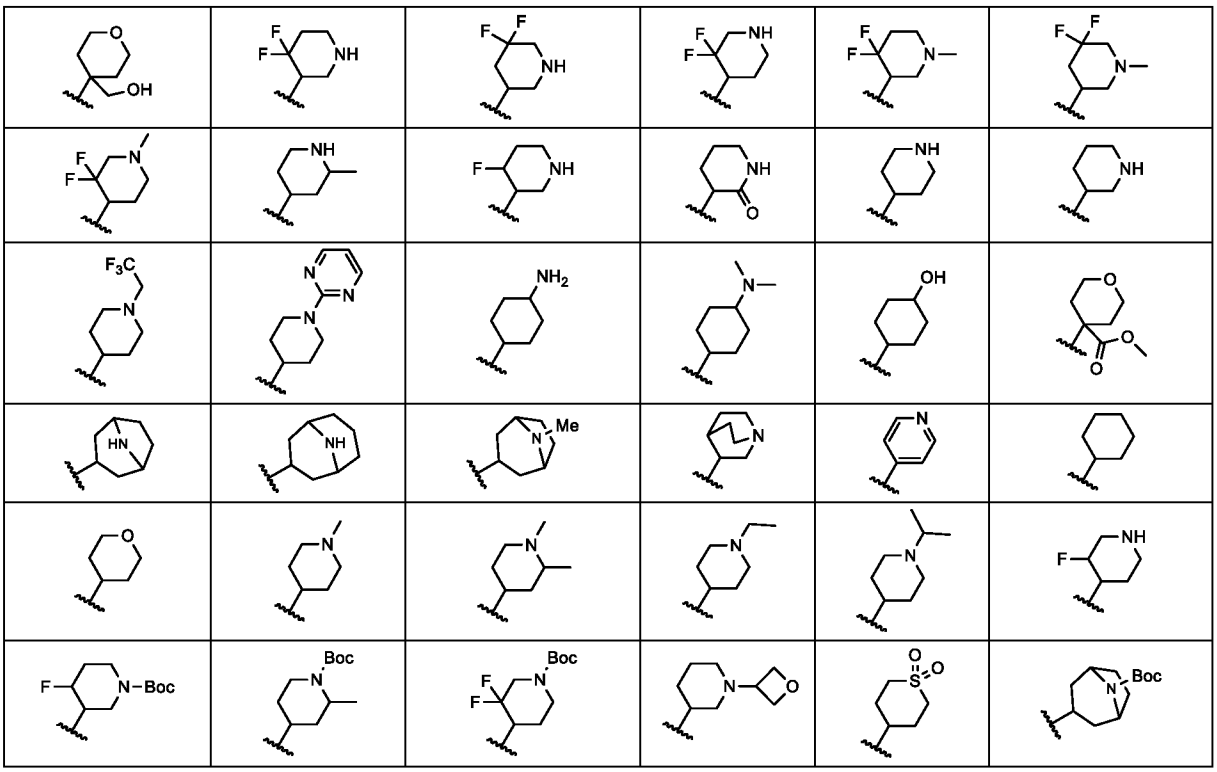
H, -F, -OH, -C_{1-3}-alkyl, -C_{1-3}-alkylene-OH, -C_{1-3}-alkylene-O-C_{1-3}-alkyl, -C_{1-3}-alkylene-CF_3, -C_{1-3}-alkylene-CO_2H, -C_{1-3}-alkylene-C(=O)O-C_{1-3}-alkyl, -C(=O)NH_2, -C(=O)NH-C_{1-3}-alkyl, or -C(=O)N(C_{1-3}-alkyl)$_2$; or $\mathbf{R^{B2}}$ and $\mathbf{R^{B3}}$ together represent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

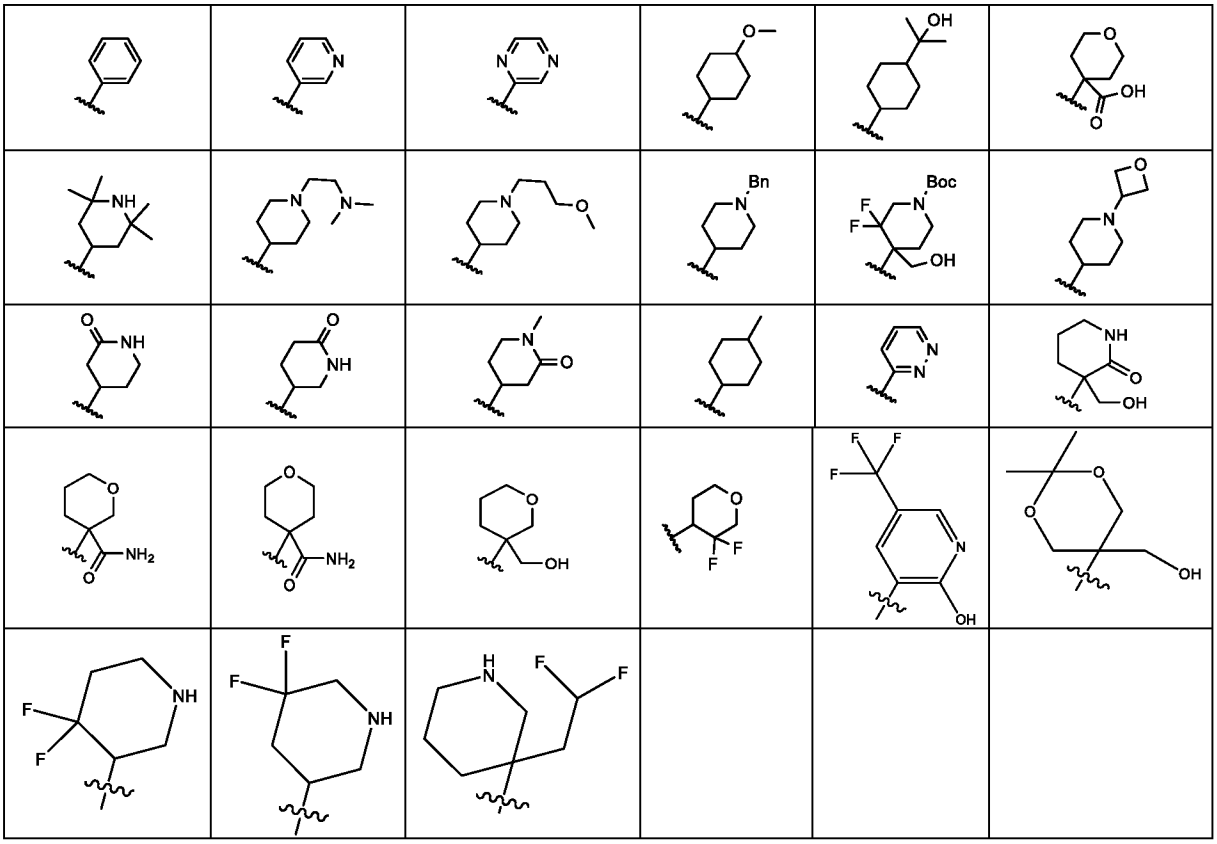
[0078] In some embodiments, $\mathbf{R^3}$ represents -H and $\mathbf{R^4}$ represents a residue according to general formula (B) as defined above, wherein

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

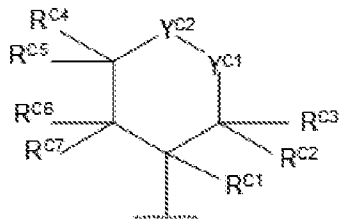
$\mathbf{R^{B1}}$, $\mathbf{R^{B2}}$, $\mathbf{R^{B3}}$, $\mathbf{R^{B4}}$, $\mathbf{R^{B5}}$, $\mathbf{R^{B6}}$, $\mathbf{R^{B7}}$, $\mathbf{R^{B8}}$ independently of one another represent -H, -F, -C_{1-3}-alkyl, -C_{1-3}-alkylene-OH, -C_{1-3}-alkylene-CF_3 or -C(=O)NH_2; or $\mathbf{R^{B2}}$ and $\mathbf{R^{B3}}$ 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 -

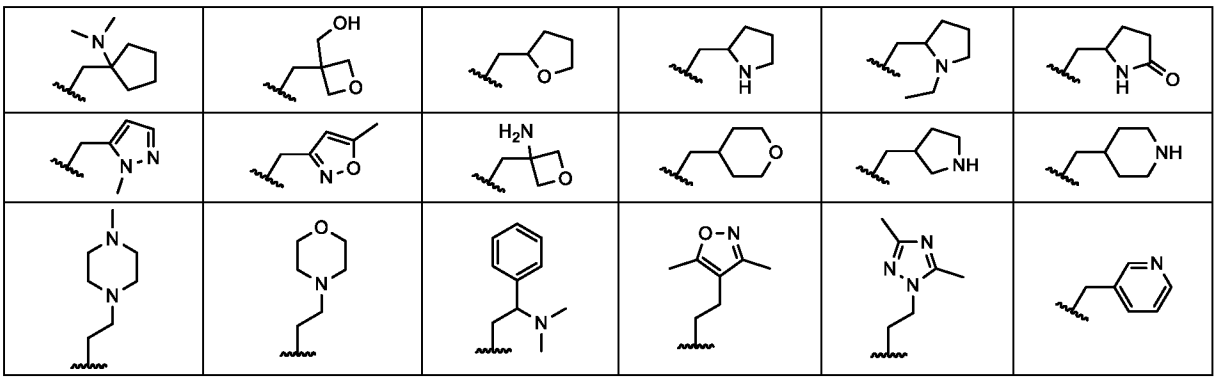
$CR^{C9}R^{C10}$- and Y^{C2} is selected from -O-, and -NR^{C8}-;

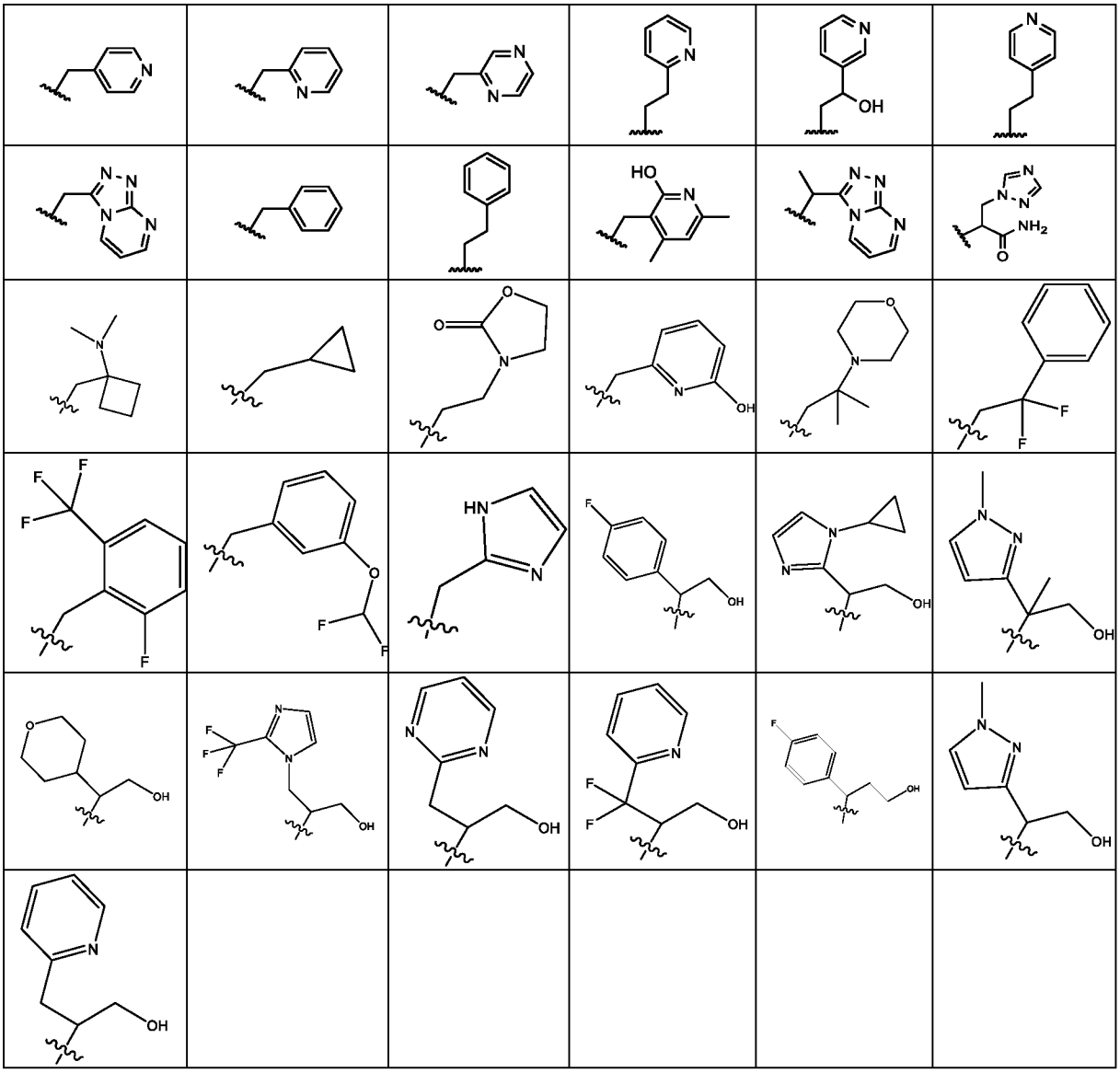
R^{C1}, R^{C2}, R^{C3}, R^{C4}, R^{C5}, R^{C6}, R^{C7}, R^{C8} ,R^{C9}, R^{C10}, R^{C11} and R^{C12} independently of one another represent -H, -F , -C_{1-3}-alkyl, -C_{1-3}-alkylene-OH, or -C(=O)NH_2; preferably with the proviso that only 1, 2 or 3 of R^{C1}, R^{C2}, R^{C3}, R^{C4}, R^{C5}, R^{C6}, 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:

.

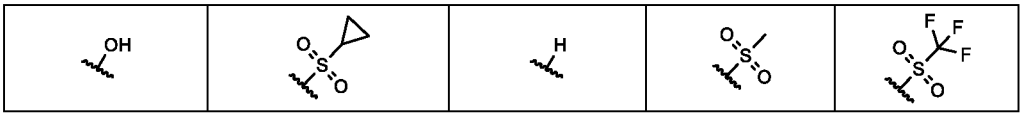
[0083] In some embodiments, R^3 represents -H and R^4 represents a 3-14-membered cycloalkyl (preferably a 3, 4, 5 or 6-membered cycloalkyl), saturated or unsaturated, unsubstituted, mono- or polysubstituted; wherein said 3-14-membered cycloalkyl is connected through -C_1-C_6-alkylene-, saturated or unsaturated, 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:

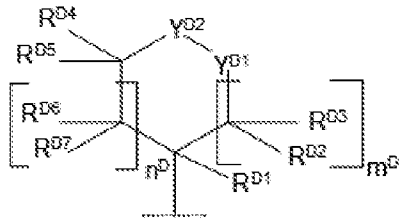


[0086] In some embodiments, **R**^{3} represents -H and **R**^{4} represents

(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

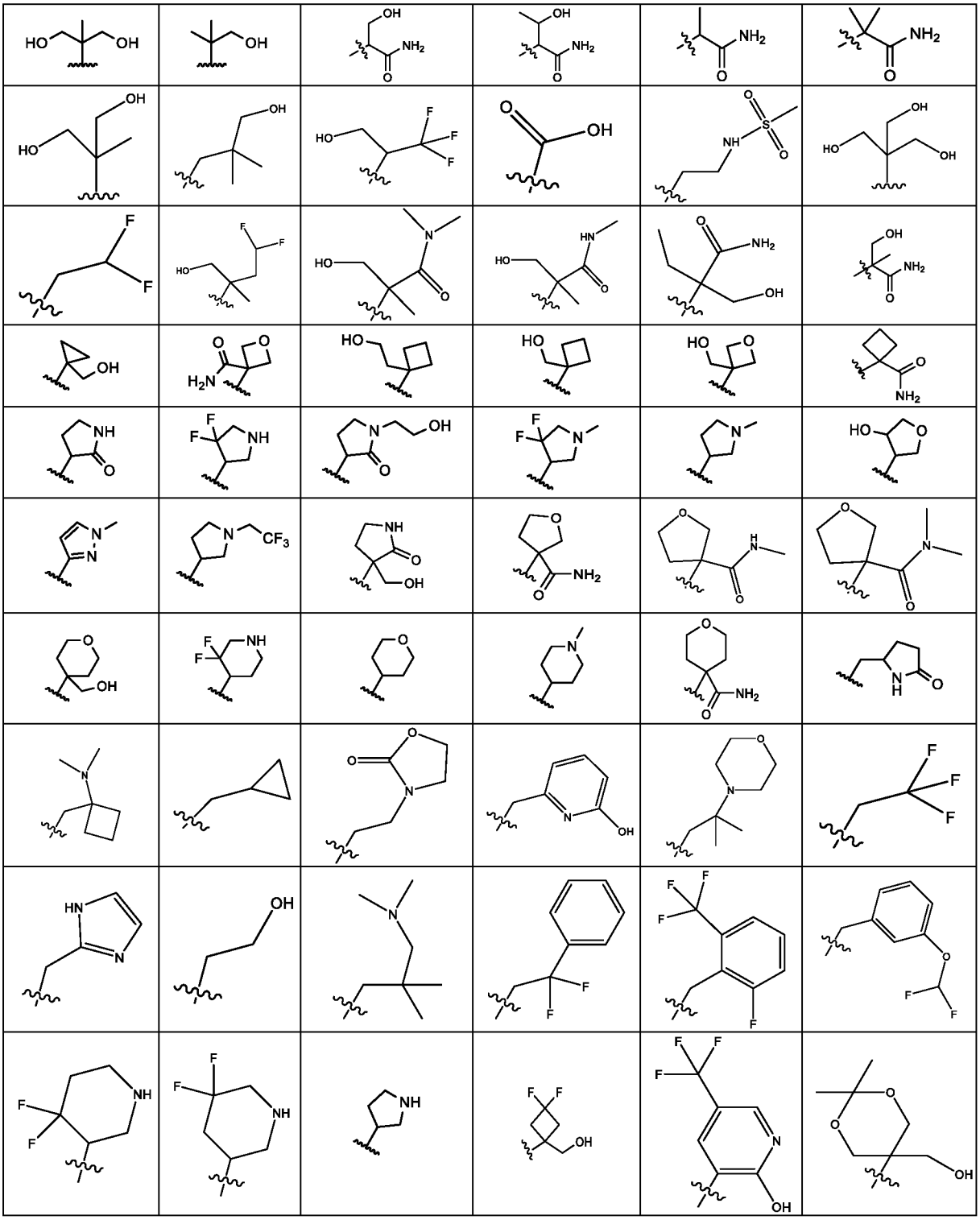
$\mathbf{m^D}$ and $\mathbf{n^D}$ independently of one another are 0, 1, 2 or 3; preferably with the proviso that $\mathbf{m^D} + \mathbf{n^D} \leq 3$;

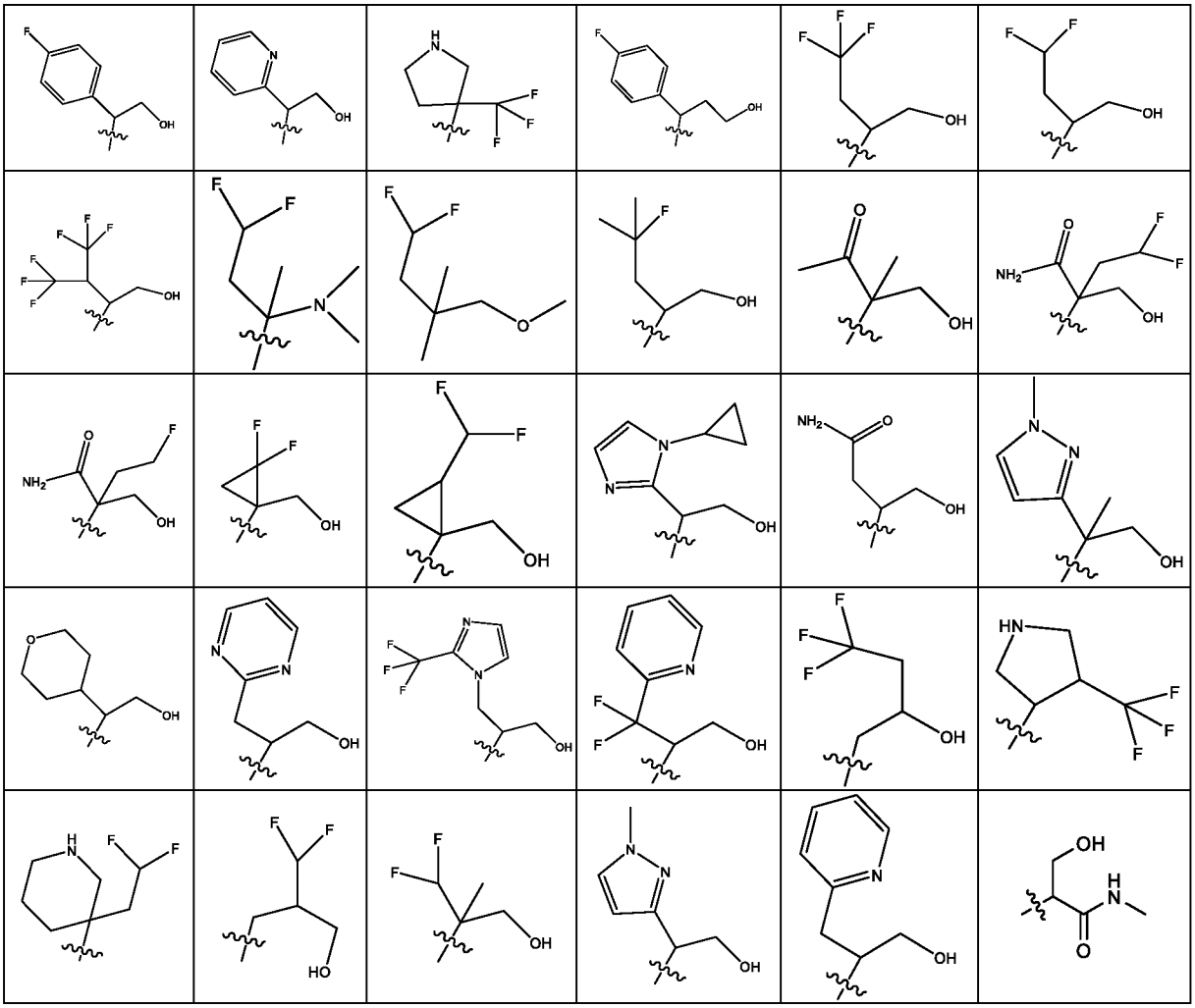
$\mathbf{Y^{D1}}$ is selected from -O-, $-NR^{D8}-$ and $-CR^{D9}R^{D10}-$ and $\mathbf{Y^{D2}}$ represents $-CR^{D11}R^{D12}-$; or $\mathbf{Y^{D1}}$ represents $-CR^{D9}R^{D10}-$ and $\mathbf{Y^{D2}}$ is selected from -O- and $-NR^{D8}-$;

$\mathbf{R^{D1}}$, $\mathbf{R^{D2}}$, $\mathbf{R^{D3}}$, $\mathbf{R^{D4}}$, $\mathbf{R^{D5}}$, $\mathbf{R^{D6}}$, $\mathbf{R^{D7}}$, $\mathbf{R^{D8}}$,$\mathbf{R^{D9}}$, $\mathbf{R^{D10}}$, $\mathbf{R^{D11}}$ 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 indolizine derivative according to the invention **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;

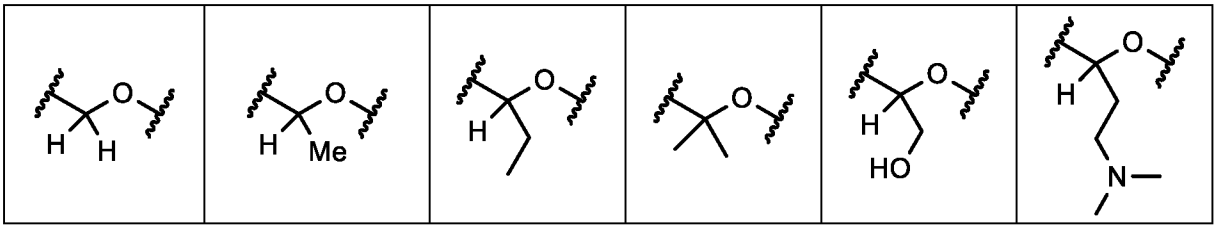
wherein said 3-14-membered cycloalkyl is optionally connected through -C_1-C_6-alkylene- or -C_1-C_6-heteroalkylene-, in each case saturated or unsaturated, unsubstituted, mono- or polysubstituted.

[0089] In some embodiments, **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)$_2$.

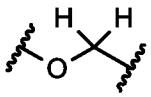
[0090] In some embodiments of the indolizine derivatives according to the invention, at least one of **R^5** and **R$^{5'}$** is not -H.

[0091] In some embodiments of the indolizine derivatives according to the invention, **R^5** and **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 indolizine 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, $\mathbf{R^6}$, $\mathbf{R^7}$ and $\mathbf{R^8}$ 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 indolizine derivatives according to the invention $\mathbf{R^6}$ represents -H, -F, -Cl, -CN, or $-C_1$-C_6-alkyl.

[0099] In some embodiments of the indolizine derivatives according to the invention, $\mathbf{R^6}$ does not represent -H.

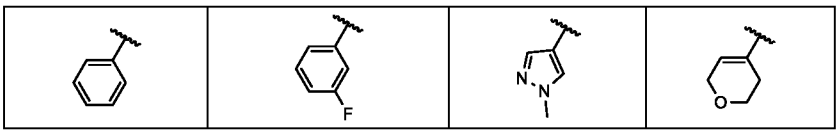
[0100] In some embodiments, $\mathbf{R^6}$ represents a residue selected from the group consisting of -H, -F, -Cl, -CN or $-CH_3$; preferably -H, -F, -CN or $-CH_3$.

[0101] In some embodiments of the indolizine derivatives according to the invention $\mathbf{R^7}$ represents -H, -F, -Cl, -CN, or $-C_1$-C_6-alkyl.

[0102] In some embodiments of the indolizine derivatives according to the invention $\mathbf{R^7}$ does not represent -H.

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

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



[0105] In someembodiments of the indolizine derivatives according to the invention $\mathbf{R^8}$ represents -H, -F, -Cl, -CN, or $-C_1$-C_6-alkyl.

[0106] In some embodiments of the indolizine derivatives according to the invention $\mathbf{R^8}$ does not represent -H.

[0107] In someembodiments, $\mathbf{R^8}$ represents a residue selected from the group consisting of -H, -F, -Cl, -CN or CH_3; preferably -F.

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

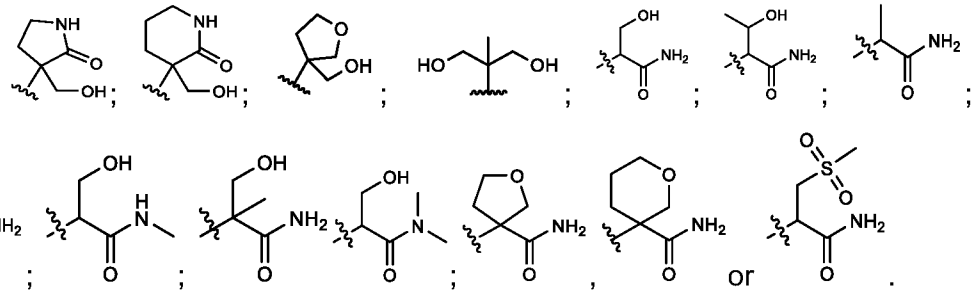
(i) $\mathbf{R^6}$, $\mathbf{R^7}$ and $\mathbf{R^8}$ each represent -H; or

(ii) two of $\mathbf{R^6}$, $\mathbf{R^7}$ and $\mathbf{R^8}$ represent -H and the other of $\mathbf{R^6}$, $\mathbf{R^7}$ and $\mathbf{R^8}$ 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 **NR^3R^4**; and/or
- **R^3** represents H; and/or
- **R^4** represents 

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

Cpd 001 -N-[4-(hydroxymethyl)oxan-4-yl]-2-methyl-6-[(4-methyl-1,3-thiazol-5-yl)methoxy]indolizine-3-carboxamide;

Cpd 002 - (2S)-2-({6-[(2-fluorophenyl)methoxy]-2-methylindolizin-3-yl}formamido)propanamide;

Cpd 003 - (2S)-2-({6-[(2-fluorophenyl)methoxy]-2-methylindolizin-3-yl}formamido)-3-hydroxypropanamide;

Cpd 004 - 2(2R)-2-({6-[(2-fluorophenyl)methoxy]-2-methylindolizin-3-yl}formamido)-3-hydroxypropanamide;

Cpd 005 - 2-({6-[(2-fluorophenyl)methoxy]-2-methylindolizin-3-yl}formamido)-3-hydroxy-2-methylpropanamide,

Cpd 006 - N-(1,3-dihydroxy-2-methylpropan-2-yl)-6-[(2-fluorophenyl)methoxy]-2-methylindolizine-3-carboxamide,

Cpd 007 - 6-[(2-fluorophenyl)methoxy]-N-[3-(hydroxymethyl)-2-oxopyrrolidin-3-yl]-2-methylindolizine-3-carboxamide,

Cpd 008 - N-(4,4-difluoropiperidin-3-yl)-6-[(2-fluorophenyl)methoxy]-2-methylindolizine-3-carboxamide,

Cpd 014 - 3-hydroxy-2-methyl-2-({2-methyl-6-[(pyridin-2-yl)methoxy]indolizin-3-yl}formamido)propanamide,

Cpd 015 - N-(1,3-dihydroxy-2-methylpropan-2-yl)-2-methyl-6-[(pyridin-2-yl)methoxy]indolizine-3-carboxamide,

Cpd 016 - N-[3-(hydroxymethyl)-2-oxopyrrolidin-3-yl]-2-methyl-6-[(pyridin-2-yl)methoxy]indolizine-3-carboxamide,

Cpd 017 - N-(4,4-difluoropiperidin-3-yl)-2-methyl-6-[(pyridin-2-yl)methoxy]indolizine-3-carboxamide,

Cpd 018 - 2-({2-methyl-6-[(pyridin-2-yl)methoxy]indolizin-3-yl}formamido)propanamide,

Cpd 019 - 2-{[6-(cyclopropylmethoxy)-2-methylindolizin-3-yl]formamido}-3-hydroxy-2-methylpropanamide,

Cpd 020 - 6-(cyclopropylmethoxy)-N-(1,3-dihydroxy-2-methylpropan-2-yl)-2-methylindolizine-3-carboxamide,

Cpd 021 - 6-(cyclopropylmethoxy)-N-[3-(hydroxymethyl)-2-oxopyrrolidin-3-yl]-2-methylindolizine-3-carboxamide,

Cpd 023 - 2-{[6-(cyclopropylmethoxy)-2-methylindolizin-3-yl]formamido}propanamide,

Cpd 025 - 6-(2,2-difluoroethoxy)-N-(1,3-dihydroxy-2-methylpropan-2-yl)-2-methylindolizine-3-carboxamide,

Cpd 027 - 6-(2,2-difluoroethoxy)-N-(4,4-difluoropiperidin-3-yl)-2-methylindolizine-3-carboxamide,

Cpd 028 - 2-{[6-(2,2-difluoroethoxy)-2-methylindolizin-3-yl]formamido}propanamide,

Cpd 029 - 3-hydroxy-2-methyl-2-({2-methyl-6-[(2-methyl-1,3-thiazol-5-yl)methoxy]indolizin-3-yl}formamido)propanamide,

Cpd 030 - N-(1,3-dihydroxy-2-methylpropan-2-yl)-2-methyl-6-[(2-methyl-1,3-thiazol-5-yl)methoxy]indolizine-3-carboxamide,

Cpd 031 - 2-({2-methyl-6-[(2-methyl-1,3-thiazol-5-yl)methoxy]indolizin-3-yl}formamido)propanamide,

Cpd 032 - N-(1-hydroxy-3-methoxy-2-methylpropan-2-yl)-2-methyl-6-[(pyridin-2-yl)methoxy]indolizine-3-carboxamide,

Cpd 033 - 3-hydroxy-2-({2-methyl-6-[(pyridin-2-yl)methoxy]indolizin-3-yl}formamido)propanamide,

Cpd 034 - 2-{[6-(benzyloxy)-2-methylindolizin-3-yl]formamido}-3-hydroxypropanamide,

Cpd 035 - 6-(benzyloxy)-N-(4,4-difluoro-1-hydroxy-2-methylbutan-2-yl)-2-methylindolizine-3-carboxamide,

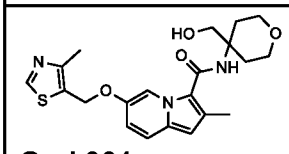
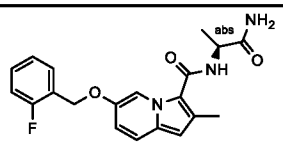
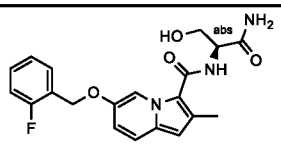
Cpd 036 - N-(4,4-difluoro-1-hydroxy-2-methylbutan-2-yl)-2-methyl-6-[(pyridin-2-

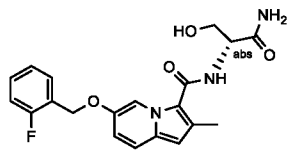
yl)methoxy]indolizine-3-carboxamide,
Cpd 037 - N-[3-(hydroxymethyl)-2-oxopyrrolidin-3-yl]-2-methyl-6-[(pyridin-3-yl)methoxy]indolizine-3-carboxamide,
Cpd 038 - N-[3-(hydroxymethyl)-2-oxopyrrolidin-3-yl]-6-[(2-methoxypyridin-3-yl)methoxy]-2-methylindolizine-3-carboxamide,
Cpd 039 - N-[3-(hydroxymethyl)-2-oxopyrrolidin-3-yl]-2-methyl-6-{[2-(trifluoromethyl)pyridin-3-yl]methoxy}indolizine-3-carboxamide,
Cpd 040 - 6-[(4-fluoro-1-methyl-1H-pyrazol-5-yl)methoxy]-N-[3-(hydroxymethyl)-2-oxopyrrolidin-3-yl]-2-methylindolizine-3-carboxamide,
Cpd 041 - 2-methyl-6-[(pyrazin-2-yl)methoxy]-N-(4,4,4-trifluoro-1-hydroxybutan-2-yl)indolizine-3-carboxamide,
Cpd 042 - 2-methyl-6-[(pyridin-3-yl)methoxy]-N-(4,4,4-trifluoro-1-hydroxybutan-2-yl)indolizine-3-carboxamide,
Cpd 043 - 6-[(2-methoxypyridin-3-yl)methoxy]-2-methyl-N-(4,4,4-trifluoro-1-hydroxybutan-2-yl)indolizine-3-carboxamide,
Cpd 044 - 2-methyl-N-(4,4,4-trifluoro-1-hydroxybutan-2-yl)-6-{[2-(trifluoromethyl)pyridin-3-yl]methoxy}indolizine-3-carboxamide,
Cpd 045 - 6-[(4-fluoro-1-methyl-1H-pyrazol-5-yl)methoxy]-2-methyl-N-(4,4,4-trifluoro-1-hydroxybutan-2-yl)indolizine-3-carboxamide,
Cpd 046 - N-[3-(hydroxymethyl)-2-oxopyrrolidin-3-yl]-2-methyl-6-[(pyrazin-2-yl)methoxy]indolizine-3-carboxamide,

[0111] The indolizine 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 indolizine derivatives according to the invention are also for use in the treatment of epilepsy.

[0112] In some embodiments, the indolizine derivatives are selected from the group consisting of compounds 001 – 046 shown in table 1 below, including stereoisomers and pharmaceutically acceptable salts thereof:

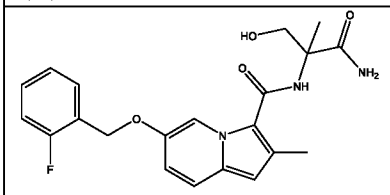
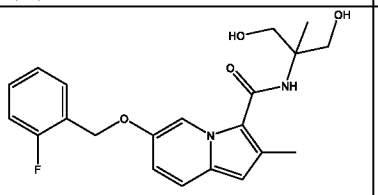
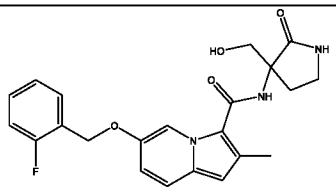
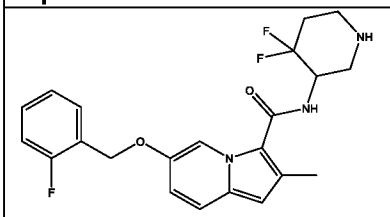
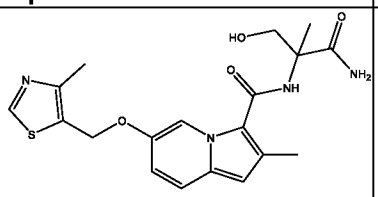
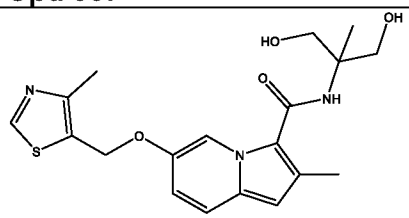
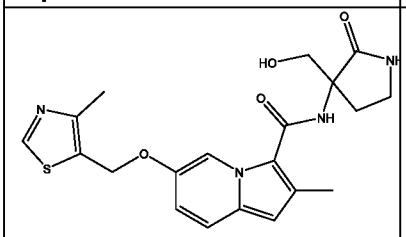
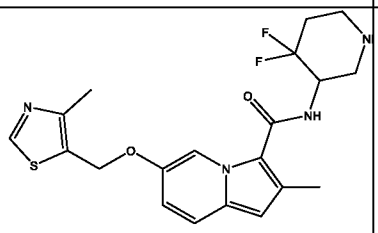
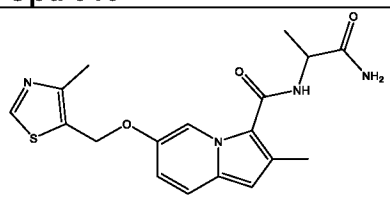
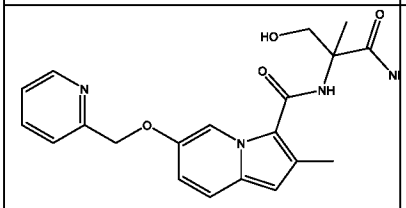
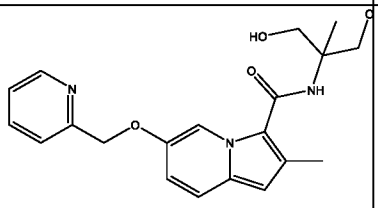
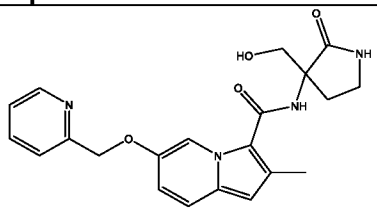
Table 1: Exemplary indolizine derivatives

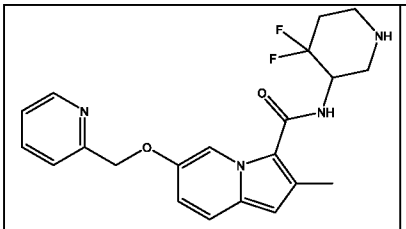
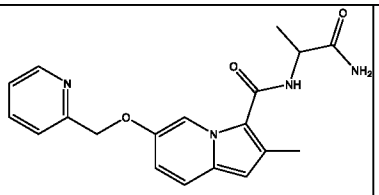
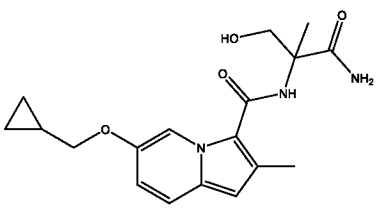
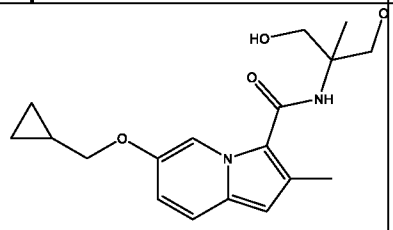
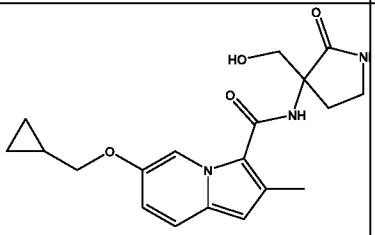
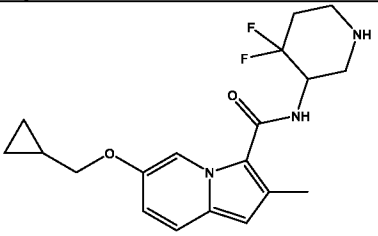
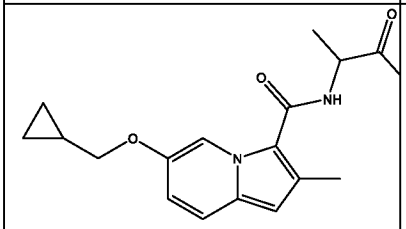
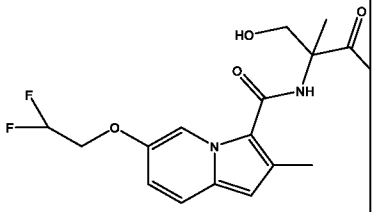
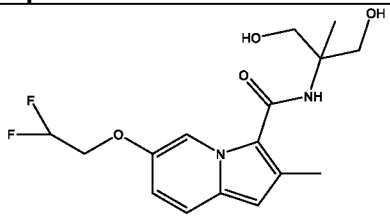
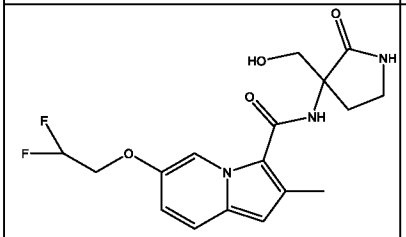
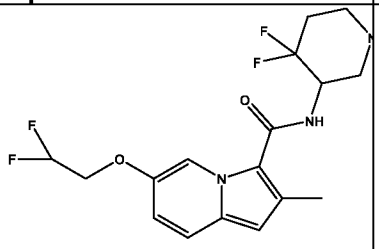
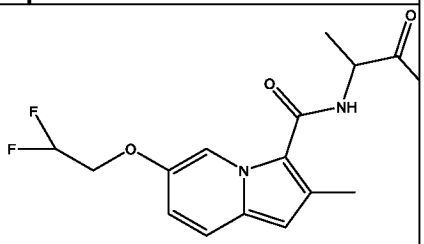
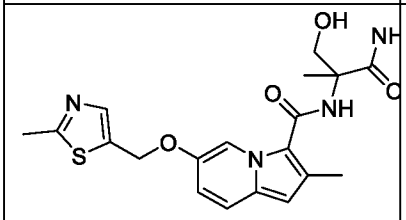
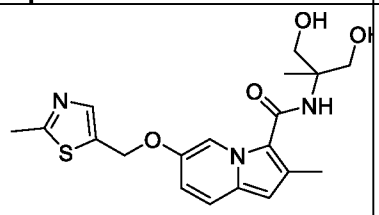
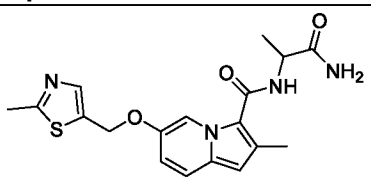
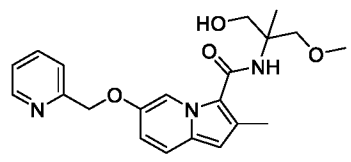
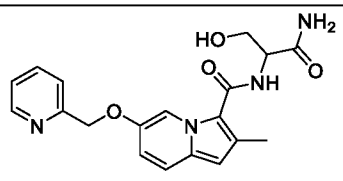
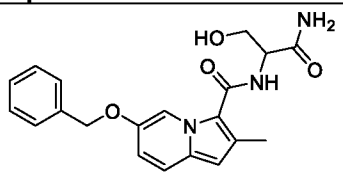
Structure and **Compound CODE**	Structure and **Compound CODE**	Structure and **Compound CODE**
 **Cpd 001**	 **Cpd 002**	 **Cpd 003**

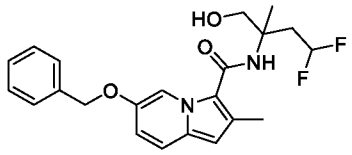
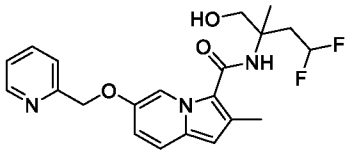
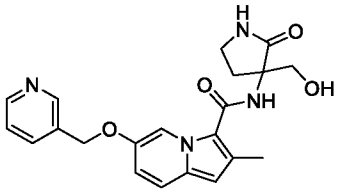
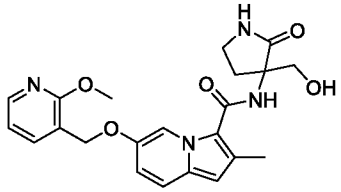
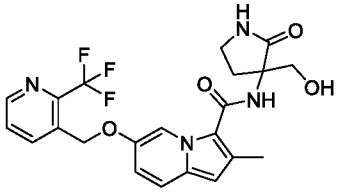
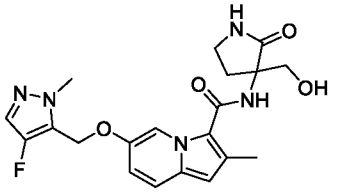
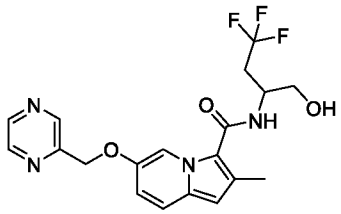
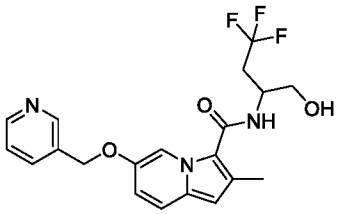
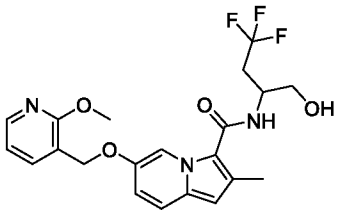
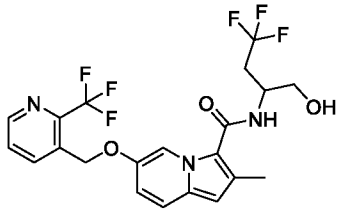
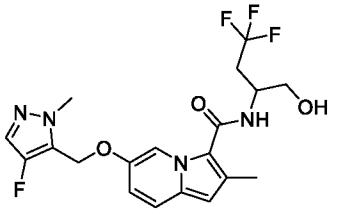
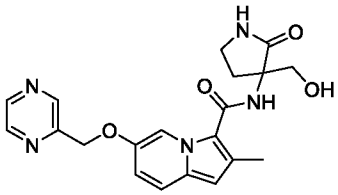
 Cpd 004		

[0113] In some embodiments, the indolizine derivatives are selected from the group consisting of compounds 005 – 046 shown in table 2 below, including stereoisomers and pharmaceutically acceptable salts thereof:

Table 2: Exemplary Indolizine derivatives

Structure and **Compound CODE**	Structure and **Compound CODE**	Structure and **Compound CODE**
 **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

[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 indolizine 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 indolizine derivatives as such, compositions comprising the indolizine derivatives, medicaments comprising the indolizine derivatives, and the indolizine 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 indolizine derivative is selected from the group consisting of cpd 001 to cpd 004 as mentioned above and the physiologically acceptable salts thereof.

[0116] In some embodiments of the invention, the indolizine derivative is selected from the group consisting of cpd 005 to cpd 046 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 indolizine 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 indolizine 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 indolizine derivative of the invention.

[0144] In an embodiment of the invention, the indolizine derivative of the invention is the sole pharmacologically active compound to be administered for therapy. In another embodiment of the invention, the indolizine 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 indolizine 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 indolizine 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 indolizine 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 indolizine derivatives of the invention may bear multiple positive or negative charges. The net charge of the indolizine 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 indolizine 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 indolizine derivatives of the invention also include physiologically acceptable salts thereof. Examples of physiologically acceptable salts of the indolizine 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 indolizine 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 indolizine 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] Indolizine 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 indolizine 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 indolizine 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 indolizine 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] Indolizine derivatives of the invention can be used to provide controlled release pharmaceutical formulations containing as active ingredient one or more indolizine 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 indolizine 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 indolizine derivatives of the invention. It may be desirable to formulate the indolizine 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 indolizine 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.

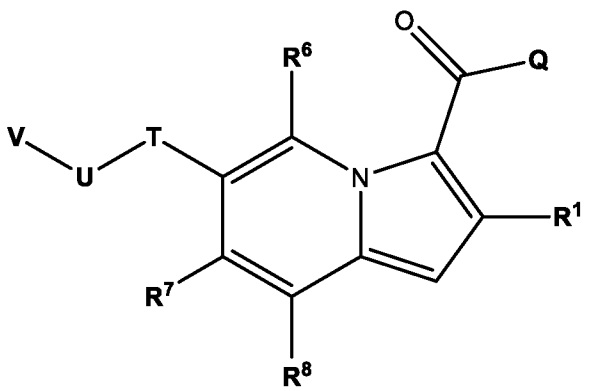
[0178] For the purpose of the invention the term “therapeutically suitable pro-drug” is defined herein as “a compound modified in such a way as to be transformed in vivo to the therapeutically active form, whether by way of a single or by multiple biological transformations, when in contact with the 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 indolizine 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}, -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; 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};

wherein

R^{W} and **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;

R^Y and 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 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)-

$NH(C_{1-6}\text{-alkyl})$, $\text{-O-C(=O)-N}(C_{1-6}\text{-alkyl})_2$, $\text{-}C_{1-6}\text{-alkylene-O-C(=O)-N}(C_{1-6}\text{-alkyl})_2$, $\text{-O-S(=O)}_2\text{-NH}_2$, $\text{-}C_{1-6}\text{-alkylene-O-S(=O)}_2\text{-NH}_2$, $\text{-O-S(=O)}_2\text{-NH}(C_{1-6}\text{-alkyl})$, $\text{-}C_{1-6}\text{-alkylene-O-S(=O)}_2\text{-NH}(C_{1-6}\text{-alkyl})$, $\text{-O-S(=O)}_2\text{-N}(C_{1-6}\text{-alkyl})_2$, $\text{-}C_{1-6}\text{-alkylene-O-S(=O)}_2\text{-N}(C_{1-6}\text{-alkyl})_2$, -NH_2, -NO, -NO_2, $\text{-}C_{1-6}\text{-alkylene-NH}_2$, $\text{-NH}(C_{1-6}\text{-alkyl})$, $\text{-N}(\text{3-14-membered cycloalkyl})(C_{1-6}\text{-alkyl})$, $\text{-N}(C_{1-6}\text{-alkyl})\text{-}C_{1-6}\text{-alkylene-OH}$, $\text{-N(H)-}C_{1-6}\text{-alkylene-OH}$, $\text{-}C_{1-6}\text{-alkylene-NH}(C_{1-6}\text{-alkyl})$, $\text{-N}(C_{1-6}\text{-alkyl})_2$, $\text{-}C_{1-6}\text{-alkylene-N}(C_{1-6}\text{-alkyl})_2$, $\text{-NH-C(=O)-}C_{1-6}\text{-alkyl}$, $\text{-}C_{1-6}\text{-alkylene-NH-C(=O)-}C_{1-6}\text{-alkyl}$, $\text{-NH-C(=O)-O-}C_{1-6}\text{-alkyl}$, $\text{-}C_{1-6}\text{-alkylene-NH-C(=O)-O-}C_{1-6}\text{-alkyl}$, -NH-C(=O)-NH_2, $\text{-}C_{1-6}\text{-alkylene-NH-C(=O)-NH}_2$, $\text{-NH-C(=O)-NH}(C_{1-6}\text{-alkyl})$, $\text{-}C_{1-6}\text{-alkylene-NH-C(=O)-NH}(C_{1-6}\text{-alkyl})$, $\text{-NH-C(=O)-N}(C_{1-6}\text{-alkyl})_2$, $\text{-}C_{1-6}\text{-alkylene-NH-C(=O)-N}(C_{1-6}\text{-alkyl})_2$, $\text{-N}(C_{1-6}\text{-alkyl})\text{-C(=O)-}C_{1-6}\text{-alkyl}$, $\text{-}C_{1-6}\text{-alkylene-N}(C_{1-6}\text{-alkyl})\text{-C(=O)-}C_{1-6}\text{-alkyl}$, $\text{-N}(C_{1-6}\text{-alkyl})\text{-C(=O)-O-}C_{1-6}\text{-alkyl}$, $\text{-}C_{1-6}\text{-alkylene-N}(C_{1-6}\text{-alkyl})\text{-C(=O)-O-}C_{1-6}\text{-alkyl}$, $\text{-N}(C_{1-6}\text{-alkyl})\text{-C(=O)-NH}_2$, $\text{-}C_{1-6}\text{-alkylene-N}(C_{1-6}\text{-alkyl})\text{-C(=O)-NH}_2$, $\text{-N}(C_{1-6}\text{-alkyl})\text{-C(=O)-NH}(C_{1-6}\text{-alkyl})$, $\text{-}C_{1-6}\text{-alkylene-N}(C_{1-6}\text{-alkyl})\text{-C(=O)-NH}(C_{1-6}\text{-alkyl})$, $\text{-N}(C_{1-6}\text{-alkyl})\text{-C(=O)-N}(C_{1-6}\text{-alkyl})_2$, $\text{-}C_{1-6}\text{-alkylene-N}(C_{1-6}\text{-alkyl})\text{-C(=O)-N}(C_{1-6}\text{-alkyl})_2$, $\text{-NH-S(=O)}_2\text{OH}$, $\text{-}C_{1-6}\text{-alkylene-NH-S(=O)}_2\text{OH}$, $\text{-NH-S(=O)}_2\text{-}C_{1-6}\text{-alkyl}$, $\text{-}C_{1-6}\text{-alkylene-NH-S(=O)}_2\text{-}C_{1-6}\text{-alkyl}$, $\text{-NH-S(=O)}_2\text{-O-}C_{1-6}\text{-alkyl}$, $\text{-}C_{1-6}\text{-alkylene-NH-S(=O)}_2\text{-O-}C_{1-6}\text{-alkyl}$, $\text{-NH-S(=O)}_2\text{-NH}_2$, $\text{-}C_{1-6}\text{-alkylene-NH-S(=O)}_2\text{-NH}_2$, $\text{-NH-S(=O)}_2\text{-NH}(C_{1-6}\text{-alkyl})$, $\text{-}C_{1-6}\text{-alkylene-NH-S(=O)}_2\text{-NH}(C_{1-6}\text{-alkyl})$, $\text{-NH-S(=O)}_2\text{N}(C_{1-6}\text{-alkyl})_2$, $\text{-}C_{1-6}\text{-alkylene-NH-S(=O)}_2\text{N}(C_{1-6}\text{-alkyl})_2$, $\text{-N}(C_{1-6}\text{-alkyl})\text{-S(=O)}_2\text{-OH}$, $\text{-}C_{1-6}\text{-alkylene-N}(C_{1-6}\text{-alkyl})\text{-S(=O)}_2\text{-OH}$, $\text{-N}(C_{1-6}\text{-alkyl})\text{-S(=O)}_2\text{-}C_{1-6}\text{-alkyl}$, $\text{-}C_{1-6}\text{-alkylene-N}(C_{1-6}\text{-alkyl})\text{-S(=O)}_2\text{-}C_{1-6}\text{-alkyl}$, $\text{-N}(C_{1-6}\text{-alkyl})\text{-S(=O)}_2\text{-O-}C_{1-6}\text{-alkyl}$, $\text{-}C_{1-6}\text{-alkylene-N}(C_{1-6}\text{-alkyl})\text{-S(=O)}_2\text{-O-}C_{1-6}\text{-alkyl}$, $\text{-N}(C_{1-6}\text{-alkyl})\text{-S(=O)}_2\text{-NH}_2$, $\text{-}C_{1-6}\text{-alkylene-N}(C_{1-6}\text{-alkyl})\text{-S(=O)}_2\text{-NH}_2$, $\text{-N}(C_{1-6}\text{-alkyl})\text{-S(=O)}_2\text{-NH}(C_{1-6}\text{-alkyl})$, $\text{-}C_{1-6}\text{-alkylene-N}(C_{1-6}\text{-alkyl})\text{-S(=O)}_2\text{-NH}(C_{1-6}\text{-alkyl})$, $\text{-N}(C_{1-6}\text{-alkyl})\text{-S(=O)}_2\text{-N}(C_{1-6}\text{-alkyl})_2$, $\text{-}C_{1-6}\text{-alkylene-N}(C_{1-6}\text{-alkyl})\text{-S(=O)}_2\text{-N}(C_{1-6}\text{-alkyl})_2$, -SH, =S, -SF_5, -SCF_3, $\text{-SCF}_2\text{H}$, -SCFH_2, $\text{-S-}C_{1-6}\text{-alkyl}$, $\text{-}C_{1-6}\text{-alkylene-S-}C_{1-6}\text{-alkyl}$, $\text{-S(=O)-}C_{1-6}\text{-alkyl}$, $\text{-}C_{1-6}\text{-alkylene-S(=O)-}C_{1-6}\text{-alkyl}$, $\text{-S(=O)}_2\text{-}C_{1-6}\text{-alkyl}$, $\text{-}C_{1-6}\text{-alkylene-S(=O)}_2\text{-}C_{1-6}\text{-alkyl}$, $\text{-S(=O)}_2\text{-OH}$, $\text{-}C_{1-6}\text{-alkylene-S(=O)}_2\text{-OH}$, $\text{-S(=O)}_2\text{-O-}C_{1-6}\text{-alkyl}$, $\text{-}C_{1-6}\text{-alkylene-S(=O)}_2\text{-O-}C_{1-6}\text{-alkyl}$, $\text{-S(=O)}_2\text{-NH}_2$, $\text{-}C_{1-6}\text{-alkylene-S(=O)}_2\text{-NH}_2$, $\text{-S(=O)}_2\text{-NH}(C_{1-6}\text{-alkyl})$, $\text{-}C_{1-6}\text{-alkylene-S(=O)}_2\text{-NH}(C_{1-6}\text{-alkyl})$, $\text{-S(=O)}_2\text{-N}(C_{1-6}\text{-alkyl})_2$, $\text{-}C_{1-6}\text{-alkylene-S(=O)}_2\text{-N}(C_{1-6}\text{-alkyl})_2$, 3-14-membered cycloalkyl, $\text{-}C_{1-6}\text{-alkylene-(3-14-membered cycloalkyl)}$, 3 to 14-membered heterocycloalkyl, $\text{-}C_{1-6}\text{-alkylene-(3 to 14-membered heterocycloalkyl)}$, -phenyl, $\text{-}C_{1-6}\text{-alkylene-phenyl}$, 5 to 14-membered heteroaryl, $\text{-}C_{1-6}\text{-alkylene-(5 to 14-membered heteroaryl)}$, -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), $\text{-S(=O)}_2\text{-(3-14-membered cycloalkyl)}$, $\text{-S(=O)}_2\text{-(3 to 14-membered heterocycloalkyl)}$, $\text{-S(=O)}_2\text{-phenyl}$, $\text{-S(=O)}_2\text{-(5 to 14-membered heteroaryl)}$.

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$\mathbf{R^3R^4}$.
5. The compound per se, or for use according to any one of Clauses 1 to 3, wherein **Q** represents -O$\mathbf{R^2}$.
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, $-SF_5$, -$\mathbf{R^Y}$, -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$\mathbf{R^Y R^Z}$.
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, $-SF_5$, -$\mathbf{R^Y}$, -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$\mathbf{R^Y R^Z}$.
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, $-SF_5$, -$\mathbf{R^Y}$, -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$\mathbf{R^Y R^Z}$.

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 oxetanel; 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 heterolalkyl 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_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)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_2F, -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_2F, -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_2F, -CHF_2, -CH_3, or -cyclopropyl, unsubstituted; preferably wherein **R**^{1} represents -CH_2F, -CHF_2, -CH_3, or -CH_2CH_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 **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 **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 **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 **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 **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 **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 $\mathbf{R^4}$ represents

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

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 **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, 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)$_2$C$_{1-6}$-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 **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.

36. The compound per se, or for use according to any one of the preceding Clauses, 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 -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 $\mathbf{R^8}$ 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 $\mathbf{R^8}$ does not represent -H.

49. The compound per se, or for use according to any one of the preceding Clauses, wherein
(i) $\mathbf{R^6}$, $\mathbf{R^7}$ and $\mathbf{R^8}$ each represent -H; or
(ii) two of $\mathbf{R^6}$, $\mathbf{R^7}$ and $\mathbf{R^8}$ represent -H and the other of $\mathbf{R^6}$, $\mathbf{R^7}$ and $\mathbf{R^8}$ represents -F, -Cl, -CN, or -CH_3; or
(iii) one of $\mathbf{R^6}$, $\mathbf{R^7}$ and $\mathbf{R^8}$ represents -H and the other of $\mathbf{R^6}$, $\mathbf{R^7}$ and $\mathbf{R^8}$ 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 004, or cpd 005 to 046, 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.

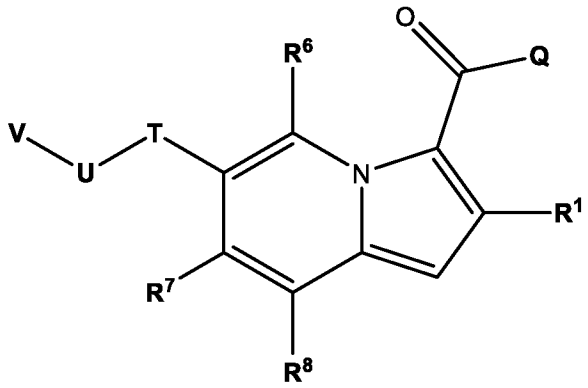
52. The compound per se, or for use according to any one of the preceding Clauses, wherein the pain is post-operative pain.

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$\mathbf{R^3R^4}$; $\mathbf{R^1}$ represents $\mathbf{R^W}$; and $\mathbf{R^W}$ represents -C_1-C_6-alkyl - and/or
(a-2) **Q** represents -N$\mathbf{R^3R^4}$; and at least one of $\mathbf{R^5}$ and $\mathbf{R^{5'}}$ represents -H; and/or
(a-3) **Q** represents -N$\mathbf{R^3R^4}$; and $\mathbf{R^6}$ represents -H; and/or
(a-4) **Q** represents -N$\mathbf{R^3R^4}$; and $\mathbf{R^8}$ represents -H;
or
(b-1)
(b-1) Q represents -N$\mathbf{R^3R^4}$; and $\mathbf{R^1}$ represents -CH_2F, -CHF_2, -CF_3, -CN, -methyl, -ethyl, -propyl or -cyclopropyl; and/or
(b-2) Q represents -N$\mathbf{R^3R^4}$; and at least one of $\mathbf{R^5}$ and $\mathbf{R^{5'}}$ does not represent -H; and/or
(b-3) Q represents -N$\mathbf{R^3R^4}$; and $\mathbf{R^3}$ 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 68 hereinafter:

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

$\mathbf{R^W}$ 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 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;

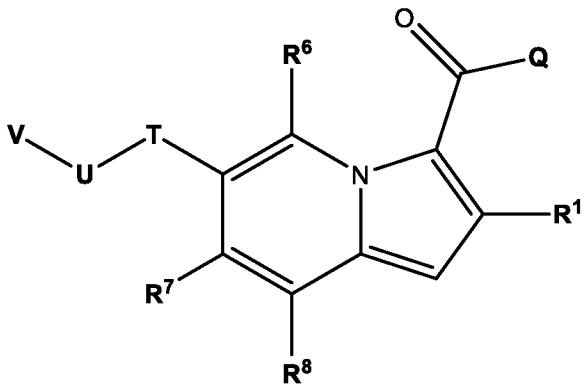
or $\mathbf{R^Y}$ and $\mathbf{R^Z}$ together form a 4, 5, 6, 7 or 8 membered heterocycle containing 1 to 3 heteroatoms selected from N, O and S, saturated or unsaturated, unsubstituted or mono- or polysubstituted;

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 the compound of 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 $-R^{10}-$;

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 a -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.

3. The compound of item 1, 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 with one or more N, O or S atom in the heterocycloalkyl ring, saturated or unsaturated

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}-;

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 a -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.

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, which may be substituted by one or more halogen atoms;

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 $-R^{10}$-; or

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 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 $-C_{1-6}$-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 a -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.

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 may form a group $-R^{10}$-.

12. The compound of any one of the preceding items, wherein R^1 and R^3 together form a straight or branched alkanediyl or alkenediyl with 1 to 4 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_{1-6}-alkyl.

13. The compound of any one of the preceding items, wherein R^1 and R^3 together form a straight or branched alkanediyl or alkenediyl with 1 to 3 carbon atoms, which may be not substituted or substituted by Halogen, C_{1-6}-alkyl or $CONR_2$, wherein the residues R may be independently of each other H or a C_{1-6}-alkyl.

14. The compound of any one of the preceding items, wherein R^1 and R^4 are not connected to form a heterocycle.

15. The compound of any one of the preceding items, wherein R^4 represents $R^{4'}$ or $-SO_2-C_{1-6}$-alkyl.

16. The compound of any one of the preceding items, wherein V represents H, C_{1-6}-alkyl or $-R^{cycl}$ wherein $-R^{cycl}$ in the 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 a 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.

17. 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 $-R^{cycl}$; and wherein-R^{cycl} in the group V may be substituted by at least one group selected from the list consisting of $-COO-C_{1-6}$-alkyl, $-CO-NR_2$, OR -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 independently of each other 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, which may be substituted by one or more halogen atoms;
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^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

R^{11} is selected from the list consisting of a -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.

18. The compound of any one of the preceding items, wherein R^6, R^7 and R^8 independently of each other represent hydrogen.

19. The compound of any one of the preceding items, wherein R^2 represents hydrogen.

20. The compound of any one of the preceding items, wherein R^3 represents hydrogen.

21. The compound of any one of the preceding items, wherein R^2 and R^3 represent hydrogen.

22. 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.

23. The compound of any one of the preceding items, wherein R^1 represents -C_{1-6}-alkyl.

24. 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 $-R^{cycl}$; and wherein R^{cycl} in group V may be substituted by at least one group selected from the list consisting of $-COO-C_{1-6}$-alkyl, $-CO-NR_2$, OR, -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 independently of each other 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

5-6-membered heteroaryl with one or more N, O or S in the heteroaryl ring; 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 a -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.

25. The compound of any one of the preceding items, wherein R^9 represents $-C_{1-6}$-alkyl, straight or branched.

26. The compound of any one of the preceding items, wherein R^{10} represents a straight or branched alkanediyl with 1 to 6 carbon atoms.

27. 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.

28. The compound of any one of the preceding items, wherein R^9 represents a straight or branched alkyl with 1 to 3 carbon atoms.

29. The compound of any one of the preceding items, wherein R^{10} represents a straight or branched alkanediyl with 1 to 3 carbon atoms.

30. 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}; and wherein R^{cycl} in group V may be substituted by at least one group selected from the list consisting of -CN, halogen O- C_{1-3}-alkyl or C_{1-3}-alkyl and the alkyl groups in the group V independently of each other 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
5-6-membered heteroaryl with one or more N, O or S in the heteroaryl ring; 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

R^{11} selected from the list consisting of OR, halogen, 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.

31. The compound of any one of the preceding items, wherein R^{cycl} comprises 1, 2 or 3 heteroatoms.

32. The compound of any one of the preceding items, wherein R^{cycl} comprises 1 or 2 heteroatoms.

33. The compound of any one of the preceding items, wherein R^{cycl} comprises 1 heteroatom.

34. 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

6-membered aryl, which may be substituted with at least one halogen; or

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

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; or

3-6-membered cycloalkyl which may be substituted by halogen or C_{1-3}-alkylene-OH; or

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 halogen or C_{1-3}-alkylene-OH; and R^6, R^7 and R^8 represent hydrogen.

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

6-membered aryl, which may be substituted with at least one halogen; or

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

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; or

3-6-membered cycloalkyl which may be substituted by halogen or C_{1-3}-alkylene-OH; or

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 halogen or C_{1-3}-alkylene-OH; and 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

6-membered aryl, which may be substituted with at least one halogen; or

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

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; or

3-6-membered cycloalkyl which may be substituted by halogen or C_{1-3}-alkylene-OH; or

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 halogen or C_{1-3}-alkylene-OH; and R^6, R^7 and R^8 represent hydrogen.

37. 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

6-membered aryl, which may be substituted with at least one halogen; or

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

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; or

3-6-membered cycloalkyl which may be substituted by halogen or C_{1-3}-alkylene-OH; or

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 halogen or C_{1-3}-alkylene-OH; and R^6, R^7 and R^8 represent hydrogen.

38. The compound of any one of items 1 to 33, wherein

Q represents OR^2 or $–NR^3R^4$;

T represents -O-;

U represents $-CH_2-$;

V represents

6-membered aryl, which may be substituted with at least one halogen; or

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

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; or

3-6-membered cycloalkyl which may be substituted by halogen or C_{1-3}-alkylene-OH; or

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 halogen or C_{1-3}-alkylene-OH; and R^6, R^7 and R^8 represent hydrogen.

39. The compound of any one of items 1 to 33, wherein

Q represents OR^2 or $–NR^3R^4$;
T represents -O-;
U represents $-CH_2-$;
V represents
6-membered aryl, which may be substituted with at least one fluorine atom; or
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;
R^1 represents -C_{1-3}-alkyl;
R^2 represents hydrogen;
R^3 represents hydrogen;
R^4 represents
C_{1-6} alkyl which may be substituted by OH or $-CONR_2$, wherein residues R are independently from each other hydrogen or methyl; or
4-7-membered heterocycloalkyl with one or more O atom in the heterocycloalkyl ring and wherein the heterocycloalkyl ring may be substituted by C_{1-3}-alkylene-OH;
and R^6, R^7 and R^8 represent hydrogen.

40. The compound of any one of items 1 to 33, wherein

Q represents OR^2 or $–NR^3R^4$;
T represents -O-;
U represents $-CH_2-$;
V represents
phenyl, which may be substituted with at least one fluorine atom; or
1,3-thiazole which may be substituted with a methyl group;
R^1 represents -C_{1-3}-alkyl;
R^2 represents hydrogen;
R^3 represents hydrogen;
R^4 represents
C_{1-3} alkyl which may be substituted by OH or $-CONH_2$; or

4-6-membered heterocycloalkyl with one O atom in the heterocycloalkyl ring and wherein the heterocycloalkyl ring may be substituted by C_{1-3}-alkylene-OH;
and R^6, R^7 and R^8 represent hydrogen.

41. The compound of any one of items 1 to 33, wherein

Q represents OR^2 or $–NR^3R^4$;
T represents -O-;
U represents $-CH_2-$;
V represents
phenyl, which is substituted with one fluorine atom; or
1,3-thiazole which is substituted with a methyl group;
R^1 represents $-C_{1-3}$-alkyl;
R^2 represents hydrogen;
R^3 represents hydrogen;
R^4 represents
C_{1-3} alkyl which may be substituted by at least one group selecetd from the group consisting of -OH and $-CONH_2$; or
an oxepan ring, which is substituted by a $-CH_2OH$ group;
and R^6, R^7 and R^8 represent hydrogen.

42. The compound of item 1, wherein **R^3** represents -H.

43. . The compound of item 2, wherein **R^4** represents a residue other than -H.

44. The compound of any one of items 1 or 42 to 43, wherein **R^1** represents -methyl or ethyl.

45. The compound of any one of items 1 or 42 to 44, wherein **T** represents -O- and **U** represents $-C\mathbf{R^5R^{5'}}-$.

46. 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.

47. The compound of any one of items 1 to 45, 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$\mathbf{R^Y R^Z}$, -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$\mathbf{R^Y R^Z}$.

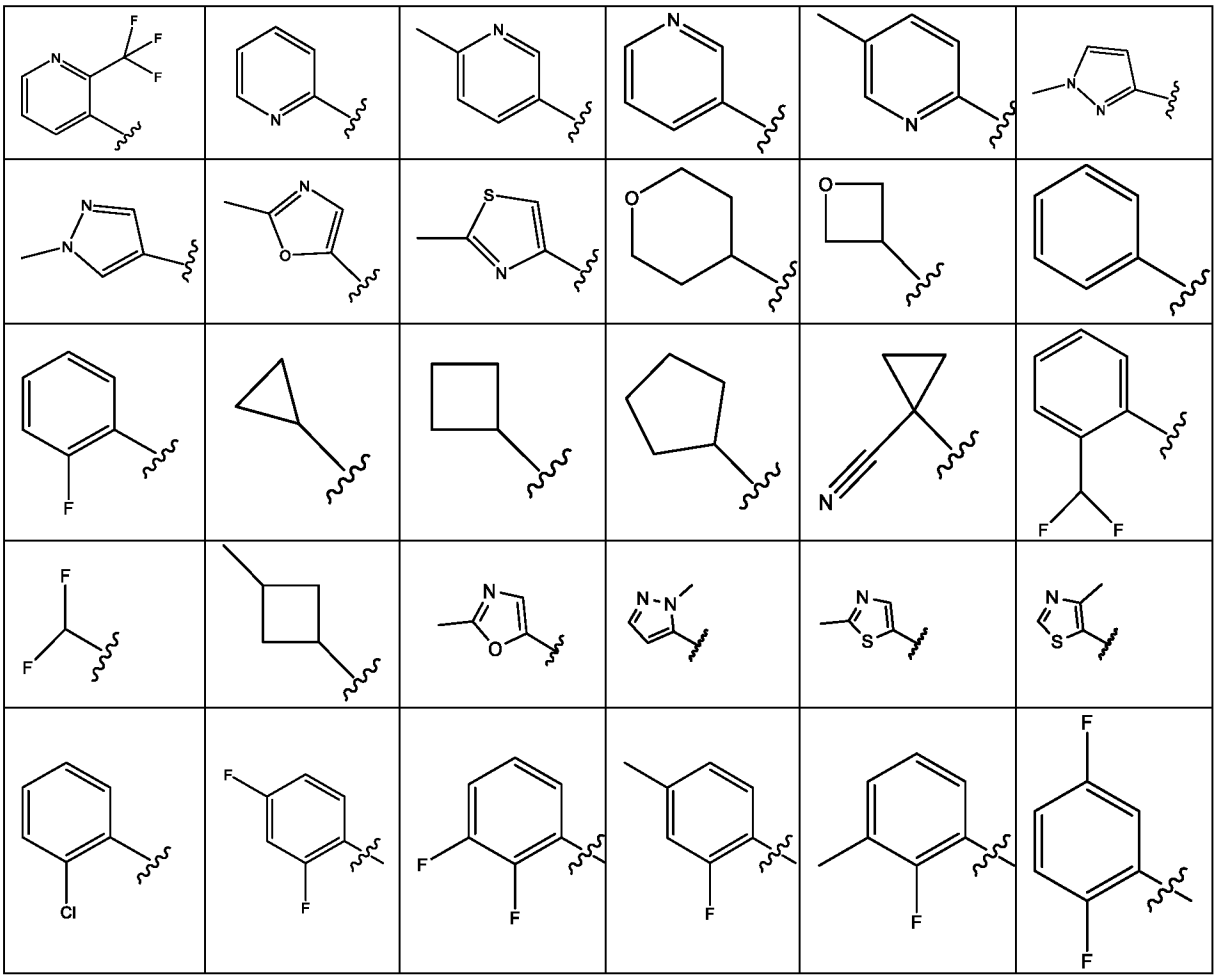
48. The compound of any one of items 1 to 45 wherein the 5-14-membered aryl within the definition of **V** is phenyl or another 5-14-membered aryl, unsubstituted, mono- or polysubstituted with substituents independently of one another selected from -F, -Cl, -Br, -I, CF_3, -CF_2H, C_1-C_6 alkyl, -CN, -NO, -NO_2, =O, =S, -SF_5, -$\mathbf{R^Y}$, -O$\mathbf{R^Y}$, -OC(=O)$\mathbf{R^Y}$, -N$\mathbf{R^Y R^Z}$, -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$\mathbf{R^Y R^Z}$.

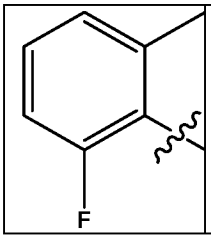
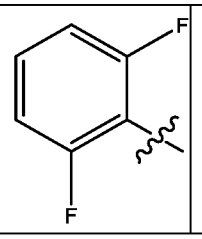
49. The compound of any one of items 1 to 45 wherein the 3-14-membered heterocycloalkyl within the definition of **V** is selected from azepane, 1,4-oxazepane, azetane, azetidine, aziridine, azocane, diazepane, dioxane, dioxolane, dithiane, dithiolane, imidazolidine, isothiazolidine, isoxalidine, morpholine, 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, 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, $-SF_5$, $-\mathbf{R}^Y$, $-O\mathbf{R}^Y$, $-OC(=O)\mathbf{R}^Y$, $-N\mathbf{R}^Y\mathbf{R}^Z$, $-N\mathbf{R}^YC(=O)\mathbf{R}^Z$, $-S\mathbf{R}^Y$, $-S(=O)\mathbf{R}^Y$, $-S(=O)_2\mathbf{R}^Y$, $-C(=O)\mathbf{R}^Y$, $-C(=O)O\mathbf{R}^Y$, or $-C(=O)N\mathbf{R}^Y\mathbf{R}^Z$.

50. The compound of any one of items 1 to 45 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 $-C(=O)N\mathbf{R}^Y\mathbf{R}^Z$.

51. The compound of any one of items 1 to 45 wherein **V** is a residue selected from the group consisting of:



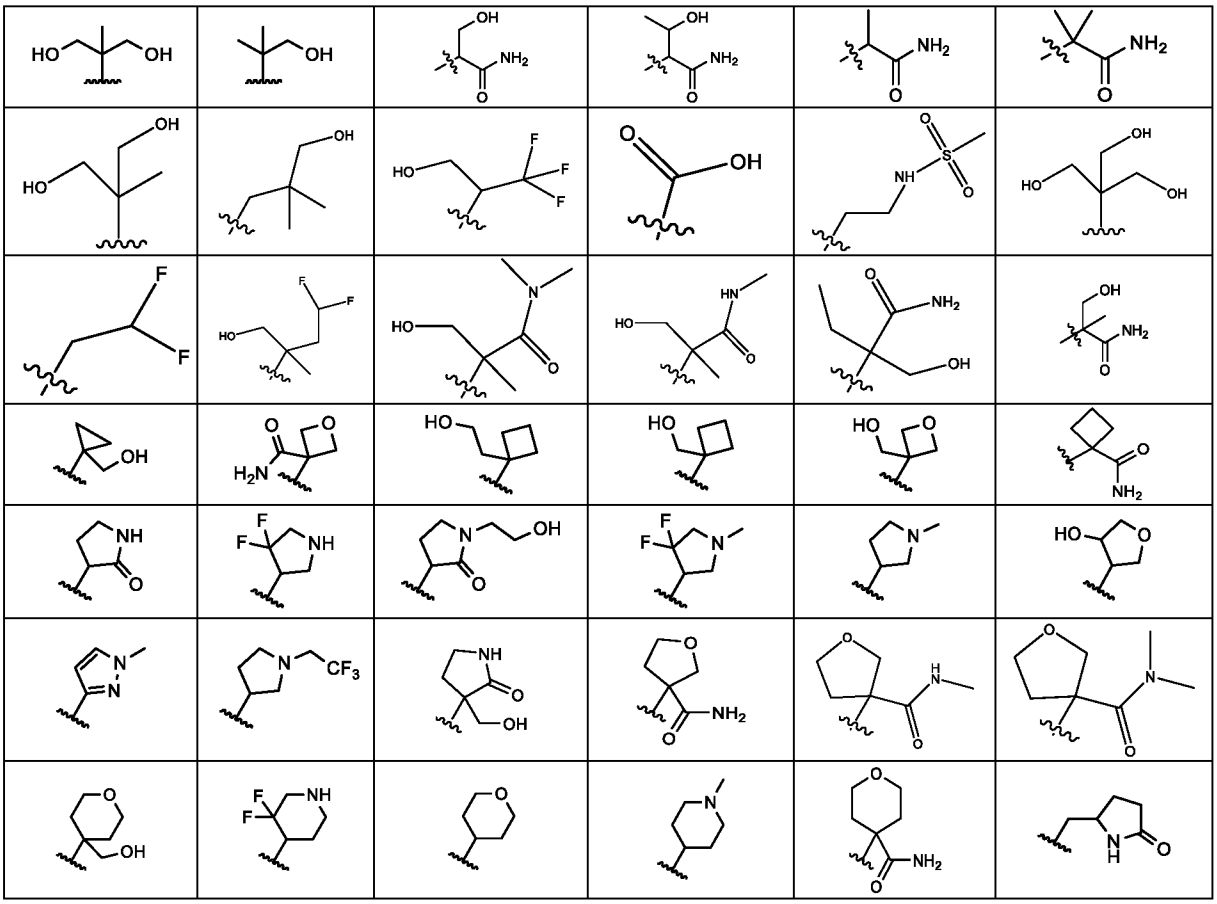
52. The compound according to any one of the preceding items, wherein $\mathbf{R^1}$ represents -H, -F, -Cl, -Br, -I, -C_{1-6}-alkyl, -O-C_{1-6}-alkyl, -C_{1-6}-alkylene-O-C_{1-6}-alkyl, -C_{1-6}-alkylene-NH(C_{1-6}-alkyl), -C_{1-6}-alkylene-N(C_{1-6}-alkyl)$_2$, -CF_3, -CF_2H, -CFH_2, -CF_2Cl, -$CFCl_2$, -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.

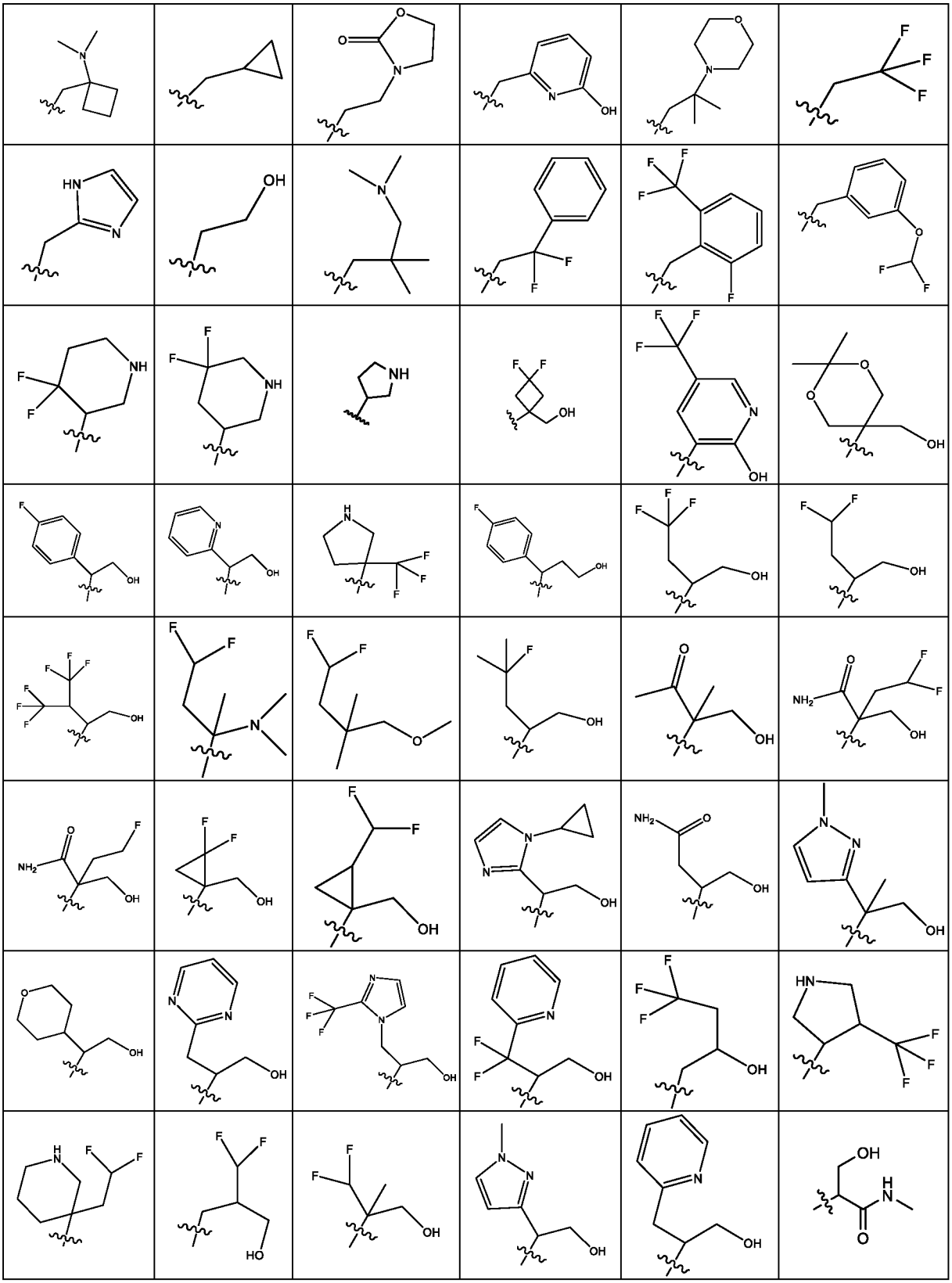
53. The compound according to any one of the preceding items, wherein $\mathbf{R^3}$ represents -H, -OH, -C_{1-6}-alkyl, -C_{1-6}-alkylene-OH, -C_{1-6}-alkylene-O-C_{1-6}-alkyl, -C_{1-6}-alkylene-NH_2, -C_{1-6}-alkylene-NH(C_{1-6}-alkyl), -C_{1-6}-alkylene-N(C_{1-6}-alkyl)$_2$, -CF_3, -CF_2H, -CFH_2, -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.

54. The compound according to any one of the preceding items, wherein $\mathbf{R^4}$ 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.

55. The compound according to any one of the preceding items wherein $\mathbf{R^4}$ 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.

56. The compound according to any one of the preceding items wherein $\mathbf{R^3}$ is H and $\mathbf{R^4}$ is a residue selected from the group consisting of:





57. 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.

58. 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.

59. The compound according to 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;

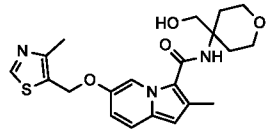
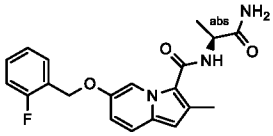
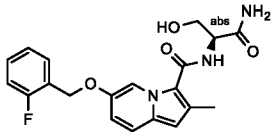
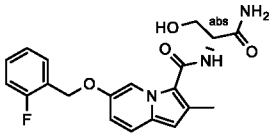
-C(=O)OC_{1-6}-alkyl unsubstituted or substituted with one or more substituents independently of one another selected from -OH, =O, -F, -Cl, -Br, -I, -SH, =S, -CN, -CF_3, -CHF_2, -CH_2F, -OCF_3, -$OCHF_2$, -OCH_2F, SF_5, -NO_2, -C(=O)OH, -NH_2, and -C(=O)NH_2;

-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;

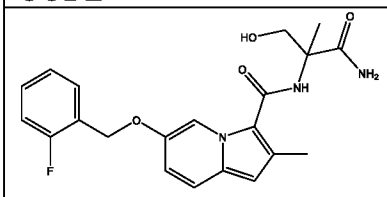
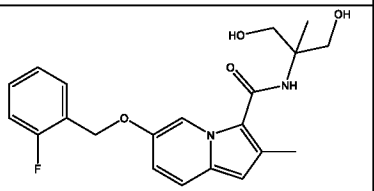
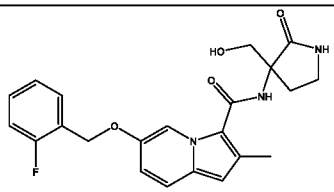
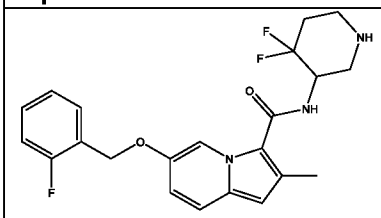
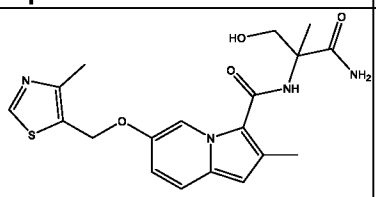
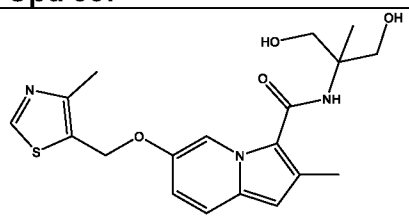
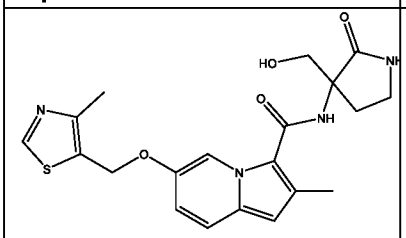
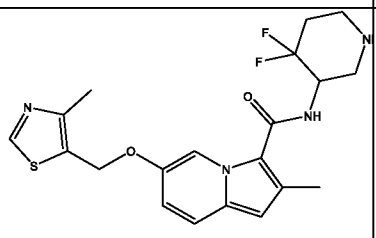
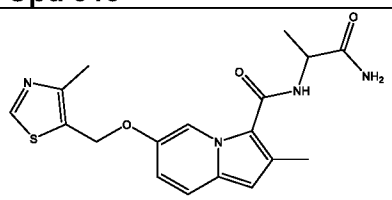
or

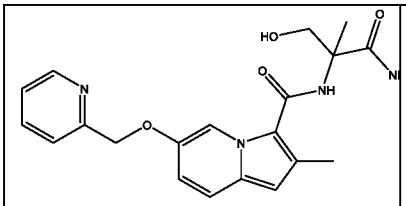
-C_{1-6}-heteroalkyl unsubstituted or substituted with one or more substituents independently of one another selected from -OH, =O, -F, -Cl, -Br, -I, -SH, =S, -CN, -CF_3, -CHF_2, -CH_2F, -OCF_3, -$OCHF_2$, -OCH_2F, SF_5, -NO_2, -C(=O)OH, -NH_2, and -C(=O)NH_2.

60. The compound of any one of the preceding items, which is selected from the group consisting of compounds 001 – 004 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**		

61. The compound of any one of the preceding items, which is selected from the group consisting of compounds 005 – 028 as shown in the table below:

Structure and **Compound CODE**	Structure and **Compound CODE**	Structure and **Compound CODE**
 **Cpd 005**	 **Cpd 006**	 **Cpd 007**
 **Cpd 008**	 **Cpd 009**	 **Cpd 010**
 **Cpd 011**	 **Cpd 012**	 **Cpd 013**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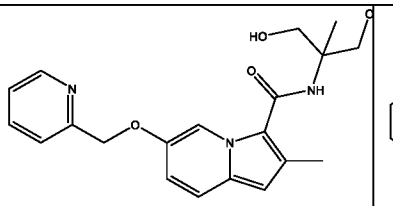
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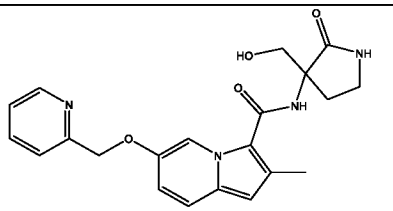
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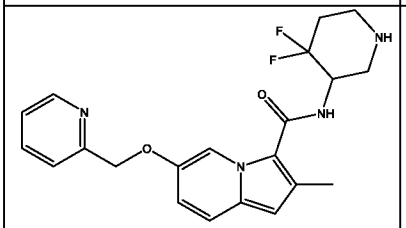
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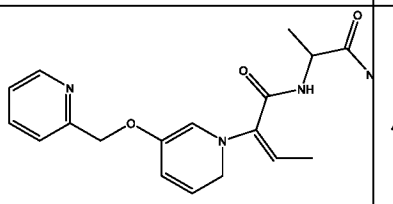
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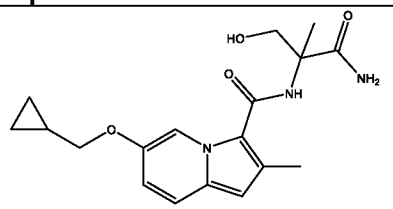
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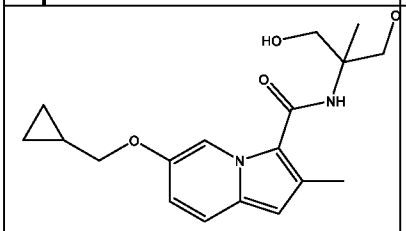
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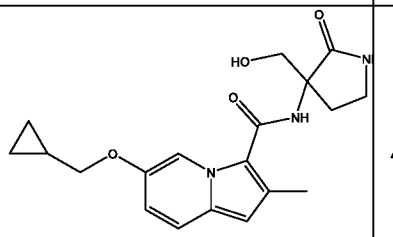
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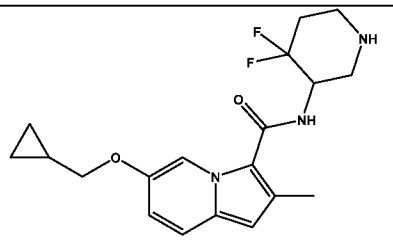
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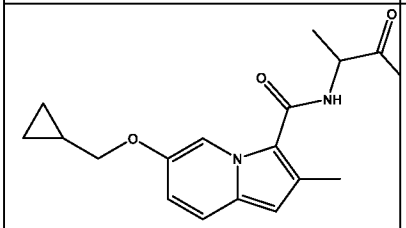
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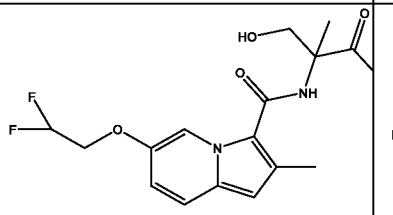
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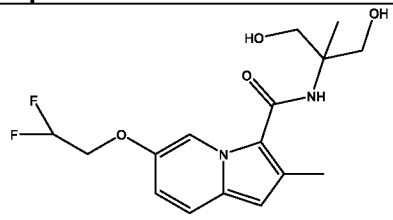
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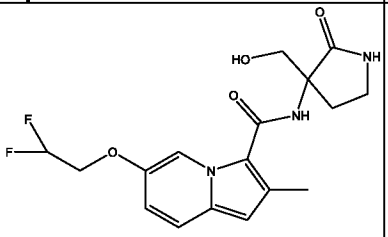
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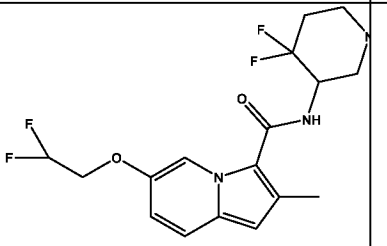
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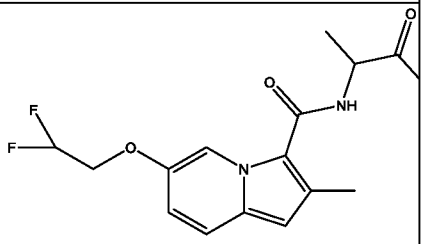
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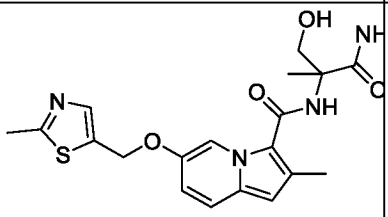
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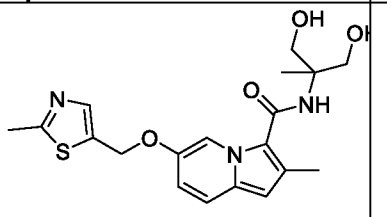
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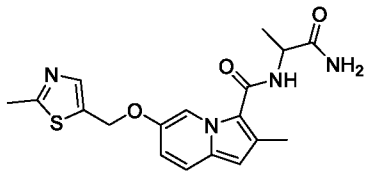
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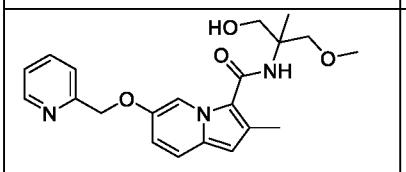
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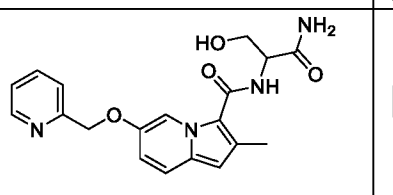
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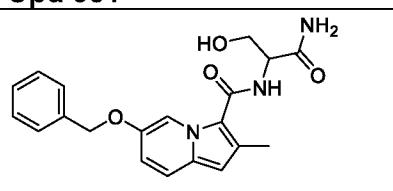
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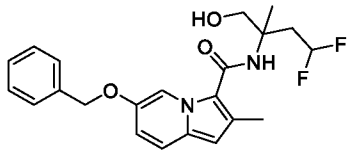
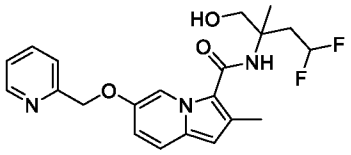
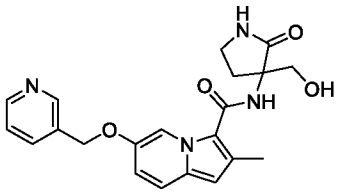
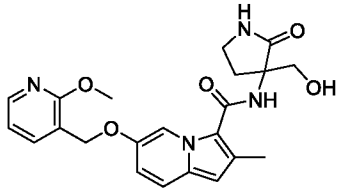
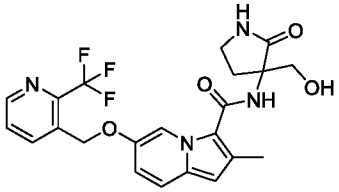
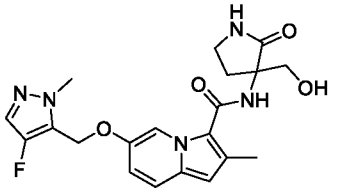
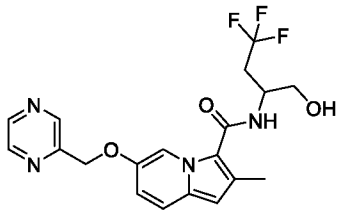
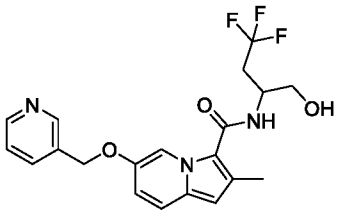
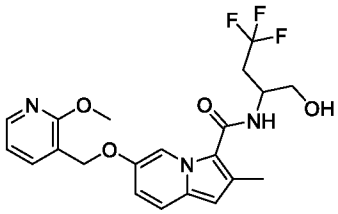
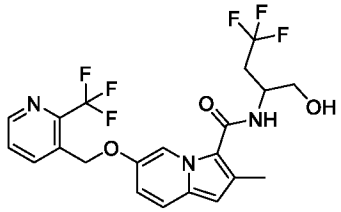
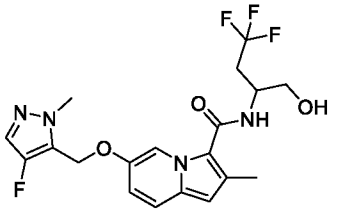
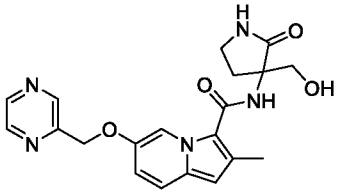
 Cpd 035	 Cpd 036	 Cpd 037
 Cpd 038	 Cpd 039	 Cpd 040
 Cpd 041	 Cpd 042	 Cpd 043
 Cpd 044	 Cpd 045	 Cpd 046

62. A pharmaceutical composition comprising a compound according to any one of the preceding items.

63. The compound according to any one of the preceding items or the pharmaceutical composition according to item 62, for use in the treatment of pain.

64. The compound or the pharmaceutical composition for use in the treatment of pain according to item 63, wherein the pain is selected from nociceptive pain, inflammatory pain, and neuropathic pain; preferably post-operative pain.

65. A method of treating of pain comprising administering a compound according to any one of items 1 to 61 or 63 to 64, or a pharmaceutical composition according to items 63 to 64, to a subject in need thereof.

66. The method of item 65 wherein the pain is selected from nociceptive pain, inflammatory pain, and neuropathic pain; preferably post-operative pain.

67. The compound according to any one of items 1 to 61 or the pharmaceutical composition according to claim 62, for use in the treatment of epilepsy.

68. A method of treating of epilepsy comprising administering a compound according to any one of items 1 to 61, or a pharmaceutical composition according to any of items 62 or 67, to a subject in need thereof.

EXAMPLES

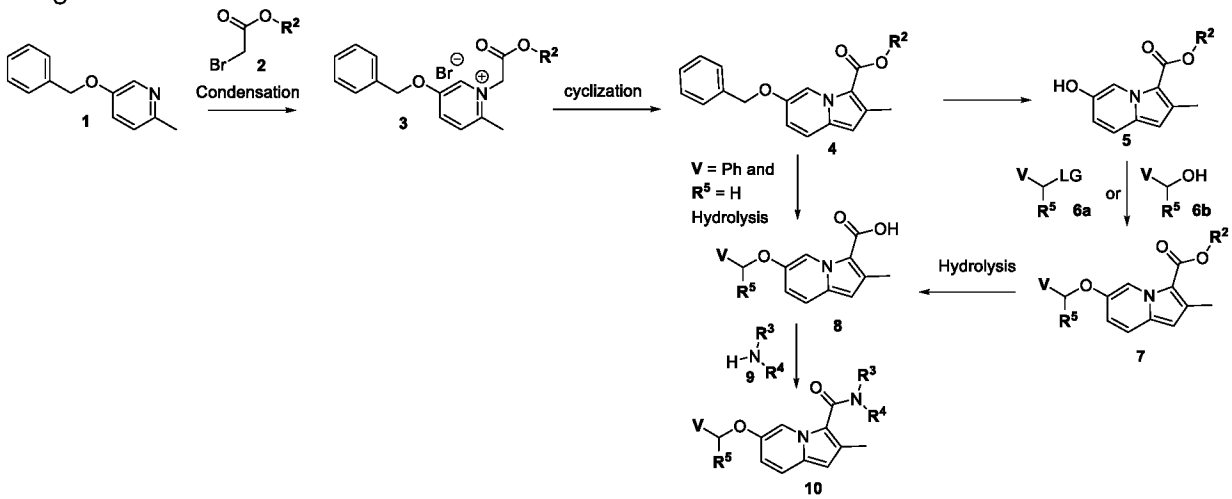
[0182] The following examples are provided for the purpose of illustrating the invention and by no means should be interpreted to limit the scope of the invention.

[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 , 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 - Diisopropylethylamine, DME - 1,2-Dimethoxyethane, DMF - N,N-Dimethylformamide, DMSO – Dimethylsulfoxide, 2,4-DNPH - 2,4-Dinitrophenylhydrazine, 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, KOTMS – Potassium trimethylsilanolate, LAH – Lithiumaluminiumhydrid, LG - Leaving group, MeOH – methanol, MgSO4 - Magnesium sulfate,

min. – Minute, Ms – Methanesulfonyl, Na_2SO_4 - Sodium sulfate, NBS - N-Bromosuccinimide, 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 - Diisoprpropylethylamine 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, SOR - Specific Optical Rotation, SPE - Solid Phase Extraction, TBDMS - Tert-Butyldimethylsilyl, TBAF - Tetrabutylammonium fluoride, TBAI - Tetrabutylammonium iodide, TEA – Triethylamine, THF - Tetrahydrofuran , TFA - Trifluoroacetic acid, TLC – thin layer chromatography, TPP – Triphenylphosphine, IPA – isopropyl alcohol, TMS – Trimethylsilyl, 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.



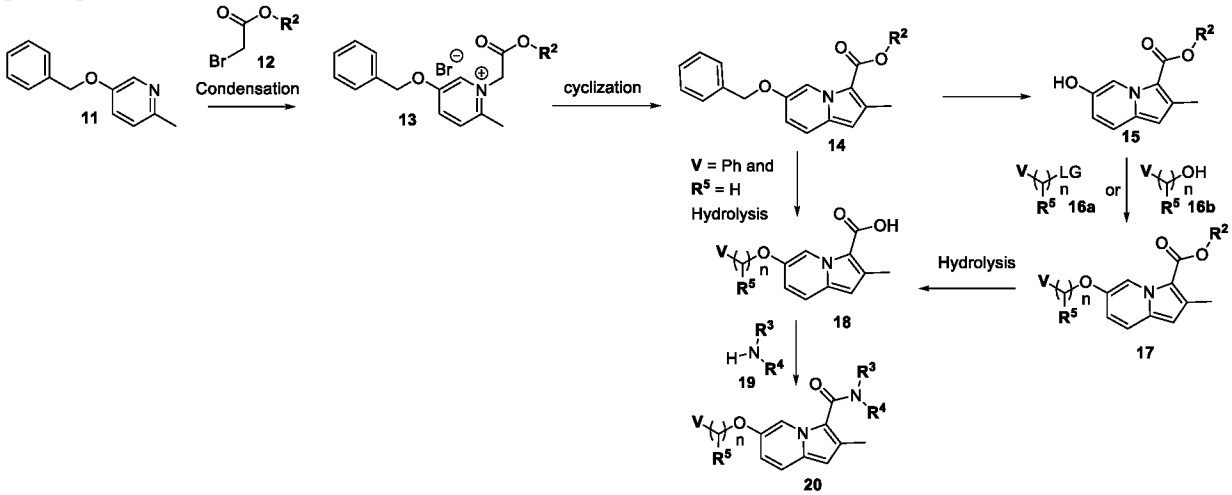
[0186] Scheme 1: all **V**, $\mathbf{R^2}$, $\mathbf{R^3}$, $\mathbf{R^4}$ and $\mathbf{R^5}$ are as described for the compounds of the present invention. At each occurrence of R^5, up to two independent substituents are contemplated (i.e. R^5 and $R^{5'}$).

[0187]

[0188] 5-(Benzyloxy)-2-methylpyridine of formula **1**, may be condensed with 2-bromoacetate derivatives **2** (commercially available or synthesized by procedures known to those skilled in the art), wherein R2 is an ester protecting group (e.g. methyl, ethyl, t-Bu and the like) in a suitable solvent (e.g., Ether, THF, and the like) to provide pyridinium salts of formula **3.** Intermediate of formula **3** may be cyclized in acetic anhydride in the presence of a base (e.g., potassium acetate, and the like) at a temperature ranging from 0 to 100°C to provide indolizine of formula **4**. Ester derivatives **4** may then be converted into the intermediate compounds of formula **5** via a hydrogenation reactions with a reducing agent (e.g., hydrogen gas, ammonium

formate, cyclohexadiene and the like) using a catalyst (more preferably Pd or Pt) in a solvent (e.g., THF, EtOH, and the like). 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, in the presence of a base (e.g., DIPEA, DBU, triethylamine, Cs_2CO_3, and the like) in a polar solvent (e.g., MeCN, 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. 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. Alternatively, benzyl derivatives **4** 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 indolizine of formula **10** by procedures known to those skilled in the art or as set forth in the examples below

[0189]

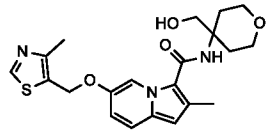
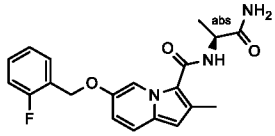
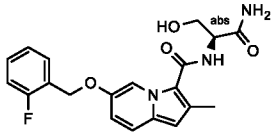


[0190] Scheme 2: all **V**, n, $\mathbf{R^2}$, $\mathbf{R^3}$, $\mathbf{R^4}$ and $\mathbf{R^5}$ are as described for the compounds of the present invention. At each occurrence of R^5, up to two independent substituents are contemplated (i.e. R^5 and $R^{5'}$). The integer n may range from 1 to 10 in some embodiments.

[0191] 5-(Benzyloxy)-2-methylpyridine of formula **11**, may be condensed with 2-bromoacetate

derivatives **12** (commercially available or synthesized by procedures known to those skilled in the art), wherein R2 is an ester protecting group (e.g. methyl, ethyl, t-Bu and the like) in a suitable solvent (e.g., Ether, THF, and the like) to provide pyridinium salts of formula **13.** Intermediate of formula **13** may be cyclized in acetic anhydride in the presence of a base (e.g., potassium acetate, and the like) at a temperature ranging from 0 to 100°C to provide indolizine of formula **14**. Ester derivatives **14** may then be converted into the intermediate compounds of formula **15** via a hydrogenation reactions with a reducing agent (e.g., hydrogen gas, ammonium formate, cyclohexadiene and the like) using a catalyst (more preferably Pd or Pt) in a solvent (e.g., THF, EtOH, and the like). 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, in the presence of a base (e.g., DIPEA, DBU, triethylamine, Cs_2CO_3, and the like) in a polar solvent (e.g., MeCN, 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. 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. Alternatively, benzyl derivatives **14** 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 indolizine of formula **20** by procedures known to those skilled in the art or as set forth in the examples below

Table 3: Exemplary Compounds

Structure and **Compound CODE**	Structure and **Compound CODE**	Structure and **Compound CODE**
 **Cpd 001**	 **Cpd 002**	 **Cpd 003**

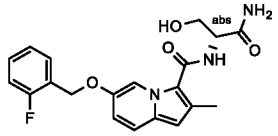
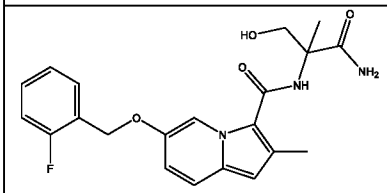
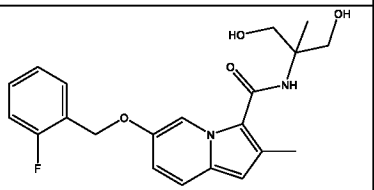
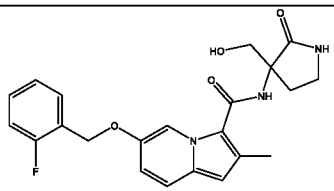
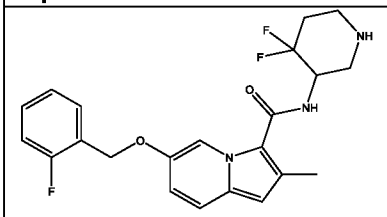
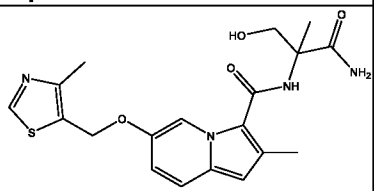
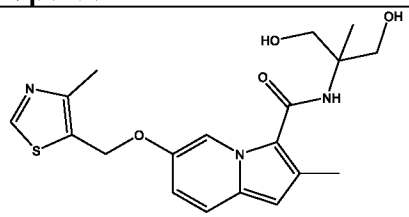
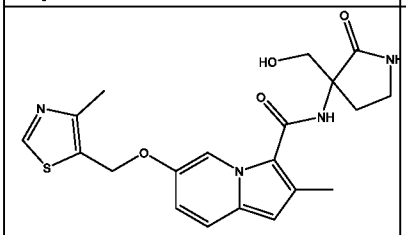
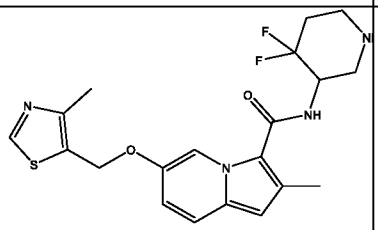
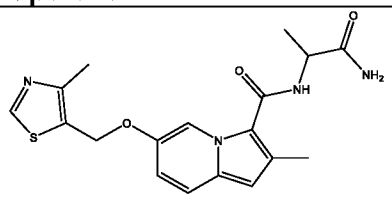
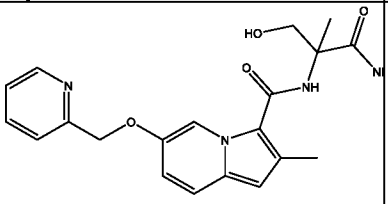
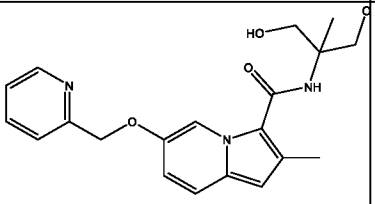
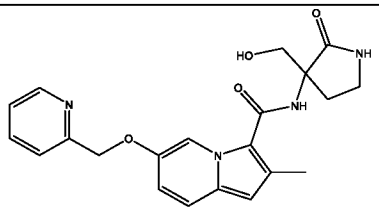
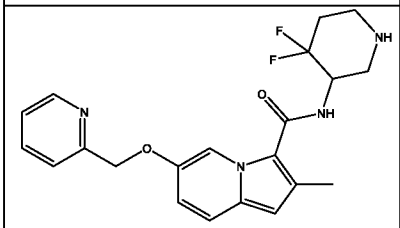
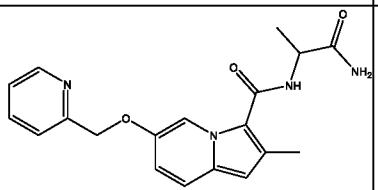
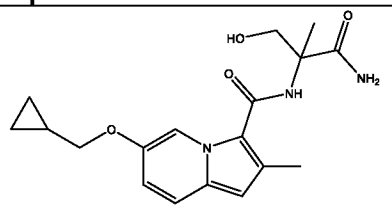
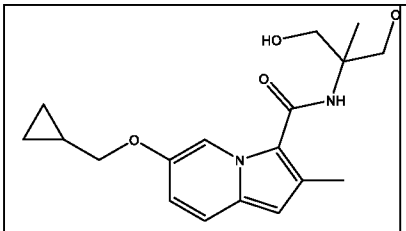
 Cpd 004		

Table 4: Exemplary Compounds

Structure and **Compound CODE**	Structure and **Compound CODE**	Structure and **Compound CODE**
 **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**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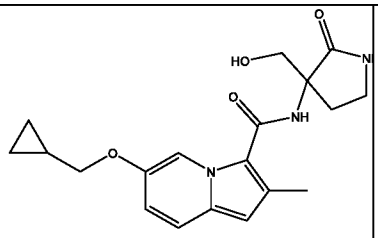
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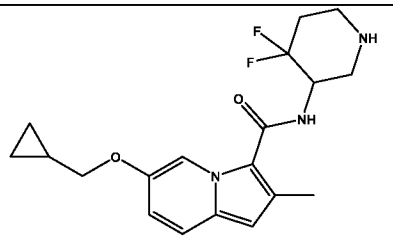
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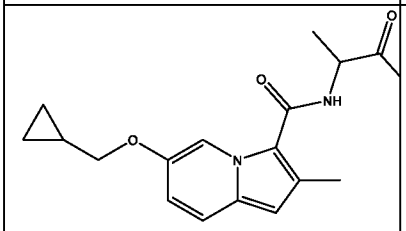
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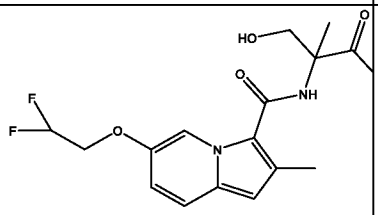
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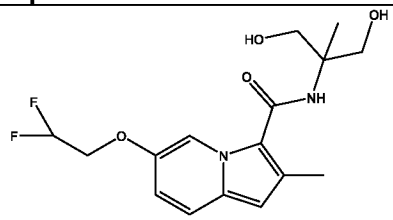
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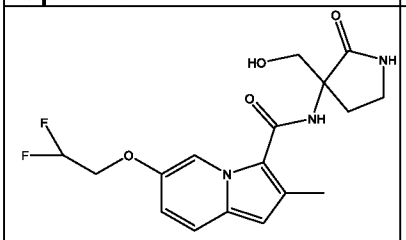
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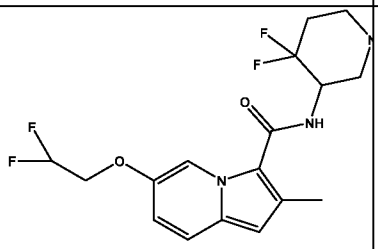
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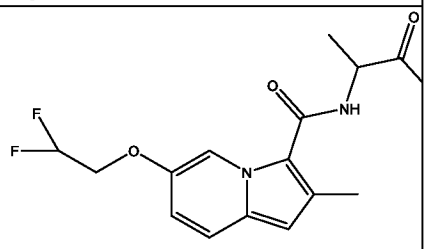
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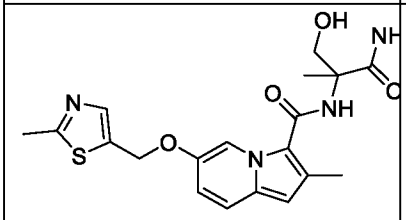
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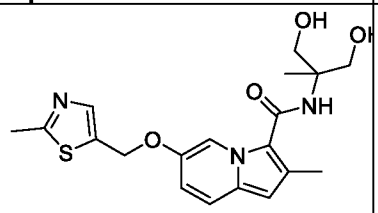
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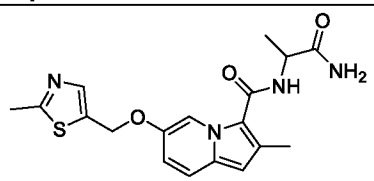
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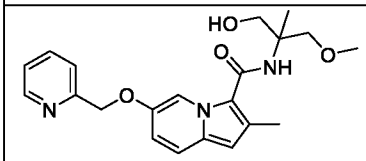
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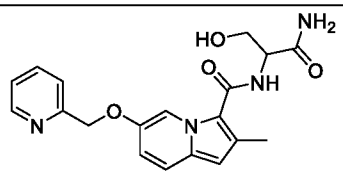
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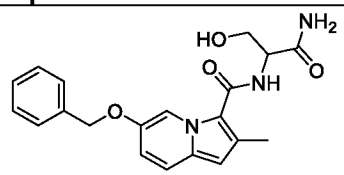
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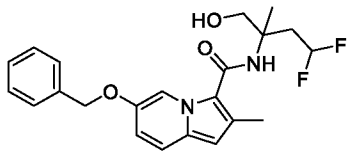
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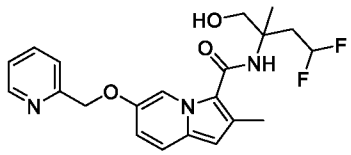
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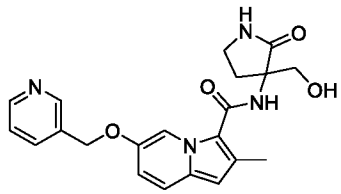
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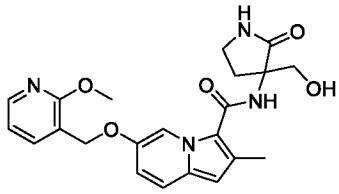
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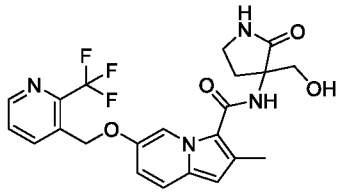
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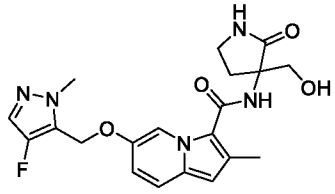
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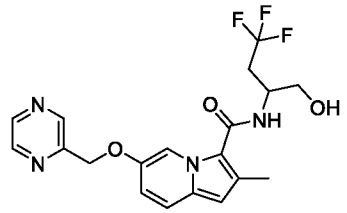
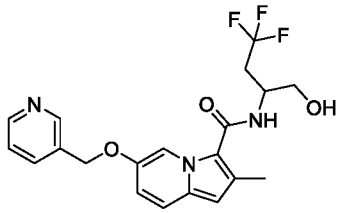
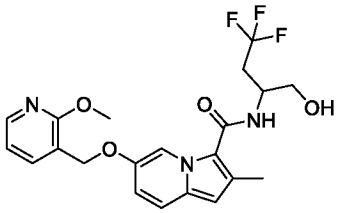
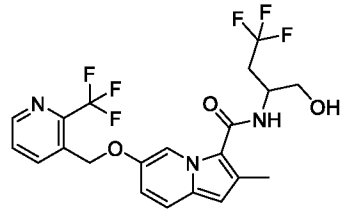
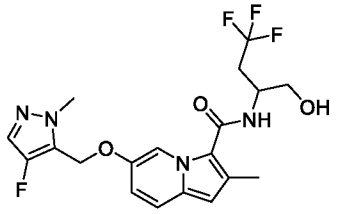
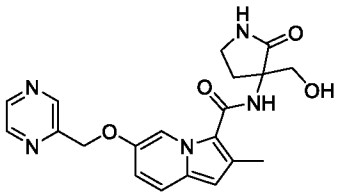
 Cpd 041	 Cpd 042	 Cpd 043
 Cpd 044	 Cpd 045	 Cpd 046

[0192] 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.

[0193] Part A represent the preparation of the compounds whereas Part B represents the pharmacological examples.

[0194] **Part A**

[0195] 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 repspectively, for example) or can be prepared using the conventional methods known to the person skilled in the art.

[0196] 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.

[0197] 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.

[0198] 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 diastereomers 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.

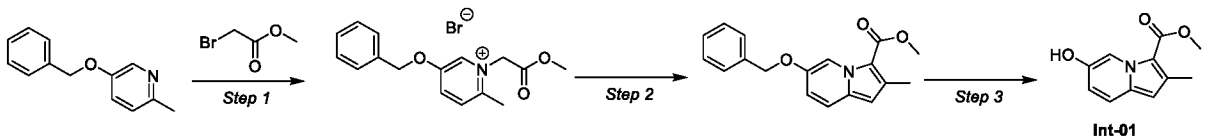
[0199] Analytical instruments employed were e.g. for NMR analysis a BRUKER 400MHz or a BRUKER 500MHz machine (Software Topspin), alternatively a BRUKER AVANCE 300MHz and 400Mhz was employed. For LC/MS analysis e.g. an Agilent 1290 infinity,Mass:6150 SQD(ESI/APCI) or an Agilent 1200 SERIES,Mass:6130 SQD(ESI/APCI) (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).

[0200] 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).

[0201] 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.

[0202] The LC/MS analysis mentioned in the experimental part were performed on Alliance Waters HPLC (equipped with a PDA detector) connected to a mass spectrometer mass spectrometer Waters 3100 Mass Detector with ESI mode; or on Acquity UPLC Waters (equipped with a PDA detector) connected to a mass spectrometer mass SQD2 Detector with ESI mode; or on Acquity UPLC Waters (equipped with a PDA detector) connected to a mass spectrometer mass Xevo TQS Detector with ESI mode.

[0203] **Synthesis of methyl 6-hydroxy-2-methylindolizine-3-carboxylate (Int-01)**



Int-01

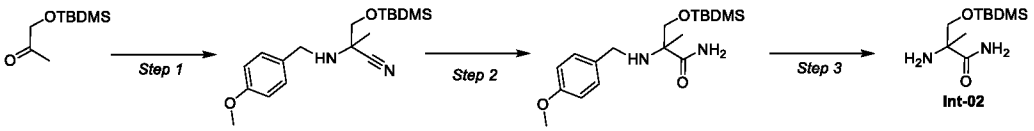
[0204] *Step 1* : To a solution of 5-(benzyloxy)-2-methylpyridine (125 g, 627 mmol) in ethanol (1000 mL) was added methyl 2-bromoacetate (65 mL, 690 mmol) at RT. The RM was stirred at 80 °C for 16 h. After completion of the reaction, the volatiles were removed under reduced pressure. The residue was triturated with pet ether (500 mL) and dried to afford benzyloxy)-1-(2-methoxy-2-oxoethyl)-2-methylpyridinium bromide (210 g, 85%).

[0205] *Step 2* : To a solution of methyl 2-(5-(benzyloxy)-2-methyl-1l4-pyridin-1-yl)acetate (105

g, 300 mmol) in acetic anhydride (500 mL) was added sodium acetate (73.8 g, 900 mmol) at RT. The RM was stirred at 150 °C for 24 h. The RM was cooled to RT, diluted with EtOAc (1000 mL), washed with sat. $NaHCO_3$ (3 x 500 mL), brine solution (400 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 methyl 6-(benzyloxy)-2-methylindolizine-3-carboxylate as a pale yellow solid (19 g, 21%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.47 (d, 2 H), 7.42 - 7.40 (m, 2 H), 7.33 - 7.39 (m, 1 H), 7.25 - 7.28 (m, 1 H), 6.88 (dd, 1 H), 6.26 (s, 1 H), 5.07 (s, 2 H), 3.91 (s, 3 H), 2.51 (s, 3 H).

[0206] *Step 3* : To a solution of methyl 6-(benzyloxy)-2-methylindolizine-3-carboxylate (5.3 g, 17.94 mmol) in methanol (500 mL) was added ammonium formate (11.31 g, 179.45 mmol) and 10% Palladium on carbon (2.5 g) at RT. The RM was stirred at RT for 2 h. The RM was filtered through a celite pad, washed with MeOH (100 mL) and the filtrate was concentrated under reduced pressure. The residue was diluted with water (250 mL), extracted with EtOAc (2 × 250 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was triturated with n-pentane (100 mL) and dried to afford methyl 6-hydroxy-2-methylindolizine-3-carboxylate methyl 6-hydroxy-2-methylindolizine-3-carboxylate (**Int-01**) as a pale yellow solid (2.2 g, 59%). ^{1}H NMR (400 MHz, DMSO-D_6) δ ppm: 9.49 (s, 1 H), 9.05 (s, 1 H), 7.42 (d, 1H), 6.83 - 6.85 (m, 1 H), 6.32 (s, 1 H), 3.81 (s, 3 H), 2.42 (s, 3 H).

[0207] **Synthesis of 2-amino-3-((tert-butyldimethylsilyl)oxy)-2-methylpropanamide (Int-02).**



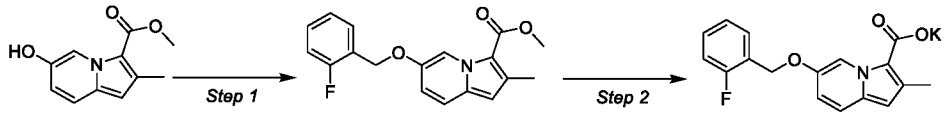
[0208] *Step 1* : To a stirred solution of 1-(tert-Butyl-dimethyl-silanyloxy)-propan-2-one (25 g, 132.7 mmol) in EtOH (250ml) was added 4-methoxy benzylamine (19.08 ml, 146 mmol) at RT. Trimethylsillylcyanide (19.93 ml, 159.286 mmol) followed by ammonium chloride (2.13 g, 39.8 mmol) were added to the RM at RT. The RM was stirred at 80°C for 16 h. The RM was concentrated under reduced pressure. The residue was partitioned between EtOAc and saturated sodium bicarbonate solution. Organic layer was washed with brine solution, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified on FCC using 10% EtOAc in Hexane as an eluent 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-d_6) 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 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 layer was dried over Na_2SO_4 and concentrated. The residue was purified on FCC on silica gel using 50% EtOAc in Hexaneas an eluent 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-d_6) 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).

[0028] *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) 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-d_6) 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).

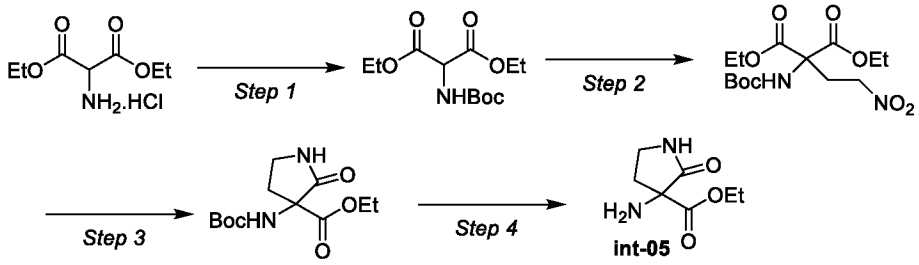
[0210] **Synthesis of methyl 6-((2-fluorobenzyl)oxy)-2-methylindolizine-3-carboxylate (Int-03) and potassium 6-((2-fluorobenzyl)oxy)-2-methylindolizine-3-carboxylate (Int-04)**



Int-01 Int-03 Int-04

[0211] *Step 1 : To a solution of methyl 6-hydroxy-2-methylindolizine-3-carboxylate (2 g, 9.75 mmol)* in THF (40 mL) were added ADDP (4.918g, 19.492 mmol), $P(nBu)_3$ (4.81 mL, 19.5 mmol) and (2-fluorophenyl)methanol (1.477 g, 11.7 mmol) at 0 °C. The RM was stirred at RT for 16 h. The RM was diluted with water (100 mL), extracted with EtOAc (2 x 50 mL). Combined organic layers were washed with saturated brine (50 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 6-((2-fluorobenzyl)oxy)-2-methylindolizine-3-carboxylate (**Int-03**) as a pale yellow solid (2.0 g, 68. 6%). ^{1}H NMR (400 MHz, DMSO-D_6) δ ppm: 9.18 (d, 1H), 7.57 - 7.61 (m, 1H), 7.53 (t, 1H), 7.45 - 7.47 (m, 1H), 7.41 - 7.43 (m, 2H), 7.24 (dd, 1H), 6.41 (s, 1H), 5.18 (d, 2H), 3.83 (s, 3H), 2.45 (s, 3H).*Step 2* : To a solution of methyl 6-((2-fluorobenzyl)oxy)-2-methylindolizine-3-carboxylate (**Int-03**) (300 mg, 0.957 mmol) in THF (10.0 mL) was added KOTMS (614 mg, 4.78 mmol) at RT. The RM was stirred at 70 °C for 16 h. After cooling to RT, solvent was removed under reduced pressure. The residue was triturated with pentane to afford 6-((2-fluorobenzyl)oxy)-2-methylindolizine-3-carboxylate as a potassium salt as a brown solid (**Int-04**) (310 mg).

[0212] **Synthesis of Ethyl 3-amino-2-oxopyrrolidine-3-carboxylate hydrochloride (**Int-05**).**



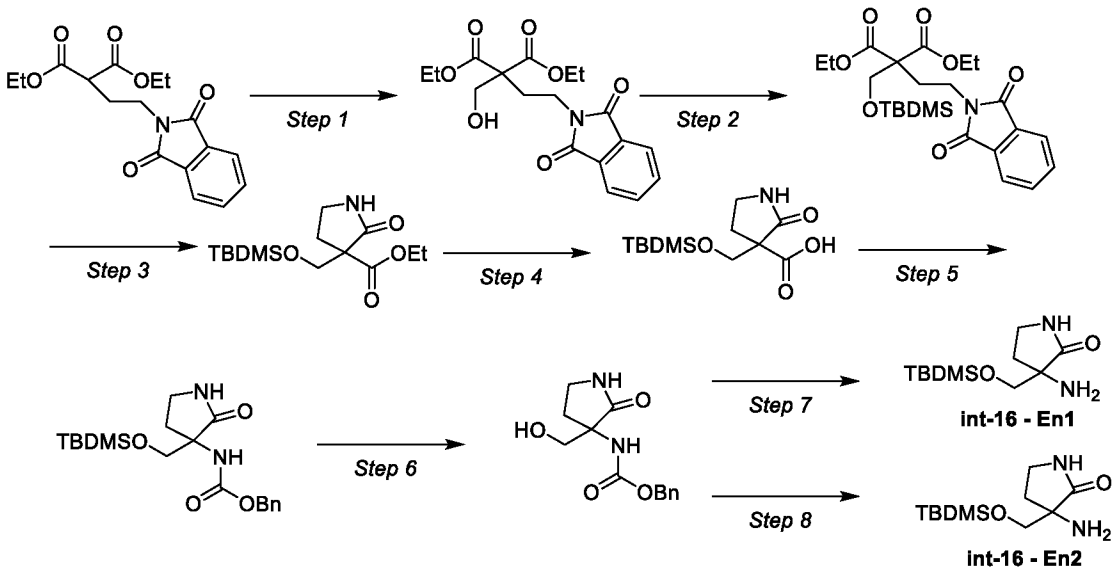
[0213] *Step 1* : Boc anhydride (35.8 mL, 155.9 mmol) was added to a solution of diethyl 2-aminomalonate *hydrochloride* (30 g, 141.7 mmol) and TEA (60.18 mL, 425.25 mmol) in DCM (400 mL) at 0 °C. The RM was stirred at RT for 16 h. The RM was diluted with ice water (500 mL) and the organic layer was separated, organic layer was washed with brine (200 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford diethyl 2-((tert-butoxycarbonyl)amino)malonate (35.8 g) as a colorless .

[0214] *Step 2* : To a solution of diethyl 2-((tert-butoxycarbonyl)amino)malonate (10 g, 36.36 mmol) and *sodium* ethoxide (1.97 g, 29.08 mmol) in ethanol (300 mL) was added a solution of nitroethene (6.64 g, 90.90 mmol) dissolved in diethyl ether (15 mL) at 0°C. The RM was slowly allowed to reach RT. Then, the RM was stirred for 2 h. The RM was diluted with ice water (500 mL) and the organic layer was separated, washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give residue. Residue was purified by RP flash chromatography using 0.1% FA in water and ACN as an eluent to afford diethyl 2-((tert-butoxycarbonyl)amino)-2-(2-nitroethyl)malonate (4.1 g).

[0215] *Step 3*: Raney-Ni (5.3 g) was added to a solution of diethyl 2-((tert-butoxycarbonyl)amino)-2-(2-nitroethyl)malonate (4.0 g, 11.49 mmol) in ethanol (50 mL) in Parr hydrogenation vessel under inert atmosphere. The RM was stirred under H_2 (70 psi) at RT for 16 h. The RM was filtered through celite pad, and the celite pad was washed with ethanol. The combined filtrate was concentrated under reduced pressure to afford ethyl 3-((tert-butoxycarbonyl)amino)-2-oxopyrrolidine-3-carboxylate (1.6 g) as a colorless oil.

[0216] *Step 4 :* HCl (4M in dioxane, 3.6 mL) was added to a stirred solution of ethyl 3-((tert-butoxycarbonyl)amino)-2-oxopyrrolidine-3-carboxylate (1.6 g, 5.9 mmol) in DCM (30 mL) at 0 °C. The RM was stirred at RT for 2 h. The RM was concentrated under vacuum. The residue was triturated with diethyl ether (10 mL), filtered and dried under vacuum to afford ethyl 3-amino-2-oxopyrrolidine-3-carboxylate hydrochloride (**Int-05**) (1.03 g) as an off-white solid.

[0217] **Synthesis of 3-Amino-3-(hydroxymethyl)pyrrolidin-2-one (**Int-06 - En1**) and (**Int-06 – En2**) .**



[0218] *Step 1* : To a stirred solution of diethyl 2-(2-(1,3-dioxoisoindolin-2-yl)ethyl)malonate (60 g, 179.99 mmol) in 1,4-Dioxane (600 mL) was added TEA (49.90 mL, 359.99 mmol) at 0 °C. After 15 minutes, formaldehyde (29.18 g, 359.99 mmol) was added at 0 °C. The RM was warmed to RT and stirred at 80 °C for 16 h. The RM was diluted with ice-cold water (200 mL) and extracted with EtOAc (2 × 300 mL). The combined organic layers were washed with brine (150 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by FCC on silica gel using a gradiant of 0 to 40% EtOAc in pet ether to afford diethyl 2-(2-(1,3-dioxoisoindolin-2-yl)ethyl)-2-(hydroxymethyl)malonate (59 g, 90%) as pale yellow gummy. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.86–7.82 (m, 2 H), 7.74–7.69 (m, 2 H), 4.25–4.18 (m, 4 H), 4.07 (d, 2 H), 3.83–3.79 (m, 2 H), 2.79 (t, 1 H), 2.33–2.30 (m, 2 H), 1.28 (t, 6 H).

[0219] *Step 2*: To a solution of diethyl 2-(2-(1,3-dioxoisoindolin-2-yl)ethyl)-2-(hydroxymethyl)malonate (68 g, 187.13 mmol) in DCM (700 mL) was added Imidazole (25.48 g, 374.27 mmol) at 0 °C. After 15 min., TBDMS chloride (33.84 g, 224.56 mmol) at 0 °C was added. The RM was stirred for 16 h at RT. The RM was diluted with ice cold water (300 mL) and extracted with DCM (2 × 500 mL). The combined organic layers were washed with brine (200 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by FCC on silica gel using a gradient of 10% EtOAc in pet ether to afford diethyl 2-(((tert-butyldimethylsilyl)oxy)methyl)-2-(2-(1,3-dioxoisoindolin-2-yl)ethyl)malonate (68 g, 77%) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.84–7.82 (m, 2 H), 7.71–7.69 (m, 2 H), 4.18–4.11 (m, 6 H), 3.76–3.72 (m, 2 H), 2.41–2.37 (m, 2 H), 1.26 (t, 6 H), 0.89 (s, 9 H), 0.08 (s, 6 H).

[0220] *Step 3* : To a stirred solution of diethyl 2-(((tert-butyldimethylsilyl)oxy)methyl)-2-(2-(1,3-dioxoisoindolin-2-yl)ethyl)malonate (68 g, 142.37 mmol) in Ethanol (700 mL) was added Hydrazine hydrate (10.69 g, 213.55 mmol) at 0 °C. The RM was stirred for 16 h at RT. The RM was diluted with ice cold water (300 mL) and extracted with EtOAc (2 x 500 mL). The combined

organic layers were washed with brine solution (200 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by FCC on silica gel using a gradient of 0-30% EtOAc in Pet. ether to afford ethyl 3-(((tert-butyldimethylsilyl)oxy)methyl)-2-oxopyrrolidine-3-carboxylate (30.7 g, 71%) as an off white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 5.76 (s, 1 H), 4.22–4.17 (m, 2 H), 4.06 (d, 1 H), 3.94 (d, 1 H), 3.46–3.42 (m, 1 H), 3.36–3.35 (m, 1 H), 2.59–2.55 (m, 1 H), 2.49–2.43 (m, 1 H), 1.27 (t, 3 H), 0.87 (d, 9 H), 0.06 (d, 6 H).

[0221] *Step 4 :* To a solution of ethyl 3-(((tert-butyldimethylsilyl)oxy)methyl)-2-oxopyrrolidine-3-carboxylate (29 g, 96.19 mmol) in EtOH (120 mL), THF (60 mL) and H_2O (30 mL) was added LiOH.H2O (20.18 g, 480.99 mmol) portion wise at 0 °C. The RM was stirred for 16 h at RT. The volatiles were removed under reduced pressure. The residue was diluted with cold water (20 mL) and then acidified with saturated aqueous Citric acid solution (pH~4). The solid was filtered, washed with water (10 mL) followed by water (10 mL), dried under vacuum to afford 3-(((tert-butyldimethylsilyl)oxy)methyl)-2-oxopyrrolidine-3-carboxylic acid (16.7 g, 63%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 7.82 (s, 1 H), 3.88 (d, 1 H), 3.70 (d, 1 H), 3.27–3.21 (m, 1 H), 3.17–3.12 (m, 1 H), 2.34–2.32 (m, 1 H), 2.24–2.22 (m, 1 H), 0.84 (s, 9 H), 0.01 (d, 6 H).

[0222] *Step 5* : To a stirred solution of 3-(((tert-butyldimethylsilyl)oxy)methyl)-2-oxopyrrolidine-3-carboxylic acid (9.5 g, 34.74 mmol) in THF (40 mL) and benzene (120 mL) were added TEA (14.65 mL, 104.24 mmol) followed by DPPA (19.12 g, 69.49 mmol) at RT. The RM was stirred at RT for 2 h. The RM was quenched with ice cold water (100 mL) and extracted with EtOAc (2 × 200 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate (2 × 50 mL), brine solution (50 mL), then dried over Na_2SO_4, filtered, and concentrated under reduced . The residue was dissolved in THF (40 mL) and benzene (120 mL). Then, Benzyl alcohol (7.51 g, 69.49 mmol) was added at RT. The RM was stirred at 55°C for 16 h. The RM was diluted with ice-cold water (100 mL) and extracted with EtOAc (2 × 200 mL). The combined organic layers were washed with brine solution (100 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by FCC on silica gel using a gradient of 0-40% EtOAc in Pet. ether to afford benzyl (3-(((tert-butyldimethylsilyl)oxy)methyl)-2-oxopyrrolidin-3-yl)carbamate (9 g, 68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.37–7.29 (m, 5 H), 5.84 (brs, 1 H), 5.42 (brs, 1 H), 5.07 (s, 2 H), 3.85 (d, 1 H), 3.67 (d, 1 H), 3.39–3.33 (m, 2 H), 2.63–2.62 (m, 1 H), 2.53–2.51 (m, 1 H), 0.88 (s, 9 H), 0.05 (d, 6 H).

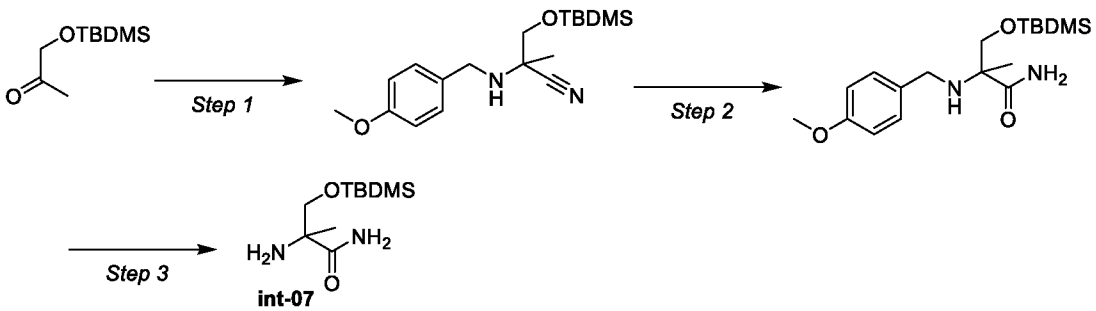
[0223] *Step 6* : To a solution of benzyl (3-(((tert-butyldimethylsilyl)oxy)methyl)-2-oxopyrrolidin-3-yl)carbamate (11 g, 29.05 mmol) in MeOH (150 mL) was added PTSA monohydrate (2.21 g, 11.62 mmol) in MeOH (50 mL) over 2 h at 0 °C. The RM was stirred for 16 h at RT. The RM was concentrated under reduced pressure. Ice-cold water (50 mL) was added to the residue. The aqueous layer was extracted with 10% MeOH in DCM (3 × 50 mL). The combined organic

layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was triturated with n-pentane (3 × 15 mL) followed by diethyl ether (15 mL), filtered and dried under vacuum to afford benzyl (3-(hydroxymethyl)-2-oxopyrrolidin-3-yl)carbamate (7 g, 91%) as an off white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 7.66 (s, 1 H), 7.38–7.29 (m, 5 H), 7.08 (s, 1 H), 4.98–4.95 (m, 3 H), 3.46–3.38 (m, 2 H), 3.18–3.15 (m, 1 H), 3.13–3.07 (m, 1 H), 2.28–2.25 (m, 2 H).Chiral separation of 3.5 g of benzyl (3-(hydroxymethyl)-2-oxopyrrolidin-3-yl)carbamate was performed by chiral SFC prep.[Preparative SFC Conditions: Column: Chiral peak IF (250 × 30 × 5µm), %CO2: 65%, %Co-solvent: 35% (100% Methanol), Total Flow: 90 g/min, Back Pressure: 100.0 bar, Temperature: 30 °C, Wavelength: 215 nm, Stack time: 7.2 min, Solubility: 100 ml of MeOH.] The collected pure fractions were concentrated under reduced pressure to afford two isomers **En1** (the first eluting) and **En2** (the second eluting).

[0224] *Step 7* : To a stirred solution of benzyl (3-(hydroxymethyl)-2-oxopyrrolidin-3-yl)carbamate **En1** (1.4 g, 5.297 mmol) in Ethanol (30 mL) was added Pd/C (450 mg) at RT. The RM was stirred under H_2 (70 psi) at RT for 16 h. The RM was filtered through a pad of Celite, and washed with MeOH (50 mL). The filtrate concentrated under reduced pressure. The residue was triturated with diethyl ether (2 × 5 mL) and dried under reduced pressure to afford 3-amino-3-(hydroxymethyl)pyrrolidin-2-one (**Int-06 – En1**) (610 mg, 88%) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 7.54 (s, 1 H), 4.73 (t, 1 H), 3.36–3.34 (m, 1 H), 3.18–3.12 (m, 2 H), 3.10–3.04 (m, 1 H), 2.22–2.15 (m, 1 H), 1.76–1.72 (m, 1 H), 1.56 (s, 2 H).

[0225] *Step 8* : To a stirred solution of benzyl (3-(hydroxymethyl)-2-oxopyrrolidin-3-yl)carbamate **En2** (1.2 g, 4.54 mmol) in Ethanol (30 mL) was added Pd/C (350 mg) at RT. The RM was stirred under H_2 (70 psi) at RT for 16 h. The RM was filtered through a pad of Celite, and washed with MeOH (50 mL). The filtrate was concentrated under reduced pressure. The residue was triturated with diethyl ether (2 × 5 mL) and dried under reduced pressure to afford 3-amino-3-(hydroxymethyl)pyrrolidin-2-one (**Int-06 – En2**) (550 mg, 93%) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 7.54 (s, 1 H), 4.73 (brs, 1 H), 3.36–3.32 (m, 1 H), 3.18–3.12 (m, 2 H), 3.10–3.04 (m, 1 H), 2.22–2.15 (m, 1 H), 1.76–1.71 (m, 1 H), 1.57 (s, 2 H).

[0226] **Synthesis of 2-amino-3-((tert-butyldimethylsilyl)oxy)-2-methylpropanamide (**Int-07**).**



[0227] *Step 1 :* To a solution of 1-((tert-butyldimethylsilyl)oxy)propan-2-one (20 g, 106.19 mmol) in EtOH (100 mL) were added (4-methoxyphenyl)methanamine (15.261 mL, 116.81

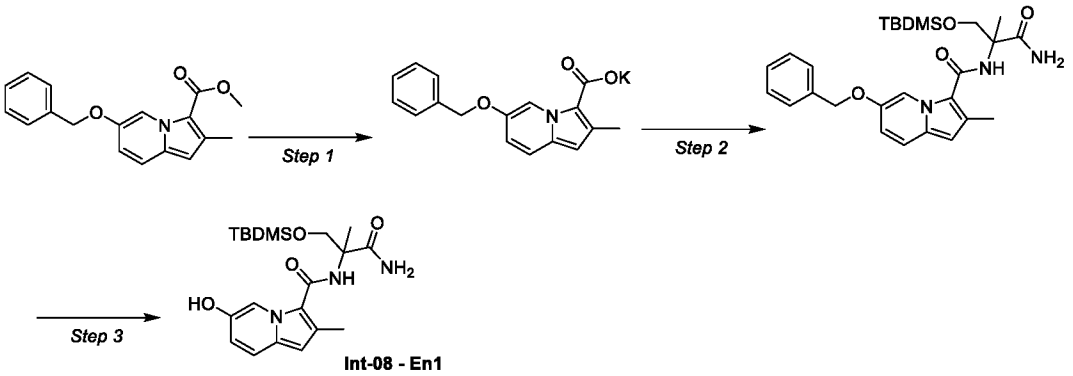
mmol), TMSCN (15.94 mL, 127.42 mmol) and NH_4Cl (1.704 g, 31.857 mmol) at RT. The RM was stirred at 80 °C for 16 h. The volatiles were removed under reduced pressure. The residue was diluted with EtOAc (200 mL), washed with saturated $NaHCO_3$ (100 ml), brine solution (100 mL), dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by FCC on silica gel using 10% EtOAc in pet ether as an eluent to afford 3-((tert-butyldimethylsilyl)oxy)-2-((4-methoxybenzyl)amino)-2-methylpropanenitrile (20 g, 56.30%). ^1H NMR (400 MHz, DMSO-D_6) δH ppm: 7.25 (d, 2 H), 6.88 (d, 2 H), 3.72 (s, 5 H), 3.65 - 3.75 (m, 1 H), 3.45 – 3.51 (m, 1 H), 2.74 – 2.77 (m, 1 H), 1.36 (s, 3 H), 0.87 (s, 9 H), 0.77 (m, 6 H).

[0228] Step 2 : To a solution of 3-((tert-butyldimethylsilyl)oxy)-2-((4-methoxybenzyl)amino)-2-methylpropanenitrile (10 g, 29.9 mmol) in DMSO (70 mL) were added K_2CO_3 (28.97 g, 209.6 mmol) and H_2O_2 (14.041 mL, 598.802 mmol) at 0° C. The RM was stirred at RT for 16 h. The RM was cooled to RT, quenched with ice-cold water (100 mL). The aqueous layer was extracted with diethyl ether (3 x 100 mL). Combined organic phases was washed with brine (50 mL), dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by FCC on silica gel using 40 to 50% EtOAc in pet ether as an eluent to afford 3-((tert-butyldimethylsilyl)oxy)-2-((4-methoxybenzyl)amino)-2-methylpropanamide as a pale yellow liquid (3.8 g, 36%). ^1H NMR (400 MHz, DMSO-D_6) δH ppm: 7.25 (d, 2 H), 7.24 (brs, 1 H), 7.07 (brs, 1 H), 6.86 (d, 2 H), 3.72 (s, 3 H), 3.68 – 3.71 (m, 1 H), 3.56 – 3.59 (m, 1 H), 3.51 (d, 2 H), 2.05 (brs, 1 H), 1.15 (s, 3 H), 0.85 (s, 9 H), 0.03 (s, 6 H).

[0229] Step 3 : To a solution of 3-((tert-butyldimethylsilyl)oxy)-2-((4-methoxybenzyl)amino)-2-methylpropanamide (10 g, 28.365 mmol) in MeOH (200 mL) was added 10% palladium hydroxide (5.178 g, 36.874 mmol) at RT. The RM was stirred at RT for 48 h under H_2 pressure (70 psi). The RM was filtered through a celite pad, washed with 10% MeOH in DCM (200 mL), filtrate was concentrated under reduced pressure. The residue was purified by FCC on silica gel using 80% EtOAc in Pet. ether as an eluent to afford 2-amino-3-((tert-butyldimethylsilyl)oxy)-2-methylpropanamide (Int-07) as an off white solid (5.5 g). ^1H NMR (400 MHz, DMSO-D_6) δ ppm: 7.25 (s, 1 H), 6.95 (s, 1 H), 3.76 (d, 1 H), 3.25 (d, 1 H), 1.77 (s, 2 H), 1.04 (s, 3 H), 0.85 (s, 9 H), 0.02 (s, 6 H).

[0230] A preparative chiral SFC was performed the racemic mixture of **Int-07** to afford **Int-07 – En1** and **Int-07 – En2.**

[0231] **Synthesis of N-(1-amino-3-((tert-butyldimethylsilyl) oxy)-2-methyl-1-oxopropan-2-yl)-6-hydroxy-2-methylindolizine-3-carboxamide (Int-08 – En1)**



Int-08 - En1

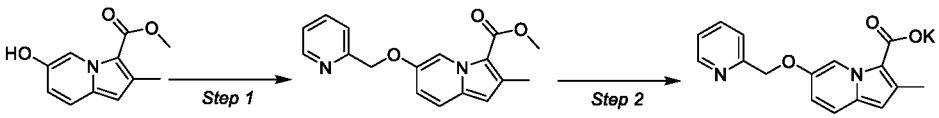
[0232] Step *1* : To a solution of methyl 6-(benzyloxy)-2-methylindolizine-3-carboxylate (1 g, 3.39 mmol) in THF (20 mL) was added KOTMS (1.08 g, 8.46 mmol) at RT. The RM was stirred at 70 °C for 5 h. The volatiles were removed under reduced pressure. The residue was triturated with n-pentane (20 mL) and dried to afford potassium 6-(benzyloxy)-2-methylindolizine-3-carboxylate (1.01 g, 93%) as an off white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 9.85 (s, 1H), 7.49–7.47 (m, 2H), 7.41–7.37 (m, 2H), 7.35–7.31 (m, 1H), 7.18 (d, 1H), 6.55 (dd, 1H), 6.07 (s, 1H), 4.98 (s, 2H), 2.45 (s, 3H).

[0233] Step 2 : To a solution of 2-amino-3-((tert-butyldimethylsilyl)oxy)-2-methylpropanamide (**Int-07 - En-1**)(0.9 g, 3.914 mmol) in DMF (20 mL) were DIPEA (2.7 mL, 15.6 mmol), potassium 6-(benzyloxy)-2-methylindolizine-3-carboxylate (1.0 g, 3.13 mmol) and HATU (1.8 g, 4.7 mmol) at 0°C. The RM was stirred at 65°C for 16 h. The RM was poured into ice water (100 mL) and extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with water (50 mL) and 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 0 to 50% EtOAc in Pet. Ether as a gradient to afford N-(1-amino-3-((tert-butyldimethylsilyl)oxy)-2-methyl-1-oxopropan-2-yl)-6-(benzyloxy)-2-methylindolizine-3-carboxamide (0.7 g, 45%) as an off white solid. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* ppm: 9.41 (s, 1 H), 7.48 (d, 2 H), 7.41–7.37 (m, 2 H), 7.35–7.33 (d, 1 H), 7.26–7.37 (m, 1 H), 6.99 (brs, 1 H), 6.86 (s, 1 H), 6.81 (dd, 1 H), 6.25 (s, 1 H), 5.36 (s, 1 H), 5.06 (s, 2 H), 4.32 (d, 1 H), 3.77 (d, 1 H), 2.59 (s, 3 H), 1.73 (s, 3 H), 0.91 (s, 9 H), 0.13 (s, 6 H).

[0234] Step 3 : To a solution of N-(1-amino-3-((tert-butyldimethylsilyl) oxy)-2-methyl-1-oxopropan-2-yl)-6-(benzyloxy)-2-methylindolizine-3-carboxamide (600 mg, 1.210 mmol) in Ethanol (20 mL) and EtOAc (5 mL) was added Pd/C (10%) (240 mg) at RT. The RM was stirred under H_2 balloon at RT for 5 h. The RM was filtered through a pad of Celite and washed with ethanol (2 x 20 mL). The filtrate was concentrated under reduced pressure to afford N-(1-amino-3-((tert-butyldimethylsilyl)oxy)-2-methyl-1-oxopropan-2-yl)-6-hydroxy-2-methylindolizine-3-carboxamide (**Int-08 – En1**) (490 mg, 99%) as a light brown solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 9.18 (s, 1 H), 9.06 (s, 1 H), 7.41 (s, 1 H), 7.33 (d, 1 H), 7.22 (s, 1 H), 7.14 (s, 1 H), 6.68 (dd, 1 H), 6.25 (s, 1 H), 4.13 (d, 1 H), 3.97 (d, 1 H), 2.55 (s, 3 H), 1.53 (s, 3 H), 0.85 (s, 9 H), 0.007 (s, 6 H).

[0235] **Int-08 – En2** was 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 **Int-08 – En1.**

[0236] **Synthesis of potassium 2-methyl-6-(pyridin-2-ylmethoxy)indolizine-3-carboxylate (Int-09)**

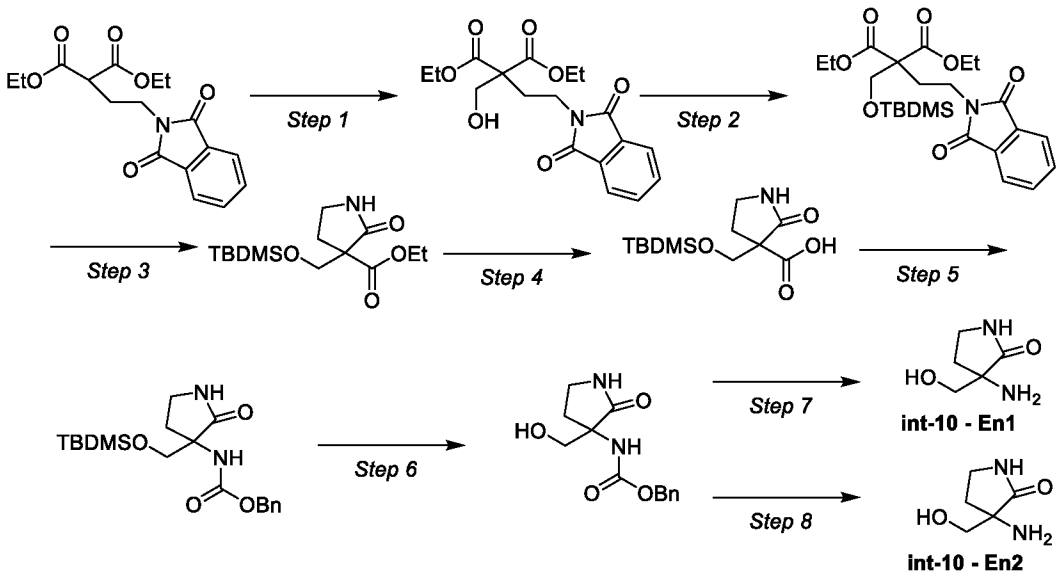


Int-01 Int-09

[0237] *Step 1* : To a solution of methyl 6-hydroxy-2-methylindolizine-3-carboxylate (2 g, 9.756 mmol) in dry THF (20 mL) were added ADDP (4.9 g, 19.512 mmol) and n-Bu_3P (4.8 mL, 19.512 mmol) at 0°C. After 10 min, pyridin-2-ylmethanol (1.2 g, 11.707 mmol) was added. The RM was stirred at RT for 2 h. The RM was diluted with cold water (50 mL), extracted with EtOAc (2 x 70 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (50 mL), brine (50 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 Hexane as an eluent to afford methyl 2-methyl-6-(pyridin-2-ylmethoxy) indolizine-3-carboxylate as a pale yellowish gummy (1.8 g, 62.26%). ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 9.37 (d, 1 H), 8.64 (d, 1 H), 7.76 - 7.72 (m, 1 H), 7.56 (d, 1 H),7.30 - 7.23 (m, 2 H), 6.94 - 6.91 (dd, 1 H), 6.27(s, 1 H), 5.21 (s, 2 H), 3.90 (s, 3 H), 2.50 (t, 3 H).

[0238] Step 2 : To a solution of methyl 2-methyl-6-(pyridin-2-ylmethoxy) indolizine-3-carboxylate (400 mg,1.350 mmol) in THF (7.0 mL) was added KOTMS (865 mg, 6.749 mmol). The RM was stirred at 70 °C for 16 h. The volatiles were removed under reduced pressure. The residue was triturated with diethyl ether (20 mL) and dried to afford potassium 2-methyl-6-(pyridin-2-ylmethoxy)indolizine-3-carboxylate (Int-09) as a pale yellow solid (350 mg). ^1H NMR (400 MHz, DMSO-D_6) δ ppm: 9.83 (d, 1 H), 8.58 - 8.57 (m, 1 H), 7.86 - 7.82 (m, 1 H), 7.58 (d, 1 H), 7.36 (m, 1 H), 7.22 (d, 1 H), 6.62 - 6.59 (dd, 1 H), 6.08 (s, 1 H), 5.06 (d, 2 H), 2.44 (s, 3 H).

[0239] **Synthesis of 3-Amino-3-(hydroxymethyl)pyrrolidin-2-one (**Int-10 - En1**) and (**Int-10 – En2**) .**



[0240] *Step 1* : To a stirred solution of diethyl 2-(2-(1,3-dioxoisoindolin-2-yl)ethyl)malonate (60 g, 179.99 mmol) in 1,4-Dioxane (600 mL) was added TEA (49.90 mL, 359.99 mmol) at 0 °C. After 15 minutes, formaldehyde (29.18 g, 359.99 mmol) was added at 0 °C. The RM was warmed to RT and stirred at 80 °C for 16 h. The RM was diluted with ice-cold water (200 mL) and extracted with EtOAc (2 × 300 mL). The combined organic layers were washed with brine (150 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by FCC on silica gel using a gradiant of 0 to 40% EtOAc in pet ether to afford diethyl 2-(2-(1,3-dioxoisoindolin-2-yl)ethyl)-2-(hydroxymethyl)malonate (59 g, 90%) as pale yellow gummy. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.86–7.82 (m, 2 H), 7.74–7.69 (m, 2 H), 4.25–4.18 (m, 4 H), 4.07 (d, 2 H), 3.83–3.79 (m, 2 H), 2.79 (t, 1 H), 2.33–2.30 (m, 2 H), 1.28 (t, 6 H).

[0241] *Step 2*: To a stirred solution of diethyl 2-(2-(1,3-dioxoisoindolin-2-yl)ethyl)-2-(hydroxymethyl)malonate (68 g, 187.13 mmol) in DCM (700 mL) was added Imidazole (25.48 g, 374.27 mmol) at 0 °C . After 15 min., tert-Butyldimethylsilyl chloride (33.84 g, 224.56 mmol) at 0 °C was added. The RM was stirred for 16 h at RT. The RM was diluted with ice cold water (300 mL) and extracted with DCM (2 × 500 mL). The combined organic layers were washed with brine (200 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by FCC on silica gel using a gradient of 10% EtOAc in pet ether to afford diethyl 2-(((tert-butyldimethylsilyl)oxy)methyl)-2-(2-(1,3-dioxoisoindolin-2-yl)ethyl)malonate (68 g, 77%) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.84–7.82 (m, 2 H), 7.71–7.69 (m, 2 H), 4.18–4.11 (m, 6 H), 3.76–3.72 (m, 2 H), 2.41–2.37 (m, 2 H), 1.26 (t, 6 H), 0.89 (s, 9 H), 0.08 (s, 6 H).

[0242] *Step 3* : To a stirred solution of diethyl 2-(((tert-butyldimethylsilyl)oxy)methyl)-2-(2-(1,3-dioxoisoindolin-2-yl)ethyl)malonate (68 g, 142.37 mmol) in Ethanol (700 mL) was added Hydrazine hydrate (10.69 g, 213.55 mmol) at 0 °C. The RM was stirred for 16 h at RT. The RM was diluted with ice cold water (300 mL) and extracted with EtOAc (2 x 500 mL). The combined

organic layers were washed with brine solution (200 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by FCC on silica gel using a gradient of 0-30% EtOAc in Pet. ether to afford ethyl 3-(((tert-butyldimethylsilyl)oxy)methyl)-2-oxopyrrolidine-3-carboxylate (30.7 g, 71%) as an off white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 5.76 (s, 1 H), 4.22–4.17 (m, 2 H), 4.06 (d, 1 H), 3.94 (d, 1 H), 3.46–3.42 (m, 1 H), 3.36–3.35 (m, 1 H), 2.59–2.55 (m, 1 H), 2.49–2.43 (m, 1 H), 1.27 (t, 3 H), 0.87 (d, 9 H), 0.06 (d, 6 H).

[0243] *Step 4 :* To a solution of ethyl 3-(((tert-butyldimethylsilyl)oxy)methyl)-2-oxopyrrolidine-3-carboxylate (29 g, 96.19 mmol) in EtOH (120 mL), THF (60 mL) and H_2O (30 mL) was added LiOH.H2O (20.18 g, 480.99 mmol) at 0 °C. The RM was stirred for 16 h at RT. The volatiles were removed under reduced pressure. The residue was diluted with cold water (20 mL) and then acidified with saturated aqueous Citric acid solution (pH~4). The solid was filtered, washed with water (10 mL) followed by water (10 mL), dried under vacuum to afford 3-(((tert-butyldimethylsilyl)oxy)methyl)-2-oxopyrrolidine-3-carboxylic acid (16.7 g, 63%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 7.82 (s, 1 H), 3.88 (d, 1 H), 3.70 (d, 1 H), 3.27–3.21 (m, 1 H), 3.17–3.12 (m, 1 H), 2.34–2.32 (m, 1 H), 2.24–2.22 (m, 1 H), 0.84 (s, 9 H), 0.01 (d, 6 H).

[0244] *Step 5* : To a stirred solution of 3-(((tert-butyldimethylsilyl)oxy)methyl)-2-oxopyrrolidine-3-carboxylic acid (9.5 g, 34.74 mmol) in THF (40 mL) and benzene (120 mL) were added TEA (14.65 mL, 104.24 mmol) followed by DPPA (19.12 g, 69.49 mmol) at RT. The RM was stirred at RT for 2 h. The RM was quenched with ice cold water (100 mL) and extracted with EtOAc (2 × 200 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate (2 × 50 mL), brine solution (50 mL), then dried over Na_2SO_4, filtered, and concentrated under reduced . The residue was dissolved in THF (40 mL) and benzene (120 mL). Then, Benzyl alcohol (7.51 g, 69.49 mmol) was added at RT. The RM was stirred at 55 °C for 16 h. The RM was diluted with ice-cold water (100 mL) and extracted with EtOAc (2 × 200 mL). The combined organic layers were washed with brine solution (100 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by FCC on silica gel using a gradient of 0-40% EtOAc in Pet. ether to afford benzyl (3-(((tert-butyldimethylsilyl)oxy)methyl)-2-oxopyrrolidin-3-yl)carbamate (9 g, 68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.37–7.29 (m, 5 H), 5.84 (brs, 1 H), 5.42 (brs, 1 H), 5.07 (s, 2 H), 3.85 (d, 1 H), 3.67 (d, 1 H), 3.39–3.33 (m, 2 H), 2.63–2.62 (m, 1 H), 2.53–2.51 (m, 1 H), 0.88 (s, 9 H), 0.05 (d, 6 H).

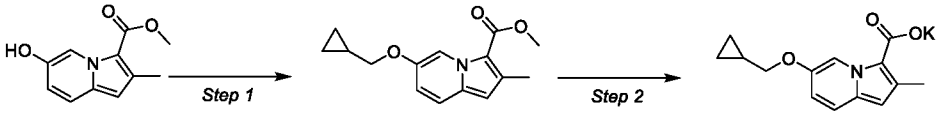
[0245] *Step 6* : To a stirred solution of benzyl (3-(((tert-butyldimethylsilyl)oxy)methyl)-2-oxopyrrolidin-3-yl)carbamate (11 g, 29.05 mmol) in MeOH (150 mL) was added PTSA monohydrate (2.21 g, 11.62 mmol) in MeOH (50 mL) over 2 h at 0 °C. The RM was stirred for 16 h at RT. The RM was concentrated under reduced pressure. The residue was quenched with ice-cold water (50 mL) and extracted with 10% MeOH in DCM (3 × 50 mL). The combined

organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was triturated with n-pentane (3 × 15 mL) followed by diethyl ether (15 mL), filtered and dried under vacuum to afford benzyl (3-(hydroxymethyl)-2-oxopyrrolidin-3-yl)carbamate (7 g, 91%) as an off white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 7.66 (s, 1 H), 7.38–7.29 (m, 5 H), 7.08 (s, 1 H), 4.98–4.95 (m, 3 H), 3.46–3.38 (m, 2 H), 3.18–3.15 (m, 1 H), 3.13–3.07 (m, 1 H), 2.28–2.25 (m, 2 H). 3.5 g of benzyl (3-(hydroxymethyl)-2-oxopyrrolidin-3-yl)carbamate was purified by chiral SFC prep.[Preparative SFC Conditions: Column: Chiral peak IF (250 × 30 × 5µm), %CO2: 65%, %Co-solvent: 35% (100% Methanol), Total Flow: 90 g/min, Back Pressure: 100.0 bar, Temperature: 30 °C, Wavelength: 215 nm, Stack time: 7.2 min, Solubility: 100 ml of MeOH.] The collected pure fractions were concentrated under reduced pressure to afford two isomers **En1** (the first eluting) and **En2** (the second eluting).

[0246] *Step 7* : To a stirred solution of benzyl (3-(hydroxymethyl)-2-oxopyrrolidin-3-yl)carbamate **En1** (1.4 g, 5.297 mmol) in Ethanol (30 mL) was added Pd/C (450 mg) at RT. The RM was stirred under H_2 (70 psi) at RT for 16 h. The RM was filtered through a pad of Celite, and washed with MeOH (50 mL). The filtrate concentrated under reduced pressure. The residue was triturated with diethyl ether (2 × 5 mL) and dried under high vacuum to afford 3-amino-3-(hydroxymethyl)pyrrolidin-2-one (**Int-10 – En1**) (610 mg, 88%) as an off-white solid. 1H NMR (400 MHz, DMSO-d6) δ ppm: 7.54 (s, 1 H), 4.73 (t, 1 H), 3.36–3.34 (m, 1 H), 3.18–3.12 (m, 2 H), 3.10–3.04 (m, 1 H), 2.22–2.15 (m, 1 H), 1.76–1.72 (m, 1 H), 1.56 (s, 2 H). UPLC: Rt = 2.29 min (98%).

[0247] *Step 8* : To a stirred solution of benzyl (3-(hydroxymethyl)-2-oxopyrrolidin-3-yl)carbamate **En2** (1.2 g, 4.54 mmol) in Ethanol (30 mL) was added Pd/C (350 mg) at RT. The RM was stirred under H_2 (70 psi) at RT for 16 h. The RM was filtered through a pad of Celite, and washed with MeOH (50 mL). The filtrate was concentrated under reduced pressure. The residue was triturated with diethyl ether (2 × 5 mL) and dried under high vacuum to afford 3-amino-3-(hydroxymethyl)pyrrolidin-2-one (**Int-10 – En2**) (550 mg, 93%) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 7.54 (s, 1 H), 4.73 (brs, 1 H), 3.36–3.32 (m, 1 H), 3.18–3.12 (m, 2 H), 3.10–3.04 (m, 1 H), 2.22–2.15 (m, 1 H), 1.76–1.71 (m, 1 H), 1.57 (s, 2 H).

[0248] **Synthesis of potassium 6-(cyclopropylmethoxy)-2-methylindolizine-3-carboxylate (Int-11)**



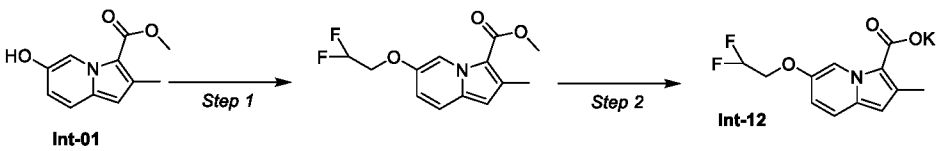
Int-01 Int-11

[0249] *Step 1* :To a solution of methyl 6-methoxy-2-methylindolizine-3-carboxylate (3 g, 14.61 mmol) and (bromomethyl)cyclopropane (2.96 g, 21.928 mmol) in ACN (50 mL) was added cesium carbonate (14.28 g, 43.857 mmol) at RT. The RM was stirred at 70 °C for 16 h. The RM was diluted with EtOAc (50 mL), washed with water (2 x 50 mL), brine (50 mL), dried over

Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by FCC on silica gel using 20% EtOAc in Pet. ether as an eluent to afford methyl 6-(cyclopropylmethoxy)-2-methylindolizine-3-carboxylate as an orange solid (3.5 g, 92%). ^{1}H NMR (400 MHz, DMSO-D_6) δ ppm: 9.06 (s, 1 H), 7.49 (d, 1 H), 6.97 (d, 1 H), 6.39 (s, 1 H), 3.82 (s, 3 H), 3.81 – 3.85 (m, 2 H), 2.50 (s, 3 H), 1.21 – 1.27 (m, 1 H), 0.56 – 0.61 (m, 2 H), 0.37 – 0.39 (m, 2 H).

[0250] *Step 2* : To a solution of methyl 6-(cyclopropylmethoxy)-2-methylindolizine-3-carboxylate (1 g, 3.85 mmol) in THF (50 mL) was added KOTMS (2.47 g, 19.28 mmol) at RT. The RM was stirred at 70 °C for 16 h. The volatiles were removed under reduced pressure. The residue was triturated with n-pentane (30 mL) and dried under vacuum to afford potassium 6-(cyclopropylmethoxy)-2-methylindolizine-3-carboxylate as a brown solid (**Int-11**) (1.6 g, 90%). ^{1}H NMR (400 MHz, DMSO-D_6) δ ppm: 9.68 (s, 1 H), 7.15 (d, 1 H), 6.48 (dd, 1 H), 6.04 (s, 1 H), 3.70 (d, 2 H), 2.43 (s, 3 H), 1.20 – 1.25 (m, 1 H), 0.54 – 0.59 (m, 2 H), 0.32 – 0.36 (m, 2 H).

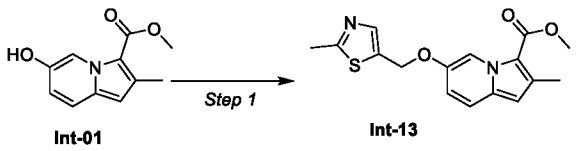
[0251] **Synthesis of potassium 6-(2,2-difluoroethoxy)-2-methylindolizine-3-carboxylate (Int-12)**



[0252] *Step 1* : To a solution of methyl 6-hydroxy-2-methylindolizine-3-carboxylate (3.0 g, 0.015 mmol) in ACN (30 mL) were added Cs_2CO_3 (11.908 g, 0.037 mmol) and 1,1-difluoro-2-iodoethane (3.366 g, 0.018 mmol) at RT. The RM was stirred at 70 °C for 16 h. After cooling to RT, the RM was diluted with water (50 mL), extracted with EtOAc (2 x 30 mL), dried over Na_2SO_4, filtered and concentrated under reduce pressure. The residue was purified by FCC on silica gel using 10% EtOAc in pet ether as a gradient to afford methyl 6-(2,2-difluoroethoxy)-2-methylindolizine-3-carboxylate as a yellow solid (2.3 g, 58.43%). ^{1}H NMR (400 MHz, DMSO-D_6) δ ppm: 9.25 (s, 1 H), 7.26 - 7.30 (m, 1 H), 6.82 - 6.85 (td, 1 H), 6.29 (s, 1 H), 5.95 - 6.25 (tt, 1 H), 4.17 - 4.24 (m, 2 H), 3.91 - 3.93 (d, 3 H), 2.50 - 2.51 (m, 3 H).

[0253] *Step 2* : To a solution of methyl 6-(2,2-difluoroethoxy)-2-methylindolizine-3-carboxylate (400 mg, 1.486 mmol) in THF (10.0 mL) was added KOTMS (952 mg, 7.428 mmol) at RT and stirred at 70 °C for 16 h. After cooling to RT, the volatiles were removed under reduced pressure. The residue was triturated with n-pentane (3 x 5 mL) and dried under reduced pressure to afford potassium 6-(2,2-difluoroethoxy)-2-methylindolizine-3-carboxylate (Int-12) (300 mg, 79%). ^{1}H NMR (400 MHz, DMSO-D_6) δ ppm: 9.81 (d, 1 H), 7.21 (d, 1 H), 6.54 - 6.57 (dd, 1 H), 6.23 - 6.38 (tt, 1 H), 6.11 (s, 1 H), 4.14 - 4.22 (m, 2 H), 2.45 (s, 3 H).

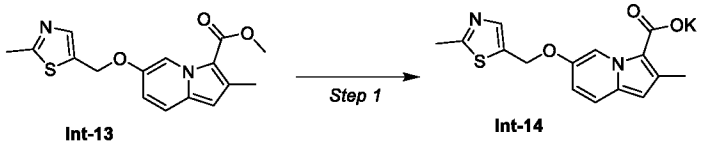
[0254] **Synthesis of methyl 2-methyl-6-((2-methylthiazol-5-yl)methoxy)indolizine-3-carboxylate (Int-13)**



Int-01 Int-13

[0255] *Step 1* : To a solution of methyl 6-hydroxy-2-methylindolizine-3-carboxylate (2 g, 9.746 mmol) in DMF (10 mL) were added Cs_2CO_3 (9.52 g, 29.23 mmol) and methyl 2-methyl-6-((2-methylthiazol-5-yl)methoxy)indolizine-3-carboxylate (1.7 g, 11.69 mmol) at 0 °C. The RM was stirred at RT for 16 h. The RM was diluted with water (50 mL), extracted with EtOAc (3 x 50 mL). Combined organic layer was washed with brine (50 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FCC on silica gel using 20% EtOAc in pet ether as a gradient to afford methyl 2-methyl-6-((2-methylthiazol-5-yl)methoxy)indolizine-3-carboxylate (Int-13) as a brown solid (1.5 g, 48.65%). ^{1}H NMR (400 MHz, DMSO-D_6) δ ppm: 9.16 (d, 1 H), 7.73 (s, 1 H), 7.52 (d, 1 H), 7.01 (dd, 1 H), 6.41 (s, 1 H), 5.33 (s, 2 H), 3.84 (s, 3 H), 2.63 (s, 3 H), 2.44 (s, 3 H).

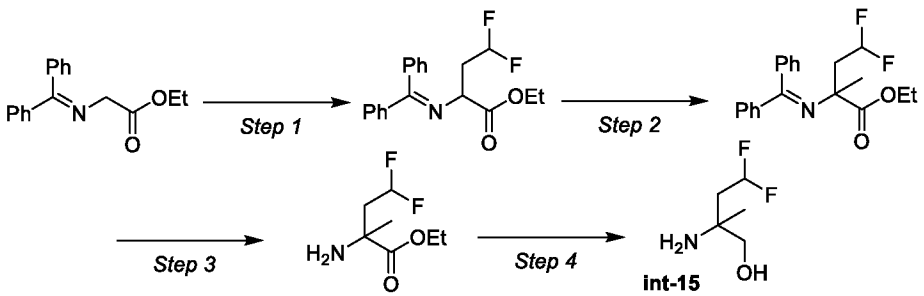
[0256] **Synthesis of potassium 2-methyl-6-((2-methylthiazol-5-yl)methoxy)indolizine-3-carboxylate (Int-14)**



Int-13 Int-14

[0257] *Step 1* : To a solution of methyl 2-methyl-6-((2-methylthiazol-5-yl)methoxy)indolizine-3-carboxylate(1.4 g, 4.425 mmol) in 1,4-Dioxane/MeOH (25 mL) was added KOH (1.241 g, 22.126 mmol) at RT and stirred at 50 °C for 16 h. After completion of the reaction, the volatiles were removed under reduced pressure. The residue was triturated with n-pentane (50.0 mL) and dried to afford potassium 2-methyl-6-((2-methylthiazol-5-yl)methoxy)indolizine-3-carboxylate (Int-14) as a brown solid (1.8 g).

[0258] **Synthesis of 2-amino-4,4-difluoro-2-methylbutan-1-ol (**Int-15**).**



int-15

[0259] *Step 1 :* To a solution of t-BuOK (13.2 g, 117.83 mmol) in DMF (150 mL) was added ethyl 2-((diphenylmethylene)amino)acetate (30 g, 112.22 mmol) at 0 °C. After 30 min, 1,1-difluoro-2-iodoethane (24.9 g, 130.18 mmol) was added over 10 min at 0 °C. The RM was stirred at 0°C for 1 h. After completion of the reaction, the RM was diluted with 5% aq NH_4Cl (100.0 mL), extracted with EtOAc (3 x 50.0 mL). Combined organic layer was washed with

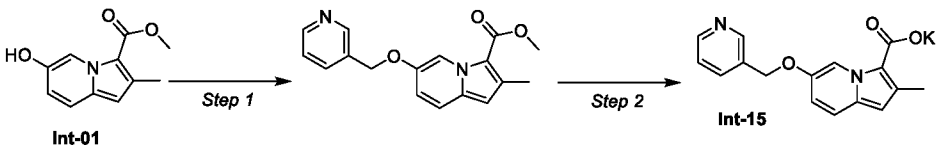
brine (100.0 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by FCC on silica gel using 5% EtOAc in pet ether as an eluent to afford ethyl 2-((diphenylmethylene)amino)-4,4-difluorobutanoate as a pale yellow liquid (30 g, 80.67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.63 - 7.65 (m, 2 H), 7.39 - 7.48 (m, 4 H), 7.31 - 7.36 (m, 2 H), 7.18 - 7.20 (m, 2 H), 5.75 - 5.91 (m, 1 H), 4.27 - 4.30 (m, 1 H), 4.14 - 4.19 (m, 2 H), 2.45 - 2.53 (m, 2 H), 1.25 (t, 3 H).

[0260] *Step 2*: To a solution of t-BuOK (7.450 g, 112.21 mmol) in DMF (30 mL) was added Ethyl N-(diphenylmethylene)glycinate (20 g, 331.36 mmol) at 0 °C. After 30 min, iodomethane (42.83 g, 141.93 mmol) was added over 10 min at 0 °C. The RM was stirred at 0°C for 1 h. After completion of the reaction, the RM was diluted with 5% aq NH_4Cl (100 mL), extracted with EtOAc (3 x 50 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 ethyl 2-((diphenylmethylene)amino)-4,4-difluoro-2-methylbutanoateas a pale yellow liquid (16 g, 76.75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.50 - 7.59 (m, 2 H), 7.36 - 7.41 (m, 4 H), 7.28 - 7.32 (m, 2 H), 7.13 - 7.15 (m, 2 H), 6.16 - 6.49 (m, 1 H), 3.69 - 3.77 (m, 2 H), 2.31 - 2.57 (m, 2 H), 1.44 (s, 3 H), 1.11 (t, 3 H).

[0261] Step 3 : To a solution of ethyl 2-((diphenylmethylene)amino)-4,4-difluoro-2-methylbutanoate (16 g, 46.32 mmol) in Pet.ether (75 mL) was added 1N HCl (150 mL) at RT. The RM was stirred at RT for 16 h. The RM was washed with EtOAc (2 x 50 mL). The aqueous solution was basified with $NaHCO_3$ (pH ~8), extracted with EtOAc (3 x 50 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to afford ethyl 2-amino-4,4-difluoro-2-methylbutanoate as a pale yellow liquid (5.910 g, 70.42%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 5.87 - 6.15 (m, 1 H), 4.17 - 4.12 (m, 2 H), 2.04 - 2.33 (m, 2 H), 1.39 (s, 3 H), 1.27 (t, 3 H).

[0262] Step 4 : To a solution of ethyl 2-amino-4,4-difluoro-2-methylbutanoate (5.6 g, 30.90 mmol) in EtOH (50 mL) was added sodium borohydride (3.508 mg, 92.72 mmol) at 0 °C. The RM was stirred at RT for 7 h. The RM was quenched with water (10 mL), extracted with EtOAc (3 x 30 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to afford 2-amino-4,4-difluoro-2-methylbutan-1-ol as a colourless gum (2.3 g, 53%). ^{1}H NMR (400 MHz, DMSO-D_6) δ ppm: 6.02 -6.33 (m, 1 H), 4.76 (t, 1 H), 3.09 - 3.19 (m, 2 H), 1.75 - 1.87 (m, 2 H), 1.48 (br, s, 2 H), 0.95 (s, 3 H).

[0263] **Synthesis of potassium 2-methyl-6-(pyridin-3-ylmethoxy) indolizine-3-carboxylate (Int-15)**

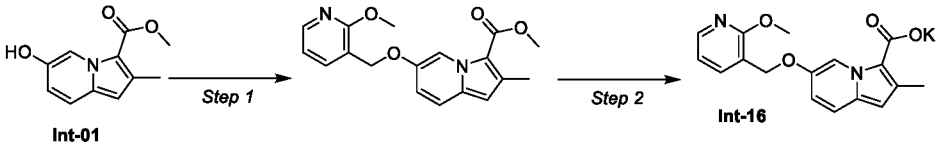


Int-01 Int-15

[0264] *Step 1* : To a stirred solution of methyl 6-hydroxy-2-methylindolizine-3-carboxylate (400 mg, 1.949 mmol) in dry THF (5 mL) were added ADDP (0.984 g, 3.898 mmol), Tri-n-butylphosphine (0.962 mL, 3.898 mmol) and Pyridin-3-ylmethanol (0.2 mL, 2.144 mmol) at 0 °C. The RM was stirred for 2 h at RT. The RM was quenched with ice cold water (30 mL) and extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (50 mL), 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 to afford methyl 2-methyl-6-(pyridin-3-ylmethoxy) indolizine-3-carboxylate (500 mg, 87%) as a pale-yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 9.33 (s, 1 H), 8.72 (s, 1 H), 8.61–8.59 (m, 1 H), 7.82–7.79 (m, 1 H),7.36–7.32 (m, 1 H), 7.29 (d, 1 H), 6.86 (dd, 1 H), 6.28 (s, 1 H), 5.09 (s, 2 H), 3.91 (s, 3 H), 2.51 (s, 3 H).

[0265] *Step 2* : To a solution of methyl 2-methyl-6-(pyridin-3-ylmethoxy) indolizine-3-carboxylate (450 mg, 1.519 mmol) in THF (7 mL) was added KOTMS (487 mg, 3.796 mmol) at RT. The RM was stirred at 70 °C for 16 h. The volatiles were removed under reduced pressure. The residue was triturated with n-pentane (30 mL), dried under reduced pressure to afford potassium 2-methyl-6-(pyridin-3-ylmethoxy) indolizine-3-carboxylate (**Int-15**) (500 mg) as a pale-yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 9.88 (d, 1 H), 8.69 (d, 1 H), 8.52–8.54 (m, 1 H), 7.92–7.89 (m, 1 H), 7.44–7.41 (m, 1 H), 7.18 (d, 1 H), 6.55 (dd, 1 H), 6.07 (s, 1 H), 5.03 (s, 2 H), 2.44 (s, 3 H).

[0266] **Synthesis of potassium 6-((2-methoxypyridin-3-yl)methoxy)-2-methylindolizine-3-carboxylate (Int-16)**



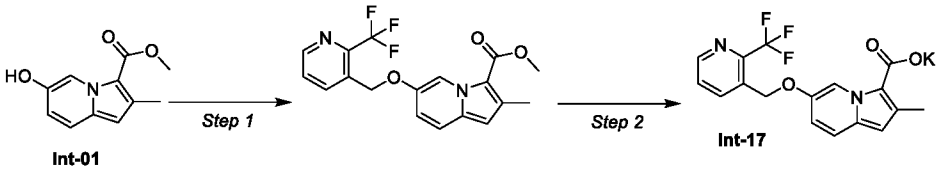
Int-01 Int-16

[0267] *Step 1* : To a stirred solution of methyl 6-hydroxy-2-methylindolizine-3-carboxylate (400 mg, 1.949 mmol) in dry THF (7 mL) were added ADDP (0.984 mg, 3.898 mmol), n-Bu_3P (0.962 mL, 3.898 mmol) and (2-methoxypyridin-3-yl) methanol (298 mg, 2.144 mmol) at 0°C. The RM was stirred at RT for 2 h. After completion of the reaction, the RM was diluted with cold water (30 mL), extracted with EtOAc (2 x 30 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (30 mL), brine (30 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 Hexane as an eluent to afford methyl 6-((2-methoxypyridin-3-yl) methoxy)-2-methylindolizine-3-carboxylate (400 mg, 63%) as a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 9.32 (d, 1 H), 8.14 (dd, 1 H), 7.80-7.77 (m, 1 H), 7.27 (t, 1 H), 6.94-6.88 (m, 2 H), 6.27 (s, 1 H), 5.06 (s, 2 H), 4.01 (s, 3 H), 3.91 (s, 3 H), 2.51 (s, 3 H).

[0268] *Step 2* : To a stirred solution of methyl 6-((2-methoxypyridin-3-yl) methoxy)-2-methylindolizine-3-carboxylate (400 mg, 1.226 mmol) in THF (7 mL) was added KOTMS (393

mg, 3.064 mmol) at RT. The RM was stirred at 70 °C for 16 h. The volatiles were removed under reduced pressure. The residue was trituration with n-pentane (5 mL) and filter to afford potassium 6-((2-methoxypyridin-3-yl)methoxy)-2-methylindolizine-3-carboxylate (**Int-16**) (500 mg) pale yellow solid ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 9.85 (s, 1 H), 8.15 (dd, 1 H), 7.86 (dd, 1 H), 7.19 (d, 1 H), 7.05-7.02 (m, 1 H), 6.56 (dd, 1 H), 6.07 (s, 1 H), 4.94 (s, 2 H), 3.93 (s, 3 H), 2.49 (s, 3 H).

[0269] **Synthesis of potassium 2-methyl-6-((2-(trifluoromethyl)pyridin-3-yl)methoxy)indolizine-3-carboxylate (Int-17)**

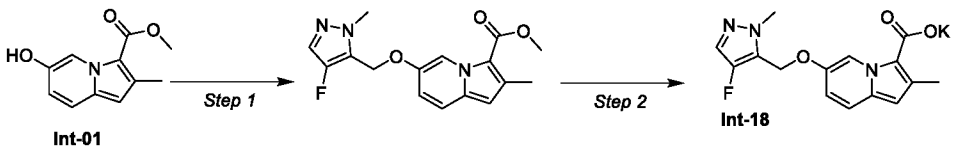


Int-01 Int-17

[0270] *Step 1* : To a stirred solution of methyl 6-hydroxy-2-methylindolizine-3-carboxylate (1.2 g, 5.848 mmol, 1 equiv.) in dry THF (20 mL) were added with ADDP (2.951 g, 11.695 mmol,), n-Bu_3P (2.886 mL, 11.695 mmol) and (2-(trifluoromethyl)pyridin-3-yl)methanol (1.346 g, 7.602 mmol) at 0 °C. The RM was stirred at RT for 16 h. The RM was diluted with cold water (50 mL) and extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with brine solution (25 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-methyl-6-((2-(trifluoromethyl)pyridin-3-yl)methoxy)indolizine-3-carboxylate (800 mg, 37%) as a gray solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 9.31 (d, 1 H), 8.68 (d, 1 H), 8.16 (dd, 1 H), 7.58–7.54 (m, 1 H), 7.31 (d, 1 H), 6.88 (dd, 1 H), 6.30 (s, 1 H), 5.29 (s, 2 H), 3.91 (s, 3 H), 2.51 (s, 3 H).

[0271] *Step 2* : To a stirred solution of methyl 2-methyl-6-((2-(trifluoromethyl)pyridin-3-yl)methoxy)indolizine-3-carboxylate (600 mg, 1.647 mmol) in THF (15 mL) was added KOTMS (550 mg, 4.117 mmol) at RT. The RM was stirred at 70 °C for 16 h. The volatiles were removed under reduced pressure. The residue was triturated with pentane (40 mL) and filtered, and dried under high vacuum to afford potassium 2-methyl-6-((2-(trifluoromethyl)pyridin-3-yl)methoxy)indolizine-3-carboxylate (**Int-17**) (850 mg) as an off white solid. ^{1}H NMR (400 MHz, CD_3OD) δ ppm: 9.42 (d, 1 H), 8.64 (d, 1 H), 8.28 (d, 1 H), 7.72–7.69 (m, 1 H), 7.24 (d, 1 H), 6.73 (dd, 1 H), 6.20 (s, 1 H), 5.26 (s, 2 H), 2.53 (s, 3 H).

[0272] **Synthesis of potassium 6-((4-fluoro-1-methyl-1H-pyrazol-5-yl) methoxy)-2-methylindolizine-3-carboxylate (Int-18)**

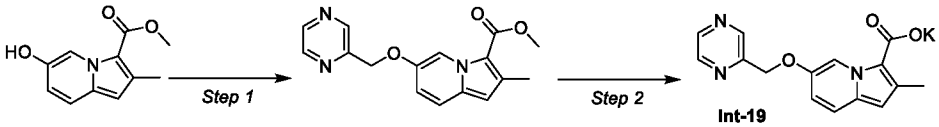


Int-01 Int-18

[0273] *Step 1* : To a stirred solution of methyl 6-hydroxy-2-methylindolizine-3-carboxylate (400 mg, 1.95 mmol) in dry THF (7 mL) were added ADDP (0.983 g, 3.9 mmol), n-Bu_3P (0.96 mL, 3.9 mmol) and (4-fluoro-1-methyl-1H-pyrazol-5-yl)methanol (0.304 g, 2.3 mmol) at 0 °C. The RM was stirred at RT for 2 h. The RM was diluted with cold water (40 mL) and extracted with EtOAc (2 × 40 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (30 mL), brine (30 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by FCC on silica gel using 0 to 50% EtOAc in Pet. ether as gradient to afford methyl 6-((4-fluoro-1-methyl-1H-pyrazol-5-yl) methoxy)-2-methylindolizine-3-carboxylate (500 mg, 81%) as a pale-yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 9.34 (d, 1 H), 7.32–7.28 (m, 2 H), 6.81 (dd, 1 H), 6.29 (s, 1 H), 5.05 (s, 2 H), 3.92 (m, 3 H), 3.89 (s, 3 H), 2.51 (s, 3 H).

[0274] *Step 2* : To a stirred solution of methyl 6-((4-fluoro-1-methyl-1H-pyrazol-5-yl) methoxy)-2-methylindolizine-3-carboxylate (450 mg, 1.42 mmol) in THF (8 mL) was added KOTMS (455 mg, 3.55 mmol) at RT. The RM was stirred at 70 °C for 16 h. The volatiles were removed under reduced pressure. The residue was triturated with n-pentane (20 mL), and dried under vacuum to afford potassium 6-((4-fluoro-1-methyl-1H-pyrazol-5-yl) methoxy)-2-methylindolizine-3-carboxylate (**Int-18**) (500 mg) as pale yellow solid. ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 9.88 (d, 1 H), 7.46–7.45 (d, 1 H), 7.20 (d, 1 H), 6.55 (dd, 1 H), 6.08 (s, 1 H), 5.03 (s, 2 H), 3.86 (s, 3 H), 2.44 (s, 3 H).

[0275] **Synthesis of potassium 2-methyl-6-(pyrazin-2-ylmethoxy)indolizine-3-carboxylate (Int-19)**



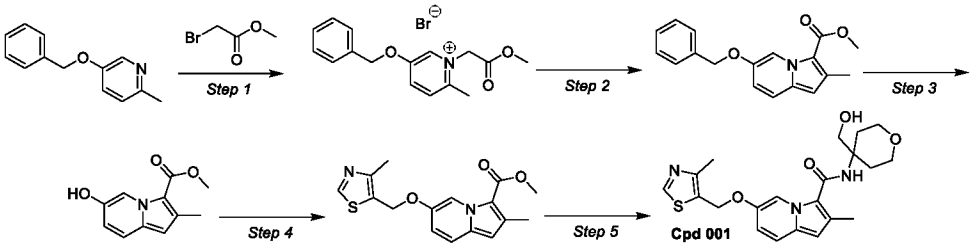
Int-01 Int-19

[0276] *Step 1* : To a stirred solution of methyl 6-hydroxy-2-methylindolizine-3-carboxylate (0.8 g, 3.9 mmol) in ACN (20 mL) was added Cesium carbonate (3.81 g, 11.7 mmol,) at 0 °C. After 5 minutes, 2-(chloromethyl)pyrazine (0.752 g, 5.848 mmol) was added at 0°C. The RM was stirred at 80 °C for 2h. The RM was diluted with water (20 mL) and extracted with EtOAc (2 × 50 mL). The combined organic layer washed with brine solution (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by FCC on silica gel using 50% EtOAc in Pet. ether as an eluent to afford methyl 2-methyl-6-(pyrazin-2-ylmethoxy)indolizine-3-carboxylate as a brown solid (700 mg, 60%). ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 9.34 (d, 1 H), 8.85 (d, 1 H), 8.61 - 8.56 (m, 2 H), 7.31 (d, 1 H), 6.92 (dd,1 H), 6.29 (s, 1 H), 5.25 (s, 2 H), 3.91 (s, 3 H), 2.51 (s, 3 H).

[0277] *Step 2*: To a solution of methyl 2-methyl-6-(pyrazin-2-ylmethoxy)indolizine-3-carboxylate (200 mg, 0.673 mmol) in THF (20 mL) was added KOTMS (258.9 mg, 2.0 mmol) at RT. The RM was stirred at 70 °C for 16 h. The volatiles were removed under reduced

pressure. The residue was triturated with n-pentane (5 mL) and filter to afford potassium 2-methyl-6-(pyrazin-2-ylmethoxy)indolizine-3-carboxylate (**Int-19**) (350 mg) as a brown solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 9.43 (s, 1 H), 8.84 (s, 1 H), 8.63 - 8.62 (m, 1 H), 8.56 (t, 1 H), 7.24 (d, 1 H), 6.72 (dd, 1 H), 6.20 (s, 1 H), 5.23 (s, 2 H), 2.52 (s, 3 H).

[0278] **Synthesis of N-[4-(hydroxymethyl)oxan-4-yl]-2-methyl-6-[(4-methyl-1,3-thiazol-5-yl)methoxy]indolizine-3-carboxamide (Cpd 001).**

[0279] 

[0280] *Step 1* : To a stirred solution of 5-(benzyloxy)-2-methylpyridine (19.5 g, 97.99 mmol) in diethyl ether (200 mL), methyl-2-bromoacetate (10.2 mL, 107.79 mmol) was added at RT. Stirred the resulting reaction mixture at RT for 18 h. Solvent was evaporated under reduced pressure and decant pet ether (50 mL) and dried to get crude 5-(benzyloxy)-1-(2-methoxy-2-oxoethyl)-2-methylpyridinium bromide (33 g) as brown viscous oil.

[0281] *Step 2* : To a stirred solution of 5-(benzyloxy)-1-(2-methoxy-2-oxoethyl)-2-methylpyridinium bromide) (33 g, 94.02 mmol) in acetic anhydride (100 mL), sodium acetate (23.13 g, 282.05 mmol) at RT. The RM was heated to 150 °C and stirred for 24 h. Reaction progress was monitored by LCMS. After completion of the reaction, RM was cooled to RT and diluted with ethyl acetate (2 l) and organic layer was washed with sat. NaHCO3 aq (3 x 400 mL), water (400 mL) and brine solution (400 ml), dried over anhydrous Na_2SO_4 and filtered. Evaporated the filtrate under reduced pressure. Crude compound was purified by silica gel (100-200 mesh) column chromatography using 5% ethyl acetate in pet ether as eluent to get methyl 6-(benzyloxy)-2-methylindolizine-3-carboxylate (6.5 g, 17% over 2 steps) as off-white solid.

[0282] *Step 3* : To a stirred solution of methyl 6-(benzyloxy)-2-methylindolizine-3-carboxylate (3 g, 10.17 mmol) in methane sulfonic acid (15 mL), DL-Ethionine (3.3 g, 20.34 mmol) was added at RT. RM was stirred for 30 min at 80 °C in pre-heated oil bath. Reaction progress was monitored by TLC. After completion of the reaction, RM was cooled to RT, poured in ice water (150 mL) and extracted with ethyl acetate (3 x 150 mL). The combined organic layers were washed with water (200 mL), brine solution (200 ml), dried over anhydrous Na_2SO_4, filtered and concentrated. The crude was purified by Grace flash column chromatography using 30% ethyl acetate in pet ether as eluent to get methyl 6-hydroxy-2-methylindolizine-3-carboxylate (1.5 g, 75%) as pale brown solid.

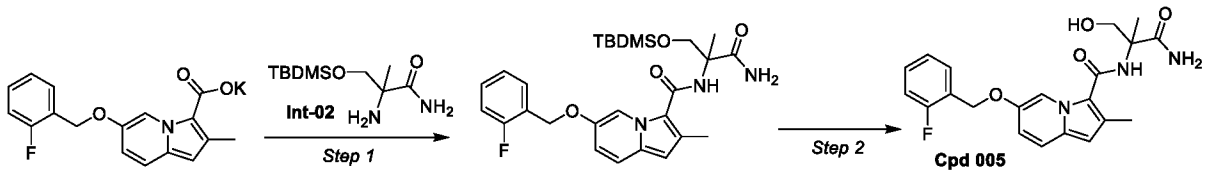
[0283] *Step 4* : To a stirred solution of methyl 6-hydroxy-2-methylindolizine-3-carboxylate (1.5 g, 7.32 mmol, 1.0 eq) in DMF (20 ml), Cs_2CO_3 (4.77 g, 14.63 mmol, 2 eq) and (4-methylthiazol-

5-yl)methyl methanesulfonate (1970-7) (1.97 g, 9.51 mmol, 1.3 eq) were added at 0 °C, then reaction mixture was stirred for 18 h at RT. Reaction progress was monitored by TLC. The reaction mixture was diluted with EtOAc (600 ml), organic layer was washed with ice water (6 x 100 mL), brine solution (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to get the crude product, which was purified by Grace flash column chromatography using eluent 20% ethyl acetate in pet-ether to afford methyl 2-methyl-6-((4-methylthiazol-5-yl)methoxy)indolizine-3-carboxylate (1970-8) (1.2 g, 37%) as off-white solid.

[0284] *Step 5* : To a stirred solution of methyl 2-methyl-6-((4-methylthiazol-5-yl)methoxy)indolizine-3-carboxylate (250 mg, 0.79 mmol, 1.0 eq) in THF (10 mL), Et_3N (0.22 mL, 1.58 mmol, 2 eq), 2,3,4,6,7,8-hexahydro-1H-pyrimido[1,2-a]pyrimidine (220 mg, 1.58 mmol, 2 eq), and (4-aminotetrahydro-2H-pyran-4-yl)methanol (207 mg, 1.58 mmol, 2 eq) were added at RT. The reaction mixture was heated to 80 °C and stirred at this tempearature for 48 h. The reaction mixture was cooled to RT and diluted with ethyl acetate (400 mL). Ethyl acetate layer was washed with water (2 x 50 mL), brine solution (50 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude. The crude was purified by column chromatography over silica gel (100-200 mesh) using 5% methanol in dichloromethane as an eluent to get crude product which was further purified in reversed phase prep-HPLC purification. Fractions obtained from Prep-HPLC were directly lyophilized to afford N-[4-(hydroxymethyl)oxan-4-yl]-2-methyl-6-[(4-methyl-1,3-thiazol-5-yl)methoxy]indolizine-3-carboxamide (**Cpd 001**) (18 mg, 5%) as off-white solid.

[0285] The following compound was 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 001**: **Cpd 002, Cpd 003 and Cpd 004.**

[0286] **Synthesis of 2-({6-[(2-fluorophenyl)methoxy]-2-methylindolizin-3-yl}formamido)-3-hydroxy-2-methylpropanamide (Cpd 005).**



[0287] *Step 1* : To a solution of potassium 6-((2-fluorobenzyl)oxy)-2-methylindolizine-3-carboxylate (**Int-04**) (0.5 g, 1.671 mmol) in DMF (10 mL) were added HATU (0.953 g, 2.506 mmol), DIPEA (0.874 mL, 5.012 mmol) and 2-amino-3-((tert-butyldimethylsilyl)oxy)-2-methylpropanamide (**Int-02**) (0.581 g, 2.506 mmol) at RT. The RM was stirred at 50 °C for 16 h. The RM was quenched with water (5 mL), extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with sat. $NaHCO_3$ solution (50 mL), brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford N-(1-amino-3-((tert-butyldimethylsilyl)oxy)-2-methyl-1-oxopropan-2-yl)-6-((2-fluorobenzyl)oxy)-2-methylindolizine-

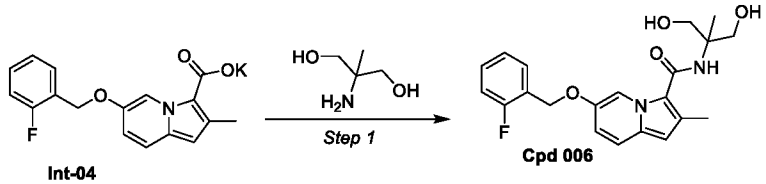
3-carboxamide as an off white solid (0.550 g, 64%). ^{1}H NMR (400 MHz, DMSO-D_6) δ ppm: 9.22 (s, 1 H), 7.59 (t, 1 H), 7.44 - 7.40 (m, 3 H), 7.28 - 7.22 (m, 4 H), 6.88 - 6.85 (m, 1 H), 7.40 - 7.36 (m, 2 H), 6.34 (s, 1 H), 5.06 (s, 2 H), 4.19 (d, 1 H), 3.98 (d, 1 H), 2.50 (s, 3 H), 1.54 (s, 3 H), 0.80 (s, 9 H), 0.04 (m, 6 H).

[0288] *Step 2* : To a solution of N-(1-amino-3-((tert-butyldimethylsilyl)oxy)-2-methyl-1-oxopropan-2-yl)-6-((2-fluorobenzyl)oxy)-2-methylindolizine-3-carboxamide (500 mg, 0.973 mmol) in THF (20.0 mL) was added TBAF (2.920 ml, 2.920 mmol) at RT for 3 h. The RM was diluted with cold water (50 mL), extracted with EtOAc (3 x 500 mL). The combined organic phases were washed with brine solution (50 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 (25 x 150mm) 5µm, FLOW: 21 ml/min, Method: (T in min./ % of B): 0/20,2/20,8/50,12/50,12.1/98,14/98,14.1/20,17/20, Solubility: ACN+Water+THF, Temperature: RT.] The desired fractions were evaporated and lyophilized to afford 2-({6-[(2-fluorophenyl)methoxy]-2-methylindolizin-3-yl}formamido)-3-hydroxy-2-methylpropanamide (**Cpd 005**) as an off-white solid (200 mg, 51%).

[0289] A preparative chiral SFC was performed on the racemic mixture of **Cpd 005** to afford **Cpd 005 – En1 and Cpd 005– En2.**

[0290] 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 005 – En1 and Cpd 005 – En2 : Cpd 014 – En1, Cpd 014 – En2, Cpd 019 – En1, Cpd 019 – En2.**

[0291] **Synthesis of N-(1,3-dihydroxy-2-methylpropan-2-yl)-6-[(2-fluorophenyl)methoxy]-2-methylindolizine-3-carboxamide (Cpd 006).**



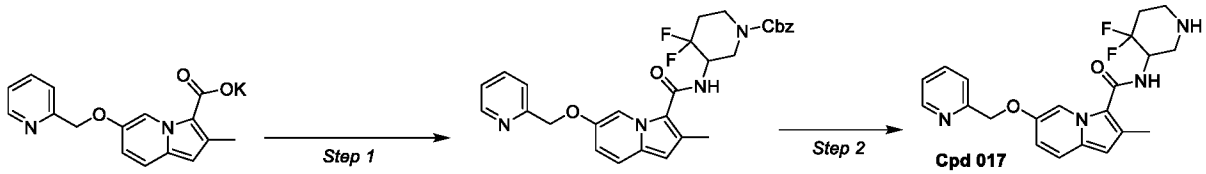
Int-04 Cpd 006

[0292] Step 1 : To a solution of potassium 6-((2-fluorobenzyl)oxy)-2-methylindolizine-3-carboxylate (**Int-04**) (300 mg, 1.0 mmol) in DMF (10 mL) were added HATU (571 mg, 1.504 mmol), DIPEA (0.526 mL, 3.0 mmol) and 2-amino-2-methylpropane-1,3-diol (158 mg, 1.504 mmol) at 0 °C. The RM was stirred at RT for 16 h. The RM was diluted with ice-cold water (50 mL), extracted with EtOAc (2 x 20 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 30% EtOAc in pet ether as an eluent. The compound was repurified by Prep. HPLC. [Prep. HPLC conditions: Mobile phase: 10mM ABC in Water, Mobile phase B: ACN, Column: YMC TRIART C18 (25 x 150mm) 5µm,

FLOW: 21 ml/min, Method: (T in min./ % of B): 0/20,2/20,8/50,12/50,12.1/98,14/98,14.1/20,17/20, Solubility: ACN+Water+THF, Temperature: RT.] The desired fractions were evaporated and lyophilized to afford N-(1,3-dihydroxy-2-methylpropan-2-yl)-6-[(2-fluorophenyl)methoxy]-2-methylindolizine-3-carboxamide (**Cpd 006**) as an off-white solid (45 mg, 11.62%).

[0293] 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 006 : Cpd 007 – En1, Cpd 007 – En2, Cpd 015, Cpd 016 – En1, Cpd 016 – En2, Cpd 018 – En1, Cpd 018 – En2, Cpd 020, Cpd 021 – En1, Cpd 021 – En2, Cpd 023 – En1, Cpd 023 – En2, Cpd 025, Cpd 028 – En1, Cpd 028 – En2, Cpd 031, Cpd 032 – En1, Cpd 032 – En2, Cpd 033 – En1, Cpd 033 – En2, Cpd 034 – En1, Cpd 034 – En2, Cpd 035 – En1, Cpd 035 – En2, Cpd 036 – En1, Cpd 036 – En2, Cpd 037 – En1, Cpd 037 – En2, Cpd 038 – En1, Cpd 038 – En2, Cpd 039 – En1, Cpd 039 – En2, Cpd 040 – En1, Cpd 040 – En2, Cpd 041 – En1, Cpd 041 – En2, Cpd 042 – En1, Cpd 042 – En2, Cpd 043 – En1, Cpd 043 – En2, Cpd 044 – En1, Cpd 044 – En2, Cpd 045 – En1, Cpd 045 – En2.**

[0294] **Synthesis of N-(4,4-difluoropiperidin-3-yl)-2-methyl-6-[(pyridin-2-yl)methoxy]indolizine-3-carboxamide (Cpd 017).**



[0295] Step 1 : To a stirred solution of potassium 2-methyl-6-(pyridin-2-ylmethoxy)indolizine-3-carboxylate (400 mg, 1.417 mmol) in DMF (8 mL) were added DIPEA (0.695 mL, 4.251 mmol), HATU (808 mg, 2.125 mmol) and benzyl 3-amino-4,4-difluoropiperidine-1-carboxylate (421 mg, 1.559 mmol) at RT. The RM was stirred at 80°C for 16 h. The RM was diluted with water (50 mL), extracted with EtOAc (2 × 50 mL). The combined organic layer was washed with saturated $NaHCO_3$ (50 mL), brine (30 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by FCC on silica gel using 20-30% EtOAc in Pet. ether as an eluent to afford benzyl 4,4-difluoro-3-(2-methyl-6-(pyridin-2-ylmethoxy) indolizine-3-carboxamido) piperidine-1-carboxylate (250 mg, 33%) as pale-yellow oil.

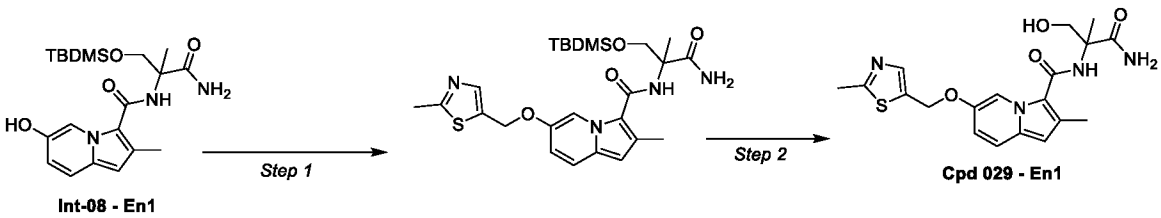
[0296] Step 2 : To a stirred solution of benzyl 4,4-difluoro-3-(2-methyl-6-(pyridin-2-ylmethoxy) indolizine-3-carboxamido) piperidine-1-carboxylate (280 mg, 0.524 mmol) in TFA (3 mL) was heated to 70 °C for 3 h. The RM was concentrated under reduced pressure. The residue was basified with saturated $NaHCO_3$ (pH ~10) and then extracted with EtOAc (2 × 20 mL). The combined organic layer was washed with saturated $NaHCO_3$ (20 mL), brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The compound was repurified by

Prep. HPLC. [Prep. HPLC conditions: Mobile phase: 10mM ABC in Water, Mobile phase B: ACN, Column: X-SELECT CSH C18 (25 x 150mm) 10µm, FLOW: 20 ml/min, Method: (T in min./ % of B): 0/25, 2/25, 10/55, 12/55, 12.1/100, 16/100, 16.1/25, 20/25, Solubility: ACN+Water+THF, Temperature: RT.] The desired fractions were evaporated and lyophilized to afford N-(4,4-difluoropiperidin-3-yl)-2-methyl-6-[(pyridin-2-yl)methoxy]indolizine-3-carboxamide (**Cpd 017**) (70 mg, 33%) as an off white solid.

[0297] A preparative chiral SFC was performed on the racemic mixture of **Cpd 017** to afford **Cpd 017 – En1 and Cpd 017– 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 017 – En1 and Cpd 017 – En2: Cpd 008, Cpd 027 – En1, Cpd 027 – En2,**

[0299] **Synthesis of 3-hydroxy-2-methyl-2-({2-methyl-6-[(2-methyl-1,3-thiazol-5-yl)methoxy]indolizin-3-yl}formamido)propanamide (Cpd 029 – En1).**



Int-08 - En1

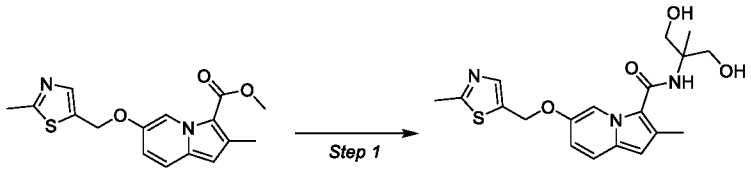
[0300] Step 1 :To a solution of N-(1-amino-3-((tert-butyldimethylsilyl)oxy)-2-methyl-1-oxopropan-2-yl)-6-hydroxy-2-methylindolizine-3-carboxamide (**Int-08 – En1**) (350 mg, 0.863 mmol) in DMF (10 mL) were added Cesium carbonate (702.9 mg, 2.157 mmol) and a solution of 5-(chloromethyl)-2-methylthiazole (140 mg, 0.949 mmol) in DMF (2 mL) at 0 °C. The RM was allowed to warm to RT and was stirred for 16 h. The RM was diluted with water (50 mL) and extracted with EtOAc (3 × 50 mL). The 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 0 to 50% EtOAc in pet. ether as a gradient. to afford N-(1-amino-3-((tert-butyldimethylsilyl)oxy)-2-methyl-1-oxopropan-2-yl)-2-methyl-6-((2-methylthiazol-5-yl)methoxy)indolizine-3-carboxamide (90 mg, 20%) as a brown solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 9.22 (s, 1H), 7.71 (s, 1H), 7.44–7.42 (m, 2H), 7.26–7.25 (m, 2H), 6.85 (dd, 1H), 6.35 (s, 1H), 5.25 (s, 2H), 4.17 (d, 1H), 3.97 (d, 1H), 2.64 (s, 3H), 2.46 (s, 3H), 1.55 (s, 3H), 0.81 (s, 9H), -0.03 (s, 6H).

[0301] Step 2 : To a solution of Pyridine (0.375 mL,4.645 mmol) in THF (6 mL) was added HF in Pyridine (0.418 mL,4.645 mmol) at 0 °C and stirred for 10 min. Then, a solution of N-(1-amino-3-((tert-butyldimethylsilyl)oxy)-2-methyl-1-oxopropan-2-yl)-2-methyl-6-((2-methylthiazol-5-yl)methoxy)indolizine-3-carboxamide (160 mg, 0.310 mmol) in THF (4 mL) at 0°C was added. The RM was stirred for 16 h at RT. The RM was diluted with water (50 mL) and extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with brine

solution (50 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: UNI HYBRID C18 (25 x 150mm) 5µm, FLOW: 20 ml/min, Method: (T in min./ % of B): /20, 2/20, 10/50, 12/50, 12.1/100, 15/100, 15.1/20, 19/20, Solubility: ACN+Water+THF, Temperature: RT.] The desired fractions were evaporated and lyophilized to afford 3-hydroxy-2-methyl-2-({2-methyl-6-[(2-methyl-1,3-thiazol-5-yl)methoxy]indolizin-3-yl}formamido)propanamide (**Cpd 029 – En1**) (25.6 mg, 20%) as an off white solid.

[0302] 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 029 – En1 : Cpd 029 – En2.**

[0303] **Synthesis of N-(1,3-dihydroxy-2-methylpropan-2-yl)-2-methyl-6-[(2-methyl-1,3-thiazol-5-yl)methoxy]indolizine-3-carboxamide (Cpd 030)**



[0304] *Step 1* : To a solution of methyl 2-methyl-6-((2-methylthiazol-5-yl)methoxy)indolizine-3-carboxylate (Int-13) (300 mg, 0.948 mmol) in THF (10 mL) were added triazabicyclodecene (263.99 mg, 1.896 mmol), TEA (0.267 mL, 1.896 mmol) at RT. After 10 min, 2-amino-2-methylpropane-1,3-diol (149.54 mg, 1.422 mmol) was added and stirred at 80 °C for 72 h. The RM was diluted with cold water (20 mL), extracted with EtOAc (2 x 15 mL). The combined organic layers were washed with sat. $NaHCO_3$ solution (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 5% MeOH in DCM as a gradient to afford N-(1,3-dihydroxy-2-methylpropan-2-yl)-2-methyl-6-[(2-methyl-1,3-thiazol-5-yl)methoxy]indolizine-3-carboxamide (Cpd 030) as a pale brown solid (90 mg, 24.37 %).

[0305] *Analytical data*

Cpd Code	[M+H]+ (m/z) :	^{1}H NMR (δ ppm)
Cpd 001	416.1	(400 MHz, DMSO-d_6): δ 8.55 (d, 1H), 7.63 (t, 1H), 7.62 - 7.54 (m, 2H), 7.50 - 7.43(m, 1H), 7.41 (s, 1H), 7.34 (s, 1H), 7.30 - 7.24 (m, 2H), 6.71 (dd, 1H), 5.25 - 5.19 (m, 2H), 4.97 (t, 1H), 4.16 - 4.12 (m, 1H), 3.79 - 3.75 (m, 1H), 2.57 (s, 3H), 2.45 - 2.37 (m, 1H), 1.75 - 1.70 (m, 1H), 0.72 (t, 3H).

Cpd 002	369.1	1H NMR (600 MHz, DMSO-D_6) δ 8.515 (dd, 1H), 7.638 – 7.579 (m, 1H), 7.500 – 7.422 (m, 2H), 7.313 – 7.232 (m, 2H), 6.696 (ddd, 1H), 6.657 (s, 1H), 5.220 (s, 2H), 5.055 (td, 2H), 3.632 (dd, 2H), 3.515 (dd, 2H), 1.314 (d, 3H).
Cpd 003	385.1	1H NMR (600 MHz, DMSO-D_6) δ 8.536 (d, 1H), 7.614 (td, 1H), 7.544 (d, 1H), 7.496 – 7.421 (m, 2H), 7.311 – 7.232 (m, 2H), 7.155 – 7.085 (m, 2H), 6.719 (dd, 1H), 5.236 (s, 2H), 5.027 – 4.969 (m, 1H), 4.447 (dt, 1H), 3.776 (ddd, 1H), 3.719 (dt, 1H), 2.555 (s, 3H).
Cpd 004	385.1	1H NMR (600 MHz, DMSO-D_6) δ 8.522 (d, 1H), 7.609 (td, 1H), 7.494 (d, 1H), 7.489 – 7.433 (m, 1H), 7.328 (s, 1H), 7.315 (s, 1H), 7.304 – 7.233 (m, 2H), 7.063 (s, 1H), 6.707 (dd, 1H), 5.246 (s, 2H), 2.551 (s, 3H), 1.558 (s, 6H).
Cpd 005 - En1	400.2	(400 MHz, DMSO-D_6) δ ppm: 9.22 (s, 1 H), 7.58 (dt, 1 H), 7.46 - 7.38 (m, 3 H), 7.28 - 7.22 (m, 3 H), 7.18 (s, 1 H), 6.85 (dd, 1 H), 6.34 (s, 1 H), 5.13 - 5.08 (m, 3 H), 3.95 - 3.91 (m, 1 H), 3.78 - 3.74 (m, 1 H), 2.52 - 2.49 (m, 3 H), 1.52 (s, 3 H).
Cpd 005 - En2	400.2	(400 MHz, DMSO-D_6) δ ppm: 9.22 (s, 1 H), 7.60 (dt, 1 H), 7.46-7.39 (m, 3 H), 7.26 - 7.22 (m, 3 H), 7.18 (s, 1 H), 6.87 - 6.84 (m, 1 H), 6.34 (s, 1 H), 5.13 - 5.08 (m, 3 H), 3.95 - 3.91 (m, 1 H), 3.78 - 3.74 (m, 1 H), 2.52 - 2.49 (m, 3 H), 1.52 (s, 3 H).
Cpd 006	387.3	(400 MHz, DMSO-D_6) δH ppm: 9.03 (d, 1 H), 7.59 (dt, 1 H), 7.39 - 7.46 (m, 2 H), 7.22 - 7.28 (m, 2 H), 6.82 (dd, 1 H), 6.64 (s, 1 H), 6.31 (s, 1 H), 5.08 (s, 2 H), 4.97 (t, 2 H), 3.64 (dd, 2 H), 3.54 (dd, 2 H), 2.44 (s, 3 H), 1.32 (s, 3 H)
Cpd 007 - En1	412.3	(400 MHz, DMSO-D6) δ ppm: 9.07 (d, 1 H), 7.80 (s, 1 H), 7.59 (t, 1 H), 7.46 - 7.40 (m, 2 H), 7.28 - 7.22 (m, 2 H), 6.90 - 6.84 (m, 2 H), 6.33 (s, 1 H), 5.25 (t, 1 H), 5.08 (s, 2 H), 3.64 - 3.56 (m, 2 H), 3.31 (s, 1 H), 3.24 - 3.18 (m, 1 H) 2.46 - 2.39 (m, 5 H)
Cpd 007 - En2	412.3	(400 MHz, DMSO-D_6) δ ppm: 9.07 (d, 1 H), 7.80 (s, 1 H), 7.59 (t, 1 H), 7.46 - 7.40 (m, 2 H), 7.28 - 7.22 (m, 2 H), 6.90 - 6.84 (m, 2 H), 6.33 (s, 1 H), 5.25 (t, 1 H), 5.08 (s, 2 H), 3.63 - 3.58 (m, 2 H), 3.31 (s, 1 H), 3.24 - 3.20 (m, 1 H) 2.47 - 2.41 (m, 5 H).
Cpd 008	418.4	(400 MHz, DMSO-D_6, VT at 90 °C) δ ppm: 8.92 (d, 1 H), 7.55–7.52 (m, 1 H), 7.43–7.38 (m, 2 H), 7.24–7.17 (m, 2 H), 6.84 (dd, 1 H), 6.32 (s, 1 H), 5.10 (s, 2 H), 4.42–4.35 (m, 1 H), 3.04–2.99 (m, 1 H), 2.92–2.88 (m, 1 H), 2.74–2.66 (m, 2 H), 2.47 (s, 3 H), 2.14–1.88 (m, 2 H), 1.33–1.21 (m, 1 H)
Cpd 014 - En1	383.3	(400 MHz, DMSO-D_6) δ ppm: 9.19 (s, 1 H), 8.59 - 8.57 (m, 1 H), 7.87 - 7.83 (m, 1 H), 7.57 (d, 1 H), 7.43 (d, 1 H), 7.38 - 7.34 (m, 1 H), 7.25 (s, 1 H), 7.18 (s, 1 H), 6.9 (dd, 1 H), 6.34 (s, 1 H), 5.11 (s, 3 H), 3.93 (dd, 1 H), 3.76 (dd, 1 H), 2.50 (s, 3 H), 1.52 (s, 3 H).

Cpd 014 - En2	383.3	(400 MHz, DMSO-D_6) δ ppm: 9.19 (s, 1 H), 8.59 - 8.57 (m, 1 H), 7.87 - 7.83 (m, 1 H), 7.57 (d, 1 H), 7.43 (d, 1 H), 7.38 - 7.34 (m, 1 H), 7.25 (s, 1 H), 7.18 (s, 1 H), 6.90 (dd, 1 H), 6.34 (s, 1 H), 5.11 (s, 3 H), 3.93 (dd, 1 H), 3.75 (dd, 1 H), 2.50 (s, 3 H), 1.52 (s, 3 H).
Cpd 015	370.3	(400 MHz, DMSO-D_6) δ ppm: 9.00 (d, 1 H), 8.59 (d, 1 H), 7.87 (t, 1 H), 7.83 (d, 1 H), 7.42 (d, 1 H), 7.34 (t, 1 H), 6.89 - 6.86 (m, 1 H), 6.42 (s, 1 H), 6.30 (s, 1 H), 5.11 (s, 2 H), 4.97 (t, 2 H), 3.65 - 3.61 (m, 2 H), 3.55 - 3.31 (m, 2 H), 2.50 (s, 3 H),1.31 (s, 3 H).
Cpd 016 - En1	395.1	(400 MHz, DMSO-D_6) δ ppm: 9.04 (s, 1 H), 8.56 (d, 1 H), 7.86 (t, 1 H), 7.80 (s, 1 H), 7.57 (d, 1 H), 7.44 (d, 1 H), 7.37 - 7.34 (m, 1 H), 6.92 - 6.89 (m, 2 H), 6.33 (s, 1 H), 5.25 (brs, 1 H), 5.11 (s, 2 H), 3.60 - 3.59 (m, 2 H), 3.31 (s, 1 H), 3.22 - 3.20 (m, 1 H) 2.47 - 2.41 (m, 5 H).
Cpd 016 - En2	395.1	(400 MHz, DMSO-D_6) δ ppm: 9.05 (s, 1 H), 8.59 - 8.57 (m, 1 H), 7.86 (t, 1 H), 7.80 (s, 1 H), 7.57 (d, 1 H), 7.44 (d, 1 H), 7.36 - 7.34 (m, 1 H), 6.92 - 6.89 (m, 2H), 6.33 (s, 1 H), 5.25 (brs, 1 H), 5.11 (s, 2 H), 3.63 - 3.56 (m, 2 H), 3.31 (s, 1 H), 3.24 - 3.20 (m, 1 H) 2.47 - 2.41 (m, 5 H).
Cpd 017 - En1	401.3	(400 MHz, DMSO-D_6) δ ppm: 8.80 (s, 1 H), 8.59–8.57 (m, 1 H), 7.86–7.82 (m, 1 H), 7.55 (d, 1 H), 7.43 (d, 1 H), 7.37–7.31 (m, 2 H), 6.88 (dd, 1 H), 6.31 (s, 1 H), 5.14 (s, 2 H), 4.40–4.33 (m, 1 H), 2.97–2.87 (m, 2 H), 2.67–2.66 (m, 2 H), 2.49 (s, 3 H), 2.09-2.06 (m, 1 H), 1.98–1.81 (m, 1 H).
Cpd 017 - En2	401.3	(400 MHz, DMSO-D_6) δ ppm: 8.80 (s, 1 H), 8.59–8.57 (m, 1 H), 7.86–7.82 (m, 1 H), 7.55 (d, 1 H), 7.43 (d, 1 H), 7.37–7.31 (m, 2 H), 6.88 (dd, 1 H), 6.31 (s, 1 H), 5.14 (s, 2 H), 4.40–4.33 (m, 1 H), 2.97–2.87 (m, 2 H), 2.67–2.66 (m, 2 H), 2.49 (s, 3 H), 2.09-2.06 (m, 1 H), 1.98–1.81 (m, 1 H).
Cpd 018 - En1	353.2	(400 MHz, DMSO-D_6) δ ppm: 9.07 (d, 1 H), 8.56 (d, 1 H) 7.86 - 7.82 (m, 1 H), 7.56 (d, 1 H), 7.49 (bs, 1 H), 7.43 (d, 1 H), 7.37 - 7.34 (m, 1 H), 7.24 (d, 1 H), 7.11 (bs, 1 H), 6.90 - 6.87 (m, 1 H), 6.32 (s, 1 H), 5.11 (s, 2 H), 4.50 - 4.43 (m, 1 H), 2.50 - 2.49 (m, 3 H), 1.36 (s, 3 H),
Cpd 018 - En2	353.2	(400 MHz, DMSO-D_6) δ ppm: 9.07 (d, 1 H), 8.58 (d, 1 H) 7.86 - 7.82 (m, 1 H), 7.56 (d, 1 H), 7.49 (bs, 1 H), 7.43 (d, 1 H), 7.37 - 7.34 (m, 1 H), 7.24 (d, 1 H), 7.10 (bs, 1 H), 6.90 - 6.87 (m, 1 H), 6.32 (s, 1 H), 5.11 (s, 2 H), 4.48 - 4.44 (m, 1 H), 2.50 - 2.49 (m, 3 H), 1.36 (s, 3 H)
Cpd 019 - En1	346.3	(400 MHz, DMSO-D_6) δ ppm: 9.05 (s, 1 H), 7.39 (d, 1 H), 7.37 (brs, 1 H), 7.21 (s, 1 H), 7.16 (s, 1H), 6.79 (dd, 1 H), 6.31 (s, 1 H), 7.10 (s, 1 H), 3.93 - 3.89 (m, 1H), 3.76 - 3.73 (m, 3 H), 2.50 (s, 3 H), 1.51 (s, 3 H), 1.24 - 1.20 (m, 1 H), 0.59 - 0.55 (m, 2 H), 0.37 - 0.33 (m, 2 H).
Cpd 019 - En2	346.3	(400 MHz, DMSO-D_6) δ ppm: 9.05 (s, 1 H), 7.39 (d, 1 H), 7.37 (brs, 1 H), 7.21 (s, 1 H), 7.16 (s, 1H), 6.79 (dd, 1 H), 6.31 (s, 1 H), 5.10 (s, 1 H), 3.91 (d, 1 H), 3.76 - 3.73 (m, 3 H), 2.50 (s, 3 H), 1.51 (s, 3 H), 1.25 - 1.19 (m, 1 H), 0.59 - 0.55 (m, 2 H), 0.37 - 0.33 (m, 2 H).

Cpd 020	333.3	(400 MHz, DMSO-D_6) δ ppm: 8.89 (s, 1 H), 7.37 (d, 1 H), 6.77 (dd, 1 H), 6.28 (s, 1 H), 4.98 (br s, 2 H), 3.76 (d, 2 H), 3.63 (d, 2 H), 3.52 (d, 2 H), 2.43 (s, 3 H), 1.31 (s, 3 H), 1.24 - 1.20 (m, 1 H), 0.59 - 0.57 (m, 2 H), 0.35 - 0.31 (m, 2 H).
Cpd 021 - En1	358.3	(400 MHz, DMSO-D_6) δ ppm: 8.91 (s, 1 H), 7.79 (s, 1 H), 7.40 (d, 1 H), 6.85 (s, 1 H), 6.80 (dd, 1 H), 6.31 (s, 1 H), 5.26 (s, 1 H), 3.76 (dd, 2 H), 3.59 (s, 2 H), 3.27 (s, 1 H), 3.23 - 3.19 (m, 1 H), 2.44 (s, 3 H), 2.42 - 2.40 (m, 2 H), 1.24 - 1.20 (m, 1 H), 0.58 - 0.55 (m, 2 H), 0.37 - 0.34 (m, 2 H).
Cpd 021 - En2	358.3	(400 MHz, DMSO-D_6) δ ppm: 8.91 (s, 1 H), 7.79 (s, 1 H), 7.34 (d, 1 H), 6.85 (s, 1 H), 6.81 - 6.78 (m, 1 H), 6.31 (s, 1 H), 5.27 (brs, 1 H), 3.76 - 3.74 (m, 2 H), 3.62 - 3.56 (m, 2 H), 3.30 - 3.17 (m, 2 H), 2.46 - 2.37 (m, 5 H), 1.24-1.2 (m, 1 H), 0.59 - 0.56 (m, 2 H), 0.39 - 0.31 (m, 2 H).
Cpd 023 - En1	316.3	(400 MHz, DMSO-D_6) δ ppm: 8.94 (s, 1 H), 7.49 (br s, 1 H), 7.39 (d, 1 H), 7.20 (d, 1 H), 7.10 (br s, 1 H), 6.78 (dd, 1 H), 6.29 (s, 1 H), 4.48 - 4.41 (m, 1 H), 3.76 (d, 2 H), 2.49 (s, 3 H), 1.36 (d, 3 H), 1.25 - 1.19 (m, 1 H), 0.59 - 0.55 (m, 2 H), 0.37 - 0.33 (m, 2 H)
Cpd 023 - En2	316.2	(400 MHz, DMSO-D_6) δ ppm: 8.94 (s, 1H), 7.49 (br s, 1H) , 7.39 (d, J = 9.6 Hz, 1H), 7.20 (d, J = 7.6 Hz, 1H), 7.10 (br s, 1H), 6.78 (dd, J1 = 2.0 Hz, J2 = 9.6 Hz, 1H), 6.29 (s, 1H), 4.48 - 4.41 (m, 1H), 3.76 (d, J = 7.2 Hz, 2H), 2.49 (s, 3H), 1.36 (d, J = 6.8 Hz, 3H), 1.25 - 1.19 (m, 1 H), 0.59 - 0.55 (m, 2 H), 0.37 - 0.33 (m, 2 H)
Cpd 025	343.3	(400 MHz, DMSO-D_6) δ ppm: 8.97 (d, 1 H), 7.43 (d, 1 H), 6.82 - 6.85 (dd, 1 H), 6.66 (s, 1 H), 6.24 - 6.53 (tt, 2 H), 4.97 (t, 2 H), 4.23 - 4.31 (dt, 2 H), 3.62 - 3.66 (m, 2 H), 3.54 (t, 2 H), 2.44 (s, 3 H), 1.32 (s, 3 H).
Cpd 027 - En1	374.2	(400 MHz, DMSO-D_6) δ ppm: 8.76 (s, 1 H), 7.44 (d, 1 H), 7.37 (d, 1 H), 6.85 (dd, 1 H), 6.52–6.24 (m, 2 H), 4.41–4.22 (m, 3 H), 2.98–2.87 (m, 2 H), 2.71–2.63 (m, 2 H), 2.45 (s, 3 H), 2.38–2.31 (m, 1 H), 2.12–2.03 (m, 1 H), 1.94–1.86 (m, 1 H).
Cpd 027 - En2	374.3	(400 MHz, DMSO-D_6) δ ppm: 8.76 (s, 1 H), 7.44 (d, 1 H), 7.37 (d, 1 H), 6.84 (dd, 1 H), 6.53–6.24 (m, 2 H), 4.41–4.22 (m, 3 H), 2.98–2.87 (m, 2 H), 2.71–2.63 (m, 2 H), 2.45 (s, 3 H), 2.38–2.31 (m, 1 H), 2.12–2.03 (m, 1 H), 1.94–1.86 (m, 1 H).
Cpd 028 - En1	326.2	(400 MHz, DMSO-D_6) δ ppm: 9.03 (d, 1 H), 7.51 (s, 1 H), 7.44 (d, 1 H), 7.31 (d, 1 H), 7.12 (s, 1 H), 6.84 - 6.87 (dd, 1 H), 6.24 - 6.53 (tt, 2 H), 4.43 - 4.50 (m, 1 H), 4.23 - 4.31 (dt, 2 H), 2.50 (t, 3 H), 1.34 (d, 3 H).
Cpd 028 - En2	326.3	(400 MHz, DMSO-D_6) δ ppm: 9.03 (d, 1 H), 7.51 (s, 1 H), 7.44 (d, 1 H), 7.31 (d, 1 H), 7.12 (s, 1 H), 6.84-6.87 (dd, 1 H), 6.24-6.53 (tt, 2 H), 4.43-4.50 (m, 1 H), 4.23-4.31 (dt, 2 H), 2.50 (t, 3 H), 1.34 (d, 3 H).

Cpd 029 - En1	403.3	(400 MHz, DMSO-D_6) δ ppm: 9.20 (s, 1 H), 7.71 (s, 1 H), 7.42 (d, 1 H), 7.38 (brs, 1 H), 7.25 (s, 1 H), 7.17 (s, 1 H), 6.83 (dd, 1 H), 6.34 (s, 1 H), 5.24 (s, 2 H), 5.16 (brs, 1 H), 3.92 (d, 1 H), 3.75 (d, 1 H), 2.63 (s, 3 H), 2.52 (s, 3 H), 1.52 (s, 3 H).
Cpd 029 - En2	403.2	400 MHz, DMSO-D_6) δ ppm: 9.20 (s, 1H), 7.71 (s, 1H), 7.42 (d, 1H), 7.37 (brs, 1H), 7.25 (s, 1H), 7.17 (s, 1H), 6.83 (dd, 1H), 6.34 (s, 1H), 5.27 (s, 2H), 5.17 (brs, 1H), 3.93 (d, 1H), 3.76 (d, 1H), 2.63 (s, 3H), 2.52 (s, 3H), 1.53 (s, 3H).
Cpd 030	390.3	(400 MHz, DMSO-D_6) δ ppm: 9.01 (d, 1 H), 7.71 (s, 1 H), 7.40 (d, 1 H), 6.79 – 6.82 (dd, 1 H), 6.64 (s, 1 H), 6.30 (s, 1 H), 5.25 (s, 2 H), 4.98 (t, 3 H), 3.62 – 3.66 (m, 2 H), 3.51 – 3.55 (m, 2 H), 2.63 (s, 3 H), 2.44 (s, 3 H), 1.32 (S, 3 H).
Cpd 031	373.1	(400 MHz, DMSO-D_6) δ ppm: 9.09 (d, 1 H), 7.72 (s, 1 H), 7.52 (s, 1 H), 7.42 (d, 1 H), 7.27 (d, 1 H), 7.13 (s, 1 H), 6.83 (dd, 1 H), 6.33 (s, 1 H), 5.26 (s, 2 H), 4.45 – 4.50 (m, 1 H), 2.64 (s, 3 H), 2.51 (s, 3 H), 1.37 (d, 3 H).
Cpd 032 - En1	384.1	(400 MHz, DMSO-D_6) δ ppm: 8.94 (s, 1 H), 8.58 - 8.57 (d, 1 H), 7.88 - 7.83 (m, 1 H), 7.58 - 7.56 (d, 1 H), 7.43 - 7.41 (d, 1 H), 7.36 (t, 1 H), 6.89 - 6.86 (m, 1 H), 6.64 (s, 1 H), 6.31 (s, 1 H), 5.11 (s, 2 H), 5.03 (d, 1 H), 3.65 - 3.60 (m, 2 H), 3.56 - 3.51 (m, 2 H), 3.30 (s, 3 H), 2.42 (s, 3 H) 1.39 (s, 3 H).
Cpd 032 - En2	384.1	(400 MHz, DMSO-D_6) δ ppm: 8.94 (s, 1 H), 8.58 - 8.57(d, 1 H), 7.88 - 7.83 (m, 1 H), 7.58 - 7.56 (d, 1 H), 7.43 - 7.41 (d, 1 H), 7.36 (t, 1 H), 6.89 - 6.86 (m, 1 H), 6.64 (s, 1 H), 6.31 (s, 1H), 5.11 (s, 2 H), 5.03 (d, 1 H), 3.65 - 3.60 (m, 2 H), 3.56 - 3.51 (m, 2 H), 3.30 (s, 3 H), 2.42 (s, 3 H) 1.39 (s, 3 H).
Cpd 033 - En1	369.2	(400 MHz, DMSO-D_6) δ ppm: 9.17 (s, 1 H), 8.59 (d, 1 H) 7.86 - 7.84 (m, 1 H), 7.56 (d, 1 H), 7.48 - 7.43 (m, 2 H), 7.37 - 7.34 (m, 1 H), 7.17 (s, 1 H), 7.06 (d, 1 H), 6.92 - 6.89 (dd, 1 H), 6.35 (s, 1 H), 5.12 (s, 2 H), 5.01 (t, 1 H), 4.47 - 4.43 (m, 1 H), 3.79 - 3.70 (m, 2 H), 2.52 (s, 3 H).
Cpd 033 - En2	369.1	(400 MHz, DMSO-D_6) δ ppm: 9.17 (d, 1 H), 8.59 - 8.57 (dd, 1 H) 7.86 - 7.82 (m, 1 H), 7.56- (d, 1 H), 7.48 - 7.43 (m, 2 H), 7.37 - 7.35 (m, 1 H), 7.17 (bs, 1 H), 7.06 (d, 1 H), 6.92 - 6.89 (dd, 1 H), 6.35 (s, 1 H), 5.12 (s, 2 H), 5.01 (t, 1 H), 4.47 - 4.43 (m, 1 H), 3.80 - 3.69 (m, 2H), 2.52 (s, 3H)
Cpd 034 - En1	368.2	(400 MHz, DMSO-D_6) δ ppm: 9.19 (s, 1H), 7.48 (d, 3 H),7.32-7.47 (m, 4 H), 7.17 (s, 1 H), 7.06 (d, 1 H), 6.85 – 6.88 (dd, 1 H), 6.34 (s, 1 H), 5.04 (s, 3 H), 4.43 - 4.48 (m, 1 H), 3.70 - 3.80 (m, 2 H), 2.49 - 2.52 (s, 3 H).
Cpd 034 - En2	368.3	(400 MHz, DMSO-D_6) δ ppm: 9.19 (s, 1H), 7.48 (d, 3 H),7.32-7.47 (m, 4 H), 7.17 (s, 1 H), 7.06 (d, 1 H), 6.85 – 6.88 (dd, 1 H), 6.34 (s, 1 H), 5.04 (s, 3 H), 4.43-4.48 (m, 1 H), 3.70-3.80 (m, 2 H), 2.49-2.52 (s, 3 H).

Cpd 035 - En1	403.2	(400 MHz, DMSO-D_6) δ ppm: 8.90 (d, 1 H), 7.49–7.41 (m, 2 H), 7.39–7.32 (m, 4 H), 6.84–6.81 (m, 2 H), 6.37–6.07 (m, 2 H), 5.21 (t, 1 H), 5.04 (s, 2 H), 3.64–3.54 (m, 2 H), 2.68–2.56 (m, 1 H), 2.42 (s, 3 H), 2.40–2.29 (m, 1 H), 1.39 (s, 3 H).
Cpd 035 - En2	403.3	(400 MHz, DMSO-D_6) δ ppm: 8.90 (d, 1 H), 7.49–7.41 (m, 2 H), 7.39–7.32 (m, 4 H), 6.84–6.81 (m, 2 H), 6.37–6.07 (m, 2 H), 5.21 (brs, 1 H), 5.04 (s, 2 H), 3.63–3.54 (m, 2 H), 2.68–2.56 (m, 1 H), 2.42 (s, 3 H), 2.40–2.29 (m, 1 H), 1.39 (s, 3 H)
Cpd 036 - En1	404.3	(400 MHz, DMSO-D_6) δ ppm: 8.86 (d, 1 H), 8.58–8.56 (m, 1 H), 7.84 (td, 1 H), 7.56 (d, 1 H), 7.41 (d, 1 H), 7.37–7.33 (m, 1 H), 6.87 (dd, 1 H), 6.83 (s, 1H), 6.36–6.07 (m, 2 H), 5.20 (brs, 1 H), 5.11 (s, 2 H), 3.63–6.54 (m, 2 H), 2.57–2.50 (m, 1 H), 2.42 (s, 3 H), 2.38–2.32 (m, 1 H), 1.38 (s, 3 H).
Cpd 036 - En2	404.3	(400 MHz, DMSO-D_6) δ ppm: 8.86 (d, 1 H), 8.58–8.56 (m, 1 H), 7.84 (td, 1 H), 7.56 (d, 1 H), 7.41 (d, 1 H), 7.37–7.33 (m, 1 H), 6.87 (dd, 1 H), 6.83 (s, 1H), 6.36–6.07 (m, 2 H), 5.20 (brs, 1 H), 5.11 (s, 2 H), 3.63–6.54 (m, 2 H), 2.57–2.50 (m, 1 H), 2.42 (s, 3 H), 2.38–2.32 (m, 1 H), 1.38 (s, 3 H).
Cpd 037 - En1	395.2	(400 MHz, DMSO-D_6) δ ppm: 9.10 (d, 1 H), 8.70 (d, 1 H), 8.55 (dd, 1 H), 7.93-7.90 (m, 1 H), 7.81 (s, 1 H), 7.45-7.42 (m, 2 H), 6.89-6.86 (m, 2 H), 6.34 (s, 1 H), 5.28 (br s, 1 H), 5.09 (s, 2H), 3.63-3.57 (m, 2H), 3.29-3.20 (m, 2 H), 2.47 (s, 3 H), 2.44-2.41 (m, 2 H)
Cpd 037 - En2	395.3	(400 MHz, DMSO-D_6) δ ppm: 9.09 (d, 1 H), 8.70 (d, 1 H), 8.56-8.55 (m, 1H), 7.93-7.90 (m, 1 H), 7.80 (s, 1 H), 7.45-7.42 (m, 2 H), 6.89-6.86 (m, 2 H), 6.34 (s, 1 H), 5.28 (t, 1 H), 5.09 (s, 2 H), 3.64 - 3.56 (m, 2 H), 3.26-3.18 (m, 2 H), 2.49-2.42(m, 5 H).
Cpd 038 - En1	425.3	(400 MHz, DMSO-D_6) δ ppm: 9.06 (d, 1 H), 8.16 (dd, 1 H), 7.85 (dd, 1 H), 7.81 (s, 1 H), 7.43 (d, 1 H), 7.05-7.02 (m, 1 H), 6.88 - 6.85 (m, 2 H), 6.33 (s, 1 H), 5.26 (t, 1 H), 4.99 (s, 2 H), 3.94 (s, 3 H), 3.62-3.56 (m, 2 H), 3.31 (s, 1 H), 3.24-3.18 (m, 1 H) 2.67 (s, 3 H) 2.47-2.42 (m, 2H)
Cpd 038 - En2	425.2	(400 MHz, DMSO-D_6) δ ppm: 9.06 (d, 1 H), 8.16 (dd, 1 H), 7.85 (dd, 1 H), 7.81 (s, 1 H), 7.43 (d, 1 H), 7.05-7.02 (m, 1 H), 6.87-6.85 (m, 2 H), 6.33 (s, 1 H), 5.26 (t, 1 H), 4.99 (s, 2 H), 3.94 (s, 3 H), 3.62-3.56 (m, 2 H), 3.31 (s, 1 H), 3.24-3.18 (m, 1 H) 2.47 (s, 3 H) 2.43-2.39 (s, 2 H).
Cpd 039 - En1	463.2	(400 MHz, DMSO-D_6) δ ppm: 9.07 (s, 1 H), 8.75 (d, 1 H), 8.27 (d, 1 H), 7.80–7.70 (m, 2 H), 7.45 (d, 1 H), 6.90 (s, 1 H), 6.87 (dd, 1H), 6.35 (s, 1 H), 5.26–5.23 (m, 3 H), 3.60 (t, 2 H), 3.31–3.28 (m, 1 H), 3.24–3.18 (m, 1 H) 2.49 (s, 3 H), 2.47–2.41 (m, 2 H).
Cpd 039 - En2	463.2	(400 MHz, DMSO-D_6) δ ppm: 9.07 (s, 1 H), 8.75 (d, 1 H), 8.27 (d, 1 H), 7.80–7.70 (m, 2 H), 7.45 (d, 1 H), 6.90 (s, 1 H), 6.87 (dd, 1H), 6.35 (s, 1 H), 5.25–5.23 (m, 3 H), 3.60–3.57(m, 2 H), 3.31–3.28 (m, 1 H), 3.24–3.18 (m, 1 H) 2.49 (s, 3 H), 2.47–2.41 (m, 2 H).

Cpd 040 - En1	416.2	(400 MHz, DMSO-D_6) δ ppm: 9.06 (s, 1 H), 7.80 (s, 1 H), 7.47–7.43 (m, 2 H), 6.9 (s, 1 H), 6.86 (dd, 1 H), 6.34 (s, 1 H), 5.25 (brs, 1 H), 5.11 (s, 2 H), 3.83 (s, 3 H), 3.63-3.57 (m, 2 H), 3.31 (m, 1 H), 3.26 (m, 1 H), 2.49 (s, 3 H), 2.47–2.41 (m, 2 H).
Cpd 040 - En2	416.2	(400 MHz, DMSO-D_6) δ ppm: 9.06 (s, 1 H), 7.80 (s, 1 H), 7.47–7.43 (m, 2 H), 6.9 (s, 1 H), 6.86 (dd, 1 H), 6.34 (s, 1 H), 5.25 (t, 1 H), 5.11 (s, 2 H), 3.83 (s, 3 H), 3.63-3.56 (m, 2 H), 3.31–3.29 (m, 1 H), 3.26–3.20 (m, 1 H), 2.49 (s, 3 H), 2.47–2.41 (m, 2 H).
Cpd 041 - En1	409.2	(400 MHz, DMSO-D_6) δ ppm: 8.84 (dd, 2 H), 8.68 - 8.64 (m, 2 H), 7.43 (d, 1 H), 7.25 (d, 1 H), 6.89 (dd, 1 H), 6.30 (s, 1 H), 5.23 (s, 2 H), 5.09 (t, 1 H), 4.37 - 4.33 (m, 1 H), 3.58 - 3.53 (m, 1 H), 3.44 - 3.38 (m, 1 H), 2.67 - 2.60 (m, 2 H), 2.43 (s, 3 H).
Cpd 041 - En2	409.2	(400 MHz, DMSO-D_6) δ ppm: 8.84 (dd, 2 H), 8.68 - 8.64 (m, 2 H), 7.43 (d, 1 H), 7.26 (d, 1 H), 6.89 (dd, 1 H), 6.31 (s, 1 H), 5.23 (s, 2 H), 5.10 (t, 1 H), 4.37 - 4.33 (m, 1 H), 3.57 - 3.53 (m, 1 H), 3.44 - 3.38 (m, 1 H), 2.67 - 2.59(m, 2 H), 2.43 (s, 3 H).
Cpd 042 - En1	408.3	(400 MHz, DMSO-D_6) δ ppm: 8.89 (s, 1 H), 8.69 (s, 1 H), 8.56–8.54 (m, 1 H), 7.90 (d, 1 H), 7.45–7.40 (m, 2 H), 7.23 (d, 1 H), 6.85 (dd, 1 H), 6.30 (s, 1 H), 5.09 (s, 3 H), 4.37–4.35 (m, 1 H), 3.58–3.54 (m, 1 H), 3.44–3.39 (m, 1 H), 2.67–2.58 (m, 2 H), 2.44 (s, 3 H).
Cpd 042 - En2	408.3	(400 MHz, DMSO-D_6) δ ppm: 8.89 (s, 1 H), 8.69 (s, 1 H), 8.56–8.54 (m, 1 H), 7.90 (d, 1 H), 7.45–7.40 (m, 2 H), 7.23 (d, 1 H), 6.85 (dd, 1 H), 6.30 (s, 1 H), 5.09 (s, 3 H), 4.37–4.35 (m, 1 H), 3.58–3.54 (m, 1 H), 3.44–3.39 (m, 1 H), 2.67–2.58 (m, 2 H), 2.44 (s, 3 H).
Cpd 043 - En1	438.2	(400 MHz, DMSO-D_6) δ ppm: 8.84 (d, 1 H), 8.16 (dd, 1 H), 7.83 (dd, 1 H), 7.42 (d, 1 H), 7.24 (d, 1 H), 7.04-7.01 (m, 1 H), 6.83 (dd, 1 H), 6.28 (s, 1 H), 5.09 (bs, 1 H), 4.99 (s, 2 H), 4.38-4.34 (bs, 1 H), 3.93 (s, 3 H), 3.58-3.54 (m, 1 H), 3.43-3.39 (m, 1 H), 2.67-2.59 (m, 2 H), 2.50 (s, 3 H).
Cpd 043 - En2	438.2	(400 MHz, DMSO-D_6) δ ppm: 8.84 (d, 1 H), 8.16 (dd, 1 H), 7.83 (dd, 1 H), 7.40 (d, 1 H), 7.24 (d, 1 H), 7.04-7.01 (m, 1 H), 6.84 (dd, 1 H), 6.29 (s, 1 H), 5.10 (bs, 1 H), 4.99 (s, 2 H), 4.36 (bs, 1 H), 3.96 (s, 3 H), 3.58-3.54 (m, 1 H), 3.43-3.39 (m, 1 H), 2.67-2.59 (m, 2 H), 2.50(s, 3 H).
Cpd 044 - En1	476.2	(400 MHz, DMSO-D_6) δ ppm: 8.83 (s, 1 H), 8.74 (d, 1 H), 8.26 (d, 1 H), 7.80–7.73 (m, 1 H), 7.43 (d, 1 H), 7.27 (d, 1 H), 6.85 (dd, 1 H), 6.31 (s, 1 H), 5.23 (s, 2 H), 5.09 (brs, 1 H), 4.37–4.33 (m, 1 H), 3.57–3.54 (m, 1 H), 3.41–3.38 (m, 1 H), 2.67–2.56 (m, 2 H), 2.43 (s, 3 H).
Cpd 044 - En2	476.2	(400 MHz, DMSO-D_6) δ ppm: 8.83 (s, 1 H), 8.74 (d, 1 H), 8.26 (d, 1 H), 7.80–7.7 (m, 1 H), 7.43 (d, 1 H), 7.27 (d, 1 H), 6.85 (dd, 1 H), 6.31 (s, 1 H), 5.23 (s, 2 H), 5.09 (brs, 1 H), 4.37–4.35 (m, 1 H), 3.56–3.54 (m, 1 H), 3.42–3.38 (m, 1 H), 2.67–2.57 (m, 2 H), 2.43 (s, 3 H).

Cpd 045 - En1	429.2	(400 MHz, DMSO-D_6) δ ppm: 8.85 (d, 1 H), 7.45 (d, 1 H), 7.42 (d, 1 H), 7.28 (d, 1 H), 6.83 (dd, 1 H), 6.31 (s, 1 H), 5.14–5.11 (m, 3 H), 4.37–4.33 (m, 1 H), 3.83 (s, 3 H), 3.59–3.53 (m, 1 H), 3.44–3.39 (m, 1 H), 2.67–2.60 (m, 2 H), 2.43 (s, 3 H)
Cpd 045 - En2	429.2	(400 MHz, DMSO-D_6) δ ppm: 8.85 (d, 1 H), 7.45 (d, 1 H), 7.42 (d, 1 H), 7.28 (d, 1 H), 6.83 (dd, 1 H), 6.31 (s, 1 H), 5.14–5.11 (m, 3 H), 4.37–4.33 (m, 1 H), 3.83 (s, 3 H), 3.59–3.53 (m, 1 H), 3.44–3.39 (m, 1 H), 2.67–2.60 (m, 2 H), 2.43 (s, 3 H).
Cpd 046 - En1	396.2	(400 MHz, DMSO-D_6) δ ppm: 9.08 (d, 1 H), 8.85 (d, 1 H), 8.69-8.68 (m, 1 H), 8.64 (d, 1 H), 7.80 (s, 1 H), 7.45 (d, 1 H), 6.93-6.90 (m, 2 H), 6.34 (s, 1 H), 5.25 (t, 1 H), 5.20 (s, 2 H), 3.61-3.59 (m, 2 H), 3.31-3.20 (m, 2 H), 2.46-2.42 (m, 5 H).
Cpd 046 - En2	396.2	(400 MHz, DMSO-D_6) δ ppm: 9.07 (d, 1 H), 8.85 (d, 1 H), 8.69-8.64 (m, 2 H), 7.81 (s, 1 H), 7.45 (d, 1 H), 6.93-6.90 (m, 2 H), 6.34 (s, 1 H), 5.25 (t, 1 H), 5.20 (s, 2 H), 3.64-3.56 (m, 2 H), 3.24 - 3.18 (m, 2 H), 2.49-2.41 (m, 5 H).

[0306] *Chiral analytical data*

Chiral SFC						
Cpd code	Column Name	co-solvent	co-solvent %	Flow [g/min]	RT [min]	*Purity [%]*
Cpd 005 - En1	C5	MeOH	30	3	9.05	99.9
Cpd 005 - En2	C5	MeOH	30	3	12.17	98
Cpd 007 - En1	C9	0.5%DEA in MeOH	25	3	4.46	99.8
Cpd 007 - En2	C9	0.5%DEA in MeOH	25	3	5.41	99.9
Cpd 014 - En1	C3	0.5%DEA in MeOH	40	3	5.52	98.6
Cpd 014 - En2	C3	0.5%DEA in MeOH	40	3	6.32	98.3
Cpd 016 - En1	C2	0.5%DEA in MeOH	40	3	7	99.9
Cpd 016 - En2	C2	0.5%DEA in MeOH	40	3	5.77	99.9
Cpd 017 - En1	C1	0.5%IPAmine in IPA	35	3	4.14	92.5
Cpd 017 - En2	C1	0.5%IPAmine in IPA	35	3	6.4	98.8
Cpd 018 - En1	C2	MeOH	40	3	4.83	99.9

Cpd 018 - En2	C2	MeOH	40	3	5.71	99.7
Cpd 019 - En1	C1	0.5%DEA in MeOH	30	3	4.01	98.4
Cpd 019 - En2	C1	0.5%DEA in MeOH	30	3	3.12	99.9
Cpd 021 - En1	C9	0.5%DEA in MeOH	30	3	2.62	99.7
Cpd 021 - En2	C9	0.5%DEA in MeOH	30	3	3.07	99.9
Cpd 023 - En1	C2	MeOH	30	3	4.99	99.9
Cpd 023 - En2	C2	MeOH	30	3	6.27	99.8
Cpd 027 - En1	C12	IPA	25	3	3.7	99.5
Cpd 027 - En2	C12	IPA	25	3	5.25	98.1
Cpd 028 - En1	C8	0.5%DEA in EtOH	10	3	3.25	99.7
Cpd 028 - En2	C8	0.5%DEA in EtOH	10	3	5.04	99.9
Cpd 029 - En1	C6	0.5%DEA in MeOH	40	3	13.19	99.5
Cpd 029 - En2	C9	0.5%DEA in MeOH	40	3	5.42	99.1
Cpd 032 - En1	C1	MeOH	30	3	3.3	99.9
Cpd 032 - En2	C1	MeOH	30	3	6.42	99.6
Cpd 033 - En1	C4	MeOH	25	3	6.59	99.9
Cpd 033 - En2	C4	MeOH	25	3	5.12	96.6
Cpd 034 - En1	C2	0.5%DEA in MeOH	35	3	2.98	99.7
Cpd 034 - En2	C2	0.5%DEA in MeOH	35	3	3.45	95.8
Cpd 035 - En1	C6	MeOH	30	3	3.34	99.9
Cpd 035 - En2	C6	MeOH	30	3	6.4	99.9
Cpd 036 - En1	C12	MeOH	30	3	7.44	99.6
Cpd 036 - En2	C12	MeOH	30	3	11.97	99.7
Cpd 037 - En1	C9	0.5%DEA in MeOH	40	3	4.15	99.9

Cpd 037 - En2	C9	0.5%DEA in MeOH	40	3	3.17	99.4
Cpd 038 - En1	C13	0.5%DEA in MeOH	40	3	4.25	9.9
Cpd 038 - En2	C13	0.5%DEA in MeOH	40	3	7.27	99.9
Cpd 039 - En1	C1	0.5%DEA in MeOH	40	3	3.38	99.8
Cpd 039 - En2	C1	0.5%DEA in MeOH	40	3	5.41	99.9
Cpd 040 - En1	C3	0.5%DEA in MeOH	30	3	8.21	99.9
Cpd 040 - En2	C3	0.5%DEA in MeOH	30	3	11.05	99.9
Cpd 041 - En1	C11	0.5%IPAmine in IPA	10	3	3.49	99.7
Cpd 041 - En2	C11	0.5%IPAmine in IPA	10	3	4.33	98.3
Cpd 042 - En1	C6	MeOH	40	3	2.54	99.9
Cpd 042 - En2	C6	MeOH	40	3	3.66	99.7
Cpd 043 - En1	C12	MeOH	30	3	1.75	99.9
Cpd 043 - En2	C12	MeOH	30	3	2.77	99.9
Cpd 044 - En1	C10	0.5%IPAmine in IPA	15	3	2.26	99.9
Cpd 044 - En2	C10	0.5%IPAmine in IPA	15	3	5.5	99.5
Cpd 045 - En1	C12	MeOH	30	3	2.35	99.9
Cpd 045 - En2	C12	MeOH	30	3	3.06	99.8
Cpd 046 - En1	C8	0.5%DEA in MeOH	20	3	1.59	99.8
Cpd 046 - En2	C7	0.5%DEA in MeOH	30	3	3.07	99.1

[0307] *Chiralpak AD-H(4.6*250 mm)5 μm = C1; Chiralpak IC (4.6*250mm)5μm = C2; Chiralpak IE-3(4.6*150mm)3μm = C3, Chiralpak IF-3(4.6*150mm)3μm = C4; Chiralpak IF (4.6*250mm)5μm = C5; Chiralpak IG-3(4.6*150 mm)3μm = C6; ChiralCel OD-3(4.6*150mm)3μm = C7; ChiralCel OJ-H(4.6*250mm)5μm = C8; (R,R) WHELK-01 (4.6*150mm)3.5μm = C9; Chiralpak IK (4.6*250mm)5μm = C10, Chiralpak AS-3 (4.6*150mm)3μm = C11; Chiralpak IG (4.6*250mm)5μm = C12; LUX AMYLOSE-2 (4.6*250mm)5μm = C13*

[0308] **Part B**

[0309] **Monitoring the TRPM3 ion channel driven Ca2+ uptake.**

[0310] 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.

[0311] 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.

[0312] 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.

[0313] Channel inhibition was calculated compared to a non-PS stimulated control versus a condition stimulated with PS (50μM) with vehicle. The ability of a 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.

[0314] The activities of the Example compounds **cpd 001-004** tested are depicted in the table below. 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.

Cpd Code	IC50
Cpd 001	B
Cpd 002	A
Cpd 003	A
Cpd 004	A

Cpd code	IC50
Cpd 005 - En1	A
Cpd 005 - En2	A
Cpd 006	A
Cpd 007 - En1	A
Cpd 007 - En2	B
Cpd 008	B

Cpd code	IC50
Cpd 023 - En2	B
Cpd 025	B
Cpd 027 - En1	B
Cpd 027 - En2	C
Cpd 028 - En1	C
Cpd 028 - En2	C

Cpd code	IC50
Cpd 037 - En2	B
Cpd 038 - En1	A
Cpd 038 - En2	B
Cpd 039 - En1	A
Cpd 039 - En2	B
Cpd 040 - En1	A

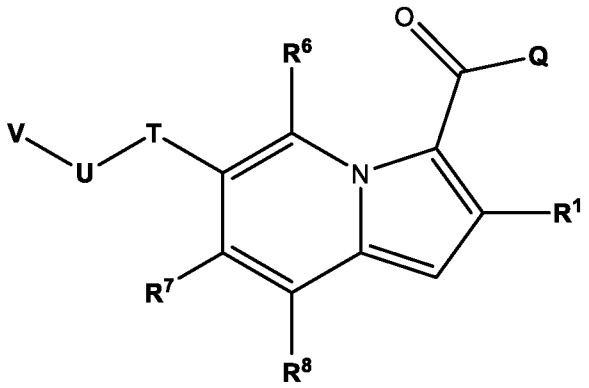
Cpd 014 - En1	A
Cpd 014 - En2	B
Cpd 015	A
Cpd 016 - En1	A
Cpd 016 - En2	B
Cpd 017 - En1	B
Cpd 017 - En2	C
Cpd 018 - En1	B
Cpd 018 - En2	B
Cpd 019 - En1	A
Cpd 019 - En2	B
Cpd 020	A
Cpd 021 - En1	A
Cpd 021 - En2	B
Cpd 023 - En1	B

Cpd 029 - En1	A
Cpd 029 - En2	B
Cpd 030	A
Cpd 031	B
Cpd 032 - En1	B
Cpd 032 - En2	A
Cpd 033 - En1	B
Cpd 033 - En2	A
Cpd 034 - En1	A
Cpd 034 - En2	A
Cpd 035 - En1	A
Cpd 035 - En2	B
Cpd 036 - En1	A
Cpd 036 - En2	B
Cpd 037 - En1	A

Cpd 040 - En2	B
Cpd 041 - En1	B
Cpd 041 - En2	C
Cpd 042 - En1	A
Cpd 042 - En2	B
Cpd 043 - En1	A
Cpd 043 - En2	C
Cpd 044 - En1	C
Cpd 044 - En2	A
Cpd 045 - En1	B
Cpd 045 - En2	C
Cpd 046 - En1	A
Cpd 046 - En2	C

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 **R^3** represents -H.

3. . The compound of claim 2, wherein **R^4** represents a residue other than -H.

4. The compound of any one of claims 1 to 3, wherein **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**R^{5}R$^{5'}$**-.

6. The compound of any one of claims 1 to 5, wherein the **R^Y** representing each of **R^5** and **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$\mathbf{R}^{Y}\mathbf{R}^{Z}$.

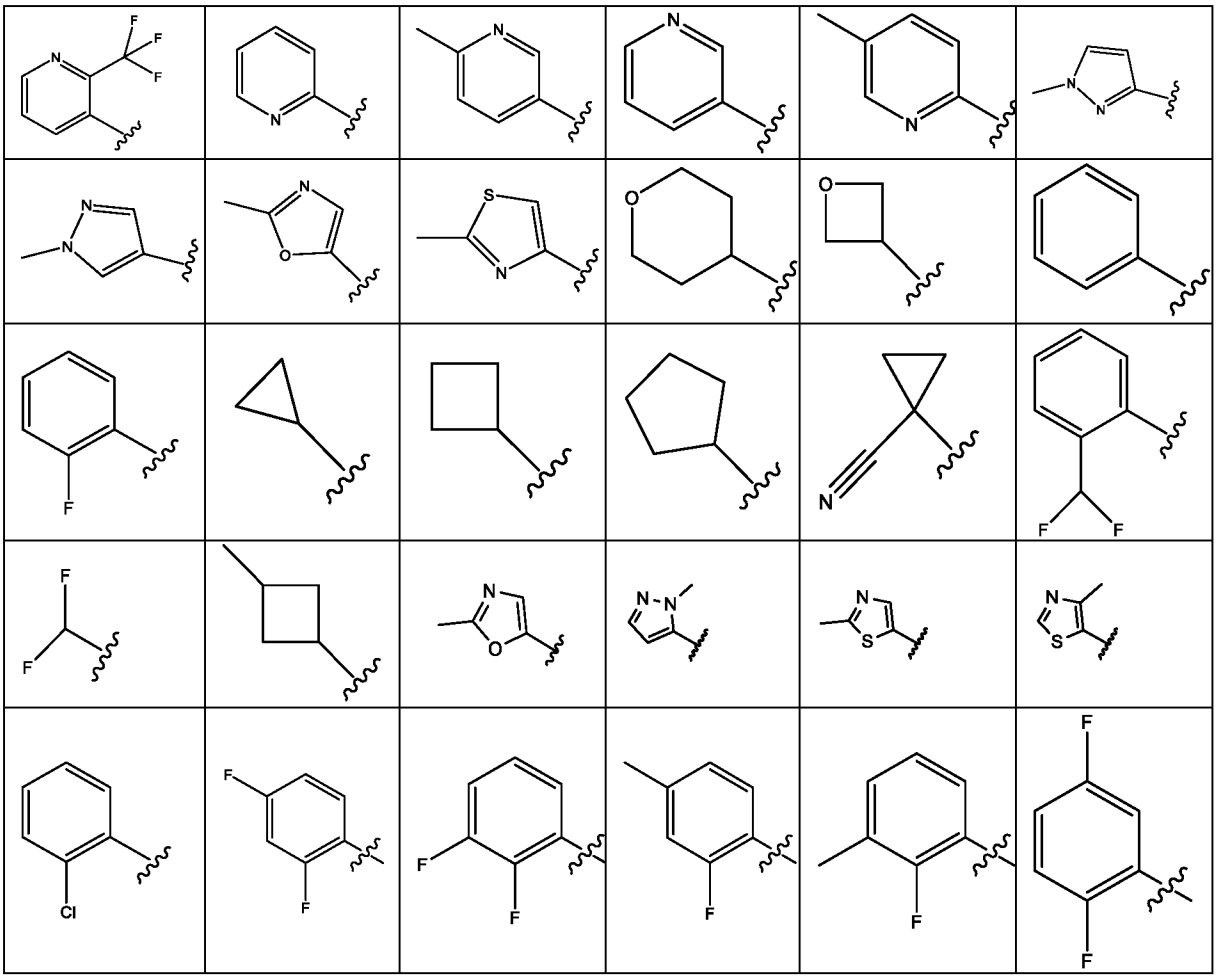
9. The compound of any one of claims 1 to 6 wherein the 5-14-membered aryl within the definition of **V** is phenyl or another 5-14-membered aryl, unsubstituted, mono- or polysubstituted with substituents independently of one another selected from -F, -Cl, -Br, -I, CF_3, -CF_2H, C_1-C_6 alkyl, -CN, -NO, -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$\mathbf{R}^{Y}\mathbf{R}^{Z}$.

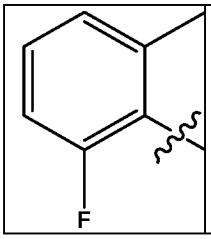
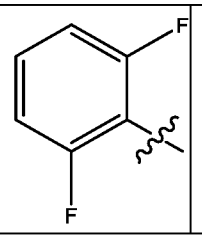
10. The compound of any one of claims 1 to 6 wherein the 3-14-membered heterocycloalkyl within the definition of **V** is selected from azepane, 1,4-oxazepane, azetane, azetidine, aziridine, azocane, diazepane, dioxane, dioxolane, dithiane, dithiolane, imidazolidine, isothiazolidine, isoxalidine, morpholine, 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, $-SF_5$, $-\mathbf{R}^Y$, $-O\mathbf{R}^Y$, $-OC(=O)\mathbf{R}^Y$, $-N\mathbf{R}^Y\mathbf{R}^Z$, $-N\mathbf{R}^YC(=O)\mathbf{R}^Z$, $-S\mathbf{R}^Y$, $-S(=O)\mathbf{R}^Y$, $-S(=O)_2\mathbf{R}^Y$, $-C(=O)\mathbf{R}^Y$, $-C(=O)O\mathbf{R}^Y$, or $-C(=O)N\mathbf{R}^Y\mathbf{R}^Z$.

11. The compound 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, $-SF_5$, $-\mathbf{R}^Y$, $-O\mathbf{R}^Y$, $-OC(=O)\mathbf{R}^Y$, $-N\mathbf{R}^Y\mathbf{R}^Z$, $-N\mathbf{R}^YC(=O)\mathbf{R}^Z$, $-S\mathbf{R}^Y$, $-S(=O)\mathbf{R}^Y$, $-S(=O)_2\mathbf{R}^Y$, $-C(=O)\mathbf{R}^Y$, $-C(=O)O\mathbf{R}^Y$, or $-C(=O)N\mathbf{R}^Y\mathbf{R}^Z$.

12. The compound of any one of claims 1 to 6 wherein **V** is a residue selected from the group consisting of:



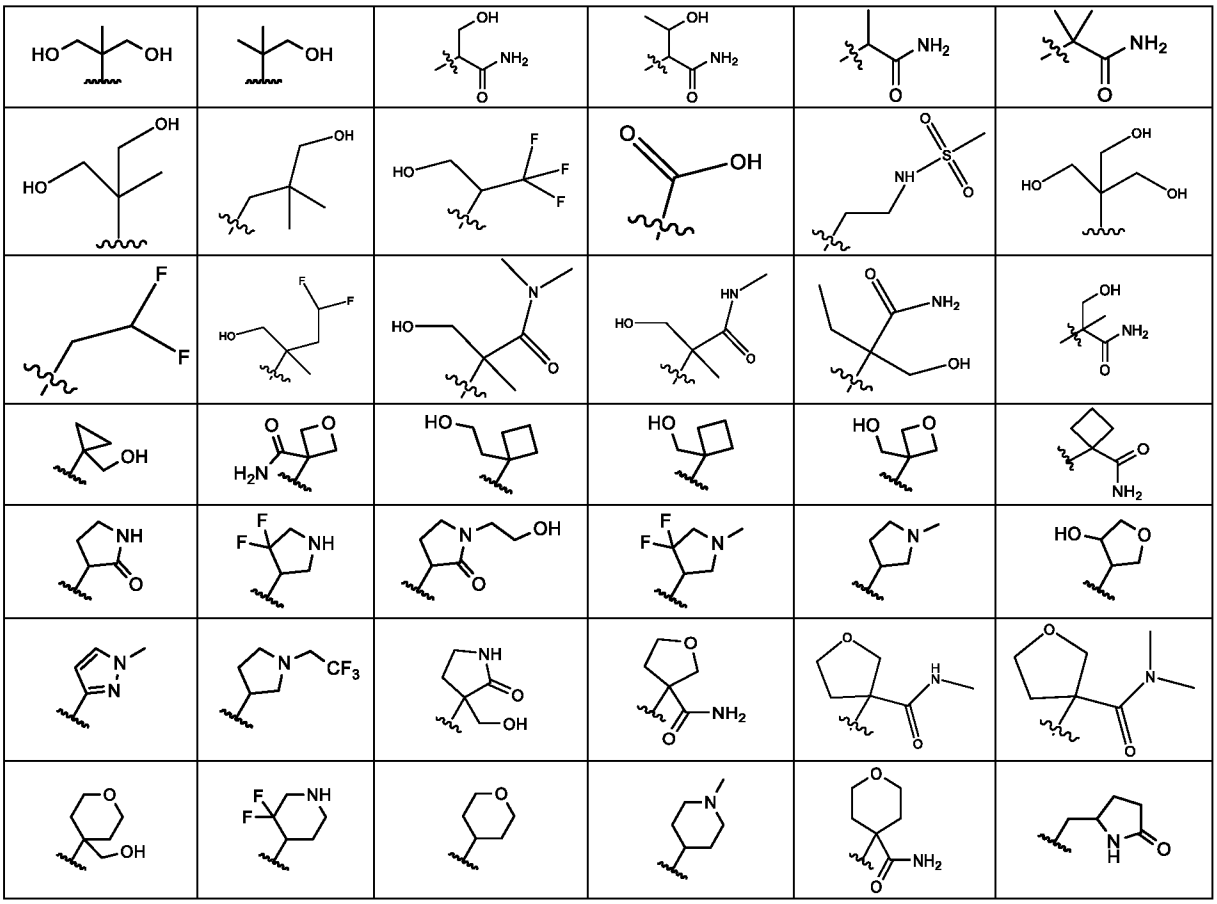
13. The compound according to claim 1 , wherein $\mathbf{R^1}$ represents -H, -F, -Cl, -Br, -I, -C_{1-6}-alkyl, -O-C_{1-6}-alkyl, -C_{1-6}-alkylene-O-C_{1-6}-alkyl, -C_{1-6}-alkylene-NH(C_{1-6}-alkyl), -C_{1-6}-alkylene-N(C_{1-6}-alkyl)$_2$, -CF_3, -CF_2H, -CFH_2, -CF_2Cl, -$CFCl_2$, -C_{1-6}-alkylene-CF_3, -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.

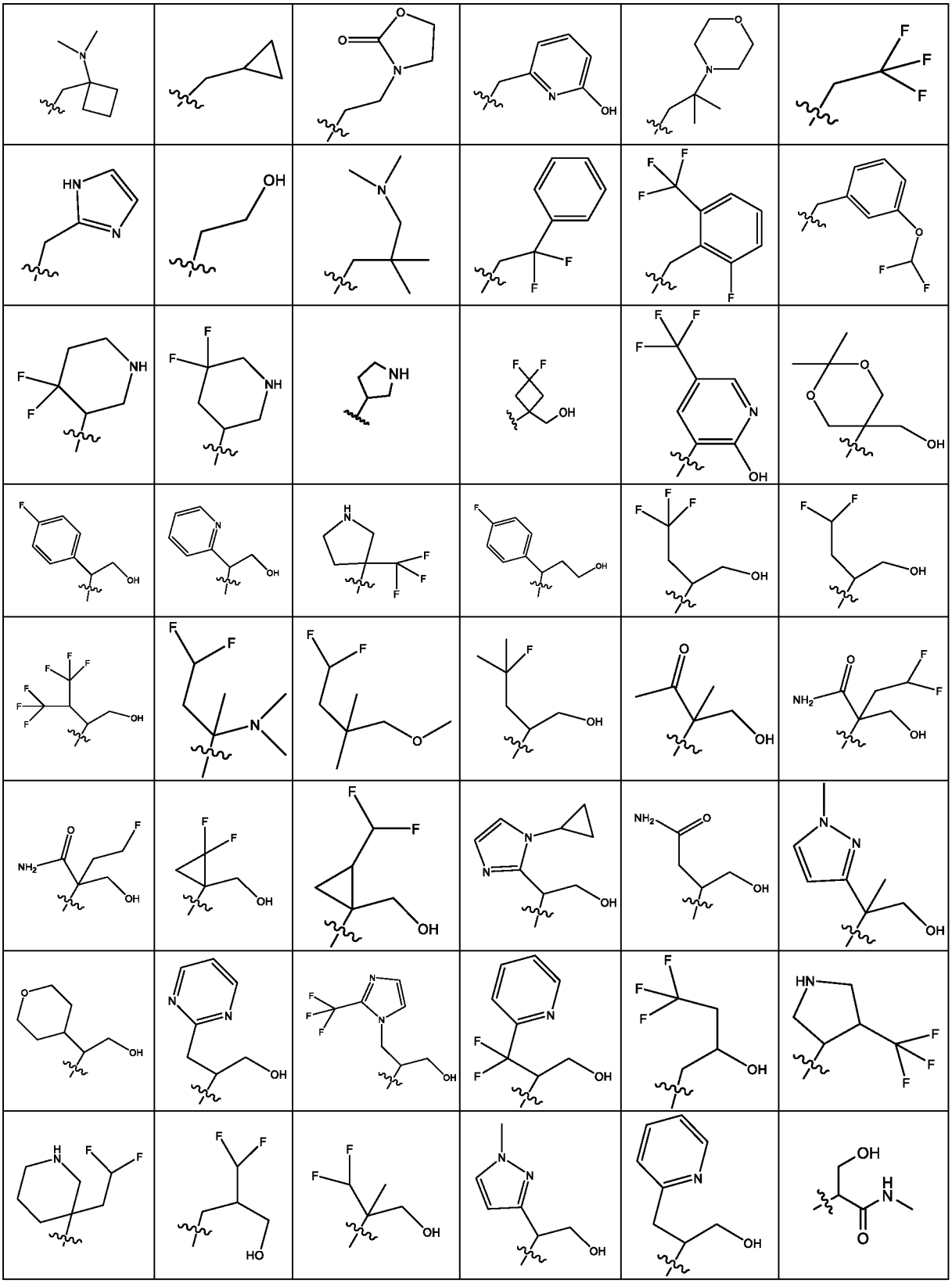
14. The compound according to claim 1 , wherein $\mathbf{R^3}$ represents -H, -OH, -C_{1-6}-alkyl, -C_{1-6}-alkylene-OH, -C_{1-6}-alkylene-O-C_{1-6}-alkyl, -C_{1-6}-alkylene-NH_2, -C_{1-6}-alkylene-NH(C_{1-6}-alkyl), -C_{1-6}-alkylene-N(C_{1-6}-alkyl)$_2$, -CF_3, -CF_2H, -CFH_2, -CF_2Cl, -$CFCl_2$, -C_{1-6}-alkylene-CF_3, -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.

15. The compound according to any one of claims 1 to 14, wherein $\mathbf{R^4}$ 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:





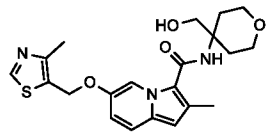
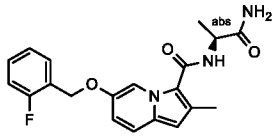
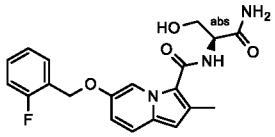
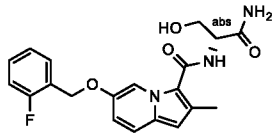
18. The compound of claim 1 wherein R^3 and R^4 together form a heterocycle selected from the group consisting of pyrrolidine, piperidine, morpholine, and piperazine, in each case

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.

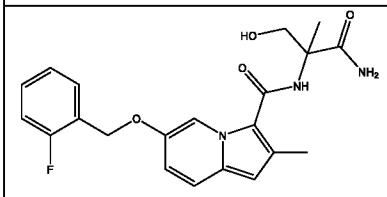
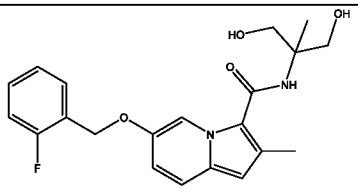
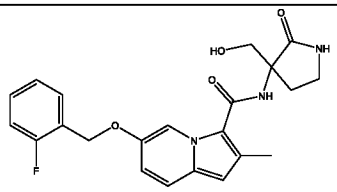
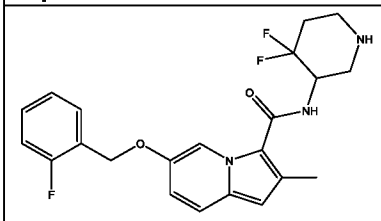
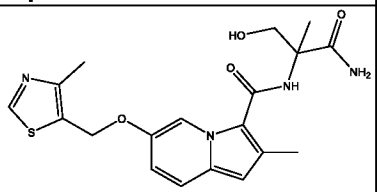
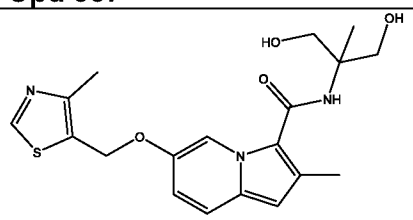
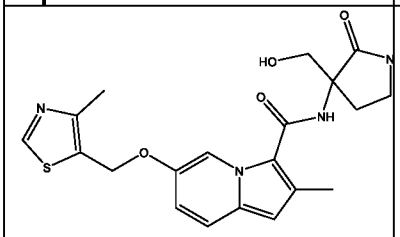
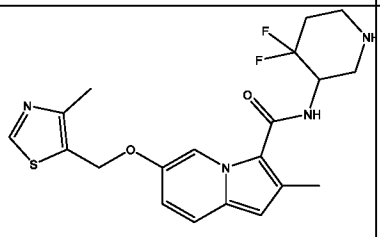
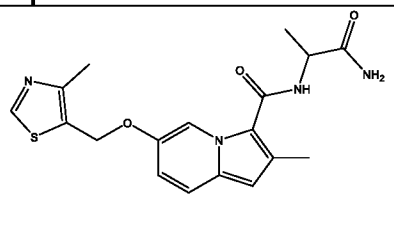
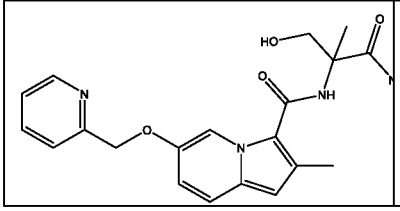
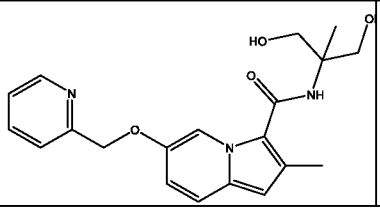
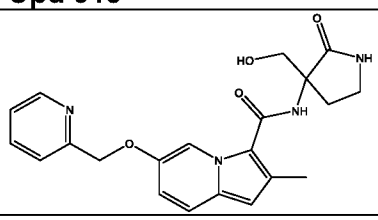
19. The compound of claim 1, wherein **R^5** and **$R^{5'}$** independently of one another represent
-H;
-C_1-C_6-alkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted;
-C_1-C_6-heteroalkyl, saturated or unsaturated, unsubstituted, mono- or polysubstituted;
3-14-membered cycloalkyl, 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 – 004 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**		

22. The compound of claim 1, which is selected from the group consisting of compounds 005 – 046 as shown in the table below:

Structure and **Compound CODE**	Structure and **Compound CODE**	Structure and **Compound CODE**
 **Cpd 005**	 **Cpd 006**	 **Cpd 007**
 **Cpd 008**	 **Cpd 009**	 **Cpd 010**
 **Cpd 011**	 **Cpd 012**	 **Cpd 013**
		

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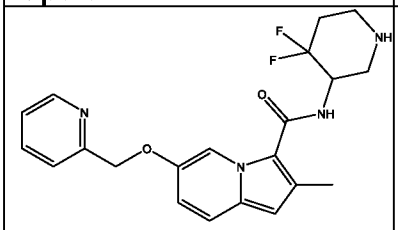
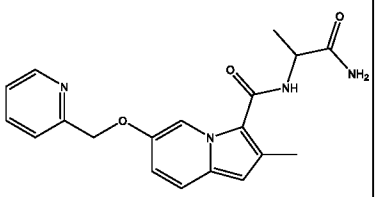
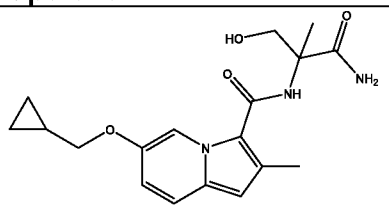
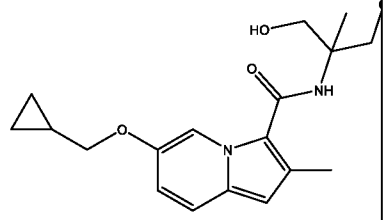
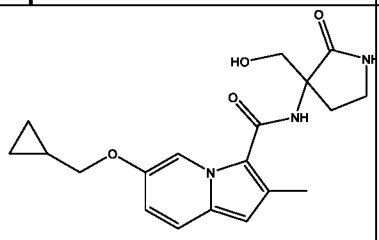
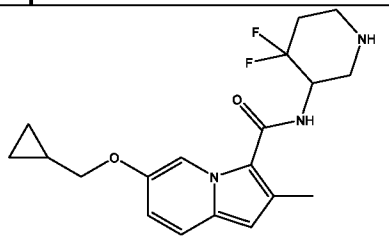
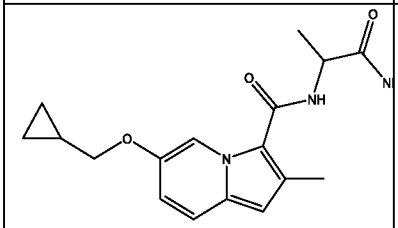
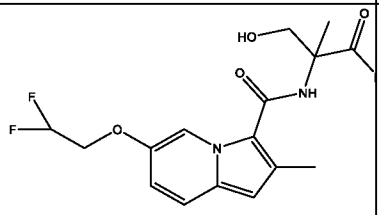
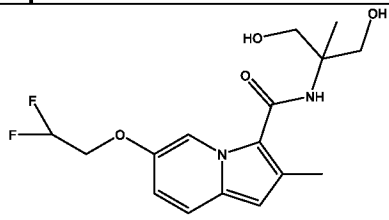
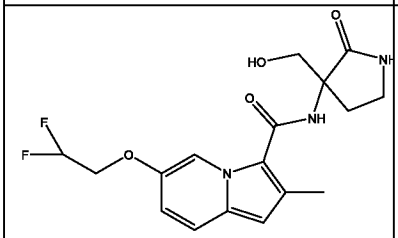
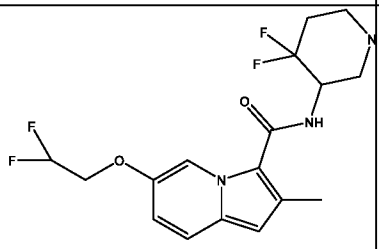
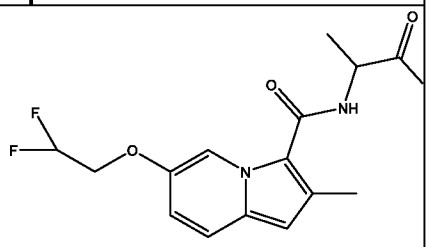
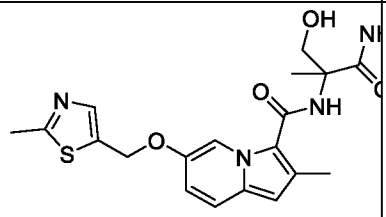
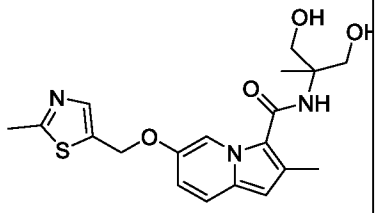
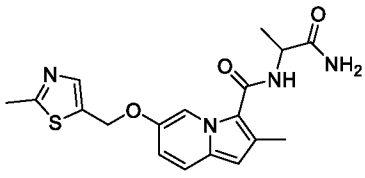
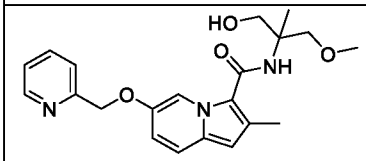
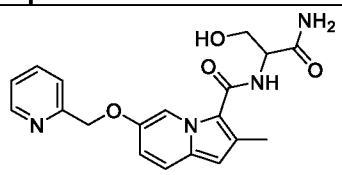
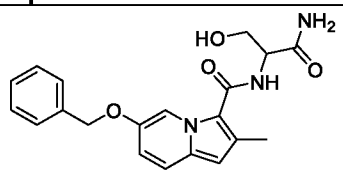
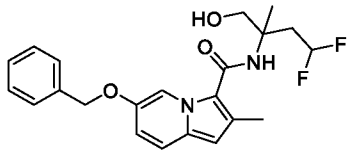
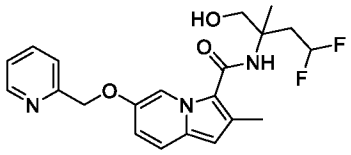
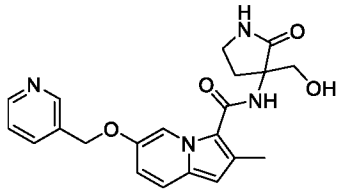
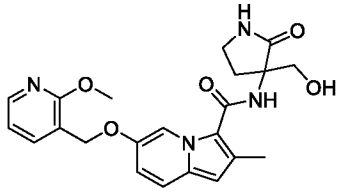
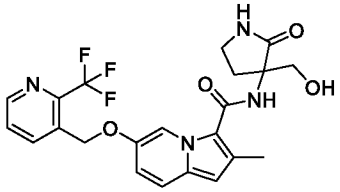
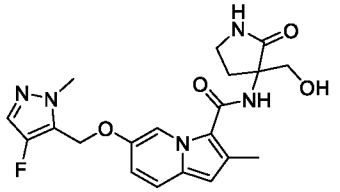
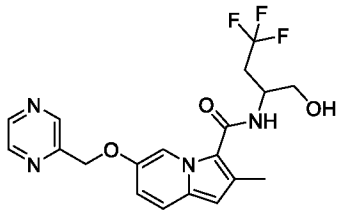
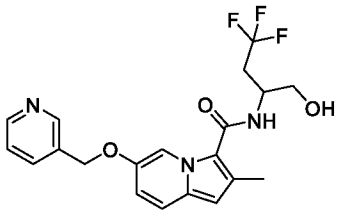
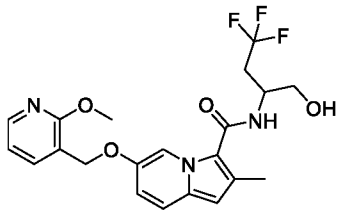
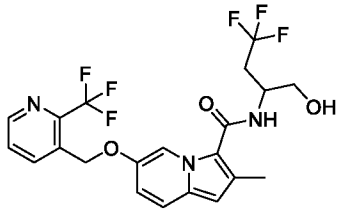
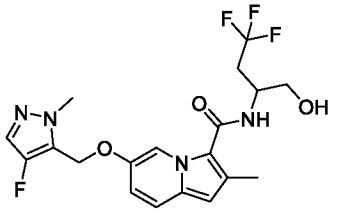
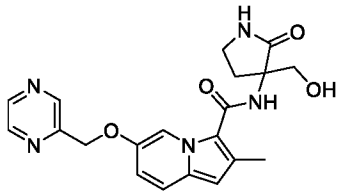
 Cpd 017	 Cpd 018	 Cpd 019
 Cpd 020	 Cpd 021	 Cpd 022
 Cpd 023	 Cpd 024	 Cpd 025
 Cpd 026	 Cpd 027	 Cpd 028
 Cpd 029	 Cpd 030	 Cpd 031
 Cpd 032	 Cpd 033	 Cpd 034

 Cpd 035	 Cpd 036	 Cpd 037
 Cpd 038	 Cpd 039	 Cpd 040
 Cpd 041	 Cpd 042	 Cpd 043
 Cpd 044	 Cpd 045	 Cpd 046

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 23 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 claim 23, 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 or 28, to a subject in need thereof.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference		FOR FURTHER ACTION
20211-WO-PCT		see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US2023/067448	25 May 2023	25 May 2022
Applicant		
KATHOLIEKE UNIVERSITEIT LEUVEN		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4. sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

   b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).

   c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☒ **Certain claims were found unsearchable** (see Box No. II).

3. ☒ **Unity of invention is lacking** (see Box No. III).

4. With regard to the **title**,

   ☒ the text is approved as submitted by the applicant.

   ☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

   ☒ the text is approved as submitted by the applicant.

   ☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

   a. the figure of the **drawings** to be published with the abstract is Figure No._____

      ☐ as suggested by the applicant.

      ☐ as selected by this Authority, because the applicant failed to suggest a figure.

      ☐ as selected by this Authority, because this figure better characterizes the invention.

   b. ☐ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2023/067448

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 6-12, 15-17, 20, 23-29
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See extra sheet(s).

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1, 5, 13, 19

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2023/067448

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - INV. - C07D 209/02; A61K 31/403 (2023.01)
ADD. - A61P 25/04, 25/08 (2023.01)

CPC - INV. - C07D 209/02; A61K 31/403 (2023.08)

ADD. - A61P 25/04, 25/08 (2023.08)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
See Search History document

Electronic database consulted during the international search (name of database and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	PUBCHEM, SID 447000577, Modify Date: 10 November 2021 [retrieved on 23 August 2023]. Retrieved from the Internet: <URL: https://pubchem.ncbi.nlm.nih.gov/substance/447000577> entire document	1, 5, 13, 19
A	WO 2018/104479 A1 (MAX-DELBRÜCK-CENTRUM FÜR MOLEKULARE MEDIZIN IN DER HELMHOLTZ-GEMEINSCHAFT) 14 June 2018 (14.06.2018) entire document	1, 5, 13, 19
P, A	WO 2022/112352 A1 (KATHOLIEKE UNIVERSITEIT LEUVEN) 02 June 2022 (02.06.2022) entire document	1, 5, 13, 19

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 September 2023	OCT 20 2023
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450 Facsimile No. 571-273-8300	Authorized officer Taina Matos Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2023/067448

Continued from Box No. III Observations where unity of invention is lacking

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees need to be paid.

Group I+: claims 1-5, 13, 14, 18, 19, 21, and 22 are drawn to compounds of formula (I), a stereo-isomeric form, a physiologically acceptable salt, solvate and/or polymorph thereof.

The first invention of Group I+ is restricted to a compound of formula (I), a stereo-isomeric form, a physiologically acceptable salt, solvate and/or polymorph thereof, wherein R1 represents –F; Q represents –OR2; R2 represents –RY; T represents –O- and U represents –CR5R5'; R5 and R5' independent of one another represent –RY; R6, R7 and R8 independently of one another represent –F; V represents 3-14-membered heterocycloalky, specifically wherein V is unsubstituted azepane, as indicated in the current specification, PCT/US23/67448, Para. [0130], attached to U via its nitrogen atom; and each RY is -H. The first named invention has been selected based on the guidance set forth in section 10.54 of the PCT International Search and Preliminary Examination Guidelines. Specifically, the first named invention was selected based on the first listed element for each of the variables presented in the claims (R1, Q, R2, T, U, R6, R7, R8, RY – claim 1; V – claim 1 and Para. [0130]). It is believed that claims 1, 5, 13, and 19 read on this first named invention and thus these claims will be searched without fee to the extent that they read on the above embodiment.

Applicant is invited to elect additional formula(e) for each additional compound to be searched in a specific combination by paying an additional fee for each set of election. Each additional elected formula(e) requires the selection of a single definition for each compound variable. An exemplary election would be a compound of formula (I), a stereo-isomeric form, a physiologically acceptable salt, solvate and/or polymorph thereof, wherein R1 represents –Cl; Q represents –OR2; R2 represents –RY; T represents –O- and U represents –CR5R5'; R5 and R5' independent of one another represent –RY; R6, R7 and R8 independently of one another represent –F; V represents 3-14-membered heterocycloalky, specifically wherein V is unsubstituted azepane, as indicated in the current specification, PCT/US23/67448, Para. [0130], attached to U via its nitrogen atom; and each RY is -H. Additional formula(e) will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined.

The inventions listed in Groups I+ do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 they lack the same or corresponding special technical features for the following reasons:

The Groups I+ formulae do not share a significant structural element requiring the selection of alternatives for the compound variables, R1, Q, R2, T, U, R6, R7, R8, V, and accordingly these groups lack unity a priori.

Additionally, even if Groups I+ were considered to share the technical features of a compound having the core structure of formula (I), a stereo-isomeric form, a physiologically acceptable salt, solvate and/or polymorph thereof, these shared technical features do not represent a contribution over the prior art as disclosed by Substance Record for SID 447000577 to PubChem (hereinafter, "PubChem").

PubChem teaches a compound having the core structure of formula (I), a stereo-isomeric form, a physiologically acceptable salt, solvate and/or polymorph thereof (Pg. 2, compound as shown).

The inventions listed in Groups I+ therefore lack unity under Rule 13 because they do not share a same or corresponding special technical feature.