

Carboxamide or sulfonamide substituted thiazoles and related derivatives as modulators for the orphan nuclear receptor ROR γ

The invention provides carboxamide or sulfonamide containing cyclic compounds, preferably thiazoles, as modulators for the orphan nuclear receptor ROR γ and methods for treating ROR γ mediated chronic inflammatory and autoimmune diseases by administering these novel ROR γ modulators to a human or a mammal in need thereof.

The retinoid-receptor related orphan receptors consist of three family members, namely ROR α (Beckerandre et al., *Biochem. Biophys. Res. Commun.* 1993, 194:1371), ROR β (Andre et al., *Gene* 1998, 516:277) and ROR γ (He et al., *Immunity* 1998, 9:797) and constitute the NR1F (ROR/RZR) subgroup of the nuclear receptor superfamily (Mangelsdorf et al., *Cell* 1995, 83:835).

The nuclear receptor superfamily shares common modular structural domains consisting of a hypervariable *N*-terminal domain, a conserved DNA binding domain (DBD), a hinge region, and a conserved ligand-binding domain (LBD). The DBD targets the receptor to specific DNA sequences (nuclear hormone response elements or NREs), and the LBD functions in the recognition of endogenous or exogenous chemical ligands. A constitutive transcriptional activation domain is found at the *N*-terminus (AF1) and a ligand regulated transcriptional activation domain is embedded within the *C*-terminal LBD of typical NRs. The nuclear receptors can exist in a transcriptional activating or repressing state when bound to their target NREs. The basic mechanism of gene activation involves ligand dependent exchange of co-regulatory proteins, namely co-activators and co-repressors (McKenna et al., *Endocrine Rev.* 1999, 20:321). A NR in the repressing state is bound to its DNA recognition element and is associated with co-repressor proteins that recruit histone-deacetylases (HDACs). In the presence of an agonist, co-repressors are exchanged for coactivators that recruit transcription factors, which contribute to assembling of a chromatin-remodelling complex, which relieves transcriptional repression and stimulates transcriptional initiation via histone acetylation. The AF-2 domain of the LBD acts as a ligand dependant molecular switch presenting interaction surfaces for co-repressor or co-activator proteins and providing with a conserved mechanism for gene activation or repression that is shared by the members of the nuclear receptor superfamily.

The members of the NR1F family of nuclear receptors (such as ROR γ) have been considered to be constitutively active transcription factors in the absence of known ligands, which is similar to the estrogen-related receptor alpha (Vanacker et al., *Mol. Endocrinol.* 1999, 13:764). Most recently, 7-oxygenated oxysterols were identified to be high affinity ligands for ROR α and ROR γ (Wang et al., *J. Biol. Chem.* 2010, 285:5013). 7-Hydroxycholesterol is a key metabolite during the conversion of cholesterol into bile acids, but to date it is not clear whether it is a true endogenous ligand for the RORs. In any case it can be expected that

inverse agonists of ROR γ should reduce the transcriptional activity of ROR γ and influence the biological pathways controlled by ROR γ .

The RORs are expressed as isoforms arising from differential splicing or alternative transcriptional start sites. So far, isoforms have been described that differ only in their N-terminal domain (A/B-domain). In humans, four different ROR α isoforms have been identified (ROR α 1-4) while only two isoforms are known for both ROR β (1 and 2) and ROR γ (1 and 2) (Andre et al., *Gene* 1998, 216:277; Villey et al., *Eur. J. Immunol.* 1999, 29:4072). ROR γ is used herein as a term describing both, ROR γ 1 and/or ROR γ 2 (also called ROR γ t).

The ROR isoforms show different tissue expression patterns and regulate different target genes and physiological pathways. For example, the ROR γ t is highly restricted to CD4⁺CD8⁺ thymocytes and to interleukin-17 (IL-17) producing T cells while other tissues express ROR γ 1 (Eberl et al., *Science* 2004, 305:248, Zhou and Littmann, *Curr. Opin. Immunol.* 2009, 21:146).

RORs exhibit a structural architecture that is typical of nuclear receptors. RORs contain four major functional domains: an amino-terminal (A/B) domain, a DNA-binding domain, a hinge domain, and a ligand-binding domain (Evans et al., *Science* 1988, 240:889). The DBD consists of two highly conserved zinc finger motifs involved in the recognition of ROR response elements (ROREs) which consist of the consensus motif AGGTCA preceded by an AT-rich sequence (Andre et al., *Gene* 1998, 216:277) which is similar to that of the nuclear receptors Rev-ErbA α and Rev-Erb β (NR1D1 and D2, respectively) (Giguere et al., *Genomics* 1995, 28:596). These recognition elements do also show high similarity to those identified for the estrogen related receptors and in particular ERR α (ERRs, NR3B1, -2, -3) (Vanacker et al., *Mol. Endocrinol.* 1999, 13:764), steroidogenic factor 1 (SF-1, NR5A) and NGFI-B (NR4A1, -2, -3) (Wilson et al., *Mol. Cell. Biol.* 1993, 13:5794).

ROR α is highly expressed in different brain regions and most highly in cerebellum and thalamus. ROR α knock-out mice show ataxia with strong cerebellar atrophy, highly similar to the symptoms displayed in the so-called staggerer mutant mouse (ROR $\alpha^{sg/sg}$). This mouse carries mutations in ROR α that results in a truncated ROR α which does not contain a LBD (Hamilton et al., *Nature* 1996, 379:736).

Analysis of ROR $\alpha^{sg/sg}$ staggerer-mice have revealed a strong impact on lipid metabolism beyond the CNS defects, namely significant decreases in serum and liver triglyceride, reduced serum HDL cholesterol levels and reduced adiposity. SREBP1c and the cholesterol transporters ABCA1 and ABCG1 are reduced in livers of staggerer mice and CHIP analysis suggest that ROR α is directly recruited to and regulates the SREBP1c promoter. In addition, PGC1 α , PGC1 β , lipin1 and β 2-adrenergic receptor were found to be increased in tissues such as liver or white and brown adipose tissue, which may help to explain the observed resistance to diet-induced obesity in staggerer mice (Lau et al., *J. Biol. Chem.* 2008, 283:18411).

ROR β expression is mainly restricted to the brain and most abundantly found in the retina. ROR β knock-out mice display a duck-like gait and retinal degeneration which leads to blindness (Andre et al., *EMBO J.* 1998, 17:3867). The molecular mechanisms behind this retinal degeneration are still poorly understood.

- 5 ROR γ (particularly ROR γ t) null-mutant mice lack lymph nodes and Peyer's patches (Eberl and Littmann, *Immunol. Rev.* 2003, 195:81) and lymphatic tissue inducer (LTi) cells are completely absent from spleen mesentery and intestine. In addition, the size of the thymus and the number of thymocytes is greatly reduced in ROR γ null mice (Sun et al., *Science* 2000, 288:2369) due to a reduction in double-positive CD4⁺CD8⁺ and single positive CD4⁺CD8⁺ or
10 CD4⁺CD8⁻ cells suggesting a very important role of ROR γ t in thymocyte development.

Thymocyte development follows a complex program involving coordinated cycles of proliferation, differentiation, cell death and gene recombination in cell populations dedicated by their microenvironment. Pluripotent lymphocyte progenitors migrating from fetal liver or adult bone marrow to the thymus are being committed to the T-cell lineage. They develop
15 through a series of steps from CD4⁻CD8⁻ double negative cells to CD4⁺CD8⁺ cells and those with low affinity towards self-MHC peptides are eliminated by negative selection. These develop further into CD4⁺CD8⁺ (killer) or CD4⁺CD8⁻ (helper) T-cell lineages. ROR γ t is not expressed in double negative and little expressed in immature single negative thymocytes (He et al., *J. Immunol.* 2000, 164:5668), while highly upregulated in double-positive thymocytes
20 and downregulated during differentiation in single-positive thymocytes. ROR γ deficiency results in increased apoptosis in CD4⁺CD8⁺ cells and the number of peripheral blood thymocytes is decreased by 6-fold (10-fold CD4⁺ and 3-fold CD8⁺ thymocytes).

Recent experiments in a model of ovalbumin (OVA)-induced inflammation in mice, as a model for allergic airway disease, demonstrated a severe impairment of the development of the
25 allergic phenotype in the ROR γ KO mice with decreased numbers of CD4⁺ cells and lower Th2 cytokine/chemokine protein and mRNA expression in the lungs after challenge with OVA (Tilley et al., *J. Immunol.* 2007, 178:3208). IFN- γ and IL-10 production were increased in splenocytes following re-stimulation with the OVA antigen compared to wt splenocytes suggesting a shift towards a Th1 type immune response on cost of a reduction of Th2 type
30 response. This suggests that down-modulation of ROR γ transcriptional activity with a ligand could result in a similar shift of the immune response towards a Th1 type response, which could be beneficial in the treatment of certain pulmonary diseases like asthma, chronic obstructive pulmonary disease (COPD) or allergic inflammatory conditions.

T-helper cells were previously considered to consist of Th1 and Th2 cells. However, a new
35 class of Th cells, the Th17 cells, which produce IL-17, were also identified as a unique class of T-cells that are considered to be pro-inflammatory. They are recognized as key players in autoimmune and inflammatory diseases since IL-17 expression has been associated with

many inflammatory diseases such as rheumatoid arthritis, systemic lupus erythematosus (SLE) and allograft rejection. (Tesmer et al., *Immunol. Rev.* 2008, 223:87).

ROR γ t is exclusively expressed in cells of the immune system and has been identified as a master regulator of Th17 cell differentiation. Expression of ROR γ t is induced by TGF-beta or IL-6 and overexpression of ROR γ t results in increased Th17 cell lineage and IL-17 expression. ROR γ t KO mice show very little Th17 cells in the intestinal lamina propria and demonstrate an attenuated response to challenges that usually lead to autoimmune disease (Ivanov et al., *Cell* 2006, 126:1121).

Inhibition of IL-17 production via inhibition of Th17 cell development may also be advantageous in atopic dermatitis and psoriasis where IL-17 is deeply involved. Interestingly, recent evidence was presented that IL-10 suppresses the expression of IL-17 secreted by both, macrophages and T-cells. In addition, the expression of the Th17 transcription factor ROR γ t was suppressed (Gu et al., *Eur. J. Immunol.* 2008, 38:1807). Moreover, IL-10 deficient mice provide a good model for inflammatory bowel disease (IBD) where a shift towards a Th1 type inflammatory response is frequently observed. Oral IL-10 delivery poses a potential treatment option for IBD.

The proinflammatory actions of IL-17 producing Th17 cells are counteracted by another T-helper cell type, so-called regulatory T-cells or Tregs. Naïve T-cells are differentiated into Tregs upon stimulation by TGF β . This results in upregulation of the transcriptional modulator FoxP3 resulting in CD4⁺FoxP3⁺ Tregs. In case the naïve T-cells are co-stimulated by IL-6, FoxP3 expression is suppressed and ROR γ t expression is induced. These CD4⁺FoxP3⁺ROR γ t⁺ T-helper cells then differentiate into IL-17 producing Th17 cells. (reviewed in Awasthi and Kuchroo, *Int. Immunol.* 2009, 21:489, and Zhou and Littmann, *Curr. Opin. Immunol.* 2009, 21:146). Several lines of evidence suggest that these Th17 cells are responsible for the etiology of a whole range of autoimmune diseases such as multiple sclerosis, rheumatoid arthritis, ankylosing spondylitis, psoriasis, Crohn's disease and other types of inflammatory bowel disease, lupus erythematosus and asthma. The severity of disease seems to correlate with the presence of IL-17⁺ Th17 cells and it is believed that interception of ROR γ t by a small molecule inverse agonist or antagonist should result in a reduction of these IL-17⁺ Th17 cells ultimately leading to alleviation of disease symptoms and outcome (Crome et al., *Clin. Exp. Immunol.* 2010, 159:109).

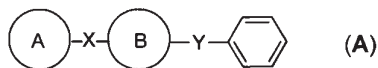
Th1 and Th17 subtype effector CD4⁺ T cells are thought to play a critical role in the pathogenesis of human and experimental crescentic glomerulonephritis (Paust et al., *Kidney Int.* 2012, doi: 10.1038/ki.2012.101). IL-17 modulators may thus be beneficial for treating acute glomerulonephritis (Velden et al., *Am. J. Physiol. Renal Physiol.* 2012, in press; Hopfer et al., *Kidney Int.* 2012, doi:10.1038/ki.2012.73).

Ligands for the RORs:

It was reported that cholesterol and its sulfated derivatives might function as ROR α ligands and in particular cholesterol-sulfate could restore transcriptional activity of ROR α in cholesterol-depleted cells (Kallen et al., *Structure* 2002, 10:1697). Previously, melatonin
5 (Missbach et al., *J. Biol. Chem.* 1998, 271:13515) and thiazolidinediones were suggested to bind to ROR α (Wiesenberg et al., *Nucleic Acid Res.* 1995, 23:327). However, none of these have been shown to be functional ligands of ROR α or of any other of the RORs. Certain retinoids including all-trans retinoid acid have been demonstrated to bind to ROR β and function as partial antagonists for ROR β but not ROR α (Stehlin-Gaon et al., *Nat. Struct. Biol.*
10 2003, 10:820).

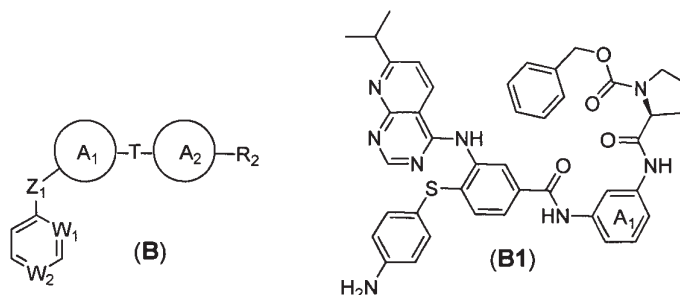
Recently, 7-oxygenated sterols such as 7-hydroxy-cholesterol and 7-keto-cholesterol were identified as highly potent modulators of ROR γ activity (Wang et al., *J. Biol. Chem.* 2010, 285:5013) in *in vitro* assays. The same group of investigators also found that a known LXR agonist, T0901317 ([N-(2,2,2-trifluoroethyl)-N-[4-[2,2,2-trifluoro-1-hydroxy-1-(trifluoro-
15 methyl)ethyl]phenyl]-benzenesulfonamide]) acts as a ROR γ inverse agonist at submicromolar potency (Kumar et al., *Mol. Pharmacol.* 2010, 77:228). In neither case, however, *in vivo* data were obtained that demonstrate a beneficial impact of these ROR γ modulating compounds. In case of the 7-oxysterols their endogenous presence as metabolites naturally produced by the body itself as well as their rapid turnover and their biological activities on many cellular
20 proteins prevent a meaningful animal study that allows drawing conclusions on the role of ROR γ . In case of the T0901317 its polypharmacodynamic properties, acting on at least six different nuclear receptors (LXR α/β , FXR, PXR, ROR α/γ) prevents its usefulness as a drug candidate for the development in an autoimmune disease application (Houck et al., *Mol. Genet. Metab.* 2004, 83:184; Xue et al., *Bioorg. Med. Chem.* 2007, 15:2156).

25 WO2011/109059 (US2011/0257196) describes compounds with anti-cancer activity of general structure (A)

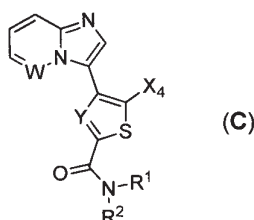


wherein cycle B can be selected from a large number of cyclic systems. However no thiazole, oxazole, thiophene or furan containing a carboxamide or sulfonamide in 2-position is
30 described in the examples.

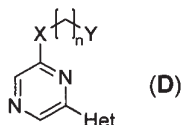
In WO2010/075376 compounds of general structure (B) for inhibiting replication of Hepatitis C virus are described. A₁ is defined to be a 3-14 membered carbo- or heterocycle, T can be e.g. CONR⁶ and SO₂NR⁶ while A₂ can be a carbo- or heterocycle. However, no thiazole, oxazole, thiophene or furan (representing A₁) is described in the examples – a typical example is e.g.
35 B1.



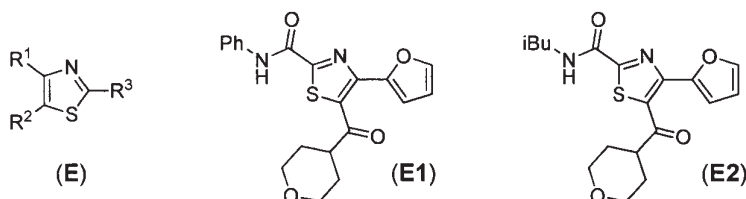
WO2010/083145 and WO2010/017046 describe compounds of general structure (C) which selectively inhibit microtubule affinity regulating kinase (MARK). The heteroaryl substituent of the thiazole (Y = N) respectively thiophene (Y = CH) is limited to imidazo[1,2-b]pyridazin-3-yl (W = N) and imidazo[1,2-a]pyridin-3-yl (W = C), while X₄ can be (CH₂)_q = 0 to 3-C₃₋₆-cycloalkyl. No thiazole or thiophene examples with X₄ equals -Z-C₃₋₁₀-cycloalkyl (Z = optionally substituted carbon, oxygen, nitrogen or sulfur) are presented (in the closest structure X₄ equals benzyl).



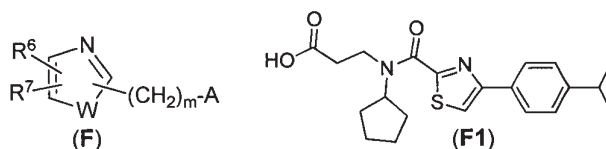
In WO2009/037247 pyrazine derivatives of general structure (D) as potassium channel modulating agents are described. 'Het' represents a heterocyclic group which can also be thiazolyl, which is optionally substituted e.g. with cycloalkyl-alkyl, amino-carbonyl and *N,N*-dialkyl-amino-carbonyl. No thiazole examples which are substituted with a carboxamide are presented.



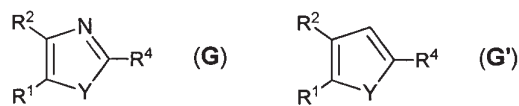
WO2007/015528 (EP1921077) and WO2006/137527 (EP1894930) describe compounds of general structure (E) for treating and/or preventing sleep disorders. R¹ is defined to be a 5-membered aromatic heterocyclic group having at least one oxygen atom, while R² can be an optionally substituted lower alkyl, NR⁴R⁵ (with R⁴ and R⁵ e.g. cycloalkyl) or COR⁶ (R⁶ e.g. cycloalkyl). Five thiazole examples with a carboxamide moiety are mentioned, e.g. compound (E1) and (E2). However, in all of those examples the group R¹ is a 5-membered oxygen-containing ring.



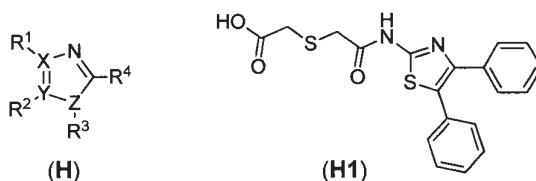
In WO2005/103022 derivatives of general structure **(F)** as melanocortin receptor modulators are described, wherein W can be a sulfur atom, m e.g. zero and A can be for example a carbox- or sulfonamide. R⁶ can be L-D²-cycloalkyl (with L e.g. bond and D² e.g. nitrogen or alkylene) and R⁷ can be L-D¹-aryl (with L and D¹ e.g. bond), therefor falling within the broadest scope of the present application. From the huge amount of examples, only two thiazoles with a directly linked carboxamide moiety are mentioned, e.g. **(F1)**. However, those compounds do not have a substituent in position 4 of the thiazole ring.



WO2005/074875 describes a keratin dyeing composition comprising (a) a medium suitable for dyeing, and (b) one or more five-membered heteroaromatic dyeing compounds, e.g. structure **(G)** or **(G')** beside many other cyclic systems, wherein Y equals sulfur or oxygen and R¹, R² and R⁴ can be alkyl, aryl, hetaryl, O-cycloalkyl and carboxamide. However no thiazole, oxazole, thiophene or furan examples which are substituted with a carboxamide or sulfonamide is presented.

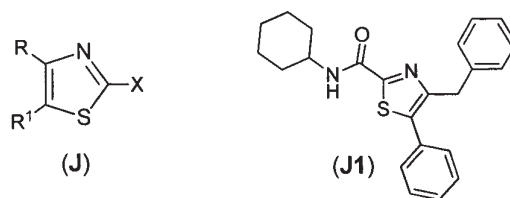


US2005/113283 claims a method of modulating an Edg-4- receptor mediated biological activity, wherein the modulator is a compound of structural formula **(H)** as presented in claim 40:

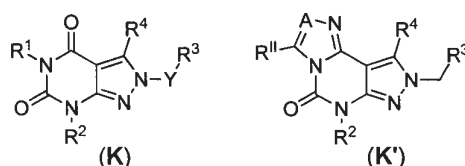


R¹ to R⁴ is selected from CONHR, CONR₂, phenyl, (CH₂)_{m=0 to 8}-R⁵ (R⁵ e.g. cycloalkyl) and others. However no thiazole or oxazole sulfon- or carboxamide is shown in the examples, only an inverse amide of structure **(H1)** is disclosed.

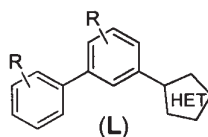
In US2005/065189 thiazoles of structure **(J)** as cannabinoid receptor modulators are described, wherein X can be a carboxamide moiety and R¹ can be a phenyl or pyridyl moiety optionally substituted with Me, Et, Pr, OMe, OEt, OH, hydroxymethyl, hydroxyethyl, halogen, CF₃, OCF₃, SO₂Me, SOMe, SO₂CF₃, phenyl or CN while R can be R¹ or alkyl-cycloalkyl. 21 thiazole examples are shown, the closest example is structure **(J1)** with an CH₂-phenyl moiety in position 4 of the thiazole ring.



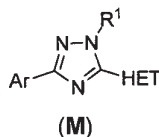
WO2005/016929 and WO2003/002567 describe compounds of general structure **(K)** and **(K')** as glutamate racemate inhibitors, wherein R^4 is broadly defined to be a monocyclic or bicyclic, saturated or unsaturated, ring system, which may contain from 5 to 12 ring atoms, 0 to 4 of which are heteroatoms independently selected from N, O or S and therefor also comprise thiazoles, oxazoles, thiophenes or furans. However no compounds were disclosed therein R^4 is a thiazole, oxazole, thiophene or furan substituted with a carbox- or sulfonamide moiety.



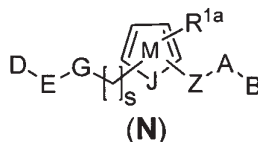
In WO2004/094395 biaryls of structure **(L)** as sodium channel blockers are described, wherein HET can be a thiazole, imidazole or oxazole moiety. The HET moiety can be substituted with sulfon- or carboxamides and alkyl-cycloalkyl. However, the thiazole or oxazole compounds disclosed therein all contain no cycloalkyl moiety.



WO2000/024739 describes insecticides and acaricides of formula **(M)**, wherein HET can be chosen from a large variety of heterocycles, however not thiophene or furan. However, no thiazole or oxazole carboxamide example is presented.

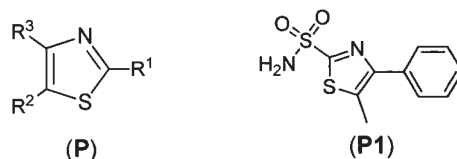


In WO1998/028282 factor Xa inhibitors of formula **(N)** are disclosed, wherein ring M may contain in addition to J other nitrogen atoms. However from the presented structures (>1000) no thiazole, oxazole, thiophene or furan at all is exemplified.

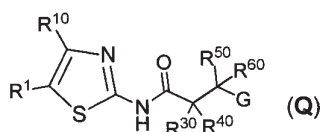


WO1995/029904 describes thiazoles of structure **(P)** as antiglaucoma agents. R^1 can be a primary sulfonamide, R^2 can be OR^4 (with R^4 as alicyclic residue), R^3 can be phenyl (optionally

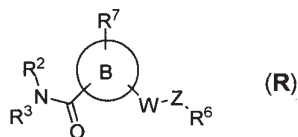
substituted with lower alkoxy, halogen or C₁₋₃ alkyl). The closest example to the compounds of the present invention is compound **(P1)**.



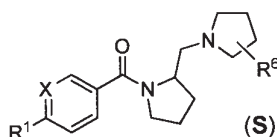
- WO2013/014205 describes thiazole-2-carboxamides of structure **(Q)** as inhibitors of the protease cathepsin A. All shown examples have an phenyl moiety in the amide residue and R¹ is always hydrogen. In WO2013/014204 the thiazole moiety is replaced by another 5-membered heterocycle, including oxazole. Again, all shown oxazole examples have an phenyl moiety in the amide residue and R¹ is always hydrogen.



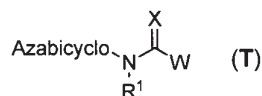
- WO2010/111059 describes P2x3 receptor antagonists for the treatment of pain of structure **(R)**, wherein R² represents H, (halo)alkyl or OH; R³ represents a broad range of optionally substituted alkyl substituents; B can be a oxazole cylyce, R⁷ represents for example an optionally substituted aryl moiety and with the rest W-Z-R⁶ a X-cycloalkyl residue (X = CR², CO or SO₂) can be constructed. However no oxazole containing a carboxamide in 2-position is described in the examples nor an oxazole, having such a hypothetical X-cycloalkyl residue.



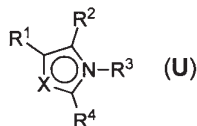
- WO2006/023462 describes 1-(hetero)aroyl-2-(pyrrolidin-1-ylmethyl)pyrrolidine as histamine H₃ receptor agents of structure **(S)**, wherein R¹ selected from a broad variety of heterocycles, including oxazole. This heterocycle can be optionally substituted with, e.g. CO-cycloalkyl, CONR⁷R⁸. However no example is described, where R¹ is an oxazole.



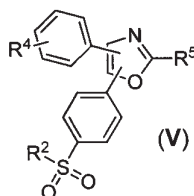
- WO2003/040147 describes the preparation of N-(azabicycyl)arylamides for therapeutic use as nicotinic acetylcholine receptor agonists of formula **(T)**, wherein R¹ is hydrogen or optionally substituted alkyl, X is oxygen or sulfur and W is a cyclic heteroeromatic moiety, which can be substituted with e.g. CO-cycloalkyl or SO₂-cycloalkyl. From the presented oxazoles no compounds with two additional substituents are shown, only some of them contain a substituted aryl as substituent.



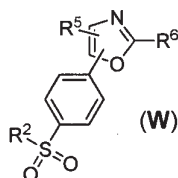
In WO2000/033836 selectin antagonists of formula (U) are disclosed, however no oxazole is presented.



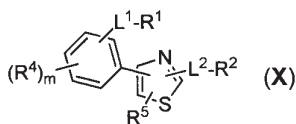
- 5 In WO1996/036617 substituted oxazoles of formula (V) as antiinflammatories are described. R⁵ can be selected from a broad range of substituents, including aminocarbonyl. R² is selected from amino and lower alkyl.



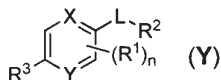
- 10 In WO1996/003392 substituted oxazoles of formula (W) for the treatment of inflammation are described. R⁶ can be selected from a broad range of substituents, including aminocarbonyl and alkylamino carbonyl. R² is selected from amino and lower alkyl. No 2-carboxamide substituted oxazoles are shown.



- 15 WO2008/154601 describes thiazole derivatives as ant-viral inhibitors of structure (X), wherein L²-R² can be a substituted carboxamide, R⁵ is selected from e.g. optionally substituted alkyl or cycloalkyl and L¹-R¹ can be a substituted sulfonamide. However, no compound is shown, wherein L¹-R¹ is a substituted sulfonamide.

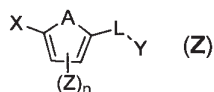


- 20 In WO2007/087429, phenyl and pyridyl compounds as Ca²⁺ ion channel inhibitors with structure (Y) are described, wherein L is selected from various linker elements including SO₂NR (R = H or alkyl) and R² can be an optionally substituted phenyl or heteroaryl. R³ can be an optionally substituted 5-membered heteroaryl, however no 2-carboxamide substituted thiazole, oxazole, thiophene or furan is shown in the examples.



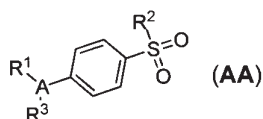
WO2005/009954 and WO2005/009539 describe compounds of structure **(Z)**, wherein A is selected from a broad range of substituents giving 5- or 6-membered aromatic cycles including thiophene and furan. L-Y can form a substituted carboxamide and X can be phenyl or pyridyl, which is optionally substituted with an alkylated sulfonamide, however such examples are not

5



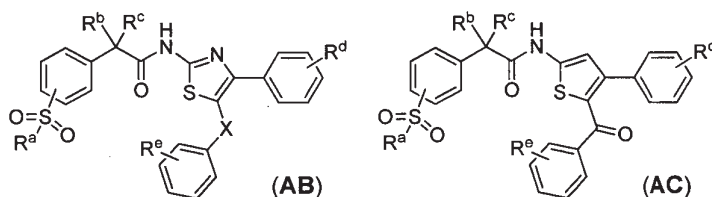
In US2003/236293 tricyclic COX-2 selective inhibitors are claimed of structure **(AA)**, wherein A can be a partially unsaturated or unsaturated heterocyclyl or carbocyclic ring. However no examples are shown, wherein A is a 2-carboxamide substituted thiazole, oxazole, thiophene or furan.

10



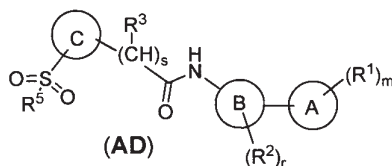
WO2012/027965 and WO2012/028100 describe thiazole compounds of structure **(AB)** as ROR_γ receptor modulators, wherein R^a represents an optionally substituted C₁₋₆-alkyl, NH₂ or NHC₁₋₃-alkyl; R^b and R^c represents H or C₁₋₆-alkyl; X is C=O and R^d and R^e are optional substituents. In WO2012/100734 compounds are described, wherein X represents O, NH, N-C₁₋₆-alkyl or C₁₋₃-alkyl, optionally substituted with OH. Similarly in WO2012/100732, the same derivatives with a thiophene core are described (structure **(AC)**).

15



In WO2013/029338 similar ROR_γ receptor modulators are described of structure **(AD)**, wherein ring A, B and C is broadly defined as phenyl or heteroaryl and R² can be selected from e.g. C₁₋₆-alkylene-cycloalkyl, heterocycloalkyl, O-heteroaryl. In the examples ring B is limited to 6-membered (hetero)aryl.

20



Modulators of the ROR_γ receptor were recently disclosed in WO2011/107248, WO2011/112263, WO2011/112264, WO2011/115892, WO2012/027965, WO2012/028100, WO2012/064744, WO2012/074547, WO2012/100732, WO2012/100734, WO2012/101261, WO2012/101263, WO2012/106995, WO2012/139775, WO2012/145254, WO2012/147916, WO2012/158784, WO2013/000869, WO2013/000871, WO2013/018695, WO2013/019621,

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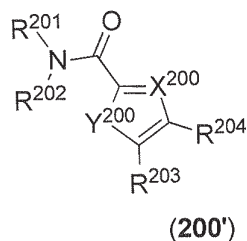
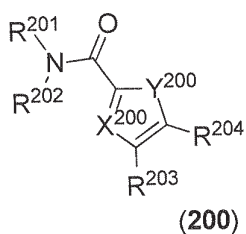
WO2013/019626, WO2013/019635, WO2013/019653, WO2013/019682, WO2013/036912, WO2013/041519, WO2013/042782, WO2013/045431 which are based upon other structural classes.

5 **Summary**

It is therefore the object of the present disclosure to provide compounds, which bind to the orphan nuclear receptors ROR γ 1 and/or ROR γ t and, thus, to open new methods for treating diseases associated with the modulation of ROR γ , such as autoimmune diseases, inflammatory skin diseases or multiple sclerosis.

10 This object is solved by claims 1 to 32.

In one aspect, there is provided a compound represented by Formula (200) and Formula (200')



15 an enantiomer, diastereomer, tautomer, *N*-oxide, solvate, formulation and pharmaceutically acceptable salt thereof,

wherein

X^{200} is N;

Y^{200} is S;

20 R^{201} and R^{202} are independently selected from H, C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl, C₃₋₁₀-cycloalkyl, C₃₋₁₀-heterocycloalkyl, C₁₋₁₀-alkylene-C₃₋₁₀-cycloalkyl, C₁₋₁₀-alkylene-C₃₋₁₀-heterocycloalkyl, C₁₋₁₀-alkylene-(5-membered heteroaryl), C₁₋₁₀-alkylene-(6-membered aryl), C₁₋₁₀-alkylene-(6-membered heteroaryl), SO₂-C₁₋₁₀-alkyl, wherein alkyl, alkenyl, alkynyl, alkylene, cycloalkyl, heterocycloalkyl, aryl and heteroaryl is unsubstituted or substituted with 1 to 7 substituents independently selected from the group consisting of oxo, CN, OR²¹¹, O-C₂₋₆-alkylene-OR²¹¹, C₁₋₆-alkyl, halo-C₁₋₆-alkyl, halogen, CO₂R²¹¹, CONR²¹¹R²¹², CONR²¹¹SO₂R²¹¹, COR²¹¹, SO_xR²¹¹, SO₃H, SO₂NR²¹¹R²¹², NR²¹¹COR²¹¹, NR²¹¹SO₂R²¹¹, NR²¹¹-CO-NR²¹¹R²¹², NR²¹¹-SO₂-NR²¹¹R²¹², C₃₋₁₀-cycloalkyl, O-C₃₋₁₀-cycloalkyl, C₃₋₁₀-heterocycloalkyl, O-C₃₋₁₀-heterocycloalkyl and NR²¹¹R²¹²;

30 or R^{201} and R^{202} when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing 1 or 2 heteroatoms selected from O, S or N, wherein the ring is unsubstituted or substituted with 1 to 4

substituents independently selected from the group consisting of halogen, oxo, CN, OR²¹¹, SO_xR²¹¹, SO₃H, NR²¹¹SO₂R²¹¹, SO₂NR²¹¹R²¹², C₀₋₆-alkylene-CO₂R²¹¹, CONR²¹¹R²¹²,
 5 CONR²¹¹SO₂R²¹¹, COR²¹¹, NR²¹¹-CO-R²¹¹, NR²¹¹-CO-NR²¹¹R²¹², NR²¹¹-SO₂-NR²¹¹R²¹², NR²¹¹R²¹², C₁₋₆-alkyl, halo-C₁₋₆-alkyl, hydroxy-C₁₋₆-alkyl, C₃₋₈-cycloalkyl, O-C₃₋₈-cycloalkyl, C₃₋₈-heterocycloalkyl and O-C₃₋₈-heterocycloalkyl,

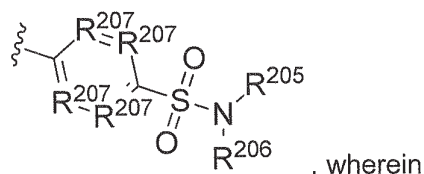
wherein cycloalkyl and heterocycloalkyl are unsubstituted or substituted with 1 to 4 substituents independently selected from the group consisting of halogen, C₁₋₃-alkyl, halo-C₁₋₃-alkyl, OH, O-C₁₋₃-alkyl, O-halo-C₁₋₃-alkyl, SO₂-C₁₋₃-alkyl, COOH and oxo;
 10

R²⁰³ is selected from C₁₋₁₀-alkyl, fluoro-C₁₋₁₀-alkyl, C₁₋₆-alkylene-C₃₋₁₀-cycloalkyl, C₁₋₆-alkylene-C₃₋₁₀-heterocycloalkyl, C₁₋₆-alkylene-(6- to 10-membered aryl), and C₁₋₆-alkylene-(5- to 10-membered heteroaryl),

wherein alkyl, alkylene, cycloalkyl, heterocycloalkyl, aryl and heteroaryl is unsubstituted or substituted with 1 to 6 substituents independently selected from the group consisting of oxo, halogen, CN, C₁₋₆-alkyl, halo-C₁₋₆-alkyl, C₃₋₆-cycloalkyl, C₃₋₆-heterocycloalkyl, OR²¹², CO₂R²¹², CONR²¹²R²¹² and COR²¹²; and
 15

wherein optionally one CH₂ unit in alkyl or alkylene can be replaced by O, SO_x, NH or N(C₁₋₃-alkyl);

20 R²⁰⁴ is



R²⁰⁵ and R²⁰⁶ is independently selected from H, C₁₋₆-alkyl, halo-C₁₋₆-alkyl, C₀₋₆-alkylene-C₃₋₈-cycloalkyl, C₀₋₆-alkylene-C₃₋₈-heterocycloalkyl, 5- or 6-membered heteroaryl and 6-membered aryl, wherein alkyl, alkylene, cycloalkyl, heterocycloalkyl, aryl and heteroaryl are unsubstituted or substituted with 1 to 6 substituents independently selected from the group consisting of halogen, CN, OH, oxo, C₁₋₃-alkyl, halo-C₁₋₃-alkyl, O-C₁₋₃-alkyl, O-halo-C₁₋₃-alkyl and SO₂-C₁₋₃-alkyl, NR²¹¹R²¹², CO₂R²¹² and CONR²¹¹R²¹²;
 25

and optionally wherein R²⁰⁵ and R²⁰⁶ when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing 1 or 2 heteroatoms selected from O, S or N, wherein the ring is unsubstituted or substituted with 1 to 4 substituents independently selected from the group consisting of fluoro, OH, oxo, C₁₋₄-alkyl and halo-C₁₋₄-alkyl;
 30

R²⁰⁷ is independently selected from N and CR²⁰⁸; or

two adjacent R²⁰⁷ form a 5- or 6-membered unsaturated or partially saturated ring containing carbon atoms and optionally containing 1 or 2 heteroatoms selected from O, S or N, wherein the ring is unsubstituted or substituted with 1 to 4 substituents independently selected from the group consisting of halogen, OH, oxo, C₁₋₄-alkyl and fluoro-C₁₋₄-alkyl;

R²⁰⁸ is independently selected from H, halogen, CN, C₁₋₆-alkyl, fluoro-C₁₋₆-alkyl, C₁₋₄-alkylene-OH, C₁₋₄-alkylene-O-C₁₋₃-alkyl, C₁₋₄-alkylene-O-fluoro-C₁₋₃-alkyl, OH, O-C₁₋₆-alkyl, O-fluoro-C₁₋₆-alkyl and C₃₋₁₀-cycloalkyl,

wherein alkylene is unsubstituted or substituted with 1 to 3 substituents selected from F and cycloalkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of F, C₁₋₃-alkyl and fluoro-C₁₋₃-alkyl;

R²¹¹ is independently selected from H, C₁₋₆-alkyl, C₀₋₆-alkylene-C₃₋₁₀-cycloalkyl and C₀₋₆-alkylene-C₃₋₁₀-heterocycloalkyl,

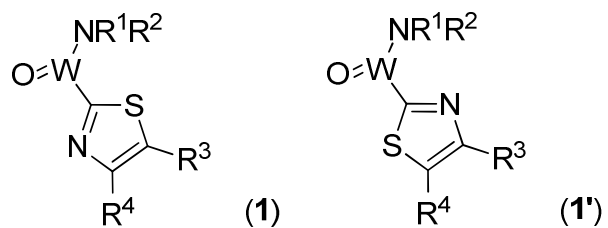
wherein alkyl, alkylene, cycloalkyl and heterocycloalkyl is unsubstituted or substituted with 1 to 6 substituents independently selected from the group consisting of halogen, CN, OH, oxo, C₁₋₃-alkyl, halo-C₁₋₃-alkyl, O-C₁₋₃-alkyl, O-halo-C₁₋₃-alkyl, NH₂, NH(C₁₋₃-alkyl), N(C₁₋₃-alkyl)₂, C₃₋₆-heterocycloalkyl, C₃₋₆-cycloalkyl and SO₂-C₁₋₃-alkyl,

wherein cycloalkyl and heterocycloalkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of F, OH, oxo, CH₃ and CF₃;

R²¹² is independently selected from H, C₁₋₆-alkyl, halo-C₁₋₆-alkyl and C₃₋₆-cycloalkyl;

x is independently selected from 0, 1 and 2.

In another aspect, there is provided a compound represented by Formula (1) or Formula (1')



an enantiomer, diastereomer, tautomer, *N*-oxide, solvate, formulation and pharmaceutically acceptable salt thereof, wherein

R¹ and R² are independently selected from H, C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl, C₃₋₁₀-cycloalkyl, C₃₋₁₀-heterocycloalkyl, C₁₋₁₀-alkylene-C₃₋₁₀-cycloalkyl, C₁₋₁₀-alkylene-C₃₋₁₀-heterocycloalkyl, C₁₋₁₀-alkylene-(5-membered heteroaryl) and SO₂-C₁₋₁₀-alkyl, wherein alkyl, alkenyl, alkynyl, alkylene, cycloalkyl, heterocycloalkyl and heteroaryl is unsubstituted or substituted with 1 to 7 substituents independently selected from the group consisting of oxo, CN, OR¹¹, O-C₂₋₆-alkylene-OR¹¹, C₁₋₆-alkyl, halo-C₁₋₆-alkyl, halogen, CO₂R¹¹, CONR¹¹R¹², CONR¹¹SO₂R¹¹, COR¹¹, SO_xR¹¹, SO₃H, SO₂NR¹¹R¹², NR¹¹COR¹¹, NR¹¹SO₂R¹¹, NR¹¹-CO-NR¹¹R¹², NR¹¹-SO₂-NR¹¹R¹², C₃₋₁₀-cycloalkyl, O-C₃₋₁₀-cycloalkyl, C₃₋₁₀-heterocycloalkyl, O-C₃₋₁₀-heterocycloalkyl and NR¹¹R¹²;

or R¹ and R² when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing 1 or 2 heteroatoms selected from O, S or N, wherein the ring is unsubstituted or substituted with 1 to 4 substituents independently selected from the group consisting of halogen, oxo, CN, OR¹¹, SO_xR¹¹, SO₃H, NR¹¹SO₂R¹¹, SO₂NR¹¹R¹², C₀₋₆-alkylene-CO₂R¹¹, CONR¹¹R¹², CONR¹¹SO₂R¹¹, COR¹¹, NR¹¹-CO-R¹¹, NR¹¹-CO-NR¹¹R¹², NR¹¹-SO₂-NR¹¹R¹², NR¹¹R¹², C₁₋₆-alkyl, halo-C₁₋₆-alkyl, hydroxy-C₁₋₆-alkyl, C₃₋₈-cycloalkyl, O-C₃₋₈-cycloalkyl, C₃₋₈-heterocycloalkyl and O-C₃₋₈-heterocycloalkyl,

wherein cycloalkyl and heterocycloalkyl are unsubstituted or substituted with 1 to 4 substituents independently selected from the group consisting of halogen, C₁₋₃-alkyl, halo-C₁₋₃-alkyl, OH, O-C₁₋₃-alkyl, O-halo-C₁₋₃-alkyl, SO₂-C₁₋₃-alkyl, COOH and oxo;

R³ is a 6-10 membered mono- or bicyclic aryl or a 5-14 membered mono-, bi- or tricyclic heteroaryl containing 1 to 5 heteroatoms independently selected from the group consisting of N, O and S,

wherein aryl and heteroaryl is unsubstituted or substituted with 1 to 5 substituents independently selected from the group consisting of halogen, C₁₋₆-alkyl, C₁₋₆-alkenyl, C₁₋₆-alkynyl, halo-C₁₋₆-alkyl, OH, O-C₁₋₆-alkyl, O-halo-C₁₋₆-alkyl, C₀₋₆-alkylene-C₃₋₁₀-cycloalkyl, C₀₋₆-alkylene-C₃₋₁₀-heterocycloalkyl, C₀₋₆-alkylene-(5- or 6-membered heteroaryl), C₁₋₆-alkylene-O-R³¹, C₀₋₆-alkylene-CN, C₀₋₆-alkylene-N(R³¹)₂, C₀₋₆-alkylene-O-C₃₋₁₀-cycloalkyl, O-C₁₋₆-alkylene-O-R³¹, C₀₋₆-alkylene-O-C₃₋₁₀-heterocycloalkyl, C₀₋₆-alkylene-COOR³¹, C₀₋₆-alkylene-C(O)R³¹, C₀₋₆-alkylene-C(O)N(R³¹)₂, C₀₋₆-alkylene-N(R³¹)C(O)R³¹, C₀₋₆-alkylene-SO-R³¹, C₀₋₆-alkylene-SO₂-R³¹, C₀₋₆-alkylene-SO₂-N(R³¹)₂, C₀₋₆-alkylene-N(R³¹)SO₂-R³¹, C₀₋₆-alkylene-SO₂-C₃₋₁₀-heterocycloalkyl and C₀₋₆-alkylene-SO₂-C₃₋₁₀-heterocycloalkyl,

- wherein alkyl, alkenyl, alkynyl, alkylene, cycloalkyl, heterocycloalkyl and the 5- or 6-membered heteroaryl is optionally substituted by 1 to 4 substituents independently selected from the group consisting of halogen, CN, C₁₋₃-alkyl, halo-C₁₋₃-alkyl, OH, oxo, =N-OR³², O-C₁₋₆-alkyl, O-halo-C₁₋₃-alkyl, N(R³¹)₂, COOH, CON(R³¹)₂, NR³¹-COR³¹, C₃₋₁₀-cycloalkyl, C₃₋₁₀-heterocycloalkyl, 6-10-membered mono- or bicyclic aryl and 6-10-membered mono- or bicyclic heteroaryl,
- or wherein two adjacent substituents complete a 3- to 8-membered saturated or partially unsaturated ring containing carbon atoms and optionally containing 1 to 3 heteroatoms selected from O, S, N, SO, SO₂ or NR³¹, wherein the ring is unsubstituted or substituted with 1 to 7 substituents independently selected from the group consisting of halogen, C₁₋₆-alkyl, halo-C₁₋₆-alkyl, C₃₋₆-cycloalkyl, C₃₋₆-heterocycloalkyl, oxo, =N-OR³², OH, O-C₁₋₆-alkyl and O-halo-C₁₋₆-alkyl;
- R⁴ is selected from (CR⁸R⁹)R⁴⁰, (C=O)R⁴⁰, OR⁴⁰, NR⁴¹R⁴⁰, SO_y-R⁷ and C₃₋₆-cycloalkyl, which is spirocyclic fused with R⁴⁰,
- wherein cycloalkyl is unsubstituted or substituted with 1 to 4 substituents independently selected from the group consisting of F, CH₃ and CF₃;
- R⁷ is selected from C₃₋₁₀-cycloalkyl and C₃₋₁₀-heterocycloalkyl,
- wherein cycloalkyl and heterocycloalkyl are unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of halogen, OH, oxo, O-C₁₋₆-alkyl, O-halo-C₁₋₆-alkyl, C₁₋₆-alkyl, halo-C₁₋₆-alkyl, cycloalkyl and heterocycloalkyl;
- R⁸ and R⁹ are independently selected from H, F, C₁₋₃-alkyl, halo-C₁₋₃-alkyl, OH, O-C₁₋₃-alkyl and O-halo-C₁₋₃-alkyl;
- R¹¹ is independently selected from H, C₁₋₆-alkyl, C₀₋₆-alkylene-C₃₋₁₀-cycloalkyl and C₀₋₆-alkylene-C₃₋₁₀-heterocycloalkyl,
- wherein alkyl, alkylene, cycloalkyl and heterocycloalkyl is unsubstituted or substituted with 1 to 6 substituents selected from the group consisting of halogen, CN, OH, oxo, C₁₋₃-alkyl, halo-C₁₋₃-alkyl, O-C₁₋₃-alkyl, O-halo-C₁₋₃-alkyl, NH₂, NH(C₁₋₃-alkyl), N(C₁₋₃-alkyl)₂, C₃₋₆-heterocycloalkyl, C₃₋₆-cycloalkyl and SO₂-C₁₋₃-alkyl,
- wherein cycloalkyl and heterocycloalkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of F, OH, oxo, CH₃ and CF₃;

R¹² is independently selected from H, C₁₋₆-alkyl, halo-C₁₋₆-alkyl and C₃₋₆-cycloalkyl;

5 R³¹ is independently selected from H, C₁₋₆-alkyl, halo-C₁₋₆-alkyl, C₀₋₆-alkylene-C₃₋₆-cycloalkyl, C₀₋₆-alkylene-C₃₋₈-heterocycloalkyl, 5- or 6-membered heteroaryl and 6-membered aryl, wherein alkyl, alkylene, cycloalkyl, heterocycloalkyl, aryl and heteroaryl are unsubstituted or substituted with 1 to 6 substituents independently selected from the group consisting of halogen, CN, OH, oxo, =N-OR³², C₁₋₃-alkyl, halo-C₁₋₃-alkyl, O-C₁₋₃-alkyl, O-halo-C₁₋₃-alkyl and SO₂-C₁₋₃-alkyl;

10 and optionally wherein two R³¹ when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing 1 or 2 heteroatoms selected from O, S or N, wherein the ring is unsubstituted or substituted with 1 to 4 substituents independently selected from the group consisting of fluoro, OH, oxo, C₁₋₄-alkyl and halo-C₁₋₄-alkyl;

R³² is independently selected from H, C₁₋₆-alkyl, halo-C₁₋₆-alkyl and C₃₋₆-cycloalkyl;

15 R⁴⁰ is C₃₋₁₀-cycloalkyl, which is unsubstituted or substituted with 1 to 5 substituents independently selected from the group consisting of halogen, OH, oxo, O-C₁₋₆-alkyl, O-halo-C₁₋₆-alkyl, C₁₋₆-alkyl, halo-C₁₋₆-alkyl, C₃₋₈-cycloalkyl and C₃₋₈-heterocycloalkyl;

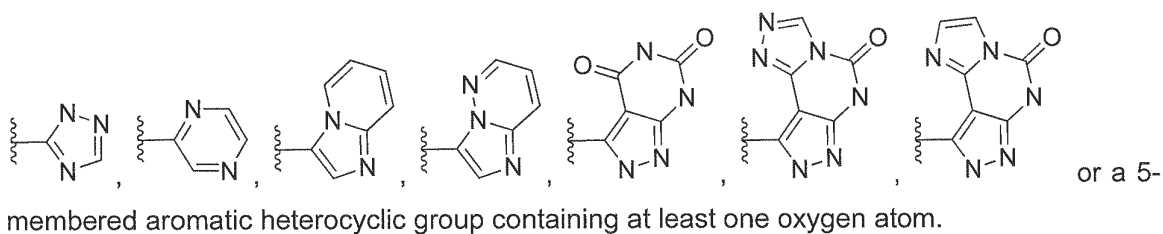
R⁴¹ is selected from H, C₁₋₆-alkyl, C₃₋₆-cycloalkyl and C₃₋₆-heterocycloalkyl,

20 wherein alkyl, cycloalkyl and heterocycloalkyl is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of OH, oxo, CN, halogen, O-C₁₋₆-alkyl, O-halo-C₁₋₆-alkyl, C₃₋₆-heterocycloalkyl and C₃₋₆-cycloalkyl;

x and y are independently selected from 0, 1 and 2;

W is selected from C or S=O;

25 with the proviso that for R³ the 5-14 membered mono-, bi- or tricyclic heteroaryl containing ring is not



In another aspect, there is provided a compound as defined above for use as medicament.

- 5 In another aspect, there is provided use of a compound as defined above in the manufacture of a medicament for the treatment or prophylaxis of a disease or disorder associated with the inhibition or activation of the ROR γ receptor, wherein the disease is selected from the group consisting of rheumatoid arthritis, ankylosing spondylitis, lupus erythematosus, psoriasis, psoriatic arthritis, atopic eczema, inflammatory bowel diseases such as Crohn's disease, mucosal leishmaniasis, systemic sclerosis, Kawasaki disease, Hashimoto's thyroiditis, chronic graft-versus-host disease, acute graft-versus-host disease, Celiac Sprue, idiopathic
- 10 thrombocytopenic thrombotic purpura, myasthenia gravis, Sjorgren's syndrome, scleroderma, ulcerative colitis, epidermal hyperplasia, glomerulonephritis, and chronic obstructive pulmonary disease.

In another aspect, there is provided a pharmaceutical composition comprising a compound as defined above and a pharmaceutically acceptable carrier or excipient.

Thus, the present disclosure provides carboxamide or sulfonamide containing cyclic compounds as ROR γ modulators, which can be used for treating or preventing a disease or disorder associated with the inactivation or activation of the ROR γ receptor.

- 5 The present disclosure relates to a ROR γ modulator which is based on a cyclic scaffold for use in the treatment or prophylaxis of a disease or disorder associated with the inhibition or activation of ROR γ .

When treating the disease or disorder associated with the modulation of the ROR γ receptor, the activity of said receptor is preferably reduced.

- 10 Preferably, the disease or disorder is selected from the group consisting of autoimmune diseases. Autoimmune diseases comprise a group of diseases with a similar etiology of an overshooting immune response against endogenous targets resulting in chronic inflammation and physical disabilities or other severe symptoms. Autoimmune diseases comprise e.g. rheumatoid arthritis, ankylosing spondylitis, lupus erythematosus, psoriasis, psoriatic arthritis,
- 15 atopic eczema, inflammatory bowel diseases such as Crohn's disease, asthma, mucosal leishmaniasis, multiple sclerosis, systemic sclerosis, type 1 diabetes, Kawasaki disease, Hashimoto's thyroiditis, chronic graft-versus-host disease, acute graft-versus-host disease, Celiac Sprue, idiopathic thrombocytopenic thrombotic purpura, myasthenia gravis, Sjorgren's

syndrome, scleroderma, ulcerative colitis, epidermal hyperplasia, glomerulonephritis, chronic obstructive pulmonary disease and amyotrophic lateral sclerosis.

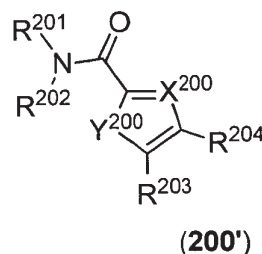
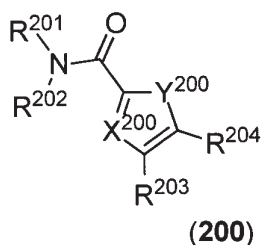
- 5 The present disclosure provides novel compounds to be used in the treatment of diseases or disorders associated with the inactivation or activation of the ROR γ receptor.

Further, the present disclosure relates to a method for treating autoimmune diseases comprising rheumatoid arthritis, ankylosing spondylitis, lupus erythematosus, psoriasis, psoriatic arthritis, atopic eczema, inflammatory bowel diseases such as Crohn's disease,
10 asthma, mucosal leishmaniasis, multiple sclerosis, systemic sclerosis, type 1 diabetes,

Kawasaki disease, Hashimoto's thyroiditis, chronic graft-versus-host disease, acute graft-versus-host disease, Celiac Sprue, idiopathic thrombocytopenic thrombotic purpura, myasthenia gravis, Sjorgren's syndrome, scleroderma, ulcerative colitis, epidermal hyperplasia, glomerulonephritis, chronic obstructive pulmonary disease and amyotrophic lateral sclerosis, said method comprising administering a sufficient amount of a compound according to Formula (1), (1'), (2), (2'), (100), (100'), (200) or (200') as shown below to a mammal in need thereof.

Detailed description of the invention

In a first alternative, the present invention provides a compound represented by Formula (200) and Formula (200')



an enantiomer, diastereomer, tautomer, *N*-oxide, solvate, formulation and pharmaceutically acceptable salt thereof,

wherein

R^{201} and R^{202} are independently selected from H, C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl, C_{3-10} -cycloalkyl, C_{3-10} -heterocycloalkyl, C_{1-10} -alkylene- C_{3-10} -cycloalkyl, C_{1-10} -alkylene- C_{3-10} -heterocycloalkyl, C_{1-10} -alkylene-(5-membered heteroaryl), C_{1-10} -alkylene-(6-membered aryl), C_{1-10} -alkylene-(6-membered heteroaryl), SO_2 - C_{1-10} -alkyl, wherein alkyl, alkenyl, alkynyl, alkylene, cycloalkyl, heterocycloalkyl, aryl and heteroaryl is unsubstituted or substituted with 1 to 7 substituents independently selected from oxo, CN, OR^{211} , $O-C_{2-6}$ -alkylene- OR^{211} , C_{1-6} -alkyl, halo- C_{1-6} -alkyl, halogen, CO_2R^{211} , $CONR^{211}R^{212}$, $CONR^{211}SO_2R^{211}$, COR^{211} , SO_xR^{211} , SO_3H , $SO_2NR^{211}R^{212}$, $NR^{211}COR^{211}$, $NR^{211}SO_2R^{211}$, $NR^{211}-CO-NR^{211}R^{212}$, $NR^{211}-SO_2-NR^{211}R^{212}$, C_{3-10} -cycloalkyl, $O-C_{3-10}$ -cycloalkyl, C_{3-10} -heterocycloalkyl, $O-C_{3-10}$ -heterocycloalkyl and $NR^{211}R^{212}$,

or R^{201} and R^{202} when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing 1 or 2 heteroatoms selected from O, S or N, wherein the ring is unsubstituted or substituted with 1 to 4 substituents independently selected from halogen, oxo, CN, OR^{211} , SO_xR^{211} , SO_3H , $NR^{211}SO_2R^{211}$, $SO_2NR^{211}R^{212}$, C_{0-6} -alkylene- CO_2R^{211} , $CONR^{211}R^{212}$, $CONR^{211}SO_2R^{211}$, COR^{211} , $NR^{211}-CO-R^{211}$, $NR^{211}-CO-NR^{211}R^{212}$, $NR^{211}-SO_2-NR^{211}R^{212}$, $NR^{211}R^{212}$, C_{1-6} -alkyl, halo- C_{1-6} -

alkyl, hydroxy-C₁₋₆-alkyl, C₃₋₈-cycloalkyl, O-C₃₋₈-cycloalkyl, C₃₋₈-heterocycloalkyl and O-C₃₋₈-heterocycloalkyl,

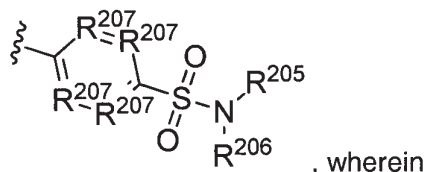
wherein cycloalkyl and heterocycloalkyl are unsubstituted or substituted with 1 to 4 substituents independently selected from halogen, C₁₋₃-alkyl, halo-C₁₋₃-alkyl, OH, O-C₁₋₃-alkyl, O-halo-C₁₋₃-alkyl, SO₂-C₁₋₃-alkyl, COOH and oxo;

R²⁰³ is selected from C₁₋₁₀-alkyl, fluoro-C₁₋₁₀-alkyl, C₀₋₆-alkylene-C₃₋₁₀-cycloalkyl, C₀₋₆-alkylene-C₃₋₁₀-heterocycloalkyl, C₀₋₆-alkylene-(6- to 10-membered aryl), C₀₋₆-alkylene-(5- to 10-membered heteroaryl),

wherein alkyl, alkylene, cycloalkyl, heterocycloalkyl, aryl and heteroaryl is unsubstituted or substituted with 1 to 6 substituents independently selected from oxo, halogen, CN, C₁₋₆-alkyl, halo-C₁₋₆-alkyl, C₃₋₆-cycloalkyl, C₃₋₆-heterocycloalkyl, OR²¹², CO₂R²¹², CONR²¹²R²¹², COR²¹², and

wherein optionally one CH₂ unit in alkyl or alkylene can be replaced by O, SO_x, NH or N(C₁₋₃-alkyl);

R²⁰⁴ is



R²⁰⁵ and R²⁰⁶ is independently selected from H, C₁₋₆-alkyl, halo-C₁₋₆-alkyl, C₀₋₆-alkylene-C₃₋₈-cycloalkyl, C₀₋₆-alkylene-C₃₋₈-heterocycloalkyl, 5- or 6-membered heteroaryl and 6-membered aryl, wherein alkyl, alkylene, cycloalkyl, heterocycloalkyl, aryl and heteroaryl are unsubstituted or substituted with 1 to 6 substituents independently selected from halogen, CN, OH, oxo, C₁₋₃-alkyl, halo-C₁₋₃-alkyl, O-C₁₋₃-alkyl, O-halo-C₁₋₃-alkyl and SO₂-C₁₋₃-alkyl, NR²¹¹R²¹², CO₂R²¹² and CONR²¹¹R²¹²;

and optionally wherein R²⁰⁵ and R²⁰⁶ when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing 1 or 2 heteroatoms selected from O, S or N, wherein the ring is unsubstituted or substituted with 1 to 4 substituents independently selected from fluoro, OH, oxo, C₁₋₄-alkyl and halo-C₁₋₄-alkyl;

R²⁰⁷ is independently selected from N and CR²⁰⁸; or

two adjacent R²⁰⁷ form a 5- or 6-membered unsaturated or partially saturated ring containing carbon atoms and optionally containing 1 or 2 heteroatoms selected from O, S or N, wherein the ring is unsubstituted or substituted with 1 to 4 substituents independently selected from halogen, OH, oxo, C₁₋₄-alkyl and fluoro-C₁₋₄-alkyl;

R^{208} is independently selected from H, halogen, CN, C_{1-6} -alkyl, fluoro- C_{1-6} -alkyl, C_{1-4} -alkylene-OH, C_{1-4} -alkylene-O- C_{1-3} -alkyl, C_{1-4} -alkylene-O-fluoro- C_{1-3} -alkyl, OH, O- C_{1-6} -alkyl, O-fluoro- C_{1-6} -alkyl, C_{3-10} -cycloalkyl,

5 wherein alkylene is unsubstituted or substituted with 1 to 3 substituents selected from F and cycloalkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from F, C_{1-3} -alkyl and fluoro- C_{1-3} -alkyl;

R^{209} is selected from H, halogen, CN, C_{1-3} -alkyl and fluoro- C_{1-3} -alkyl;

R^{211} is independently selected from H, C_{1-6} -alkyl, C_{0-6} -alkylene- C_{3-10} -cycloalkyl and C_{0-6} -alkylene- C_{3-10} -heterocycloalkyl,

10 wherein alkyl, alkylene, cycloalkyl and heterocycloalkyl is unsubstituted or substituted with 1 to 6 substituents selected from the group consisting of halogen, CN, OH, oxo, C_{1-3} -alkyl, halo- C_{1-3} -alkyl, O- C_{1-3} -alkyl, O-halo- C_{1-3} -alkyl, NH_2 , $NH(C_{1-3}\text{-alkyl})$, $N(C_{1-3}\text{-alkyl})_2$, C_{3-6} -heterocycloalkyl, C_{3-6} -cycloalkyl and SO_2 - C_{1-3} -alkyl,

15 wherein cycloalkyl and heterocycloalkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of F, OH, oxo, Me and CF_3 ;

R^{212} is independently selected from H, C_{1-6} -alkyl, halo- C_{1-6} -alkyl and C_{3-6} -cycloalkyl;

X^{200} is selected from N and CR^{209} ;

Y^{200} is selected from O and S;

20 x is independently selected from 0, 1 and 2;

with the proviso, that 4-phenyl-5-(4-sulfamoylphenyl)oxazole-2-carboxamide is excluded.

In a preferred embodiment of the first alternative, the present invention provides a compound of Formula (200) and Formula (200'), wherein compounds with

Y^{200} is S; X^{200} is N;

25 R^{203} is selected from $(CR^8R^9)R^{40}$, $(C=O)R^{40}$, C_{3-} cycloalkylene- R^{40} , OR^{40} , $NR^{41}R^{40}$ and SO_y-R^7 , wherein

R^7 is selected from C_{3-10} -cycloalkyl and C_{3-10} -heterocycloalkyl,

30 wherein cycloalkyl and heterocycloalkyl are unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of halogen, OH, oxo, O- C_{1-6} -alkyl, O-halo- C_{1-6} -alkyl, C_{1-6} -alkyl, halo- C_{1-6} -alkyl, cycloalkyl and heterocycloalkyl;

R^8 and R^9 are independently selected from H, F, C_{1-3} -alkyl, halo- C_{1-3} -alkyl, OH, O- C_{1-3} -alkyl and O-halo- C_{1-3} -alkyl;

R^{40} is C_{3-10} -cycloalkyl, which is unsubstituted or substituted with 1 to 5 substituents independently selected from the group consisting of halogen, OH, oxo, O- C_{1-6} -alkyl, O-halo- C_{1-6} -alkyl, C_{1-6} -alkyl and halo- C_{1-6} -alkyl; and

y is selected from 0, 1 and 2;

5 are excluded.

In a further preferred embodiment in combination with any of the above or below embodiments of the first alternative R^{201} is selected from H, C_{1-10} -alkyl, C_{3-10} -cycloalkyl, C_{3-10} -heterocycloalkyl, C_{1-10} -alkylene- C_{3-10} -cycloalkyl, C_{1-10} -alkylene- C_{3-10} -heterocycloalkyl, C_{1-10} -alkylene-(5-membered heteroaryl), C_{1-10} -alkylene-(6-membered aryl), C_{1-10} -alkylene-(6-membered heteroaryl), SO_2 - C_{1-10} -alkyl, wherein alkyl, alkenyl, alkynyl, alkylene, cycloalkyl, heterocycloalkyl, aryl and heteroaryl is unsubstituted or substituted with 1 to 7 substituents independently selected from oxo, CN, OR^{211} , O- C_{2-6} -alkylene- OR^{211} , C_{1-6} -alkyl, halo- C_{1-6} -alkyl, halogen, CO_2R^{211} , $CONR^{211}R^{212}$, $CONR^{211}SO_2R^{211}$, COR^{211} , SO_xR^{211} , SO_3H , $SO_2NR^{211}R^{212}$, $NR^{211}COR^{211}$, $NR^{211}SO_2R^{211}$, $NR^{211}-CO-NR^{211}R^{212}$, $NR^{211}-SO_2-NR^{211}R^{212}$, C_{3-10} -cycloalkyl, O- C_{3-10} -cycloalkyl, C_{3-10} -heterocycloalkyl, O- C_{3-10} -heterocycloalkyl and $NR^{211}R^{212}$;

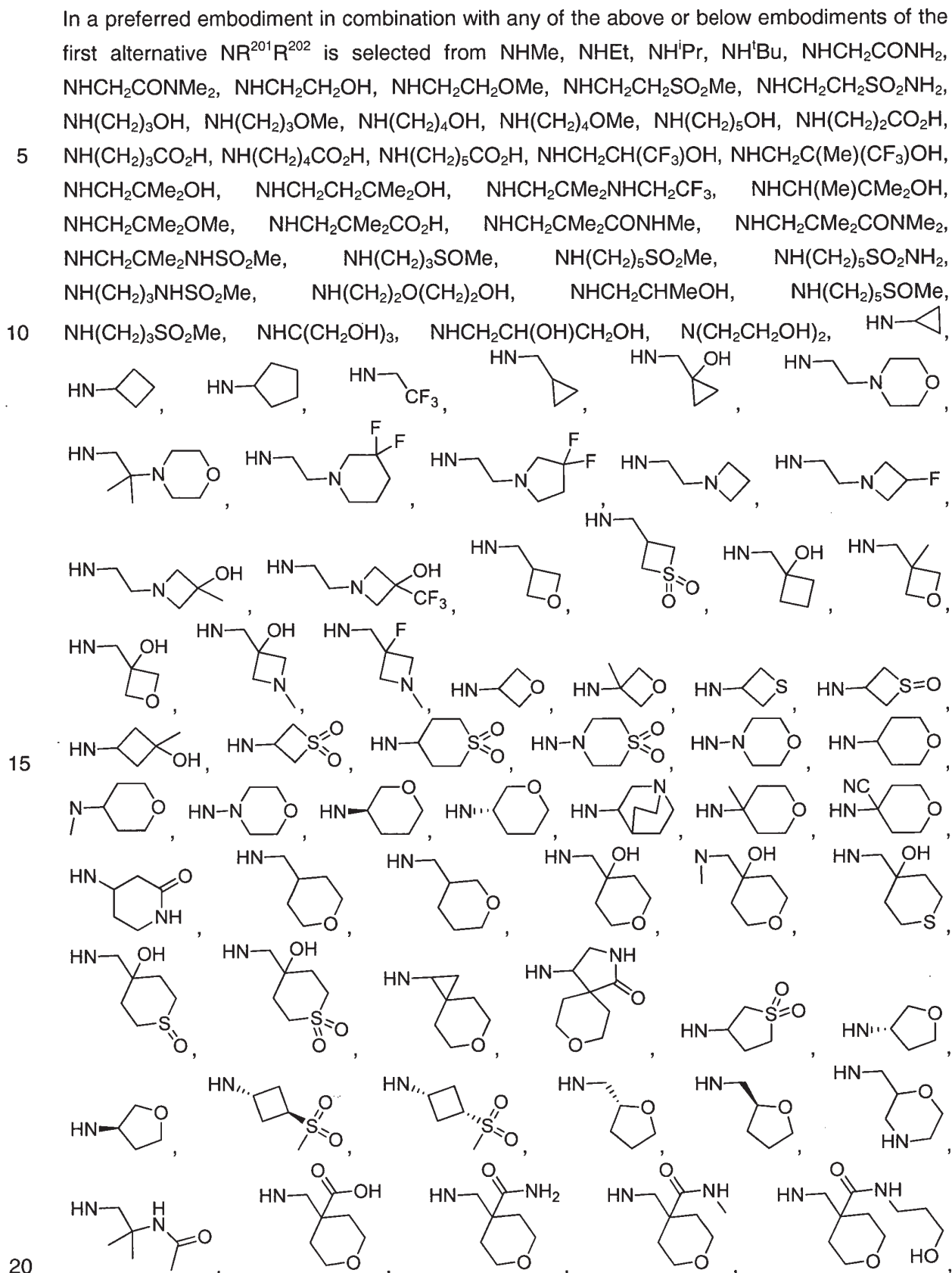
R^{202} is selected from H, C_{1-6} -alkyl, halo- C_{1-6} -alkyl and hydroxy- C_{1-6} -alkyl, more preferably R^{202} is hydrogen;

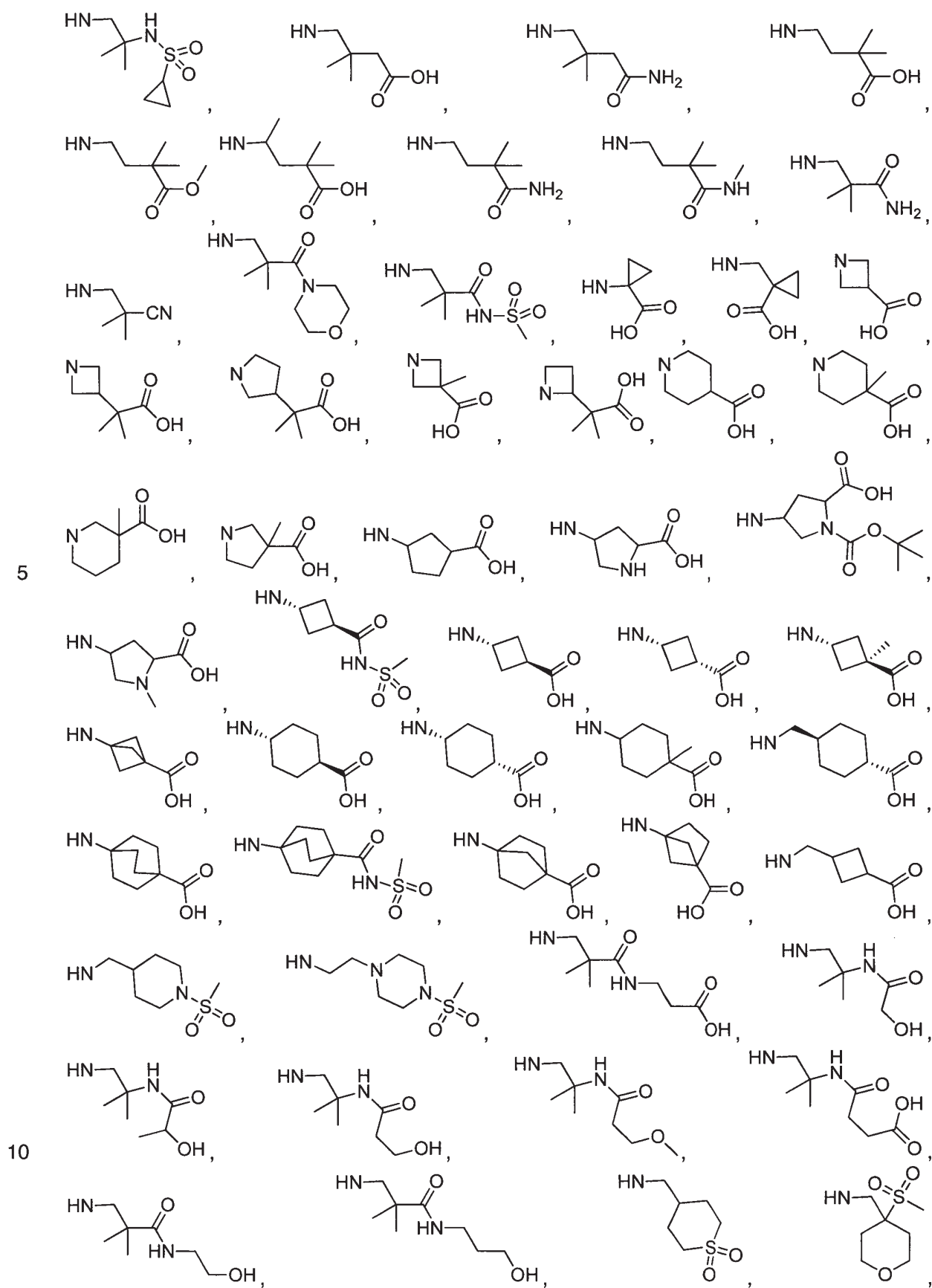
or R^{201} and R^{202} when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing 1 or 2 heteroatoms selected from O, S or N, wherein the ring is unsubstituted or substituted with 1 to 4 substituents independently selected from halogen, oxo, CN, OR^{211} , SO_xR^{211} , SO_3H , $NR^{211}SO_2R^{211}$, $SO_2NR^{211}R^{212}$, C_{0-6} -alkylene- CO_2R^{211} , $CONR^{211}R^{212}$, $CONR^{211}SO_2R^{211}$, COR^{211} , $NR^{211}-CO-R^{211}$, $NR^{211}-CO-NR^{211}R^{212}$, $NR^{211}-SO_2-NR^{211}R^{212}$, $NR^{211}R^{212}$, C_{1-6} -alkyl, halo- C_{1-6} -alkyl, hydroxy- C_{1-6} -alkyl, C_{3-8} -cycloalkyl, O- C_{3-8} -cycloalkyl, C_{3-8} -heterocycloalkyl and O- C_{3-8} -heterocycloalkyl,

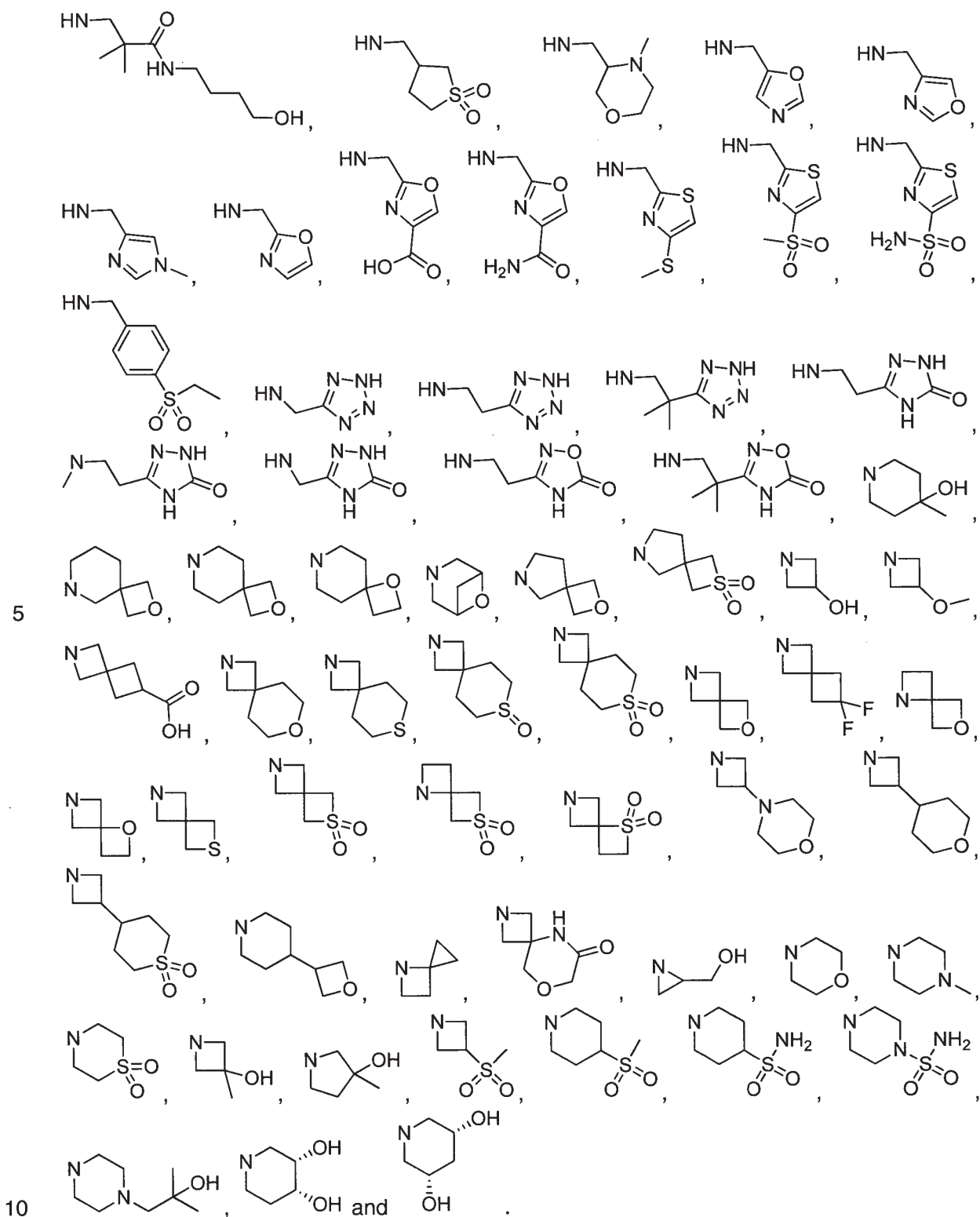
wherein cycloalkyl and heterocycloalkyl are unsubstituted or substituted with 1 to 4 substituents independently selected from halogen, C_{1-3} -alkyl, halo- C_{1-3} -alkyl, OH, O- C_{1-3} -alkyl, O-halo- C_{1-3} -alkyl, SO_2 - C_{1-3} -alkyl, COOH and oxo.

More preferably, R^{201} and R^{202} when taken together with the nitrogen to which they are attached complete a 4- to 6-membered ring containing carbon atoms and optionally containing one additional nitrogen atom, wherein the ring is unsubstituted or substituted with 1 to 4 substituents independently selected from fluoro, oxo, OR^{211} , SO_2R^{211} , $NR^{211}SO_2R^{211}$, $SO_2NR^{211}R^{212}$, C_{0-6} -alkylene- CO_2H , $CONR^{211}R^{212}$, COR^{211} , $NR^{211}R^{212}$, C_{1-6} -alkyl, halo- C_{1-6} -alkyl, hydroxy- C_{1-6} -alkyl, C_{3-8} -cycloalkyl and C_{3-8} -heterocycloalkyl,

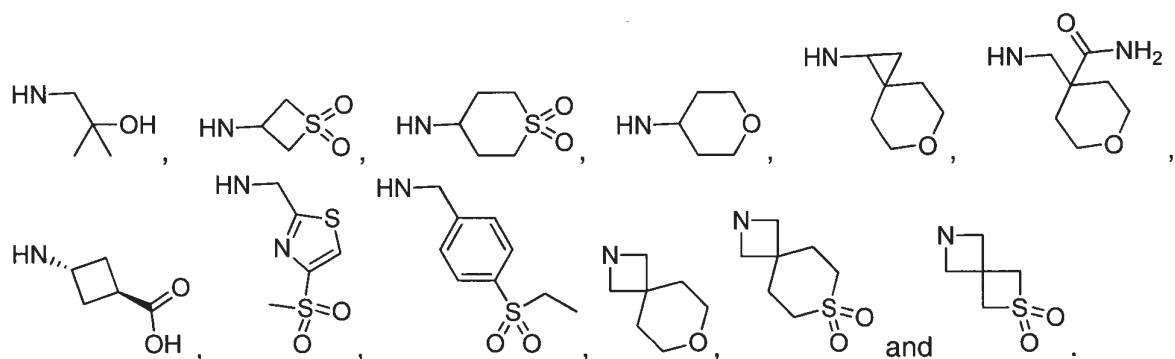
wherein cycloalkyl and heterocycloalkyl are unsubstituted or substituted with 1 to 4 substituents independently selected from halogen, C_{1-3} -alkyl, halo- C_{1-3} -alkyl, SO_2 - C_{1-3} -alkyl, COOH and oxo.



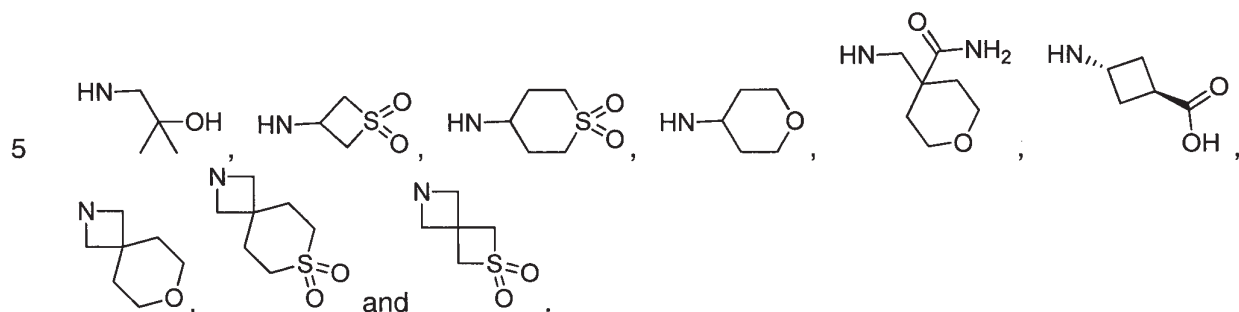




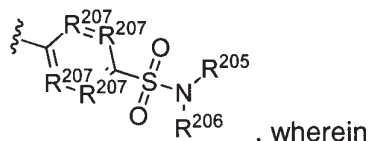
In a more preferred embodiment in combination with any of the above or below embodiments of the first alternative $\text{NR}^{201}\text{R}^{202}$ is selected from



In an even more preferred embodiment in combination with any of the above or below embodiments of the first alternative NR²⁰¹R²⁰² is selected from



In another preferred embodiment in combination with any of the above or below embodiments of the first alternative R²⁰⁴ is



- 10 R²⁰⁵ and R²⁰⁶ is independently selected from H, C₁₋₆-alkyl, halo-C₁₋₆-alkyl, C₀₋₆-alkylene-C₃₋₈-cycloalkyl, C₀₋₆-alkylene-C₃₋₈-heterocycloalkyl, 5- or 6-membered heteroaryl and 6-membered aryl, wherein alkyl, alkylene, cycloalkyl, heterocycloalkyl, aryl and heteroaryl are unsubstituted or substituted with 1 to 6 substituents independently selected from halogen, CN, OH, oxo, C₁₋₃-alkyl, halo-C₁₋₃-alkyl, O-C₁₋₃-alkyl, O-halo-C₁₋₃-alkyl and SO₂-C₁₋₃-alkyl, NR²¹¹R²¹², CO₂R²¹² and CONR²¹¹R²¹²;

and optionally wherein R²⁰⁵ and R²⁰⁶ when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing 1 or 2 heteroatoms selected from O, S or N, wherein the ring is unsubstituted or substituted with 1 to 4 substituents independently selected from fluoro, OH, oxo, C₁₋₄-alkyl and halo-C₁₋₄-alkyl;

R^{207} is independently selected from N and CR^{208} ; or

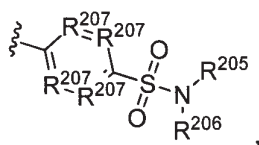
two adjacent R²⁰⁷ form a 5- or 6-membered unsaturated or partially saturated ring containing carbon atoms and optionally containing 1 or 2 heteroatoms selected from O, S or N, wherein

the ring is unsubstituted or substituted with 1 to 4 substituents independently selected from halogen, OH, oxo, C₁₋₄-alkyl and fluoro-C₁₋₄-alkyl;

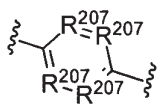
R²⁰⁸ is independently selected from H, halogen, CN, C₁₋₆-alkyl, fluoro-C₁₋₆-alkyl, C₁₋₄-alkylene-OH, C₁₋₄-alkylene-O-C₁₋₃-alkyl, C₁₋₄-alkylene-O-fluoro-C₁₋₃-alkyl, OH, O-C₁₋₆-alkyl, O-fluoro-C₁₋₆-alkyl, C₃₋₁₀-cycloalkyl,

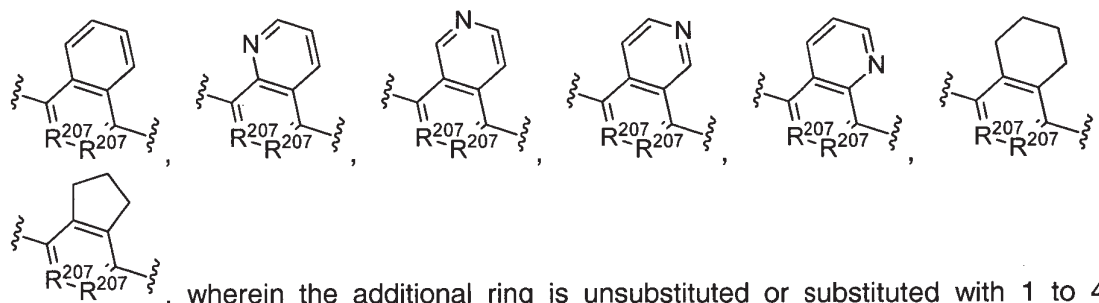
wherein alkylene is unsubstituted or substituted with 1 to 3 substituents selected from F and cycloalkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from F, C₁₋₃-alkyl and fluoro-C₁₋₃-alkyl.

In a more preferred embodiment in combination with any of the above or below embodiments of the first alternative R²⁰⁴ is



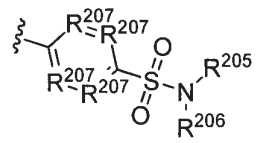
wherein all R²⁰⁷ are CR²⁰⁸ or one R²⁰⁷ is N and the three other R²⁰⁷ are CR²⁰⁸; or

wherein  is selected from



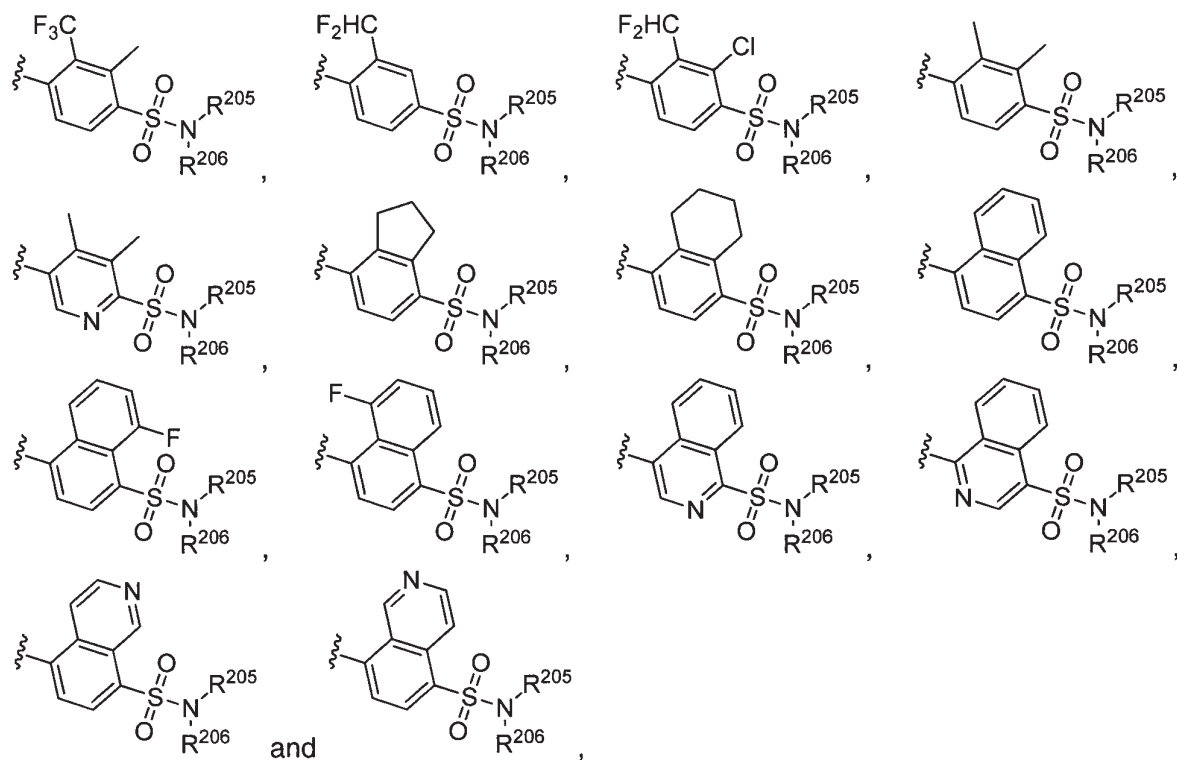
wherein the additional ring is unsubstituted or substituted with 1 to 4 substituents independently selected from halogen, OH, oxo, C₁₋₄-alkyl and fluoro-C₁₋₄-alkyl.

In an even more preferred embodiment in combination with any of the above or below embodiments of the first alternative R²⁰⁴ is



wherein all R²⁰⁷ are CR²⁰⁸ or one R²⁰⁷ is N and the three other R²⁰⁷ are CR²⁰⁸; and

wherein one R²⁰⁸ is independently selected from or two adjacent R²⁰⁸ are independently selected from fluoro, chloro, methyl, CHF₂, CF₃, CMe₂OH, OCHF₂ and OCF₃ while the remaining R²⁰⁸ residues are hydrogen; or

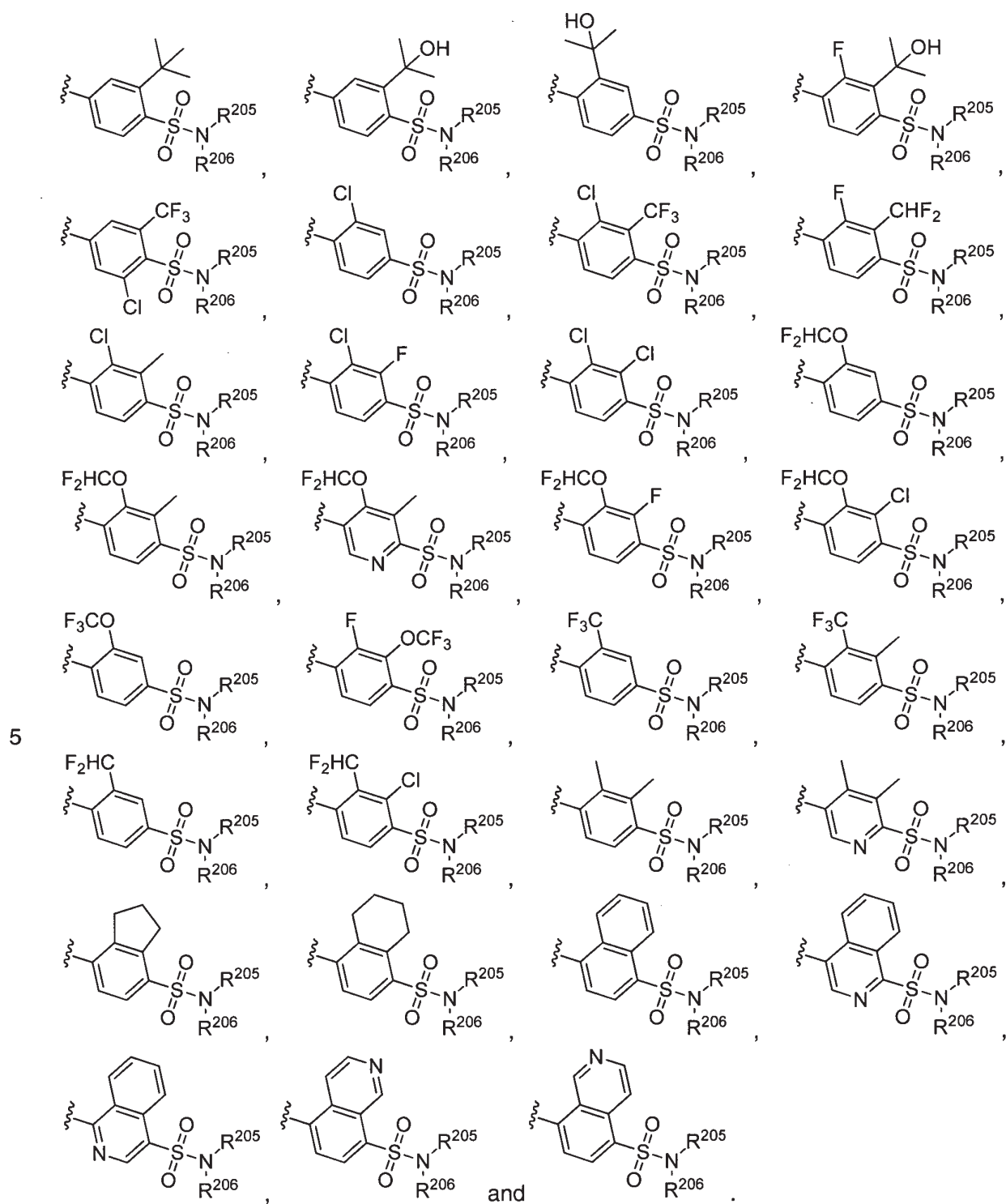


5 wherein

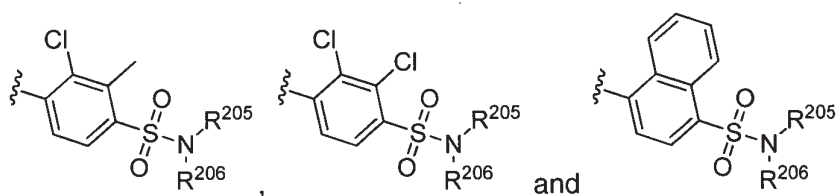
R^{205} and R^{206} is independently selected from H, C₁₋₆-alkyl, halo-C₁₋₆-alkyl, C₀₋₆-alkylene-C₃₋₈-cycloalkyl, C₀₋₆-alkylene-C₃₋₈-heterocycloalkyl, 5- or 6-membered heteroaryl and 6-membered aryl, wherein alkyl, alkylene, cycloalkyl, heterocycloalkyl, aryl and heteroaryl are unsubstituted or substituted with 1 to 6 substituents independently selected from halogen, CN, OH, oxo, C₁₋₃-alkyl, halo-C₁₋₃-alkyl, O-C₁₋₃-alkyl, O-halo-C₁₋₃-alkyl and SO₂-C₁₋₃-alkyl, NR²¹¹R²¹², CO₂R²¹² and CONR²¹¹R²¹²;

and optionally wherein R^{205} and R^{206} when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing 1 or 2 heteroatoms selected from O, S or N, wherein the ring is unsubstituted or substituted with 1 to 4 substituents independently selected from fluoro, OH, oxo, C₁₋₄-alkyl and halo-C₁₋₄-alkyl.

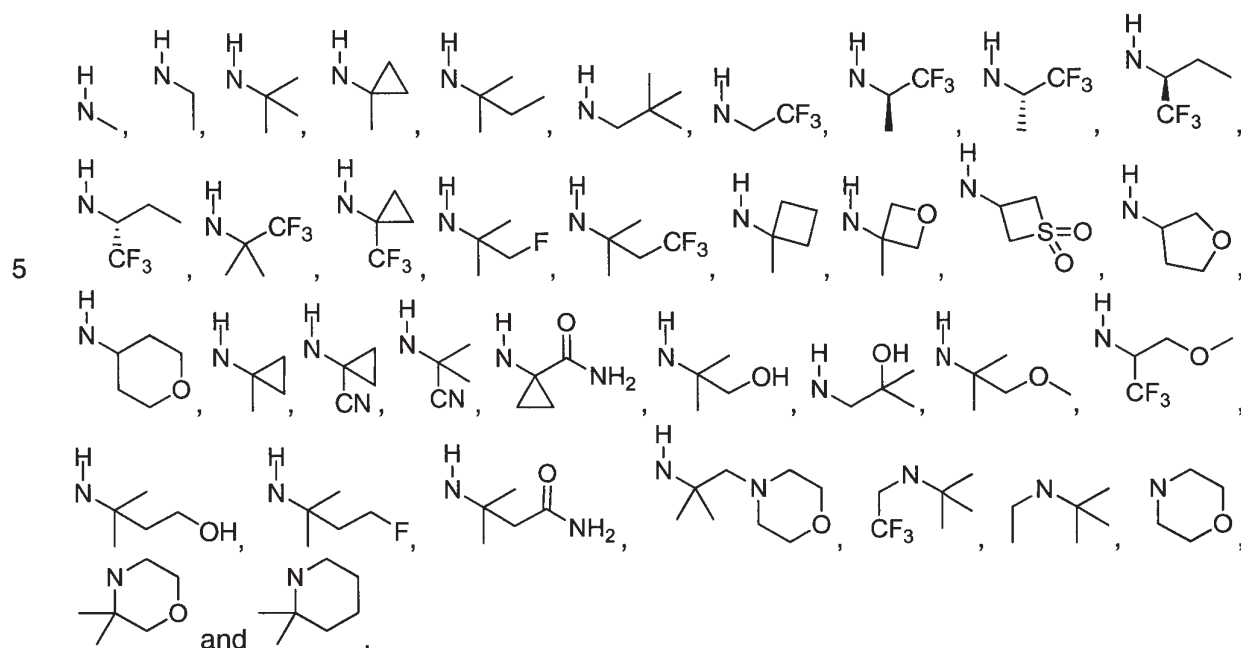
More preferably in combination with any of the above or below embodiments of the first alternative, R^{204} is selected from



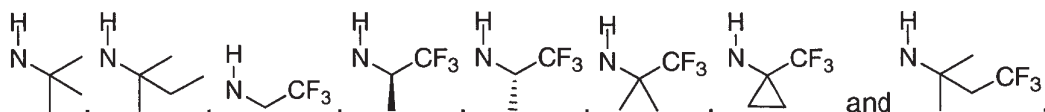
Even more preferably in combination with any of the above or below embodiments of the first
10 alternative, R²⁰⁴ is selected from



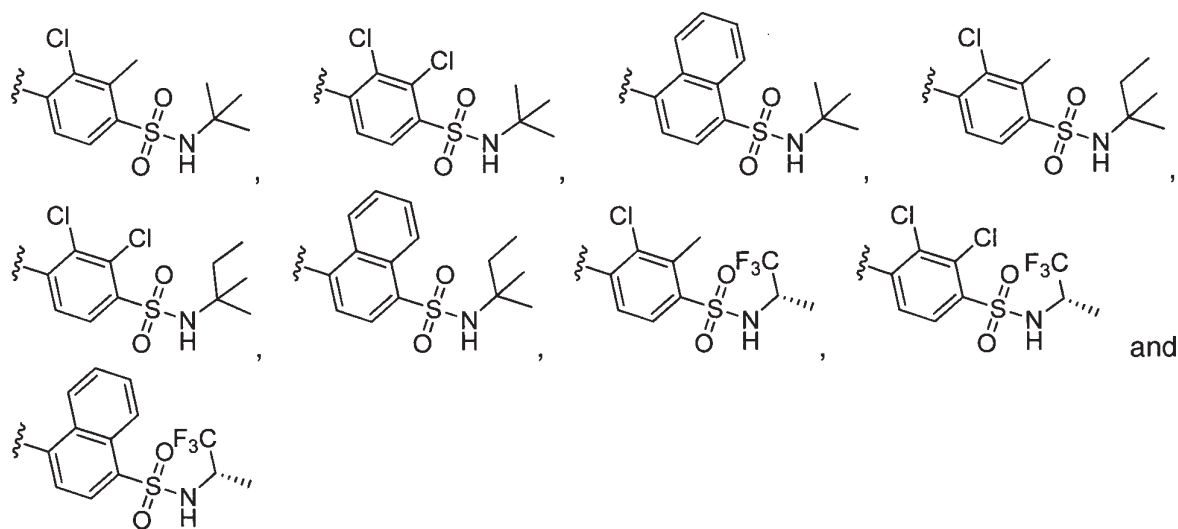
In another preferred embodiment in combination with any of the above or below embodiments of the first alternative NR²⁰⁵R²⁰⁶ is selected from



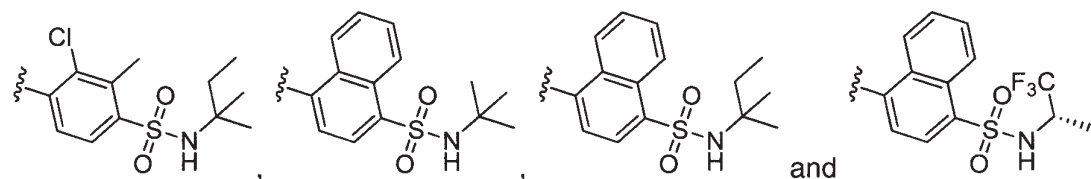
In a more preferred embodiment in combination with any of the above or below embodiments
10 of the first alternative NR²⁰⁵R²⁰⁶ is preferably



In another preferred embodiment in combination with any of the above or below embodiments of the first alternative R²⁰⁴ is selected from



In a more preferred embodiment in combination with any of the above or below embodiments
 5 of the first alternative R^{204} is selected from



In another preferred embodiment in combination with any of the above or below embodiments
 of the first alternative R^{203} is selected from C_{1-10} -alkyl, fluoro- C_{1-10} -alkyl, C_{0-6} -alkylene- C_{3-10} -
 cycloalkyl, C_{0-6} -alkylene- C_{3-10} -heterocycloalkyl, C_{0-6} -alkylene-(6- to 10-membered aryl), C_{0-6} -
 10 alkylene-(5- to 10-membered heteroaryl),

wherein alkyl, alkylene, cycloalkyl, heterocycloalkyl, aryl and heteroaryl is unsubstituted
 or substituted with 1 to 6 substituents independently selected from oxo, halogen, CN, C_{1-6} -
 alkyl, halo- C_{1-6} -alkyl, C_{3-6} -cycloalkyl, C_{3-6} -heterocycloalkyl, OR^{212} , CO_2R^{212} ,
 $CONR^{212}R^{212}$, COR^{212} ; and

15 wherein optionally one CH_2 unit in alkyl or alkylene can be replaced by O, SO_x , NH or $N(C_{1-3}$ -
 alkyl).

In an equally preferred embodiment in combination with any of the above or below
 embodiments of the first alternative, R^{203} is selected from C_{1-10} -alkyl, fluoro- C_{1-10} -alkyl, C_{0-6} -
 alkylene- C_{3-10} -cycloalkyl, C_{0-6} -alkylene- C_{3-10} -heterocycloalkyl, C_{0-6} -alkylene-(5- to 10-
 20 membered heteroaryl),

wherein alkyl, alkylene, cycloalkyl, heterocycloalkyl and heteroaryl is unsubstituted or
 substituted with 1 to 6 substituents independently selected from oxo, halogen, CN, C_{1-6} -
 alkyl, halo- C_{1-6} -alkyl, C_{3-6} -cycloalkyl, C_{3-6} -heterocycloalkyl, OR^{212} , CO_2R^{212} , $CONR^{212}R^{212}$,
 COR^{212} ; and

wherein optionally one CH₂ unit in alkyl or alkylene can be replaced by O, SO_x, NH or N(C₁₋₃-alkyl).

- In a more preferred embodiment in combination with any of the above or below embodiments of the first alternative, R²⁰³ is selected from C₁₋₁₀-alkyl, fluoro-C₁₋₁₀-alkyl, C₀₋₆-alkylene-C₃₋₁₀-cycloalkyl and C₀₋₆-alkylene-C₃₋₁₀-heterocycloalkyl,

wherein alkyl, alkylene, cycloalkyl and heterocycloalkyl is unsubstituted or substituted with 1 to 6 substituents independently selected from oxo, halogen, CN, C₁₋₆-alkyl, halo-C₁₋₆-alkyl, C₃₋₆-cycloalkyl, C₃₋₆-heterocycloalkyl, OR²¹², CO₂R²¹², CONR²¹²R²¹², COR²¹², and

- wherein optionally one CH₂ unit in alkyl or alkylene can be replaced by O, SO_x, NH or N(C₁₋₃-alkyl).

- In a more preferred embodiment in combination with any of the above or below embodiments of the first alternative R²⁰³ is selected from C₁₋₈-alkyl, fluoro-C₁₋₈-alkyl, C₀₋₂-alkylene-C₃₋₈-cycloalkyl, C₀₋₂-alkylene-C₃₋₈-heterocycloalkyl, C₀₋₂-alkylene-(6- to 10-membered aryl), C₀₋₂-alkylene-(5- to 10-membered heteroaryl),

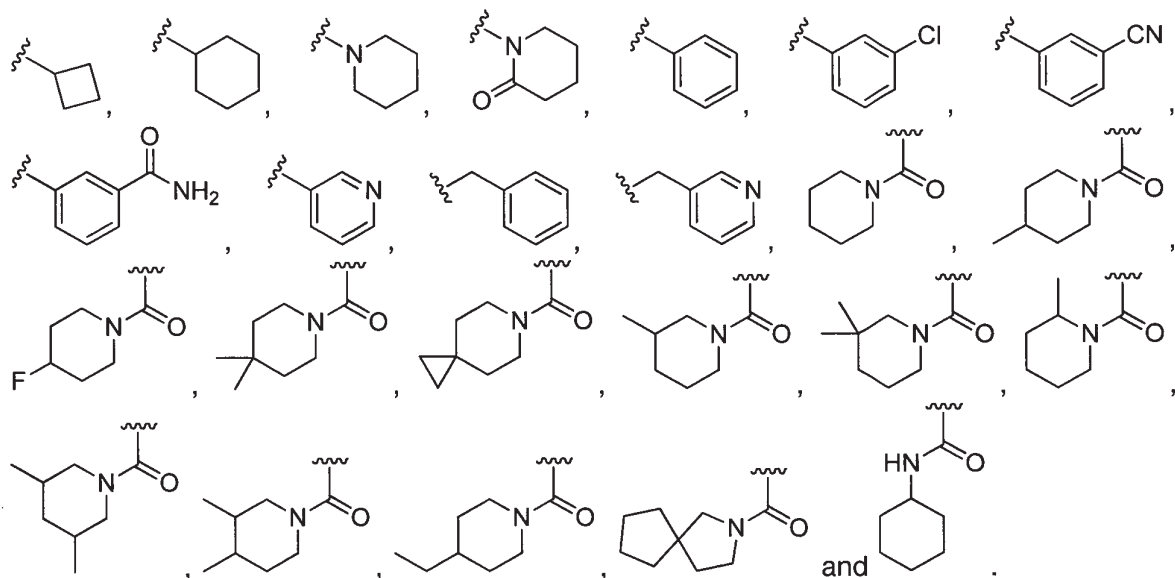
wherein alkyl, alkylene, cycloalkyl, heterocycloalkyl, aryl and heteroaryl is unsubstituted or substituted with 1 to 6 substituents independently selected from oxo, fluoro, chloro, CN, CONH₂, C₁₋₃-alkyl, fluoro-C₁₋₃-alkyl, C₃₋₆-cycloalkyl, C₃₋₆-heterocycloalkyl and OC₁₋₄-alkyl.

- In a more preferred embodiment in combination with any of the above or below embodiments of the first alternative R²⁰³ is selected from C₁₋₈-alkyl, fluoro-C₁₋₆-alkyl, C₃₋₈-cycloalkyl, C₃₋₈-heterocycloalkyl, 6-membered aryl, 6-membered heteroaryl, CH₂-(6-membered aryl), CH₂-(6-membered heteroaryl), CO-(6-membered aryl), CO-(6-membered heteroaryl) and CO-NR^aR^b (wherein R^aR^b form a 4- to 8-membered saturated heterocycloalkyl),

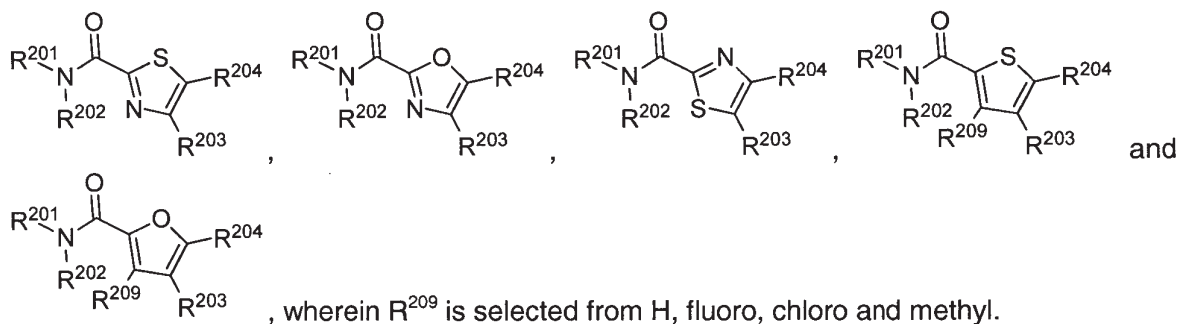
- wherein cycloalkyl and heterocycloalkyl is unsubstituted or optionally substituted with 1 to 4 substituents independently selected from oxo, C₁₋₃-alkyl, fluoro-C₁₋₃-alkyl and C₃₋₈-cycloalkyl; and

wherein aryl and heteroaryl is optionally substituted with 1 to 3 substituents independently selected from fluoro, chloro, CN, C₁₋₃-alkyl and fluoro-C₁₋₃-alkyl.

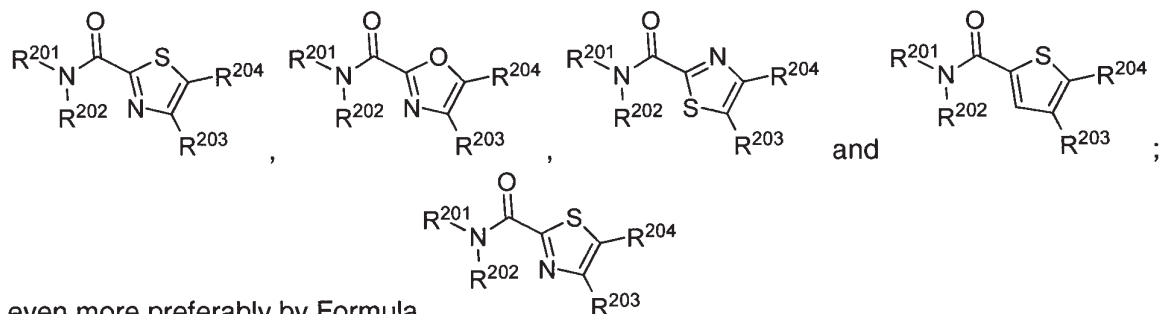
- In a more preferred embodiment in combination with any of the above or below embodiments of the first alternative R²⁰³ is selected from CHF₂, CH₂CH₃, CH₂CH₂CH₃, CMe₃, CH₂OCMe₃,



- 5 In another preferred embodiment in combination with any of the above or below embodiments of the first alternative the compound is represented by a Formula selected from



- 10 In a more preferred embodiment in combination with any of the above or below embodiments of the first alternative the compound is represented by a Formula selected from



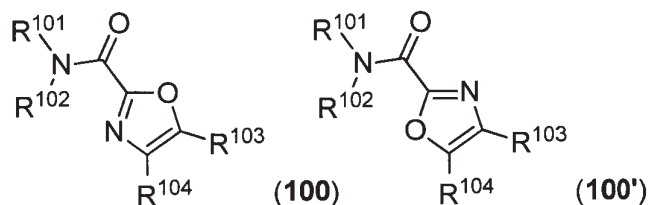
The invention also provides the compound of the first alternative of the invention for use as a medicament.

- 15 Also provided is the compound of the first alternative of the invention for use in the treatment or prophylaxis of a disease or disorder associated with the inhibition or activation of the ROR γ receptor.

Also provided is the compound of the first alternative of the invention in treating ROR γ mediated inflammatory and autoimmune diseases. Preferably, the disease is selected from the group consisting of rheumatoid arthritis, ankylosing spondylitis, lupus erythematosus, psoriasis, psoriatic arthritis, atopic eczema, inflammatory bowel diseases such as Crohn's disease, asthma, mucosal leishmaniasis, multiple sclerosis, systemic sclerosis, type 1
 5 diabetes, Kawasaki disease, Hashimoto's thyroiditis, chronic graft-versus-host disease, acute graft-versus-host disease, Celiac Sprue, idiopathic thrombocytopenic thrombotic purpura, myasthenia gravis, Sjorgren's syndrome, scleroderma, ulcerative colitis, epidermal hyperplasia, glomerulonephritis, chronic obstructive pulmonary disease and amyotrophic
 10 lateral sclerosis.

Also provided is a pharmaceutical composition comprising the compound of the first alternative of the invention and a pharmaceutically acceptable carrier.

In a second alternative, the present invention provides a compound represented by Formula
 15 (100) and Formula (100')



an enantiomer, diastereomer, tautomer, *N*-oxide, solvate, formulation and pharmaceutically acceptable salt thereof,

wherein

- 20 R¹⁰¹ and R¹⁰² are independently selected from H, C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl, C₃₋₁₀-cycloalkyl, C₃₋₁₀-heterocycloalkyl, C₁₋₁₀-alkylene-C₃₋₁₀-cycloalkyl, C₁₋₁₀-alkylene-C₃₋₁₀-heterocycloalkyl, C₁₋₁₀-alkylene-(5-membered heteroaryl), C₁₋₁₀-alkylene-(6-membered aryl), C₁₋₁₀-alkylene-(6-membered heteroaryl), SO₂-C₁₋₁₀-alkyl, wherein alkyl, alkenyl, alkynyl, alkylene, cycloalkyl, heterocycloalkyl, aryl and heteroaryl is unsubstituted or substituted with 1
 25 to 7 substituents independently selected from oxo, CN, OR¹¹¹, O-C₂₋₆-alkylene-OR¹¹¹, C₁₋₆-alkyl, halo-C₁₋₆-alkyl, halogen, CO₂R¹¹¹, CONR¹¹¹R¹¹², CONR¹¹¹SO₂R¹¹¹, COR¹¹¹, SO_xR¹¹¹, SO₃H, SO₂NR¹¹¹R¹¹², NR¹¹¹COR¹¹¹, NR¹¹¹SO₂R¹¹¹, NR¹¹¹-CO-NR¹¹¹R¹¹², NR¹¹¹-SO₂-NR¹¹¹R¹¹², C₃₋₁₀-cycloalkyl, O-C₃₋₁₀-cycloalkyl, C₃₋₁₀-heterocycloalkyl, O-C₃₋₁₀-heterocycloalkyl and NR¹¹¹R¹¹²;
 30 or R¹⁰¹ and R¹⁰² when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing 1 or 2 heteroatoms selected from O, S or N, wherein the ring is unsubstituted or substituted with 1 to 4 substituents independently selected from halogen, oxo, CN, OR¹¹¹, SO_xR¹¹¹, SO₃H,

$\text{NR}^{111}\text{SO}_2\text{R}^{111}$, $\text{SO}_2\text{NR}^{111}\text{R}^{112}$, C_{0-6} -alkylene- $\text{CO}_2\text{R}^{111}$, $\text{CONR}^{111}\text{R}^{112}$, $\text{CONR}^{111}\text{SO}_2\text{R}^{111}$, COR^{111} , $\text{NR}^{111}\text{-CO-R}^{111}$, $\text{NR}^{111}\text{-CO-NR}^{111}\text{R}^{112}$, $\text{NR}^{111}\text{-SO}_2\text{-NR}^{111}\text{R}^{112}$, $\text{NR}^{111}\text{R}^{112}$, C_{1-6} -alkyl, halo- C_{1-6} -alkyl, hydroxy- C_{1-6} -alkyl, C_{3-8} -cycloalkyl, O- C_{3-8} -cycloalkyl, C_{3-8} -heterocycloalkyl and O- C_{3-8} -heterocycloalkyl,

- 5 wherein cycloalkyl and heterocycloalkyl are unsubstituted or substituted with 1 to 4 substituents independently selected from halogen, C_{1-3} -alkyl, halo- C_{1-3} -alkyl, OH, O- C_{1-3} -alkyl, O-halo- C_{1-3} -alkyl, $\text{SO}_2\text{-C}_{1-3}$ -alkyl, COOH and oxo;

R^{103} is a 6-10 membered mono- or bicyclic aryl or a 5-14 membered mono-, bi- or tricyclic heteroaryl containing 1 to 5 heteroatoms independently selected from the group consisting of

10 N, O and S,

- wherein aryl and heteroaryl is optionally substituted with 1 to 5 substituents independently selected from halogen, C_{1-6} -alkyl, C_{1-6} -alkenyl, C_{1-6} -alkynyl, halo- C_{1-6} -alkyl, OH, O- C_{1-6} -alkyl, O-halo- C_{1-6} -alkyl, C_{0-6} -alkylene- C_{3-10} -cycloalkyl, C_{0-6} -alkylene- C_{3-10} -heterocycloalkyl, C_{0-6} -alkylene-(5- or 6-membered heteroaryl), C_{1-6} -alkylene-O- R^{131} , C_{0-6} -alkylene-CN, C_{0-6} -alkylene- $\text{N}(\text{R}^{131})_2$, O- C_{3-10} -cycloalkyl, O- C_{1-6} -alkylene-O- R^{131} , O- C_{3-10} -heterocycloalkyl, C_{0-6} -alkylene-COOR¹³¹, C_{0-6} -alkylene-C(O)R¹³¹, C_{0-6} -alkylene-C(O)N(R¹³¹)₂, C_{0-6} -alkylene-N(R¹³¹)C(O)R¹³¹, C_{0-6} -alkylene-SO-R¹³¹, C_{0-6} -alkylene-SO₂-R¹³¹, C_{0-6} -alkylene-SO₂-N(R¹³¹)₂, C_{0-6} -alkylene-N(R¹³¹)SO₂-R¹³¹, C_{0-6} -alkylene-SO₂- C_{3-10} -heterocycloalkyl and C_{0-6} -alkylene-SO₂- C_{3-10} -heterocycloalkyl,
- 15

- 20 wherein alkylene, cycloalkyl, heterocycloalkyl and the 5- or 6-membered heteroaryl is optionally substituted by 1 to 4 substituents independently selected from the group consisting of halogen, CN, C_{1-3} -alkyl, halo- C_{1-3} -alkyl, OH, oxo, =N-OR¹³², O- C_{1-3} -alkyl and O-halo- C_{1-3} -alkyl,

- or wherein two adjacent substituents completing a 3- to 8-membered saturated or partially unsaturated ring containing carbon atoms and optionally containing 1 to 3 heteroatoms selected from O, S or N, wherein the ring is unsubstituted or substituted with 1 to 7 substituents independently selected from halogen, C_{1-6} -alkyl, halo- C_{1-6} -alkyl, C_{3-6} -cycloalkyl, C_{3-6} -heterocycloalkyl, oxo, =N-OR¹³², OH, O- C_{1-6} -alkyl and O-halo- C_{1-6} -alkyl;
- 25

- 30 R^{104} is selected from $(\text{CR}^{108}\text{R}^{109})\text{R}^{140}$, $(\text{C=O})\text{R}^{140}$, OR¹⁴⁰, $\text{SO}_y\text{-R}^{107}$ and C_{3-6} -cycloalkyl, which is spirocyclic fused with R^{140} ,

wherein cycloalkyl is unsubstituted or substituted with 1 to 4 substituents independently selected from the group consisting of F, methyl and CF₃;

R^{107} is selected from C_{3-10} -cycloalkyl and C_{3-10} -heterocycloalkyl,

wherein cycloalkyl and heterocycloalkyl are unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of halogen, OH, oxo, O-C₁₋₆-alkyl, O-halo-C₁₋₆-alkyl, C₁₋₆-alkyl, halo-C₁₋₆-alkyl, cycloalkyl and heterocycloalkyl;

5 R¹⁰⁸ is independently selected from H, F, C₁₋₃-alkyl, halo-C₁₋₃-alkyl, OH, O-C₁₋₃-alkyl and O-halo-C₁₋₃-alkyl;

R¹⁰⁹ is selected from H, F, C₁₋₃-alkyl and halo-C₁₋₃-alkyl;

R¹¹¹ is independently selected from H, C₁₋₆-alkyl, C₀₋₆-alkylene-C₃₋₁₀-cycloalkyl and C₀₋₆-alkylene-C₃₋₁₀-heterocycloalkyl,

10 wherein alkyl, alkylene, cycloalkyl and heterocycloalkyl is unsubstituted or substituted with 1 to 6 substituents selected from the group consisting of halogen, CN, OH, oxo, C₁₋₃-alkyl, halo-C₁₋₃-alkyl, O-C₁₋₃-alkyl, O-halo-C₁₋₃-alkyl, NH₂, NH(C₁₋₃-alkyl), N(C₁₋₃-alkyl)₂, C₃₋₆-heterocycloalkyl, C₃₋₆-cycloalkyl and SO₂-C₁₋₃-alkyl,

15 wherein cycloalkyl and heterocycloalkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of F, OH, oxo, Me and CF₃;

R¹¹² is independently selected from H, C₁₋₆-alkyl, halo-C₁₋₆-alkyl and C₃₋₆-cycloalkyl;

20 R¹³¹ is independently selected from H, C₁₋₆-alkyl, halo-C₁₋₆-alkyl, C₀₋₆-alkylene-C₃₋₈-cycloalkyl, C₀₋₆-alkylene-C₃₋₈-heterocycloalkyl, 5- or 6-membered heteroaryl and 6-membered aryl, wherein alkyl, alkylene, cycloalkyl, heterocycloalkyl, aryl and heteroaryl are unsubstituted or substituted with 1 to 6 substituents independently selected from halogen, CN, OH, oxo, =N-OR¹³², C₁₋₃-alkyl, halo-C₁₋₃-alkyl, O-C₁₋₃-alkyl, O-halo-C₁₋₃-alkyl and SO₂-C₁₋₃-alkyl;

25 and optionally wherein two R¹³¹ when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing 1 or 2 heteroatoms selected from O, S or N, wherein the ring is unsubstituted or substituted with 1 to 4 substituents independently selected from fluoro, OH, oxo, C₁₋₄-alkyl and halo-C₁₋₄-alkyl;

R¹³² is independently selected from H, C₁₋₆-alkyl and halo-C₁₋₆-alkyl and C₃₋₆-cycloalkyl;

30 R¹⁴⁰ is C₃₋₁₀-cycloalkyl, which is unsubstituted or substituted with 1 to 5 substituents independently selected from the group consisting of halogen, OH, oxo, O-C₁₋₆-alkyl, O-halo-C₁₋₆-alkyl, C₁₋₆-alkyl, halo-C₁₋₆-alkyl, C₃₋₈-cycloalkyl and C₃₋₈-heterocycloalkyl;

x and y are independently selected from 0, 1 and 2.

In a further preferred embodiment in combination with any of the above or below embodiments of the second alternative R¹⁰¹ is selected from H, C₁₋₁₀-alkyl, C₃₋₁₀-cycloalkyl, C₃₋₁₀-heterocycloalkyl, C₁₋₁₀-alkylene-C₃₋₁₀-cycloalkyl, C₁₋₁₀-alkylene-C₃₋₁₀-heterocycloalkyl, C₁₋₁₀-alkylene-(5-membered heteroaryl), C₁₋₁₀-alkylene-(6-membered aryl), C₁₋₁₀-alkylene-(6-

35

membered heteroaryl), wherein alkyl, alkenyl, alkynyl, alkylene, cycloalkyl, heterocycloalkyl, aryl and heteroaryl is unsubstituted or substituted with 1 to 7 substituents independently selected from oxo, CN, OR¹¹¹, O-C₂₋₆-alkylene-OR¹¹¹, C₁₋₆-alkyl, halo-C₁₋₆-alkyl, halogen, CO₂R¹¹¹, CONR¹¹¹R¹¹², CONR¹¹¹SO₂R¹¹¹, COR¹¹¹, SO_xR¹¹¹, SO₃H, SO₂NR¹¹¹R¹¹²,
 5 NR¹¹¹COR¹¹¹, NR¹¹¹SO₂R¹¹¹, NR¹¹¹-CO-NR¹¹¹R¹¹², NR¹¹¹-SO₂-NR¹¹¹R¹¹², C₃₋₈-cycloalkyl, O-C₃₋₈-cycloalkyl, C₃₋₈-heterocycloalkyl, O-C₃₋₈-heterocycloalkyl and NR¹¹¹R¹¹²;

R¹⁰² are selected from the group consisting of H, C₁₋₃-alkyl, fluoro-C₁₋₃-alkyl and hydroxy-C₁₋₃-alkyl, more preferably R¹⁰² is hydrogen;

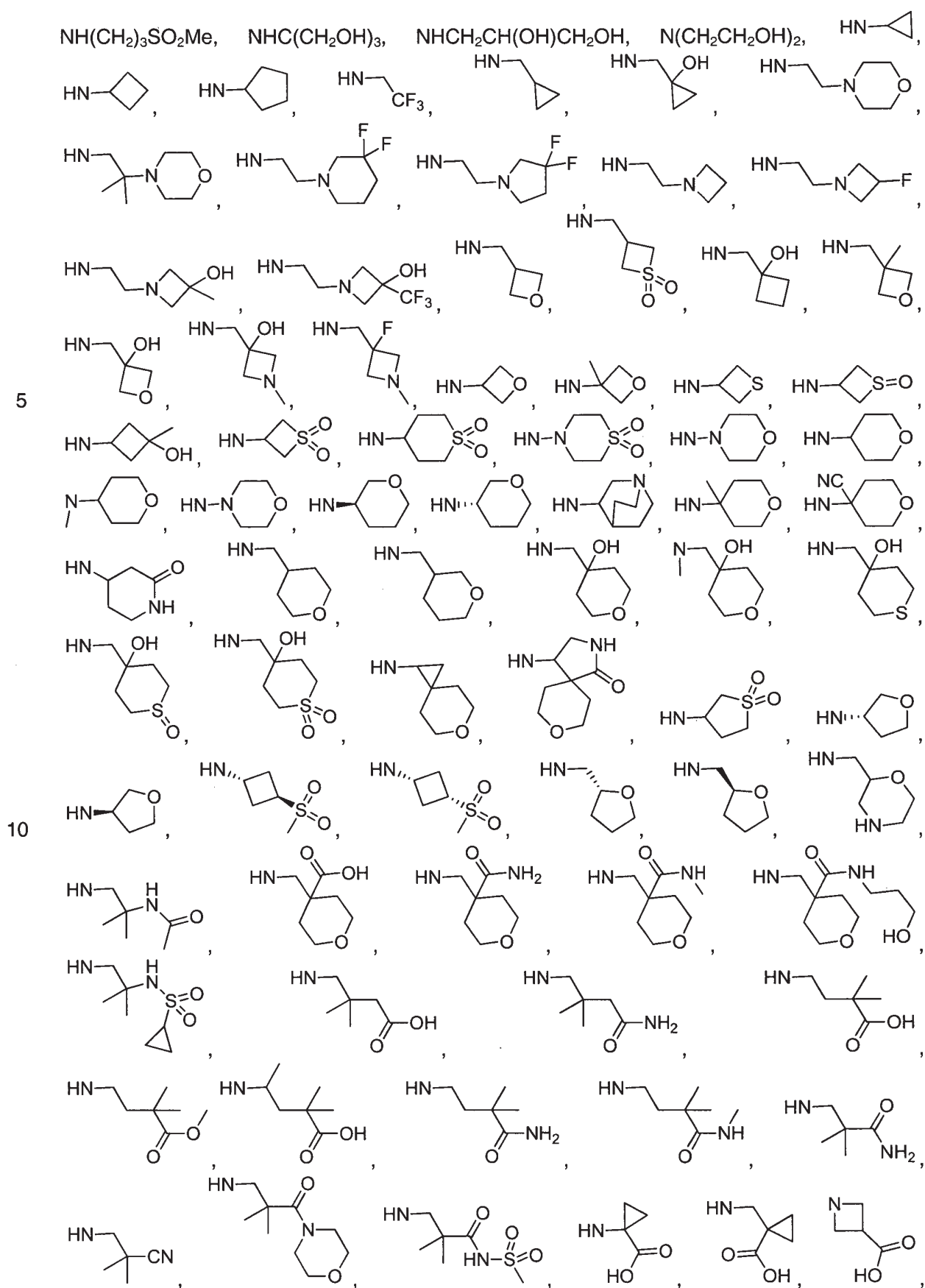
or R¹⁰¹ and R¹⁰² when taken together with the nitrogen to which they are attached complete a
 10 3- to 8-membered ring containing carbon atoms and optionally containing 1 or 2 heteroatoms selected from O, S or N, wherein the ring is unsubstituted or substituted with 1 to 4 substituents independently selected from halogen, oxo, CN, OR¹¹¹, SO_xR¹¹¹, SO₃H, NR¹¹¹SO₂R¹¹¹, SO₂NR¹¹¹R¹¹², C₀₋₆-alkylene-CO₂R¹¹¹, CONR¹¹¹R¹¹², CONR¹¹¹SO₂R¹¹¹, COR¹¹¹, NR¹¹¹-CO-R¹¹¹, NR¹¹¹-CO-NR¹¹¹R¹¹², NR¹¹¹-SO₂-NR¹¹¹R¹¹², NR¹¹¹R¹¹², C₁₋₆-alkyl, halo-C₁₋₆-
 15 alkyl, hydroxy-C₁₋₆-alkyl, C₃₋₈-cycloalkyl, O-C₃₋₈-cycloalkyl, C₃₋₈-heterocycloalkyl and O-C₃₋₈-heterocycloalkyl,

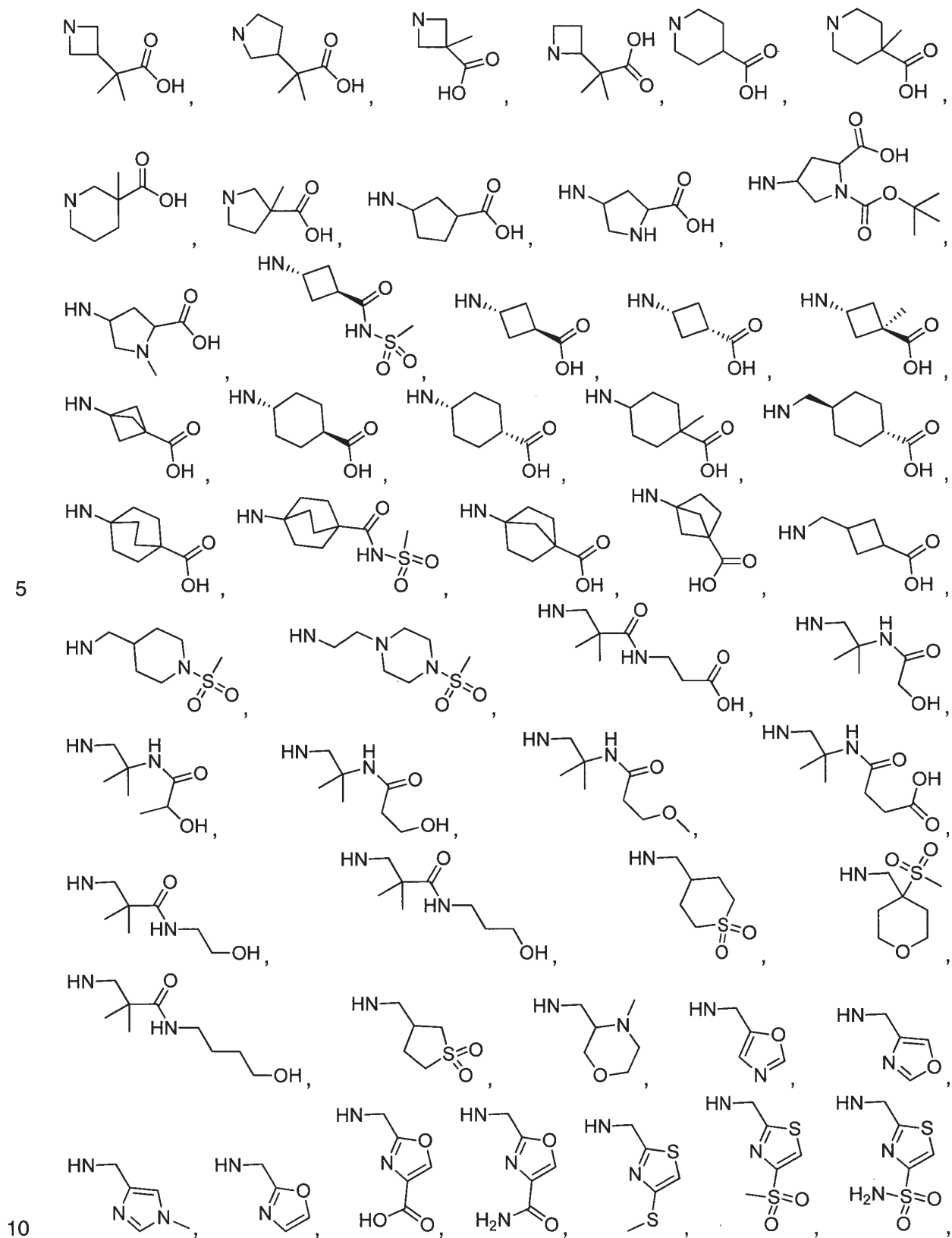
wherein cycloalkyl and heterocycloalkyl are unsubstituted or substituted with 1 to 4 substituents independently selected from halogen, C₁₋₃-alkyl, halo-C₁₋₃-alkyl, OH, O-C₁₋₃-alkyl, O-halo-C₁₋₃-alkyl, SO₂-C₁₋₃-alkyl, COOH and oxo.

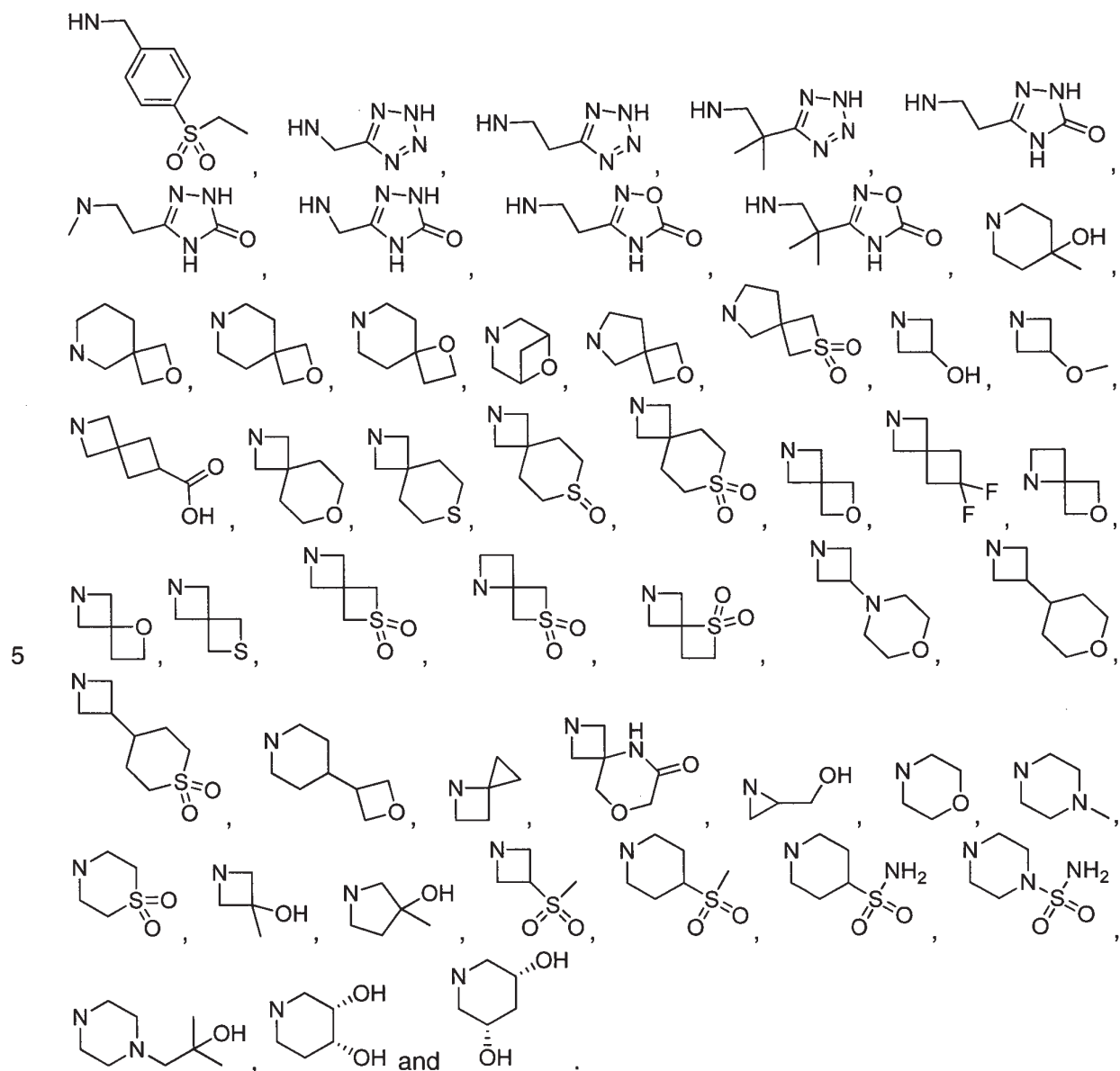
20 More preferably, R¹⁰¹ and R¹⁰² when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing 1 or 2 heteroatoms selected from O, S or N, wherein the ring is unsubstituted or substituted with 1 to 4 substituents independently selected from fluoro, oxo, OR¹¹¹, SO₂R¹¹¹, NR¹¹¹SO₂R¹¹¹, SO₂NR¹¹¹R¹¹², C₀₋₆-alkylene-CO₂H, CONR¹¹¹R¹¹², COR¹¹¹, NR¹¹¹R¹¹², C₁₋₆-alkyl,
 25 halo-C₁₋₆-alkyl, hydroxy-C₁₋₆-alkyl, C₃₋₈-cycloalkyl and C₃₋₈-heterocycloalkyl,

wherein cycloalkyl and heterocycloalkyl are unsubstituted or substituted with 1 to 4 substituents independently selected from halogen, C₁₋₃-alkyl, halo-C₁₋₃-alkyl, SO₂-C₁₋₃-alkyl, COOH and oxo.

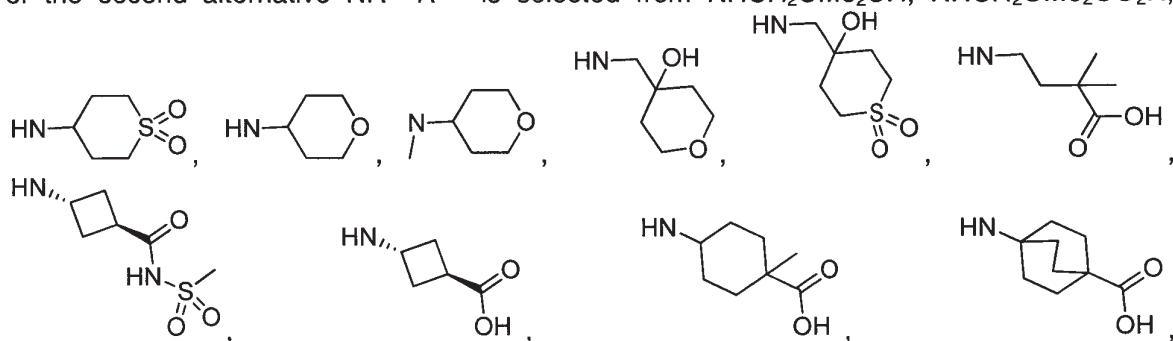
In a preferred embodiment in combination with any of the above or below embodiments of the
 30 second alternative NR¹⁰¹R¹⁰² is selected from NHMe, NEt, NHⁱPr, NHⁱBu, NHCH₂CONH₂, NHCH₂CONMe₂, NHCH₂CH₂OH, NHCH₂CH₂OMe, NHCH₂CH₂SO₂Me, NHCH₂CH₂SO₂NH₂, NH(CH₂)₃OH, NH(CH₂)₃OMe, NH(CH₂)₄OH, NH(CH₂)₄OMe, NH(CH₂)₅OH, NH(CH₂)₂CO₂H, NH(CH₂)₃CO₂H, NH(CH₂)₄CO₂H, NH(CH₂)₅CO₂H, NHCH₂CH(CF₃)OH, NHCH₂C(Me)(CF₃)OH, NHCH₂CMe₂OH, NHCH₂CH₂CMe₂OH, NHCH₂CMe₂NHCH₂CF₃, NHCH(Me)CMe₂OH,
 35 NHCH₂CMe₂OMe, NHCH₂CMe₂CO₂H, NHCH₂CMe₂CONHMe, NHCH₂CMe₂CONMe₂, NHCH₂CMe₂NHSO₂Me, NH(CH₂)₃SOMe, NH(CH₂)₅SO₂Me, NH(CH₂)₅SO₂NH₂, NH(CH₂)₃NHSO₂Me, NH(CH₂)₂O(CH₂)₂OH, NHCH₂CHMeOH, NH(CH₂)₅SOMe,

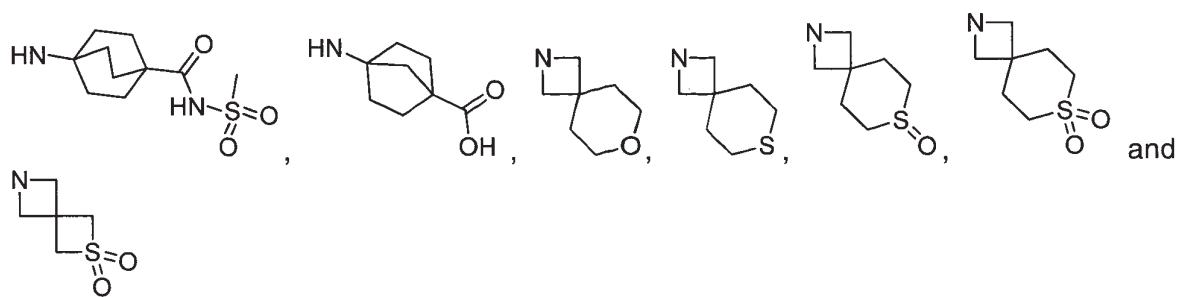




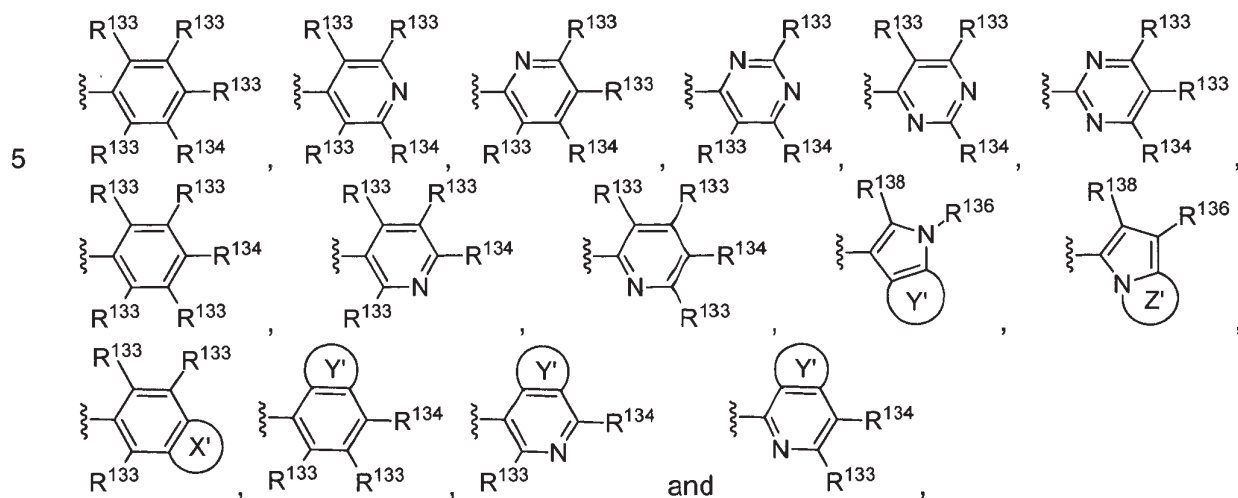


In a more preferred embodiment in combination with any of the above or below embodiments of the second alternative $\text{NR}^{101}\text{R}^{102}$ is selected from $\text{NHCH}_2\text{CMe}_2\text{OH}$, $\text{NHCH}_2\text{CMe}_2\text{CO}_2\text{H}$,





In another preferred embodiment in combination with any of the above or below embodiments of the second alternative R^{103} is selected from



wherein

R^{133} is independently selected from H, halogen, CN, C_{1-6} -alkyl, fluoro- C_{1-6} -alkyl, C_{1-4} -alkylene-OH, C_{1-4} -alkylene-O- C_{1-3} -alkyl, C_{1-4} -alkylene-O-fluoro- C_{1-3} -alkyl, OH, O- C_{1-6} -alkyl, O-fluoro- C_{1-6} -alkyl, NH- C_{1-6} -alkyl, NH-fluoro- C_{1-6} -alkyl, C_{3-10} -cycloalkyl,

wherein alkylene is unsubstituted or substituted with 1 to 3 substituents selected from F and cycloalkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from F, C_{1-3} -alkyl and fluoro- C_{1-3} -alkyl;

R^{134} are independently selected from H, halogen, CN, C_{1-6} -alkyl, fluoro- C_{1-6} -alkyl, C_{1-4} -alkylene-OH, C_{1-4} -alkylene-O- C_{1-3} -alkyl, C_{1-4} -alkylene-O-fluoro- C_{1-3} -alkyl, OH, O- C_{1-6} -alkyl, O-fluoro- C_{1-6} -alkyl, NH- C_{1-6} -alkyl, NH-fluoro- C_{1-6} -alkyl, C_{3-10} -cycloalkyl, C_{0-6} -alkylene- C_{3-10} -heterocycloalkyl, 5-membered heteroaryl, 6-membered heteroaryl, $C(O)N(R^{137})_2$ and $SO_2N(R^{137})_2$,

wherein alkylene is unsubstituted or substituted with 1 to 3 substituents selected from F and cycloalkyl, heterocycloalkyl and heteroaryl is unsubstituted or substituted with 1 to 3 substituents independently selected from F, C_{1-3} -alkyl, fluoro- C_{1-3} -alkyl, OH, O- C_{1-3} -alkyl, fluoro-O- C_{1-3} -alkyl;

R^{135} is selected from halogen, C_{1-6} -alkyl, halo- C_{1-6} -alkyl, C_{3-6} -cycloalkyl, C_{3-6} -heterocycloalkyl, oxo, $=N-OR^{132}$, OH, O- C_{1-6} -alkyl and O-halo- C_{1-6} -alkyl;

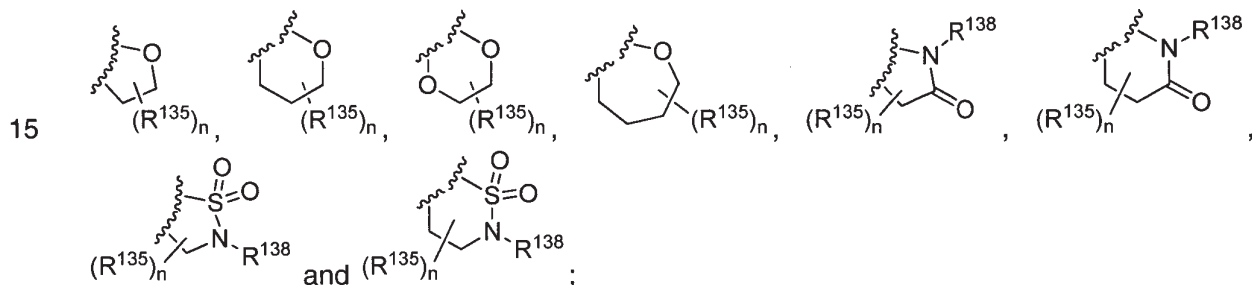
R^{136} is selected from C_{1-6} -alkyl, fluoro- C_{1-6} -alkyl, $C(O)N(R^{137})_2$, $SO_2N(R^{137})_2$;

- 5 R^{137} is independently selected from H, C_{1-6} -alkyl, halo- C_{1-6} -alkyl, C_{0-4} -alkylene- C_{3-6} -cycloalkyl, C_{0-4} -alkylene- C_{3-6} -heterocycloalkyl, wherein alkyl and alkylene is unsubstituted or substituted with 1 to 4 substituents selected from halogen, OH, O- C_{1-3} -alkyl, CN; and cycloalkyl or heterocycloalkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from F, CN, OH, oxo, C_{1-3} -alkyl and fluoro- C_{1-3} -alkyl;

- 10 or wherein two R^{137} when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing 1 or 2 heteroatoms selected from O, S or N, wherein the ring is unsubstituted or substituted with 1 to 4 substituents independently selected from fluoro, OH, oxo, C_{1-4} -alkyl and halo- C_{1-4} -alkyl;

R^{138} is selected from H, C_{1-3} -alkyl and fluoro- C_{1-3} -alkyl;

X' is an annelated saturated heterocycle selected from the group consisting of

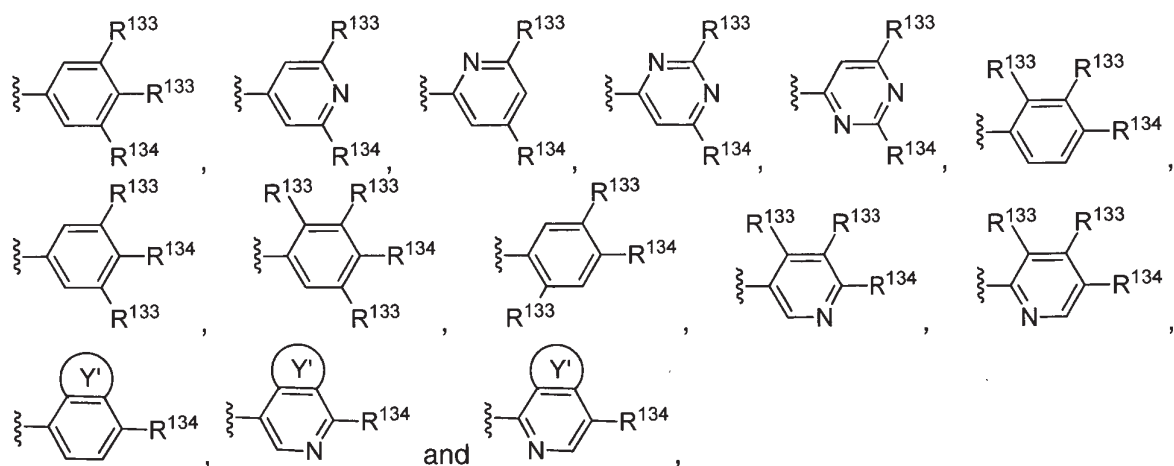


- 20 Y' is an annelated 5- or 6-membered carbocycle, an annelated 6-membered aryl or an annelated 6-membered heteroaryl containing 1 to 2 nitrogen atoms, wherein the carbocycle, aryl or heteroaryl is unsubstituted or substituted with 1 to 3 substituents selected from fluoro, C_{1-3} -alkyl and fluoro- C_{1-3} -alkyl;

Z' is an annelated 6-membered cycle forming a heteroaryl containing 1 to 2 nitrogen atoms, wherein the heteroaryl is unsubstituted or substituted with 1 to 3 substituents selected from fluoro, C_{1-3} -alkyl and fluoro- C_{1-3} -alkyl;

n is selected from 1 to 4.

- 25 In a more preferred embodiment in combination with any of the above or below embodiments of the second alternative R^{103} is selected from



wherein

- 5 R^{133} is independently selected from H, halogen, CN, C_{1-6} -alkyl, fluoro- C_{1-6} -alkyl, C_{1-4} -alkylene-OH, C_{1-4} -alkylene-O- C_{1-3} -alkyl, C_{1-4} -alkylene-O-fluoro- C_{1-3} -alkyl, OH, O- C_{1-6} -alkyl, O-fluoro- C_{1-6} -alkyl, NH- C_{1-6} -alkyl, NH-fluoro- C_{1-6} -alkyl, C_{3-10} -cycloalkyl, $C(O)N(R^{137})_2$,

wherein alkylene is unsubstituted or substituted with 1 to 3 substituents selected from F and cycloalkyl is unsubstituted or substituted with 1 to 3 substituents independently
10 selected from F, C_{1-3} -alkyl and fluoro- C_{1-3} -alkyl;

R^{134} is selected from C_{1-4} -alkylene-OH, C_{1-4} -alkylene-O- C_{1-3} -alkyl, C_{1-4} -alkylene-O-fluoro- C_{1-3} -alkyl, C_{3-10} -cycloalkyl, $C(O)N(R^{137})_2$, $SO_2N(R^{137})_2$,

wherein alkylene is unsubstituted or substituted with 1 to 3 substituents selected from F and cycloalkyl is unsubstituted or substituted with 1 to 3 substituents independently
15 selected from F, C_{1-3} -alkyl and fluoro- C_{1-3} -alkyl;

R^{137} is independently selected from H, C_{1-6} -alkyl, halo- C_{1-6} -alkyl, C_{0-4} -alkylene- C_{3-6} -cycloalkyl, C_{0-4} -alkylene- C_{3-6} -heterocycloalkyl,

wherein alkyl and alkylene is unsubstituted or substituted with 1 to 4 substituents selected from halogen, OH, O- C_{1-3} -alkyl, CN, $CONH_2$; and

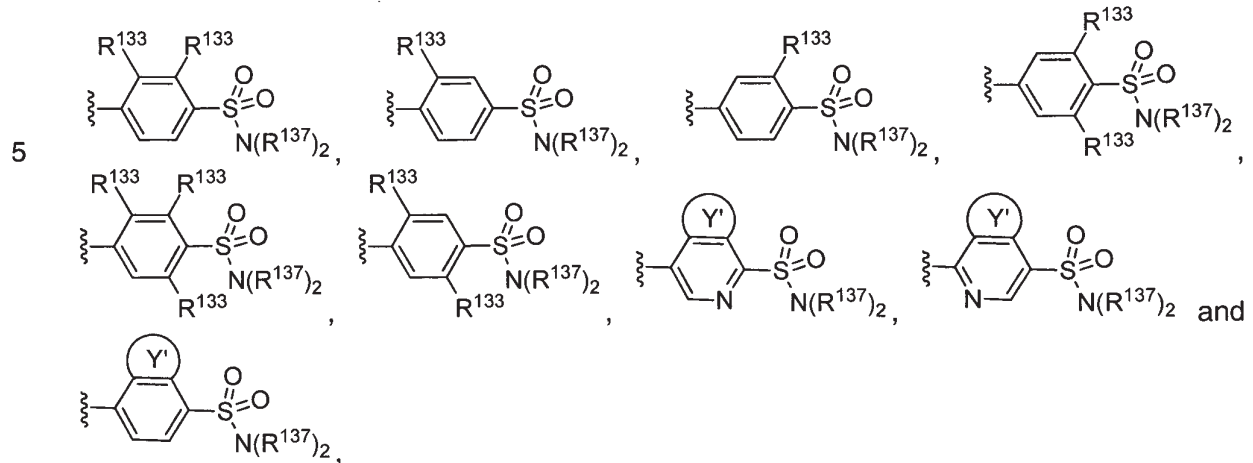
wherein cycloalkyl or heterocycloalkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from F, CN, OH, oxo, O- C_{1-3} -alkyl, C_{1-3} -alkyl and fluoro- C_{1-3} -alkyl;

or wherein two R^{137} when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing 1 or 2
25 heteroatoms selected from O, S or N, wherein the ring is unsubstituted or substituted with 1 to 4 substituents independently selected from fluoro, OH, oxo, C_{1-4} -alkyl and halo- C_{1-4} -alkyl;

Y' is an annelated 5- or 6-membered carbocycle, an annelated 6-membered aryl or an annelated 6-membered heteroaryl containing 1 to 2 nitrogen atoms, wherein the carbocycle,

aryl or heteroaryl is unsubstituted or substituted with 1 to 3 substituents selected from fluoro, methyl and CF₃.

In an even more preferred embodiment in combination with any of the above or below embodiments of the second alternative R¹⁰³ is selected from



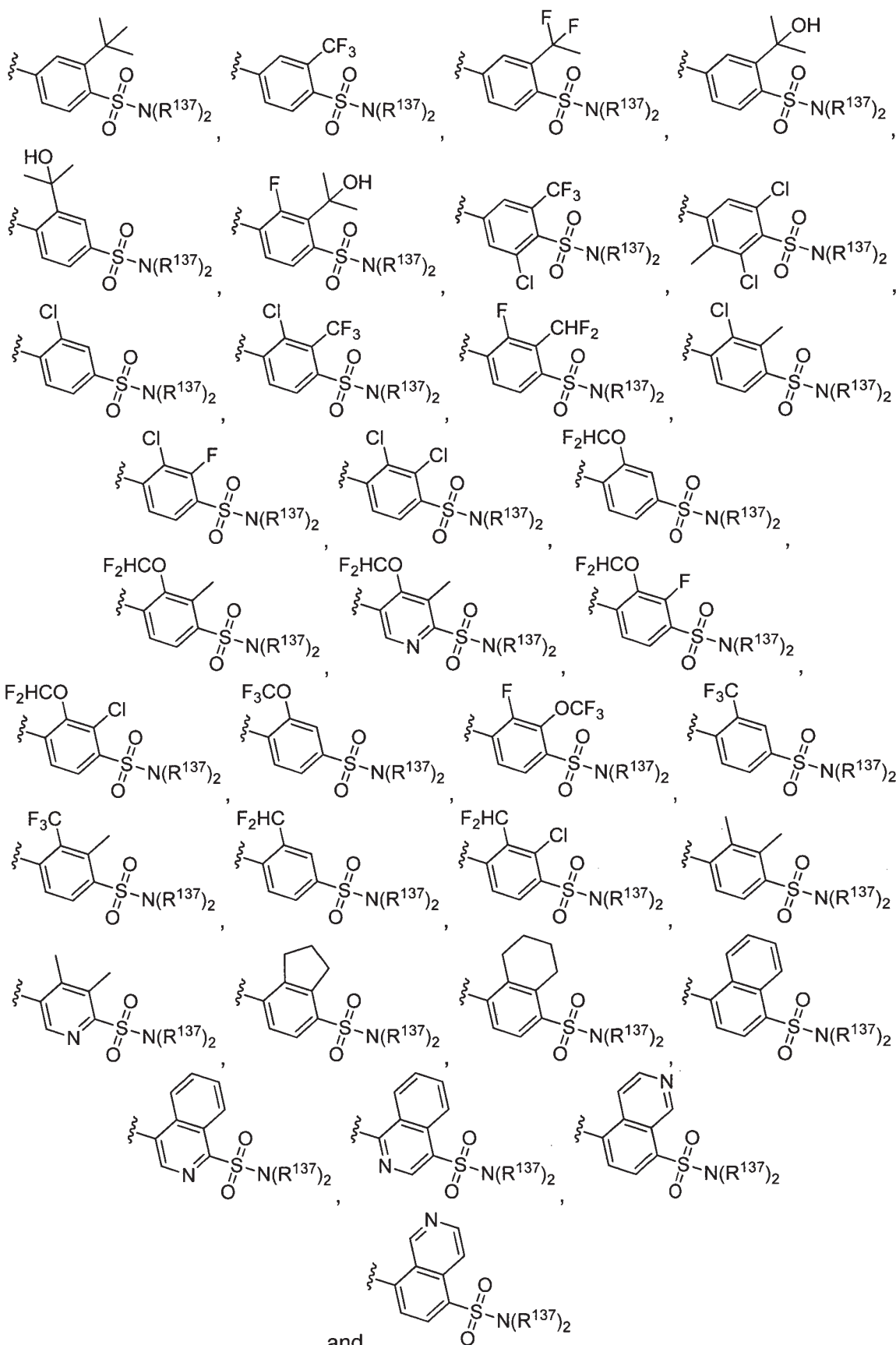
wherein R¹³³ is independently selected from H, halogen, C₁₋₆-alkyl, fluoro-C₁₋₆-alkyl, C₁₋₄-alkylene-OH, C₁₋₄-alkylene-O-C₁₋₃-alkyl, O-C₁₋₆-alkyl, and O-fluoro-C₁₋₆-alkyl, more preferably R³³ is independently selected from fluoro, chloro, CF₃, CHF₂, OCF₃, OCHF₂, methyl, butyl and CMe₂OH;

one R¹³⁷ is selected from H, C₁₋₆-alkyl, fluoro-C₁₋₆-alkyl and the other R¹³⁷ is selected from C₁₋₆-alkyl, fluoro-C₁₋₆-alkyl, C₀₋₄-alkylene-C₃₋₆-cycloalkyl, C₀₋₄-alkylene-C₃₋₆-heterocycloalkyl, wherein alkyl and alkylene is unsubstituted or substituted with a substituent selected from halogen, OH, O-C₁₋₃-alkyl, CN, CONH₂; and cycloalkyl or heterocycloalkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from F, CN, CONH₂, OH, oxo, C₁₋₃-alkyl and fluoro-C₁₋₃-alkyl,

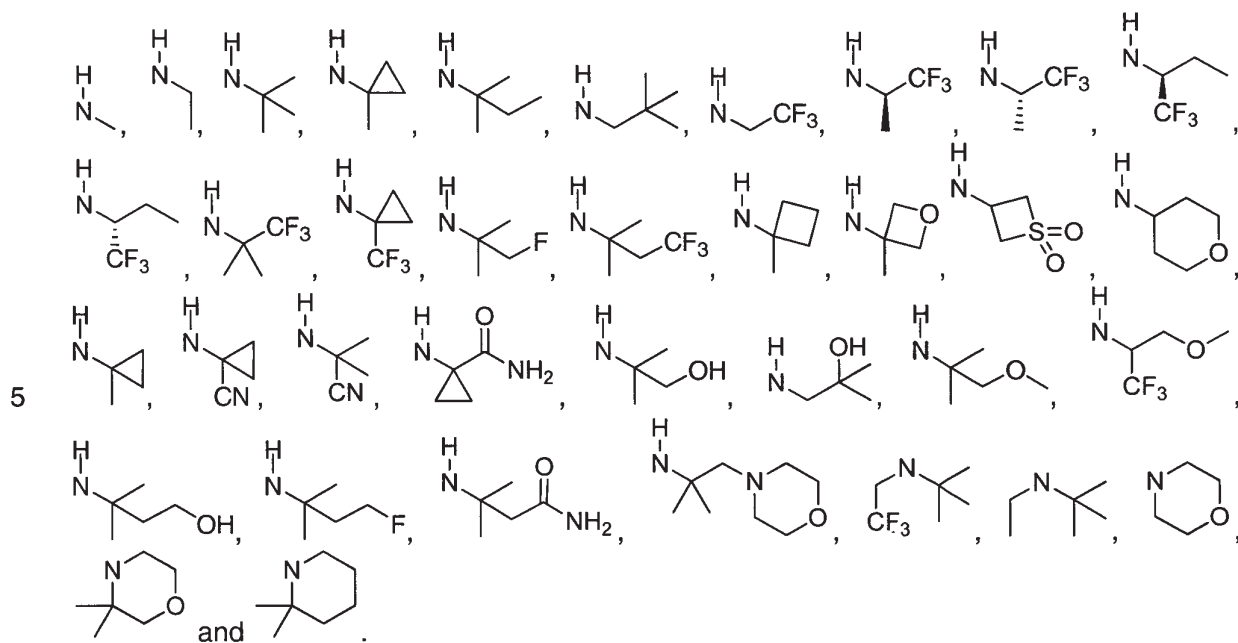
or wherein two R¹³⁷ when taken together with the nitrogen to which they are attached may complete a 3- to 8-membered ring containing carbon atoms and optionally containing 1 or 2 heteroatoms selected from O, S or N, wherein the ring is unsubstituted or substituted with 1 to 4 substituents independently selected from fluoro, OH, oxo, C₁₋₄-alkyl and halo-C₁₋₄-alkyl;

Y' is an annelated 5- or 6-membered carbocycle, an annelated 6-membered aryl or an annelated 6-membered heteroaryl containing 1 to 2 nitrogen atoms, wherein the carbocycle, aryl or heteroaryl is unsubstituted or substituted with 1 to 3 substituents selected from fluoro, methyl and CF₃.

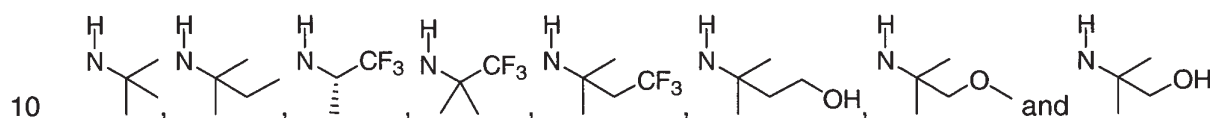
In a most preferred embodiment in combination with any of the above or below embodiments of the second alternative R¹⁰³ is selected from



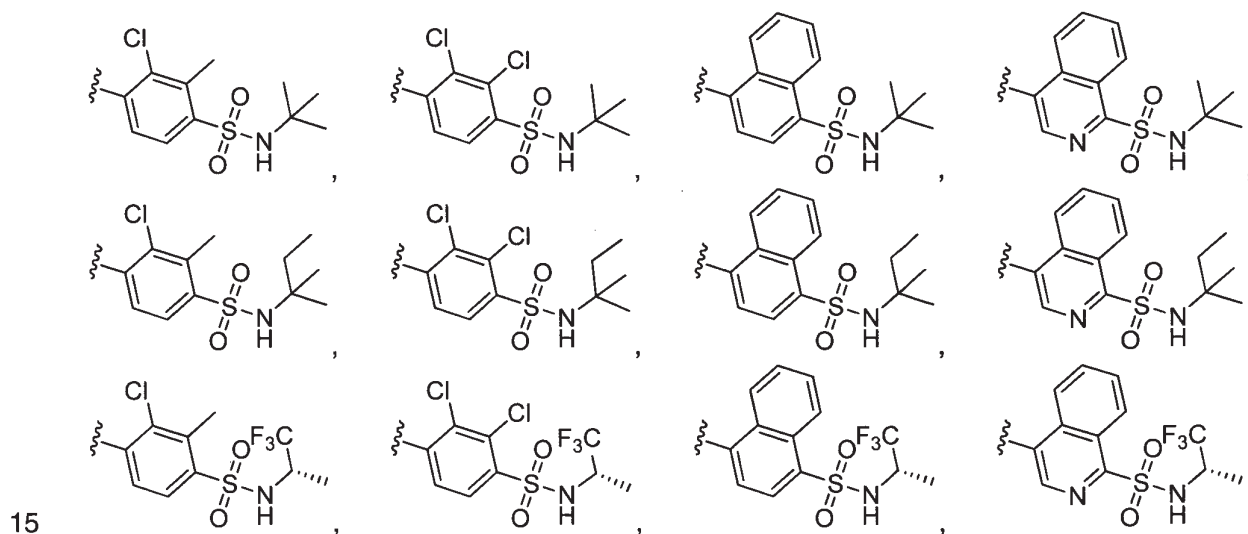
In another preferred embodiment in combination with any of the above or below embodiments of the second alternative $N(R^{137})_2$ is selected from

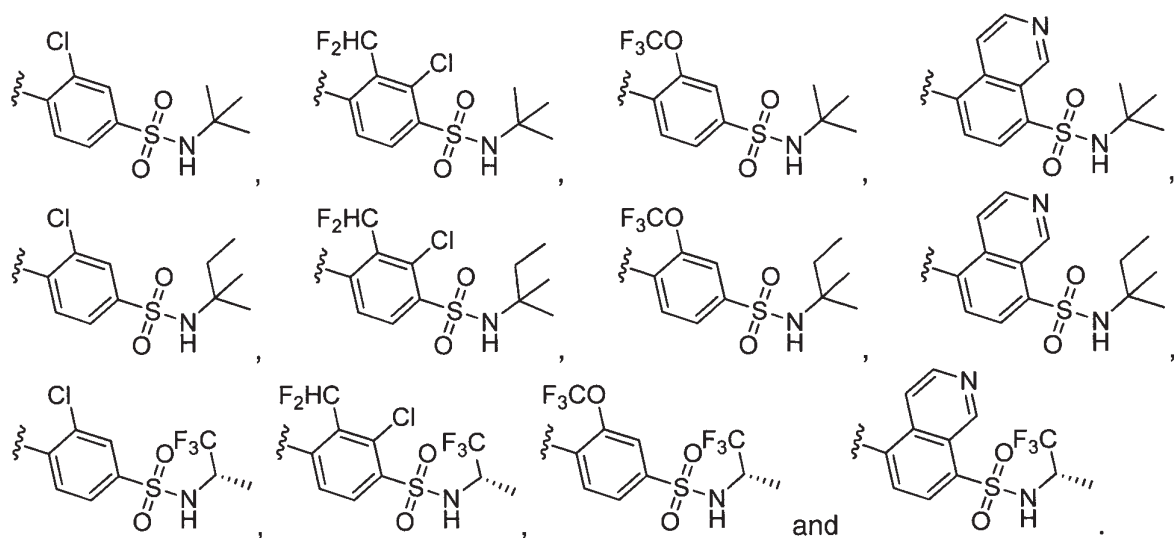


In a more preferred embodiment in combination with any of the above or below embodiments of the second alternative $N(R^{137})_2$ is selected from

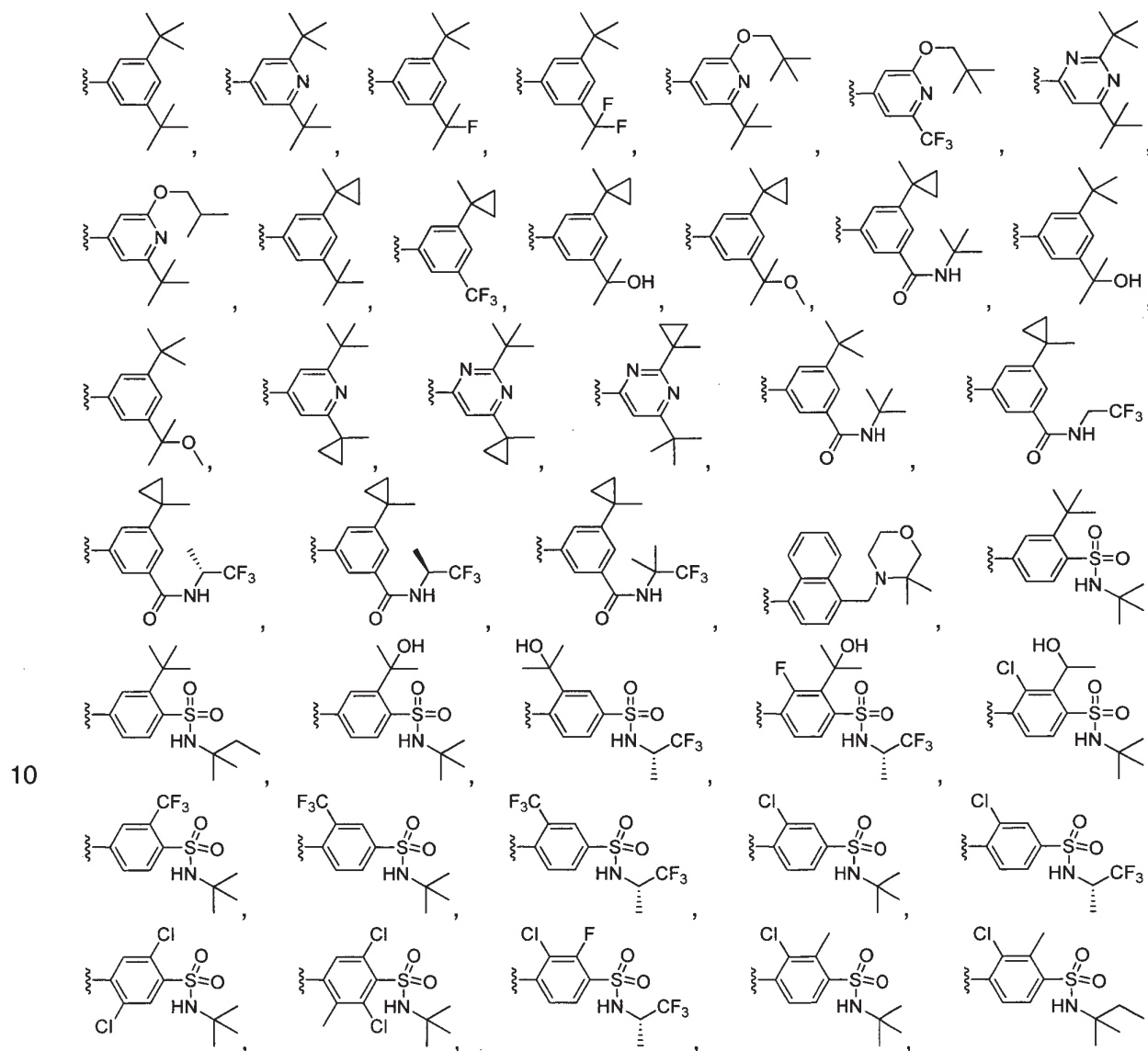


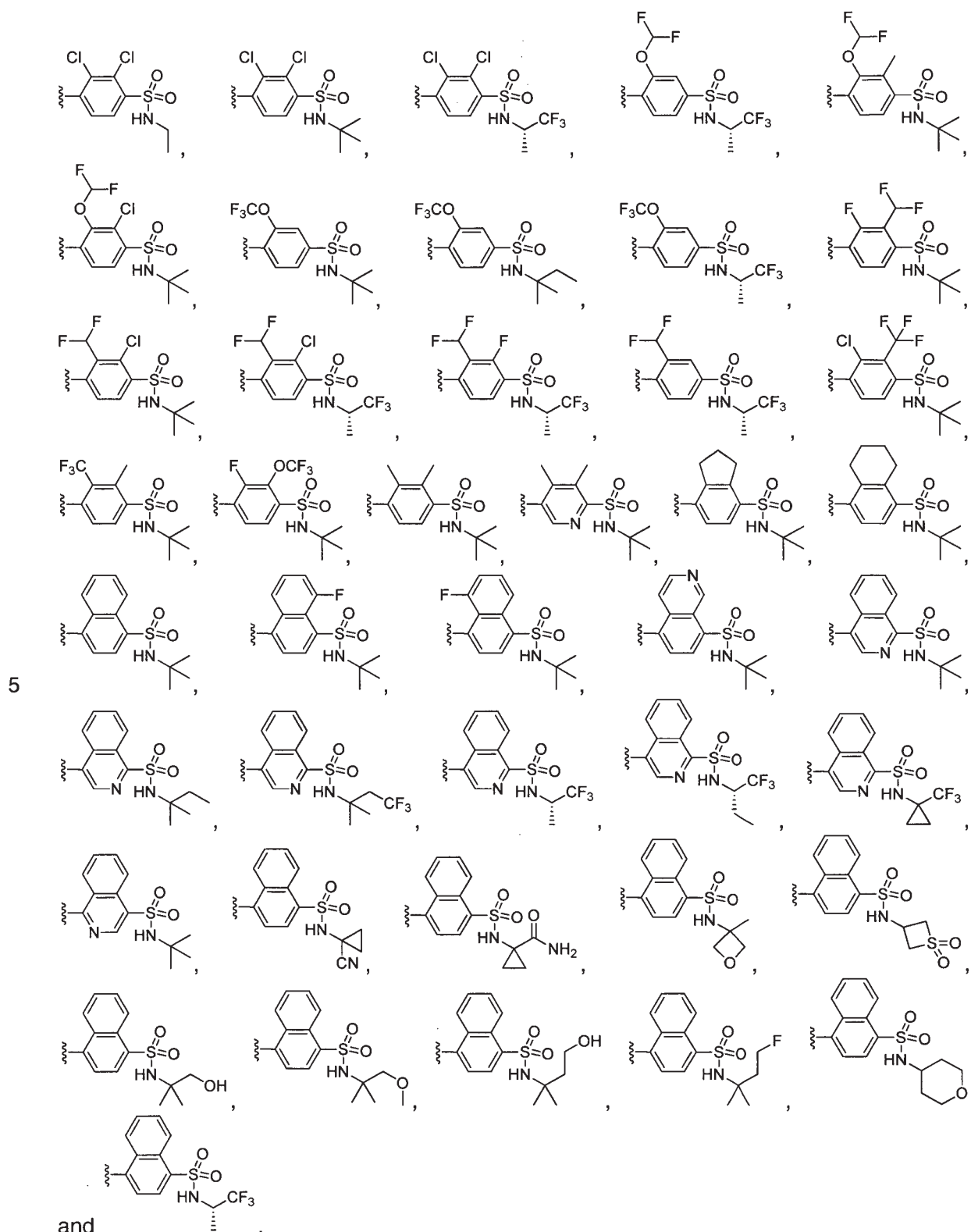
In another preferred embodiment in combination with any of the above or below embodiments of the second alternative R¹⁰³ is selected from



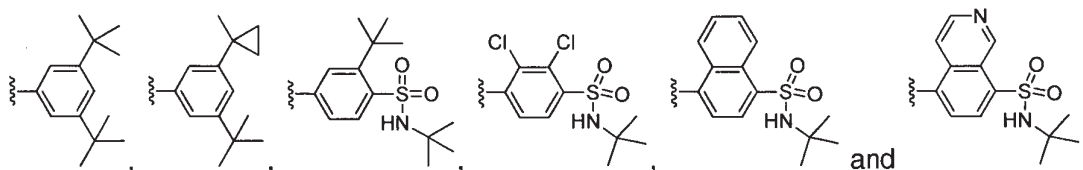


In an alternative preferred embodiment in combination with any of the above or below
5 embodiments of the second alternative R¹⁰³ is selected from

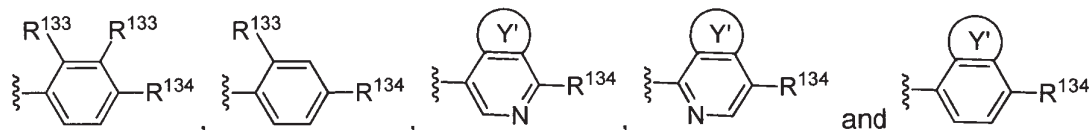




10 In a more preferred embodiment in combination with any of the above or below embodiments of the second alternative R¹⁰³ is selected from



In another preferred embodiment in combination with any of the above or below embodiments of the third alternative R^{103} is selected from



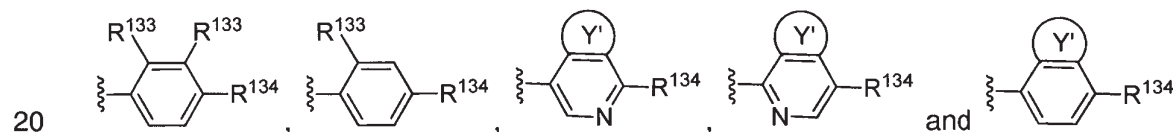
- 5 wherein R^{133} is independently selected from H, halogen, C_{1-6} -alkyl, fluoro- C_{1-6} -alkyl, C_{1-4} -alkylene-OH, C_{1-4} -alkylene-O- C_{1-3} -alkyl, O- C_{1-6} -alkyl, and O-fluoro- C_{1-6} -alkyl, more preferably R^{133} is independently selected from fluoro, chloro, CF_3 , CHF_2 , OCF_3 , $OCHF_2$, methyl, t butyl and CMe_2OH ;

R^{134} is selected from C_{1-6} -alkyl, halo- C_{1-6} -alkyl and C_{0-6} -alkylene- C_{3-10} -heterocycloalkyl,

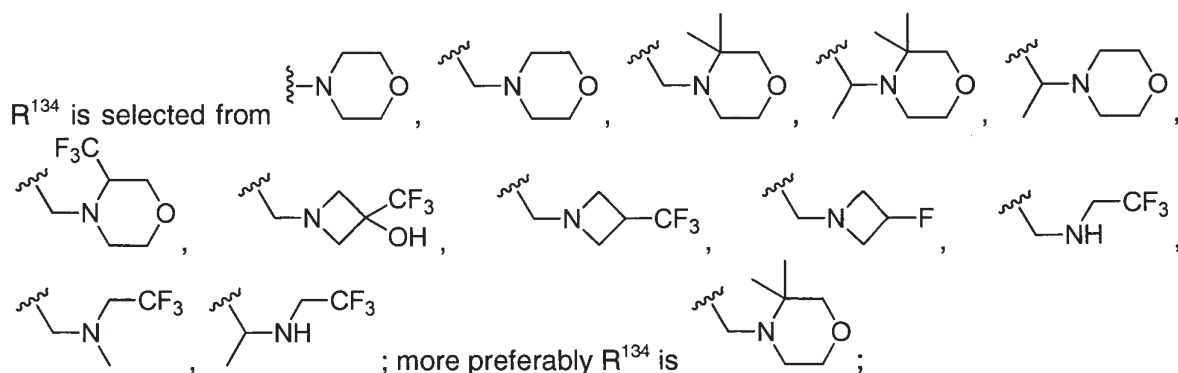
- 10 wherein alkyl, alkylene and heterocycloalkyl are unsubstituted or substituted by 1 to 3 substituents independently selected from the group consisting of halogen, C_{1-6} -alkyl, halo- C_{1-6} -alkyl, OH, oxo, $N(R^{131})_2$, O- C_{1-6} -alkyl, C_{3-10} -cycloalkyl, C_{3-10} -heterocycloalkyl; and

- 15 Y' is selected from an annelated 5- or 6-membered carbocycle, an annelated 6-membered aryl or an annelated 6-membered heteroaryl containing 1 to 2 nitrogen atoms, wherein the carbocycle, aryl or heteroaryl is unsubstituted or substituted with 1 to 3 substituents selected from fluoro, methyl or CF_3 .

In more preferred embodiment in combination with any of the above or below embodiments of the third alternative R^{103} is selected from



20 wherein R^{133} is independently selected from H, halogen, C_{1-6} -alkyl, fluoro- C_{1-6} -alkyl, C_{1-4} -alkylene-OH, C_{1-4} -alkylene-O- C_{1-3} -alkyl, O- C_{1-6} -alkyl, and O-fluoro- C_{1-6} -alkyl, more preferably R^{133} is independently selected from fluoro, chloro, CF_3 , CHF_2 , OCF_3 , $OCHF_2$, methyl, t butyl and CMe_2OH ;



Y' is selected from an annelated 5- or 6-membered carbocycle, an annelated 6-membered aryl or an annelated 6-membered heteroaryl containing 1 to 2 nitrogen atoms, wherein the carbocycle, aryl or heteroaryl is unsubstituted or substituted with 1 to 3 substituents selected from fluoro, methyl or CF₃.

In another preferred embodiment in combination with any of the above or below embodiments of the second alternative R¹⁰⁴ is selected from (CR¹⁰⁸R¹⁰⁹)R¹⁴⁰ and (C=O)R¹⁴⁰;

10 R¹⁰⁸ is independently selected from H, F, C₁₋₃-alkyl, halo-C₁₋₃-alkyl, OH, O-C₁₋₃-alkyl and O-halo-C₁₋₃-alkyl;

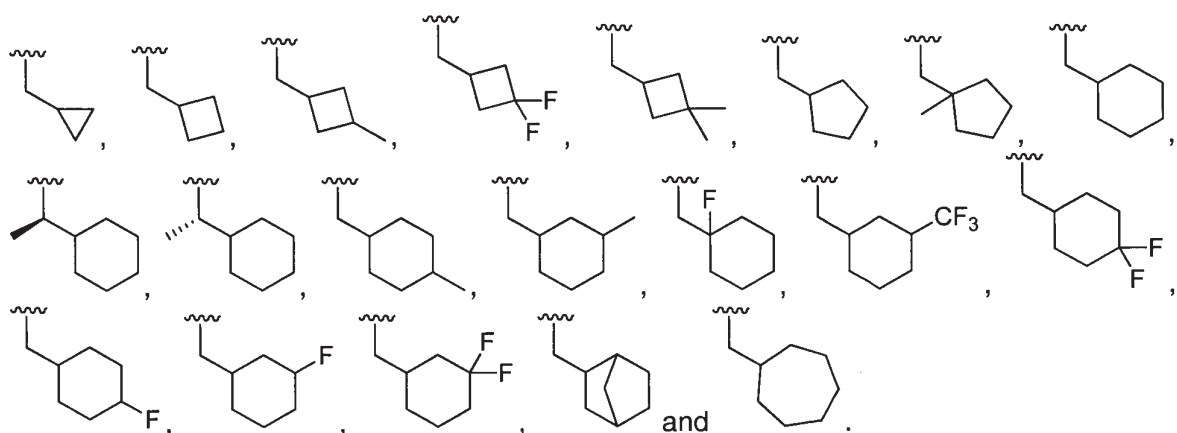
R^{109} is selected from H, F and methyl;

R¹⁴⁰ is C₃₋₁₀-cycloalkyl, which is unsubstituted or substituted with 1 to 5 substituents independently selected from the group consisting of halogen, OH, oxo, O-C₁₋₆-alkyl, O-halo-C₁₋₆-alkyl, C₁₋₆-alkyl, halo-C₁₋₆-alkyl, cycloalkyl and heterocycloalkyl.

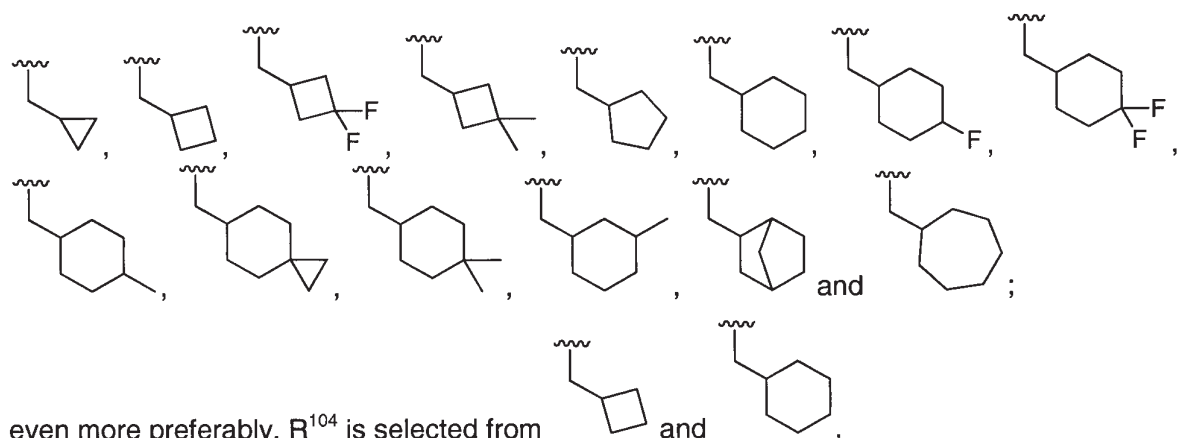
In a more preferred embodiment in combination with any of the above or below embodiments of the second alternative, R^{104} is $(CR^{108}R^{109})R^{140}$; R^{108} is selected from H, F, methyl and O-methyl; R^{109} is selected from H, F and methyl; and R^{140} is C_{3-8} -cycloalkyl, which is unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of F, methyl and CF_3 .

In an even more preferred embodiment in combination with any of the above or below embodiments of the second alternative, R¹⁰⁴ is (CH₂)R¹⁴⁰, wherein R¹⁴⁰ is C₃₋₈-cycloalkyl, which is unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of fluoro, methyl and CF₃.

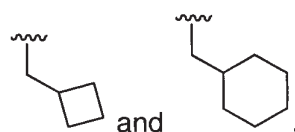
25 In another preferred embodiment in combination with any of the above or below embodiments
of the second alternative R¹⁰⁴ is selected from



- In a more preferred embodiment in combination with any of the above or below embodiments
 5 of the second alternative, R^{104} is selected from

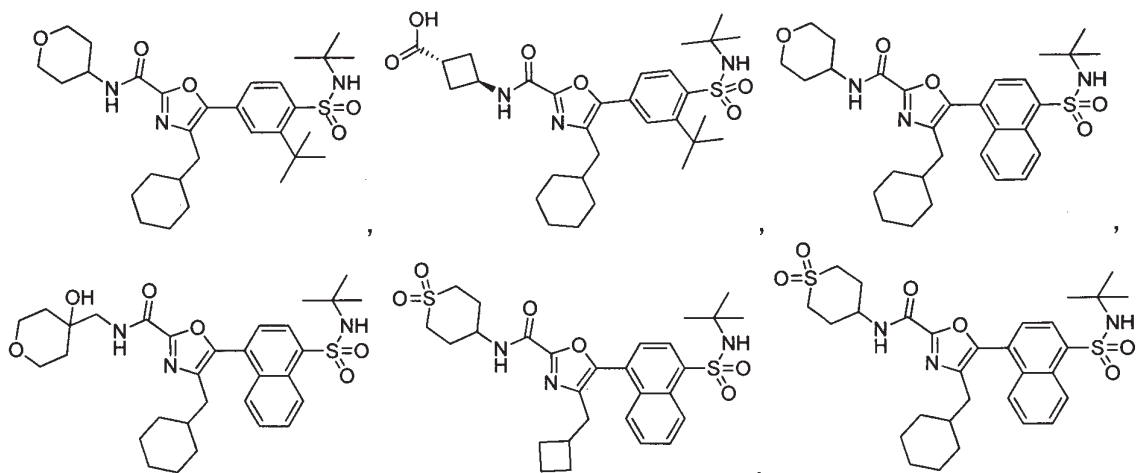


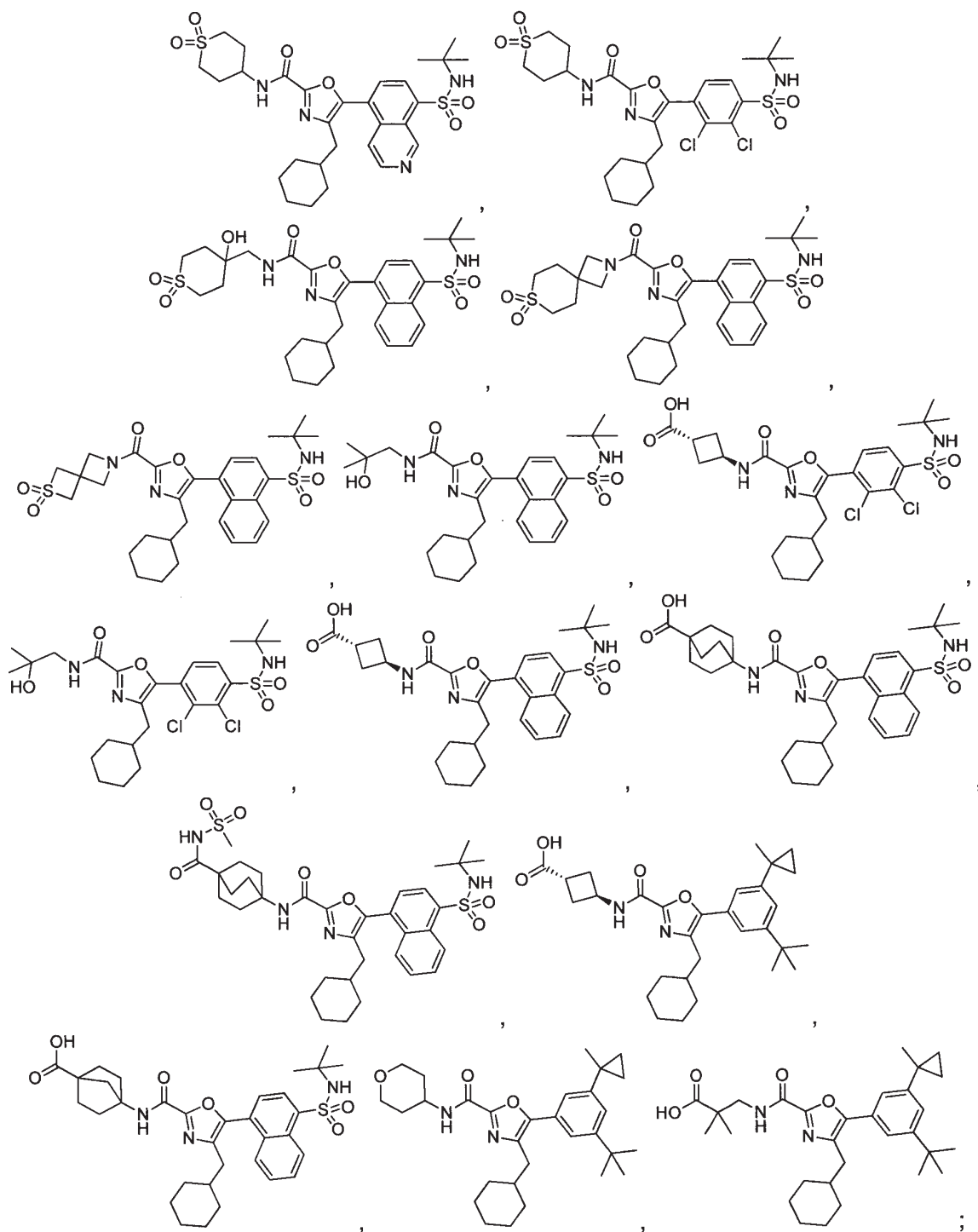
even more preferably, R^{104} is selected from



- In another preferred embodiment in combination with any of the above or below embodiments
 10 of the second alternative the compound is represented by Formula (100).

In yet another preferred embodiment in combination with any of the above or below
 embodiments of the second alternative, the compound of Formula (100) is selected from the
 group consisting of





and an enantiomer, diastereomer, tautomer, *N*-oxide, solvate and pharmaceutically acceptable salt thereof.

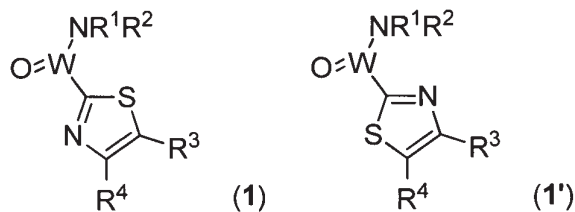
The invention also provides the compound of the second alternative of the invention for use as
10 a medicament.

Also provided is the compound of the second alternative of the invention for use in the treatment or prophylaxis of a disease or disorder associated with the inhibition or activation of the ROR γ receptor.

Also provided is the compound of the second alternative of the invention in treating ROR γ mediated inflammatory and autoimmune diseases. Preferably, the disease is selected from the group consisting of rheumatoid arthritis, ankylosing spondylitis, lupus erythematosus, psoriasis, psoriatic arthritis, atopic eczema, inflammatory bowel diseases such as Crohn's disease, asthma, mucosal leishmaniasis, multiple sclerosis, systemic sclerosis, type 1 diabetes, Kawasaki disease, Hashimoto's thyroiditis, chronic graft-versus-host disease, acute graft-versus-host disease, Celiac Sprue, idiopathic thrombocytopenic thrombotic purpura, myasthenia gravis, Sjorgren's syndrome, scleroderma, ulcerative colitis, epidermal hyperplasia, glomerulonephritis, chronic obstructive pulmonary disease and amyotrophic lateral sclerosis.

Also provided is a pharmaceutical composition comprising the compound of the second alternative of the invention and a pharmaceutically acceptable carrier.

In a third alternative, the present invention provides a compound represented by Formula (1) or Formula (1')



an enantiomer, diastereomer, tautomer, *N*-oxide, solvate, formulation and pharmaceutically acceptable salt thereof,

R^1 and R^2 are independently selected from H, C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl, C_{3-10} -cycloalkyl, C_{3-10} -heterocycloalkyl, C_{1-10} -alkylene- C_{3-10} -cycloalkyl, C_{1-10} -alkylene- C_{3-10} -heterocycloalkyl, C_{1-10} -alkylene-(5-membered heteroaryl), SO_2 - C_{1-10} -alkyl, wherein alkyl, alkenyl, alkynyl, alkylene, cycloalkyl, heterocycloalkyl and heteroaryl is unsubstituted or substituted with 1 to 7 substituents independently selected from oxo, CN, OR^{11} , $\text{O}-\text{C}_{2-6}$ -alkylene- OR^{11} , C_{1-6} -alkyl, halo- C_{1-6} -alkyl, halogen, CO_2R^{11} , $\text{CONR}^{11}\text{R}^{12}$, $\text{CONR}^{11}\text{SO}_2\text{R}^{11}$, COR^{11} , SO_xR^{11} , SO_3H , $\text{SO}_2\text{NR}^{11}\text{R}^{12}$, $\text{NR}^{11}\text{COR}^{11}$, $\text{NR}^{11}\text{SO}_2\text{R}^{11}$, $\text{NR}^{11}-\text{CO}-\text{NR}^{11}\text{R}^{12}$, $\text{NR}^{11}-\text{SO}_2-\text{NR}^{11}\text{R}^{12}$, C_{3-10} -cycloalkyl, $\text{O}-\text{C}_{3-10}$ -cycloalkyl, C_{3-10} -heterocycloalkyl, $\text{O}-\text{C}_{3-10}$ -heterocycloalkyl and $\text{NR}^{11}\text{R}^{12}$;

or R^1 and R^2 when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing 1 or 2 heteroatoms selected from O, S or N, wherein the ring is unsubstituted or substituted with 1 to 4

substituents independently selected from halogen, oxo, CN, OR¹¹, SO_xR¹¹, SO₃H, NR¹¹SO₂R¹¹, SO₂NR¹¹R¹², C₀₋₆-alkylene-CO₂R¹¹, CONR¹¹R¹², CONR¹¹SO₂R¹¹, COR¹¹, NR¹¹-CO-R¹¹, NR¹¹-CO-NR¹¹R¹², NR¹¹-SO₂-NR¹¹R¹², NR¹¹R¹², C₁₋₆-alkyl, halo-C₁₋₆-alkyl, hydroxy-C₁₋₆-alkyl, C₃₋₈-cycloalkyl, O-C₃₋₈-cycloalkyl, C₃₋₈-heterocycloalkyl and O-C₃₋₈-heterocycloalkyl,

5 wherein cycloalkyl and heterocycloalkyl are unsubstituted or substituted with 1 to 4 substituents independently selected from halogen, C₁₋₃-alkyl, halo-C₁₋₃-alkyl, OH, O-C₁₋₃-alkyl, O-halo-C₁₋₃-alkyl, SO₂-C₁₋₃-alkyl, COOH and oxo;

R³ is a 6-10 membered mono- or bicyclic aryl or a 5-14 membered mono-, bi- or tricyclic heteroaryl containing 1 to 5 heteroatoms independently selected from the group consisting of

10 N, O and S,

wherein aryl and heteroaryl is optionally substituted with 1 to 5 substituents independently selected from halogen, C₁₋₆-alkyl, C₁₋₆-alkenyl, C₁₋₆-alkynyl, halo-C₁₋₆-alkyl, OH, O-C₁₋₆-alkyl, O-halo-C₁₋₆-alkyl, C₀₋₆-alkylene-C₃₋₁₀-cycloalkyl, C₀₋₆-alkylene-C₃₋₁₀-heterocycloalkyl, C₀₋₆-alkylene-(5- or 6-membered heteroaryl), C₁₋₆-alkylene-O-R³¹, C₀₋₆-alkylene-CN, C₀₋₆-alkylene-N(R³¹)₂, C₀₋₆-alkylene-O-C₃₋₁₀-cycloalkyl, O-C₁₋₆-alkylene-O-R³¹, C₀₋₆-alkylene-O-C₃₋₁₀-heterocycloalkyl, C₀₋₆-alkylene-COOR³¹, C₀₋₆-alkylene-C(O)R³¹, C₀₋₆-alkylene-C(O)N(R³¹)₂, C₀₋₆-alkylene-N(R³¹)C(O)R³¹, C₀₋₆-alkylene-SO-R³¹, C₀₋₆-alkylene-SO₂-R³¹, C₀₋₆-alkylene-SO₂-N(R³¹)₂, C₀₋₆-alkylene-N(R³¹)SO₂-R³¹, C₀₋₆-alkylene-SO₂-C₃₋₁₀-heterocycloalkyl and C₀₋₆-alkylene-SO₂-C₃₋₁₀-heterocycloalkyl,

20 wherein alkyl, alkenyl, alkynyl, alkylene, cycloalkyl, heterocycloalkyl and the 5- or 6-membered heteroaryl is optionally substituted by 1 to 4 substituents independently selected from the group consisting of halogen, CN, C₁₋₃-alkyl, halo-C₁₋₃-alkyl, OH, oxo, =N-OR³², O-C₁₋₆-alkyl, O-halo-C₁₋₃-alkyl, N(R³¹)₂, COOH, CON(R³¹)₂, NR³¹-COR³¹, C₃₋₁₀-cycloalkyl, C₃₋₁₀-heterocycloalkyl, 6-10-membered
25 mono- or bicyclic aryl and 6-10-membered mono- or bicyclic heteroaryl,

or wherein two adjacent substituents completing a 3- to 8-membered saturated or partially unsaturated ring containing carbon atoms and optionally containing 1 to 3 heteroatoms selected from O, S, N, SO, SO₂, or NR³¹, wherein the ring is unsubstituted or substituted with 1 to 7 substituents independently selected from halogen, C₁₋₆-alkyl, halo-C₁₋₆-alkyl, C₃₋₆-cycloalkyl, C₃₋₆-heterocycloalkyl, oxo, =N-OR³², OH, O-C₁₋₆-alkyl and O-halo-C₁₋₆-alkyl;

30 R⁴ is selected from (CR⁸R⁹)R⁴⁰, (C=O)R⁴⁰, OR⁴⁰, NR⁴¹R⁴⁰, SO_y-R⁷ and C₃₋₆-cycloalkyl, which is spirocyclic fused with R⁴⁰,

wherein cycloalkyl is unsubstituted or substituted with 1 to 4 substituents independently
35 selected from the group consisting of F, methyl and CF₃;

R⁷ is selected from C₃₋₁₀-cycloalkyl and C₃₋₁₀-heterocycloalkyl,

wherein cycloalkyl and heterocycloalkyl are unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of halogen, OH, oxo, O-C₁₋₆-alkyl, O-halo-C₁₋₆-alkyl, C₁₋₆-alkyl, halo-C₁₋₆-alkyl, cycloalkyl and heterocycloalkyl;

5 R⁸ and R⁹ are independently selected from H, F, C₁₋₃-alkyl, halo-C₁₋₃-alkyl, OH, O-C₁₋₃-alkyl and O-halo-C₁₋₃-alkyl;

R¹¹ is independently selected from H, C₁₋₆-alkyl, C₀₋₆-alkylene-C₃₋₁₀-cycloalkyl and C₀₋₆-alkylene-C₃₋₁₀-heterocycloalkyl,

10 wherein alkyl, alkylene, cycloalkyl and heterocycloalkyl is unsubstituted or substituted with 1 to 6 substituents selected from the group consisting of halogen, CN, OH, oxo, C₁₋₃-alkyl, halo-C₁₋₃-alkyl, O-C₁₋₃-alkyl, O-halo-C₁₋₃-alkyl, NH₂, NH(C₁₋₃-alkyl), N(C₁₋₃-alkyl)₂, C₃₋₆-heterocycloalkyl, C₃₋₆-cycloalkyl and SO₂-C₁₋₃-alkyl,

wherein cycloalkyl and heterocycloalkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of F, OH, oxo, Me and CF₃;

15 R¹² is independently selected from H, C₁₋₆-alkyl, halo-C₁₋₆-alkyl and C₃₋₆-cycloalkyl;

R³¹ is independently selected from H, C₁₋₆-alkyl, halo-C₁₋₆-alkyl, C₀₋₆-alkylene-C₃₋₈-cycloalkyl, C₀₋₆-alkylene-C₃₋₈-heterocycloalkyl, 5- or 6-membered heteroaryl and 6-membered aryl, wherein alkyl, alkylene, cycloalkyl, heterocycloalkyl, aryl and heteroaryl are unsubstituted or substituted with 1 to 6 substituents independently selected from halogen, CN, OH, oxo, =N-OR³², C₁₋₃-alkyl, halo-C₁₋₃-alkyl, O-C₁₋₃-alkyl, O-halo-C₁₋₃-alkyl and SO₂-C₁₋₃-alkyl;

20 and optionally wherein two R³¹ when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing 1 or 2 heteroatoms selected from O, S or N, wherein the ring is unsubstituted or substituted with 1 to 4 substituents independently selected from fluoro, OH, oxo, C₁₋₄-alkyl and halo-C₁₋₄-alkyl;

R³² is independently selected from H, C₁₋₆-alkyl and halo-C₁₋₆-alkyl and C₃₋₆-cycloalkyl;

R⁴⁰ is C₃₋₁₀-cycloalkyl, which is unsubstituted or substituted with 1 to 5 substituents independently selected from the group consisting of halogen, OH, oxo, O-C₁₋₆-alkyl, O-halo-C₁₋₆-alkyl, C₁₋₆-alkyl, halo-C₁₋₆-alkyl, C₃₋₈-cycloalkyl and C₃₋₈-heterocycloalkyl;

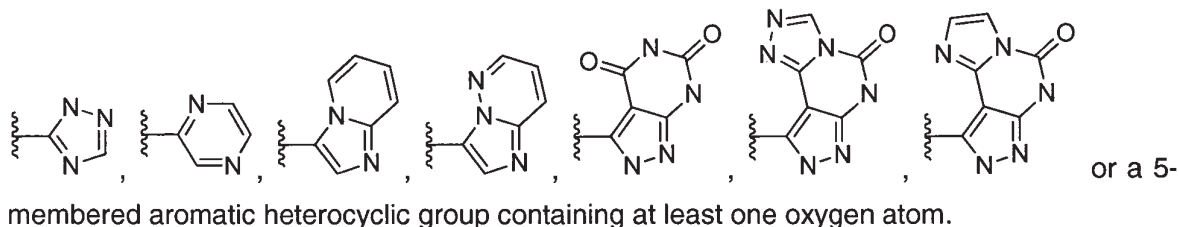
30 R⁴¹ is selected from H, C₁₋₆-alkyl, C₃₋₆-cycloalkyl and C₃₋₆-heterocycloalkyl,

wherein alkyl, cycloalkyl and heterocycloalkyl is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of OH, oxo, CN, halogen, O-C₁₋₆-alkyl, O-halo-C₁₋₆-alkyl, C₃₋₆-heterocycloalkyl and C₃₋₆-cycloalkyl;

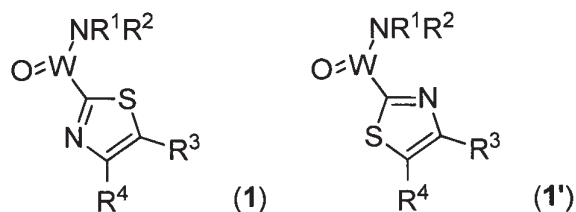
x and y are independently selected from 0, 1 and 2;

35 W is selected from C or S=O;

with the proviso that for R³ the 5-14 membered mono-, bi- or tricyclic heteroaryl containing ring is not



- 5 In an alternative preferred embodiment of the third alternative the compound is represented by Formula (1) or Formula (1')



an enantiomer, diastereomer, tautomer, solvate, formulation and pharmaceutically acceptable salt thereof,

- 10 wherein

R¹ and R² are independently selected from H, C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl, C₀₋₁₀-alkylene-C₃₋₁₀-cycloalkyl, C₀₋₁₀-alkylene-C₃₋₁₀-heterocycloalkyl, C₀₋₁₀-alkylene-(5-membered monocyclic heteroaryl), SO₂-C₁₋₁₀-alkyl, wherein alkyl, alkenyl, alkynyl, alkylene, cycloalkyl, heterocycloalkyl and heteroaryl is unsubstituted or substituted with 1 to 7 substituents independently selected from oxo, CN, OR¹¹, O-C₂₋₆-alkylene-OR¹¹, C₁₋₆-alkyl, halo-C₁₋₆-alkyl, halogen, CO₂R¹¹, CONR¹¹R¹², CONR¹¹SO₂R¹², COR¹¹, SO_yR¹¹, SO₃H, SO₂NR¹¹R¹², NR¹¹COR¹¹, NR¹¹SO₂R¹¹, NR¹¹-CO-NR¹¹R¹², NR¹¹-SO₂-NR¹¹R¹², C₃₋₆-cycloalkyl, O-C₃₋₆-cycloalkyl, C₃₋₆-heterocycloalkyl, O-C₃₋₆-heterocycloalkyl and NR¹¹R¹²;

or R¹ and R² when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing 1 or 2 heteroatoms selected from O, S or N, wherein the ring is unsubstituted or substituted with 1 to 4 substituents independently selected from halogen, oxo, CN, OR¹¹, SO_yR¹¹, SO₃H, NR¹¹SO₂R¹¹, SO₂NR¹¹R¹², CO₂R¹¹, CONR¹¹R¹², CONR¹¹SO₂R¹², COR¹¹, NR¹¹-CO-R¹¹, NR¹¹-CO-NR¹¹R¹², NR¹¹-SO₂-NR¹¹R¹², NR¹¹R¹², C₁₋₆-alkyl, halo-C₁₋₆-alkyl, hydroxy-C₁₋₆-alkyl, C₃₋₆-cycloalkyl, O-C₃₋₆-cycloalkyl, C₃₋₆-heterocycloalkyl and O-C₃₋₆-heterocycloalkyl,

wherein cycloalkyl and heterocycloalkyl are unsubstituted or substituted with 1 to 3 substituents selected from oxo, OH, methyl, CF₃ and fluoro;

R³ is a 6-10 membered mono- or bicyclic aryl or a 5-14 membered mono-, bi- or tricyclic heteroaryl containing 1 to 5 heteroatoms independently selected from the group consisting of N, O and S

wherein aryl and heteroaryl are unsubstituted or substituted with 1 to 5 substituents independently selected from halogen, CN, C₁₋₆-alkyl, C₁₋₆-alkenyl, C₁₋₆-alkynyl, halo-C₁₋₆-alkyl, OH, O-C₁₋₆-alkyl, O-halo-C₁₋₆-alkyl, C₀₋₆-alkylene-C₃₋₁₀-cycloalkyl, C₀₋₆-alkylene-O-C₃₋₁₀-cycloalkyl, C₀₋₆-alkylene-C₃₋₁₀-heterocycloalkyl, C₀₋₆-alkylene-COOR³¹, C₀₋₆-alkylene-C(O)R³¹, C₀₋₆-alkylene-C(O)N(R³¹)₂, C₀₋₆-alkylene-SO₂-N(R³¹)₂, C₀₋₆-alkylene-SO₂-R³¹, C₀₋₆-alkylene-(5-membered heteroaryl), C₀₋₆-alkylene-(6-membered heteroaryl),

wherein alkyl, alkenyl, alkynyl, alkylene, cycloalkyl, heterocycloalkyl and heteroaryl are unsubstituted or substituted by 1 to 3 substituents independently selected from the group consisting of C₁₋₆-alkyl, halo-C₁₋₆-alkyl, halogen, OH, oxo, =N-OR³², N(R³¹)₂, O-C₁₋₆-alkyl, O-halo-C₁₋₆-alkyl, COOH, CON(R³¹)₂, CN, NR³¹-COR³¹, C₃₋₁₀-cycloalkyl, C₃₋₁₀-heterocycloalkyl, 6-10-membered mono- or bicyclic aryl, 6-10-membered mono- or bicyclic heteroaryl,

or wherein two adjacent substituents may complete a 3- to 8-membered saturated or partially unsaturated ring containing carbon atoms and optionally containing 1 to 3 members selected from O, S, SO, SO₂ or NR³¹, wherein the ring is unsubstituted or substituted with one to four substituents independently selected from halogen, oxo, =N-OR³², OH, O-C₁₋₆-alkyl, O-halo-C₁₋₆-alkyl, C₁₋₆-alkyl, C₃₋₆-cycloalkyl and halo-C₁₋₆-alkyl;

R⁴ is selected from (CR⁸R⁹)R⁴⁰, (C=O)R⁴⁰, C₃-cycloalkylene-R⁴⁰, OR⁴⁰, NR⁴¹R⁴⁰ and SO_y-R⁷;

R⁷ is selected from C₃₋₁₀-cycloalkyl and C₃₋₁₀-heterocycloalkyl,

wherein cycloalkyl and heterocycloalkyl are unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of halogen, OH, oxo, O-C₁₋₆-alkyl, O-halo-C₁₋₆-alkyl, C₁₋₆-alkyl, halo-C₁₋₆-alkyl, cycloalkyl and heterocycloalkyl;

R⁸ and R⁹ are independently selected from H, F, C₁₋₃-alkyl, halo-C₁₋₃-alkyl, OH, O-C₁₋₃-alkyl and O-halo-C₁₋₃-alkyl,

R¹¹ and R³¹ independently selected from H, C₁₋₆-alkyl, C₃₋₁₀-cycloalkyl, C₃₋₁₀-heterocycloalkyl, phenyl, 5-6-membered heteroaryl containing 1 to 4 heteroatoms independently selected from N, O and S

wherein alkyl, cycloalkyl and heterocycloalkyl is unsubstituted or substituted with 1 to 5 substituents selected from the group consisting of C₁₋₆-alkyl, halo-C₁₋₆-alkyl, OH, O-C₁₋₆-alkyl, O-halo-C₁₋₆-alkyl, phenyl, heteroaryl, halogen, NH₂, NH(C₁₋₆-alkyl), N(C₁₋₆-alkyl)₂, C₃₋₁₀-heterocycloalkyl and C₃₋₁₀-cycloalkyl, COOH, SO₂-C₁₋₃-alkyl, SO₂-C₁₋₃-fluoroalkyl, oxo and CN,

wherein cycloalkyl and heterocycloalkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of C₁₋₆-alkyl, halo-C₁₋₆-alkyl, OH, O-C₁₋₆-alkyl, O-halo-C₁₋₆-alkyl, phenyl, heteroaryl, halogen, NH₂, NH(C₁₋₆-alkyl), N(C₁₋₆-alkyl)₂ and C₃₋₁₀-cycloalkyl,

wherein phenyl and heteroaryl are unsubstituted or substituted with 1 to 4 substituents independently selected from the group consisting of OH, O-C₁₋₆-alkyl, O-halo-C₁₋₆-alkyl, halogen, C₁₋₆-alkyl, halo-C₁₋₆-alkyl, NH₂, NH(C₁₋₆-alkyl), N(C₁₋₆-alkyl)₂ and C₃₋₁₀-cycloalkyl;

5 R¹² and R³² are independently selected from H, C₁₋₆-alkyl, halo-C₁₋₆-alkyl and C₃₋₁₀-cycloalkyl;

R⁴⁰ is C₃₋₁₀-cycloalkyl, which is unsubstituted or substituted with 1 to 5 substituents independently selected from the group consisting of halogen, OH, oxo, O-C₁₋₆-alkyl, O-halo-C₁₋₆-alkyl, C₁₋₆-alkyl and halo-C₁₋₆-alkyl;

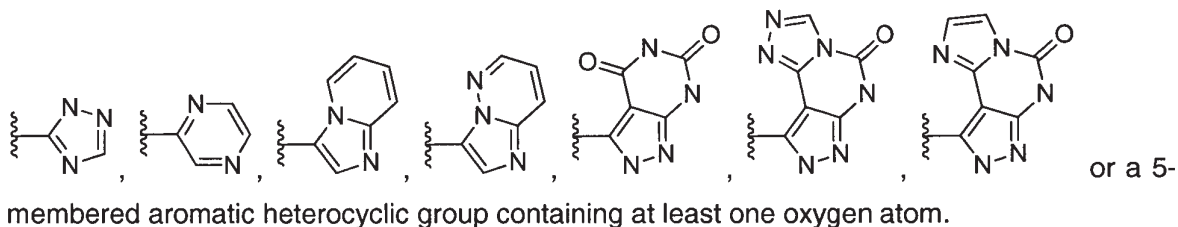
R⁴¹ is selected from H, C₁₋₆-alkyl, C₃₋₆-cycloalkyl and C₃₋₆-heterocycloalkyl,

10 wherein alkyl, cycloalkyl and heterocycloalkyl is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of OH, oxo, CN, halogen, O-C₁₋₆-alkyl, O-halo-C₁₋₆-alkyl, C₃₋₆-heterocycloalkyl and C₃₋₆-cycloalkyl;

y is independently selected from 0, 1 and 2;

W is selected from C or S=O;

15 with the proviso that for R³ the 5-14 membered mono-, bi- or tricyclic heteroaryl containing ring
is not



In a preferred embodiment in combination with any of the above or below embodiments of the third alternative W is a carbon atom.

In a preferred embodiment in combination with any of the above or below embodiments of the third alternative R^4 is selected from $(CR^8R^9)R^{40}$, $(CO)R^{40}$ and OR^{40} :

R⁸ is selected from H, F, methyl, trifluoromethyl and O-methyl;

R⁹ is selected from H, F and methyl;

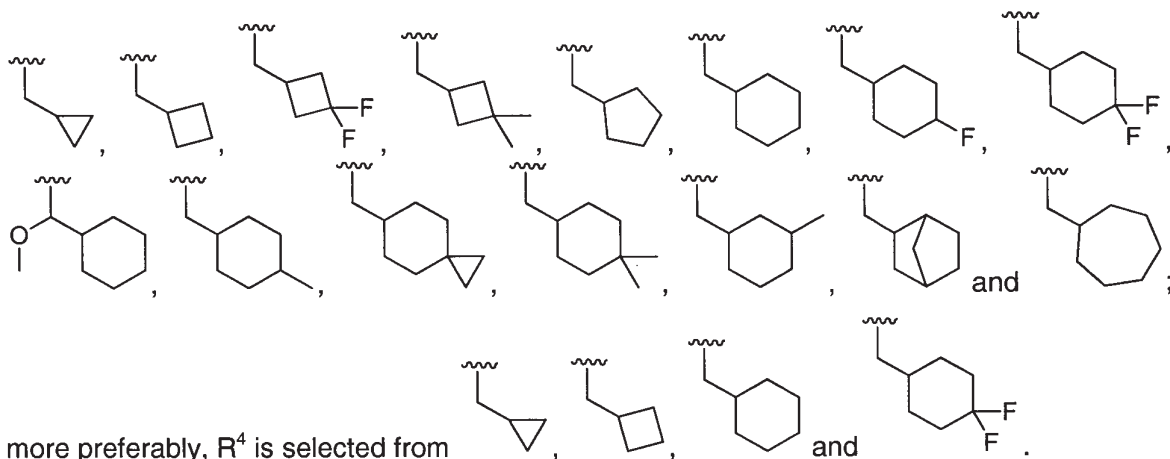
25 R⁴⁰ is C₃₋₈-cycloalkyl, which is unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of fluoro, methyl and trifluoromethyl.

In a more preferred embodiment in combination with any of the above or below embodiments of the third alternative R⁴ is selected from (CR⁸R⁹)R⁴⁰ and OR⁴⁰; R⁸ is selected from H, F, methyl, CF₃ and OMe; R⁹ is selected from H, F and methyl; and R⁴⁰ is C₃₋₈-cycloalkyl, which is unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of fluoro, methyl and CF₃.

In an even more preferred embodiment in combination with any of the above or below embodiments of the third alternative R^4 is $(CR^8R^9)R^{40}$; R^8 is selected from H, F, methyl and O-methyl; R^9 is selected from H, F and methyl; and R^{40} is C_{3-8} -cycloalkyl, which is unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of fluoro, methyl and CF_3 .

In a most preferred embodiment in combination with any of the above or below embodiments of the third alternative R^4 is $(CH_2)R^{40}$, wherein R^{40} is C_{3-8} -cycloalkyl, which is unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of fluoro, methyl and CF_3 .

- 10 In an alternative preferred embodiment in combination with any of the above or below embodiments of the third alternative R^4 is selected from



- 15 In a preferred embodiment in combination with any of the above or below embodiments of the third alternative R^1 is selected from H, C_{1-10} -alkyl, C_{3-10} -cycloalkyl, C_{3-10} -heterocycloalkyl, C_{1-10} -alkylene- C_{3-10} -cycloalkyl, C_{1-10} -alkylene- C_{3-10} -heterocycloalkyl, C_{1-10} -alkylene-(5-membered heteroaryl), wherein alkyl, alkenyl, alkynyl, alkylene, cycloalkyl and heterocycloalkyl is unsubstituted or substituted with 1 to 7 substituents independently selected from oxo, CN, OR^{11} , $O-C_{2-6}$ -alkylene- OR^{11} , C_{1-6} -alkyl, halo- C_{1-6} -alkyl, halogen, CO_2R^{11} , $CONR^{11}R^{12}$, $CONR^{11}SO_2R^{11}$, COR^{11} , SO_xR^{11} , SO_3H , $SO_2NR^{11}R^{12}$, $NR^{11}COR^{11}$, $NR^{11}SO_2R^{11}$, $NR^{11}-CO-NR^{11}R^{12}$, $NR^{11}-SO_2-NR^{11}R^{12}$, C_{3-10} -cycloalkyl, $O-C_{3-10}$ -cycloalkyl, C_{3-10} -heterocycloalkyl, $O-C_{3-10}$ -heterocycloalkyl and $NR^{11}R^{12}$;

R^2 is selected from H, C_{1-6} -alkyl, halo- C_{1-6} -alkyl and hydroxy- C_{1-6} -alkyl;

- 25 or R^1 and R^2 when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing 1 or 2 heteroatoms selected from O, S or N, wherein the ring is unsubstituted or substituted with 1 to 4 substituents independently selected from halogen, oxo, CN, OR^{11} , SO_xR^{11} , SO_3H , $NR^{11}SO_2R^{11}$, $SO_2NR^{11}R^{12}$, C_{0-6} -alkylene- CO_2R^{11} , $CONR^{11}R^{12}$, $CONR^{11}SO_2R^{11}$, COR^{11} , NR^{11} .

CO-R¹¹, NR¹¹-CO-NR¹¹R¹², NR¹¹-SO₂-NR¹¹R¹², NR¹¹R¹², C₁₋₆-alkyl, halo-C₁₋₆-alkyl, hydroxy-C₁₋₆-alkyl, C₃₋₈-cycloalkyl, O-C₃₋₈-cycloalkyl, C₃₋₈-heterocycloalkyl and O-C₃₋₈-heterocycloalkyl,

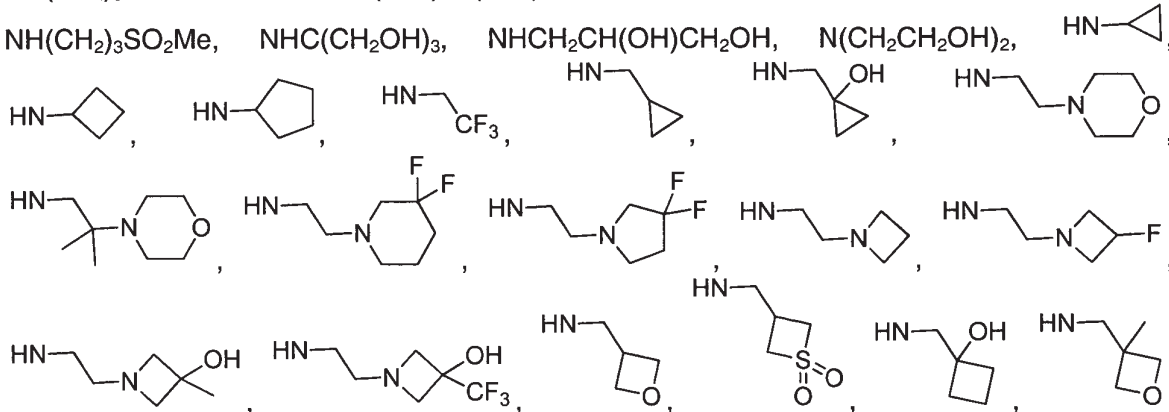
wherein cycloalkyl and heterocycloalkyl are unsubstituted or substituted with 1 to 4 substituents independently selected from halogen, C₁₋₃-alkyl, halo-C₁₋₃-alkyl, OH, O-C₁₋₃-alkyl, O-halo-C₁₋₃-alkyl, SO₂-C₁₋₃-alkyl, COOH and oxo.

In an alternative preferred embodiment in combination with any of the above or below embodiments of the third alternative R¹ is selected from H, C₁₋₁₀-alkyl, C₀₋₁₀-alkylene-C₃₋₁₀-cycloalkyl, and C₀₋₁₀-alkylene-C₃₋₁₀-heterocycloalkyl, wherein alkyl, alkylene, cycloalkyl and heterocycloalkyl is unsubstituted or substituted with 1 to 7 substituents independently selected from oxo, OR¹¹, C₁₋₆-alkyl, halo-C₁₋₆-alkyl, halogen, CO₂R¹¹, CONR¹¹R¹², CONR¹¹SO₂R¹², COR¹¹, NR¹¹COR¹¹, NR¹¹SO₂R¹¹, NR¹¹-CO-NR¹¹R¹², NR¹¹-SO₂-NR¹¹R¹², C₃₋₆-cycloalkyl, O-C₃₋₆-cycloalkyl, C₃₋₆-heterocycloalkyl and O-C₃₋₆-heterocycloalkyl;

R² is selected from the group consisting of H, C₁₋₆ alkyl and halo-C₁₋₆ alkyl;

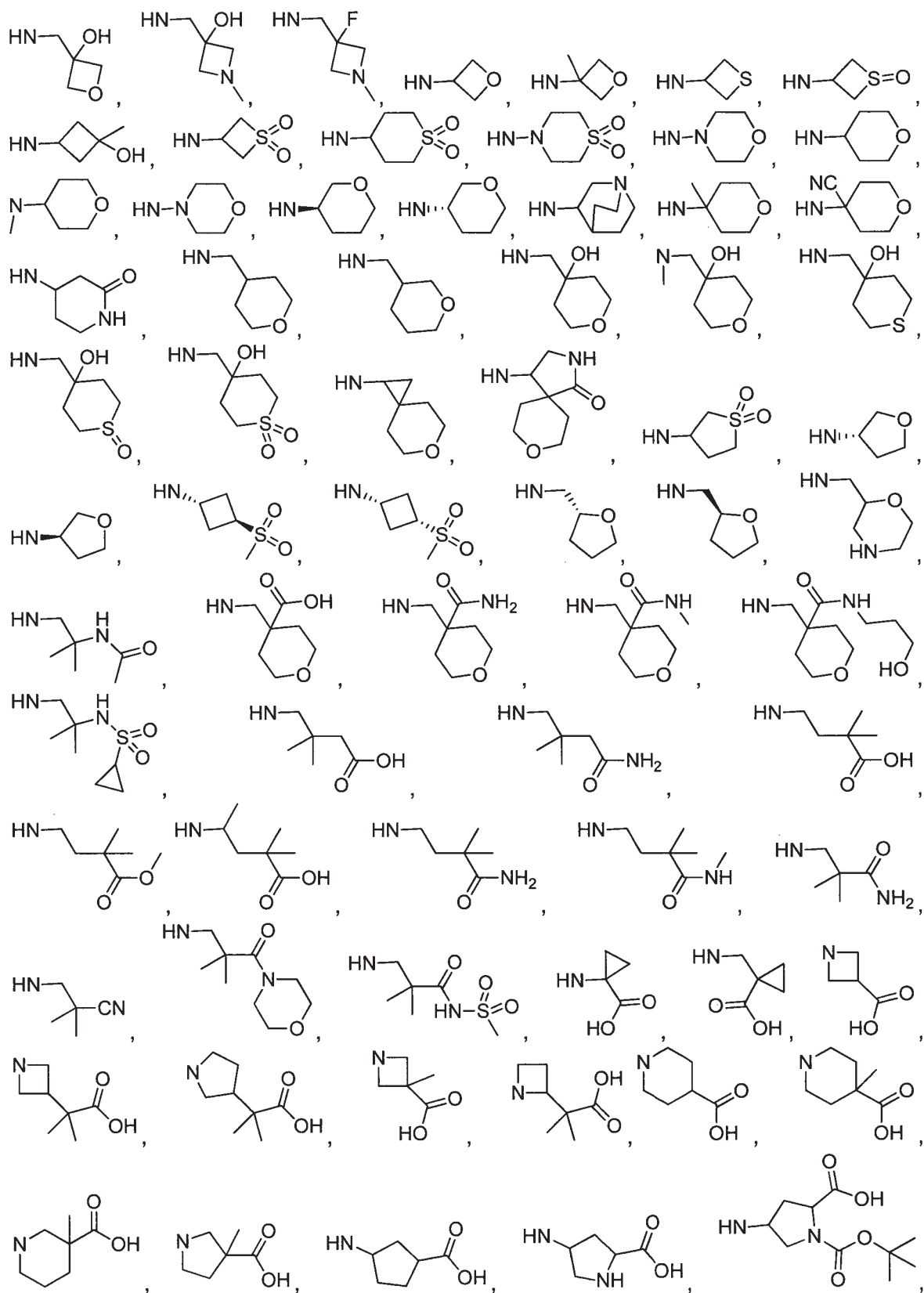
or R¹ and R² when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing 1 or 2 heteroatoms selected from O, S or N, wherein the ring is unsubstituted or substituted with 1 to 4 substituents independently selected from fluoro, oxo, C₁₋₆-alkyl.

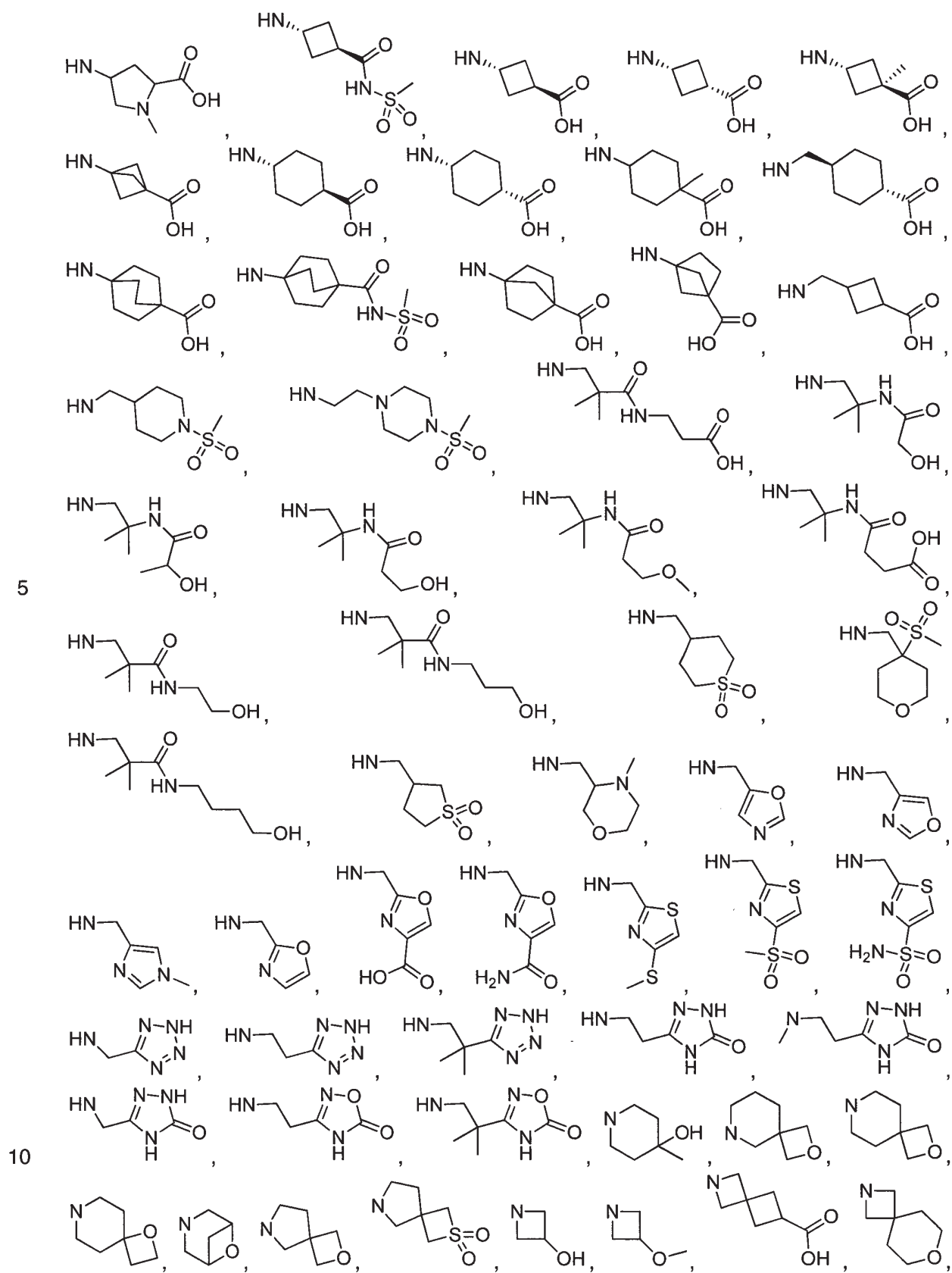
In a preferred embodiment in combination with any of the above or below embodiments of the third alternative NR¹R² is selected from NHMe, NH₂Et, NHⁱPr, NH^tBu, NHCH₂CONH₂, NHCH₂CONMe₂, NHCH₂CH₂OH, NHCH₂CH₂OMe, NHCH₂CH₂SO₂Me, NHCH₂CH₂SO₂NH₂, NH(CH₂)₃OH, NH(CH₂)₃OMe, NH(CH₂)₄OH, NH(CH₂)₄OMe, NH(CH₂)₅OH, NH(CH₂)₂CO₂H, NH(CH₂)₃CO₂H, NH(CH₂)₄CO₂H, NH(CH₂)₅CO₂H, NHCH₂CH(CF₃)OH, NHCH₂C(Me)(CF₃)OH, NHCH₂CMe₂OH, NHCH₂CH₂CMe₂OH, NHCH₂CMe₂NHCH₂CF₃, NHCH(Me)CMe₂OH, NHCH₂CMe₂OMe, NHCH₂CMe₂CO₂H, NHCH₂CMe₂CONHMe, NHCH₂CMe₂CONMe₂, NHCH₂CMe₂NHSO₂Me, NH(CH₂)₃SOMe, NH(CH₂)₅SO₂Me, NH(CH₂)₅SO₂NH₂, NH(CH₂)₃NHSO₂Me, NH(CH₂)₂O(CH₂)₂OH, NHCH₂CHMeOH, NH(CH₂)₅SOMe, NH(CH₂)₃SO₂Me, NHC(CH₂OH)₃, NHCH₂CH(OH)CH₂OH, N(CH₂CH₂OH)₂, HN-

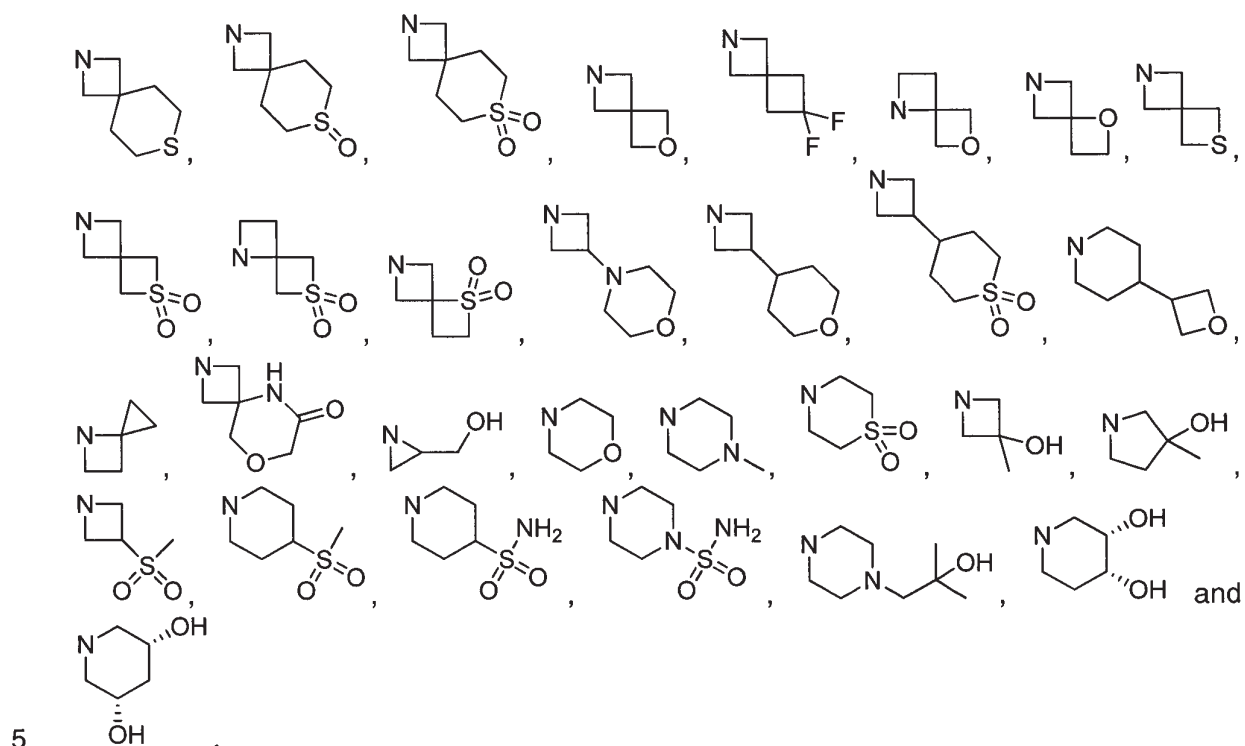


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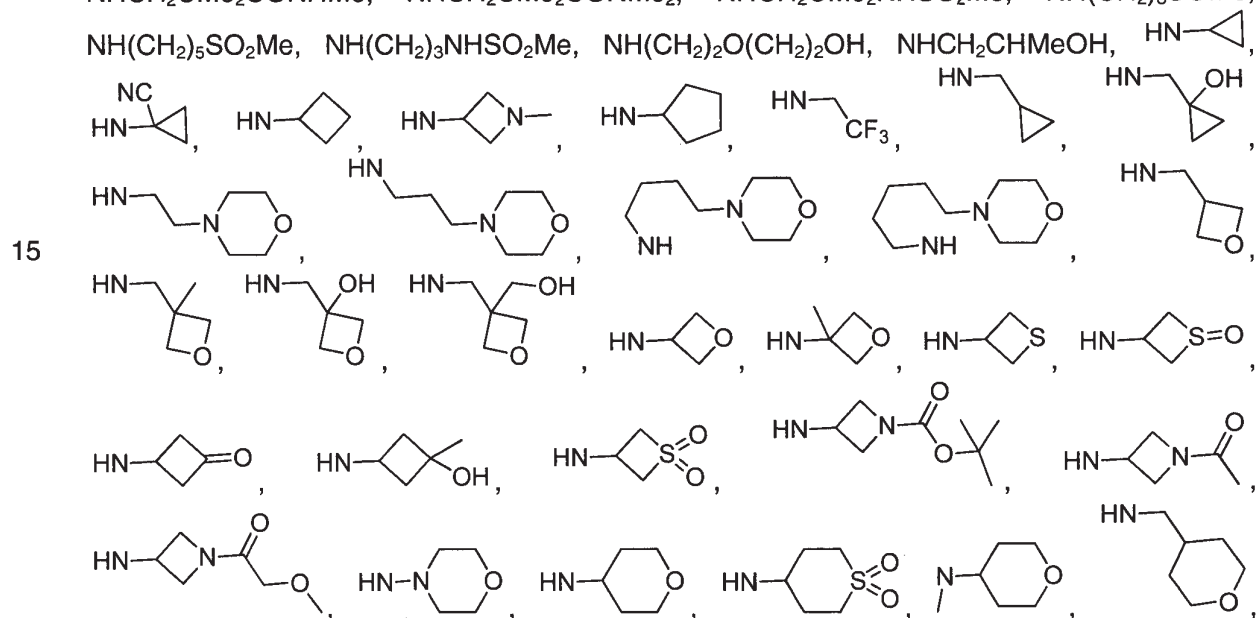
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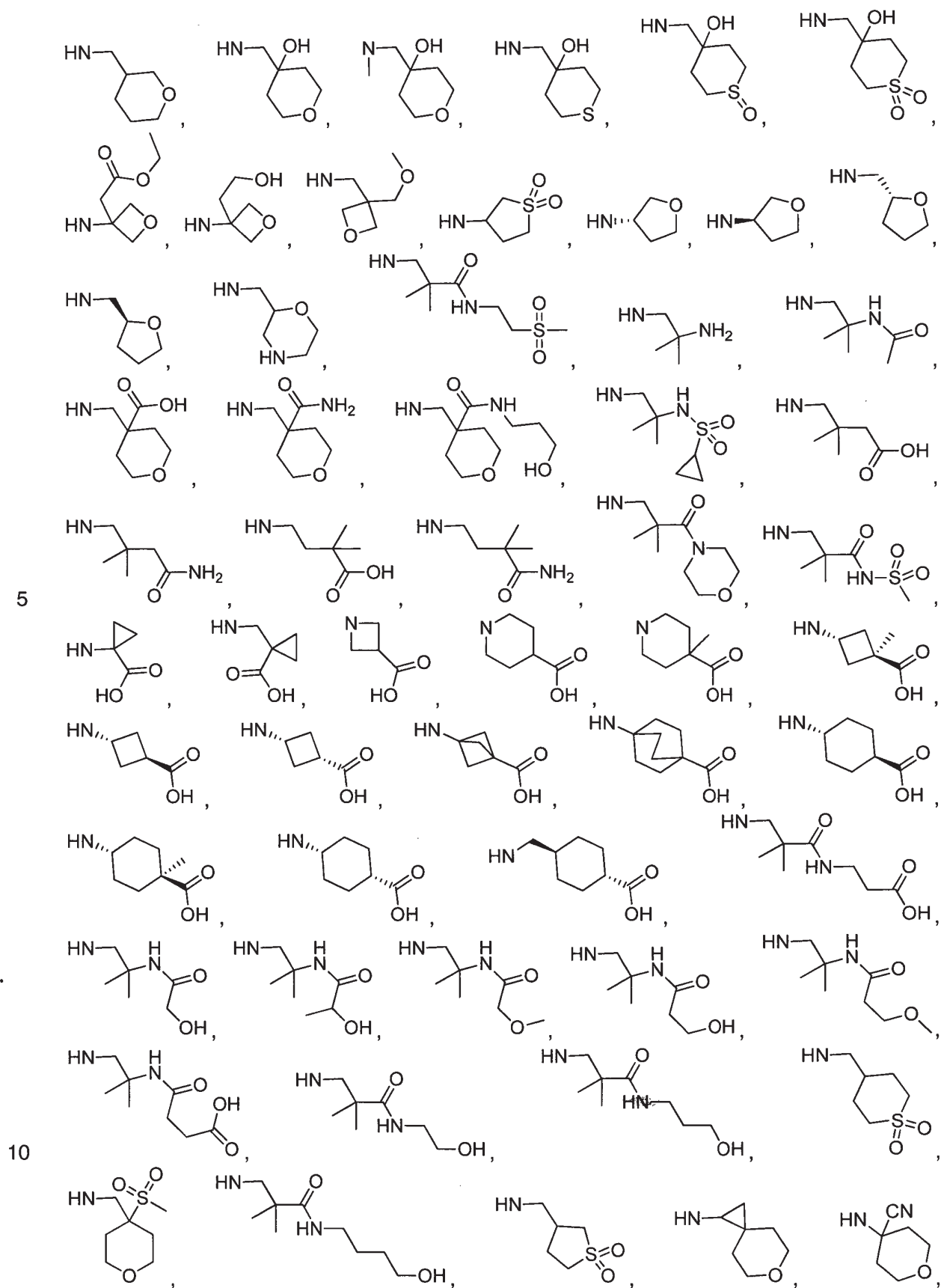


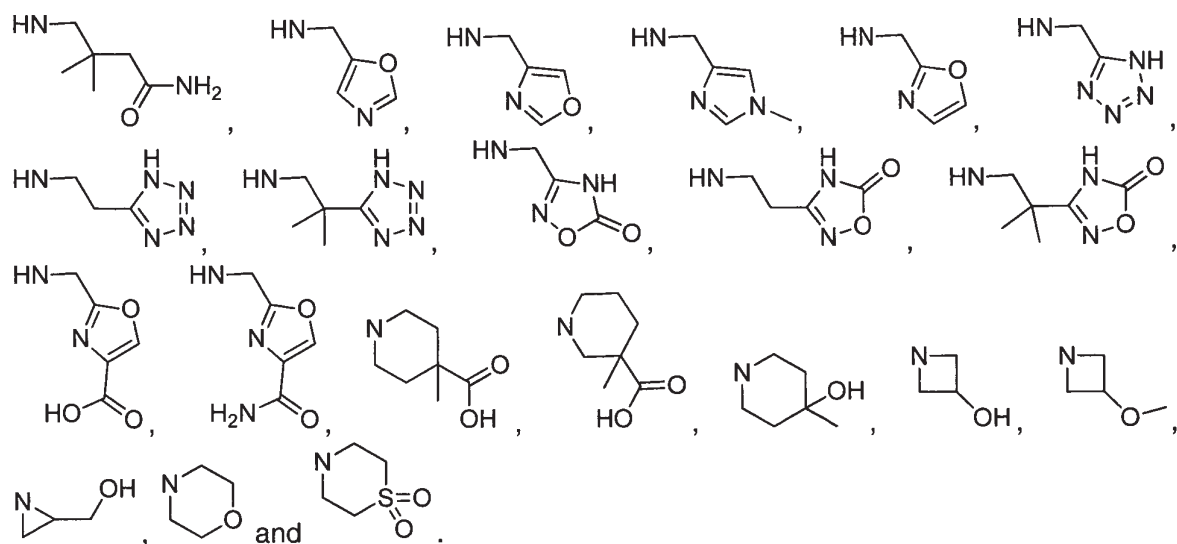




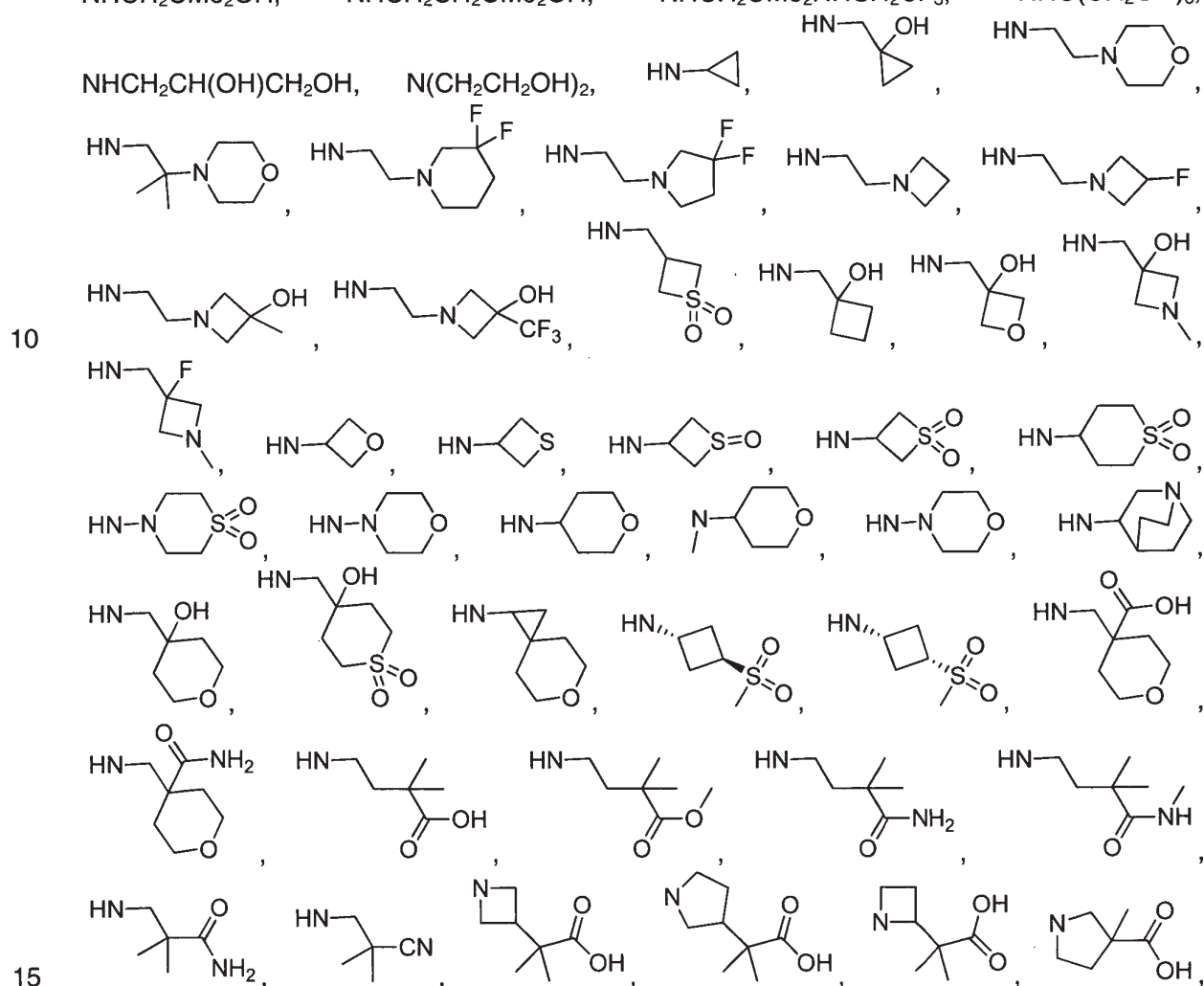
In an alternative preferred embodiment in combination with any of the above or below embodiments of the third alternative NR^1R^2 is selected from NH_2 , NHMe , NH^iEt , NH^iPr , NH^iBu , $\text{NHCH}_2\text{CONH}_2$, $\text{NHCH}_2\text{CONMe}_2$, $\text{NHCH}_2\text{CH}_2\text{OH}$, $\text{NHCH}_2\text{CH}(\text{CF}_3)\text{OH}$, $\text{NHCH}_2\text{C}(\text{CF}_3)_2\text{OH}$, $\text{NHCH}_2\text{CH}_2\text{OMe}$, $\text{NHCH}_2\text{CH}_2\text{SO}_2\text{Me}$, $\text{NHCH}_2\text{CH}_2\text{SO}_2\text{NH}_2$, $\text{NH}(\text{CH}_2)_3\text{OH}$, $\text{NH}(\text{CH}_2)_3\text{OMe}$, $\text{NH}(\text{CH}_2)_4\text{OH}$, $\text{NH}(\text{CH}_2)_4\text{OMe}$, $\text{NH}(\text{CH}_2)_5\text{OH}$, $\text{NH}(\text{CH}_2)_2\text{CO}_2\text{H}$, $\text{NH}(\text{CH}_2)_3\text{CO}_2\text{H}$, $\text{NH}(\text{CH}_2)_4\text{CO}_2\text{H}$, $\text{NH}(\text{CH}_2)_5\text{CO}_2\text{H}$, $\text{NHCH}_2\text{CMe}_2\text{OH}$, $\text{NHCH}(\text{Me})\text{CMe}_2\text{OH}$, $\text{NHCH}_2\text{CMe}_2\text{OMe}$, $\text{NHCH}_2\text{CMe}_2\text{CO}_2\text{H}$, $\text{NHCH}_2\text{CMe}_2\text{CONHMe}$, $\text{NHCH}_2\text{CMe}_2\text{CONMe}_2$, $\text{NHCH}_2\text{CMe}_2\text{NH}\text{SO}_2\text{Me}$, $\text{NH}(\text{CH}_2)_3\text{SOMe}$, $\text{NH}(\text{CH}_2)_5\text{SO}_2\text{Me}$, $\text{NH}(\text{CH}_2)_3\text{NH}\text{SO}_2\text{Me}$, $\text{NH}(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{OH}$, $\text{NHCH}_2\text{CHMeOH}$, HN ,

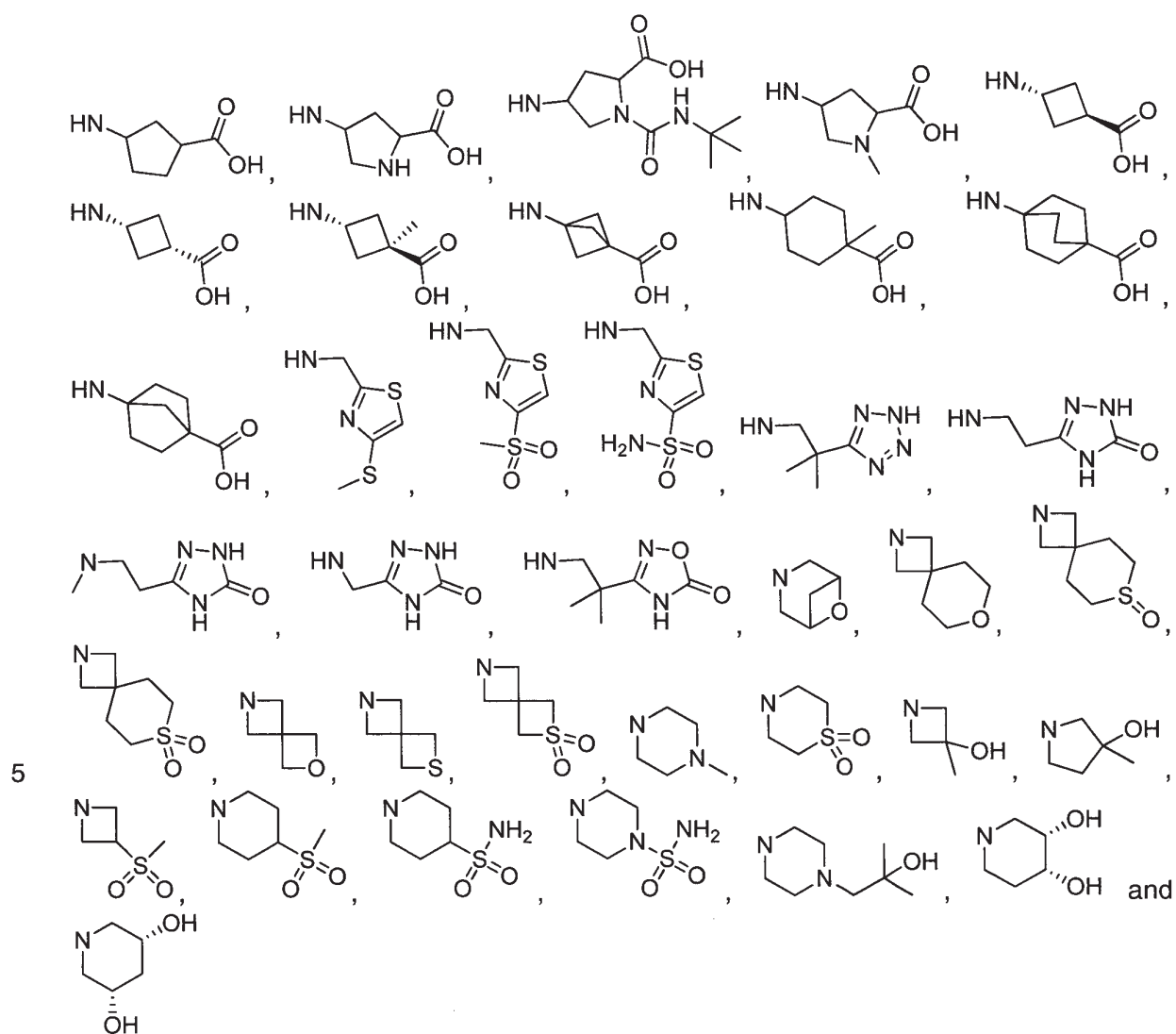




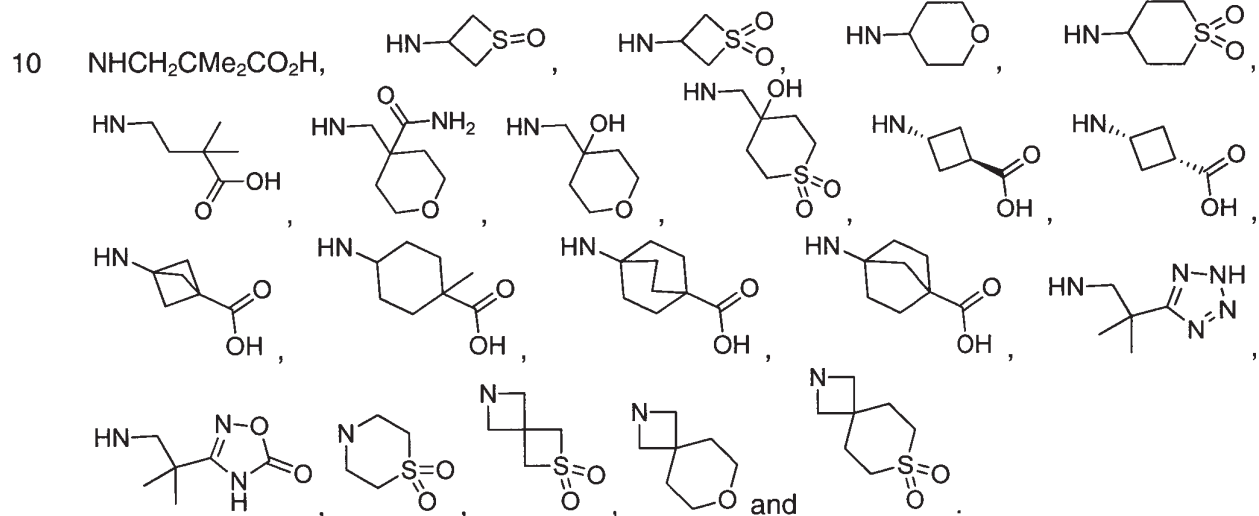


5 In a more preferred embodiment in combination with any of the above or below embodiments of the third alternative NR^1R^2 is selected from $\text{NHCH}_2\text{CH}(\text{CF}_3)\text{OH}$, $\text{NHCH}_2\text{C}(\text{Me})(\text{CF}_3)\text{OH}$, $\text{NHCH}_2\text{CMe}_2\text{OH}$, $\text{NHCH}_2\text{CH}_2\text{CMe}_2\text{OH}$, $\text{NHCH}_2\text{CMe}_2\text{NHCH}_2\text{CF}_3$, $\text{NHC}(\text{CH}_2\text{OH})_3$,

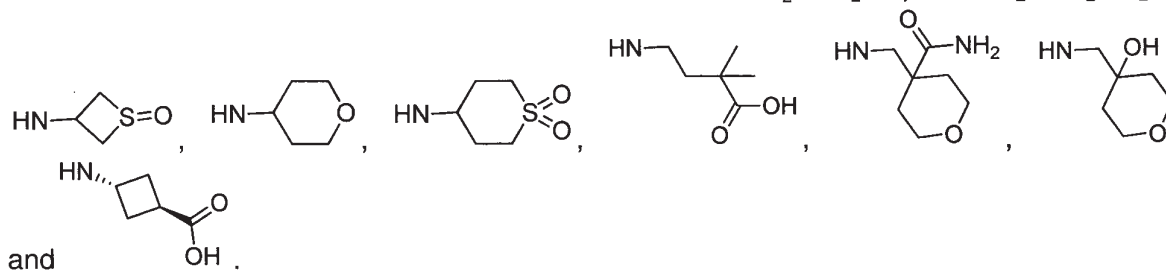




In an even more preferred embodiment in combination with any of the above or below embodiments of the third alternative NR^1R^2 is selected from $\text{NHCH}_2\text{CMe}_2\text{OH}$,



In a most preferred embodiment in combination with any of the above or below embodiments of the third alternative NR^1R^2 is selected from $\text{NHCH}_2\text{CMe}_2\text{OH}$, $\text{NHCH}_2\text{CMe}_2\text{CO}_2\text{H}$,



- 5 In another preferred embodiment in combination with any of the above or below embodiments of the third alternative R^3 is a 6-10 membered mono- or bicyclic aryl or a 5-10 membered mono- or bicyclic heteroaryl containing 1 to 4 heteroatoms independently selected from the group consisting of N, O and S

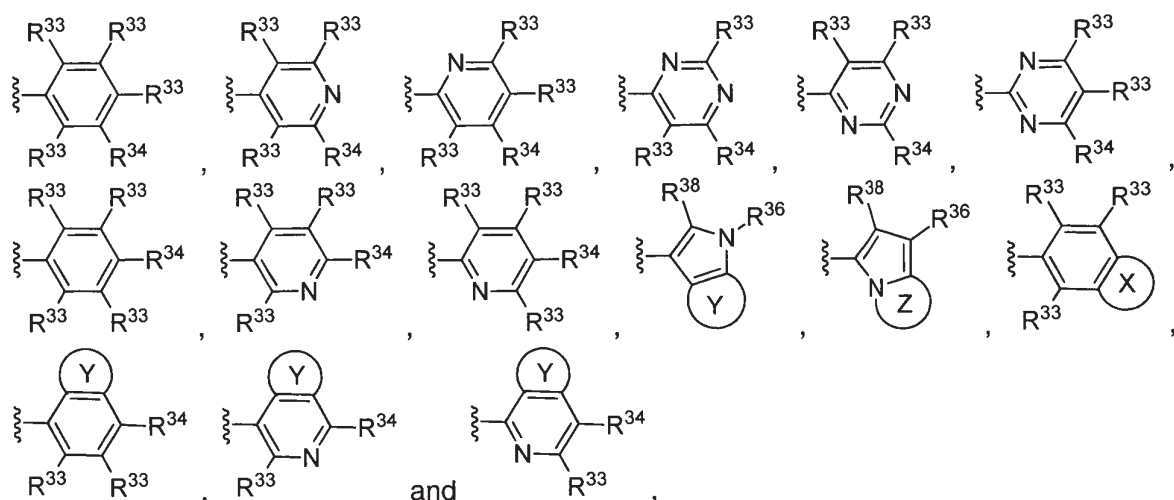
10 wherein aryl and heteroaryl are unsubstituted or substituted with 1 to 5 substituents independently selected from halogen, CN, C_{1-6} -alkyl, halo- C_{1-6} -alkyl, OH, O- C_{1-6} -alkyl, O-halo- C_{1-6} -alkyl, C_{0-6} -alkylene- C_{3-10} -cycloalkyl, C_{0-6} -alkylene-O- C_{3-10} -cycloalkyl, C_{0-6} -alkylene- C_{3-10} -heterocycloalkyl, C_{0-6} -alkylene- COOR^{31} , C_{0-6} -alkylene- C(O)R^{31} , C_{0-6} -alkylene- $\text{C(O)N(R}^{31})_2$, C_{0-6} -alkylene- $\text{SO}_2\text{-N(R}^{31})_2$, C_{0-6} -alkylene- $\text{SO}_2\text{-R}^{31}$, C_{0-6} -alkylene-(5-membered heteroaryl), C_{0-6} -alkylene-(6-membered heteroaryl),

15 wherein alkyl, alkylene, cycloalkyl, heterocycloalkyl and heteroaryl are unsubstituted or substituted by 1 to 3 substituents independently selected from the group consisting of halogen, OH, oxo, $=\text{N-OR}^{32}$, $\text{N(R}^{31})_2$, O- C_{1-6} -alkyl, COOH , $\text{CON(R}^{31})_2$, CN, $\text{NR}^{31}\text{-COR}^{31}$, C_{3-10} -cycloalkyl, C_{3-10} -heterocycloalkyl, 6-10-membered mono- or bicyclic aryl, 6-10-membered mono- or bicyclic heteroaryl,

20 or wherein two adjacent substituents may complete a 3- to 8-membered saturated or partially unsaturated ring containing carbon atoms and optionally containing 1 to 3 members selected from O, S, SO, SO_2 or NR^{31} , wherein the ring is unsubstituted or substituted with 1 to 4 substituents independently selected from halogen, oxo, $=\text{N-OR}^{32}$, OH, O- C_{1-6} -alkyl, O-halo- C_{1-6} -alkyl, C_{1-6} -alkyl, C_{3-6} -cycloalkyl and halo- C_{1-6} -alkyl.

25 In a more preferred embodiment in combination with any of the above or below embodiments of the third alternative R^3 is a 6-membered aryl, a 10-membered bicyclic aryl, a 6-membered heteroaryl or 10-membered bicyclic heteroaryl containing 1 or 2 nitrogen atom wherein aryl and heteroaryl may be unsubstituted or substituted as above.

30 In another preferred embodiment in combination with any of the above or below embodiments of the third alternative R^3 is selected from



wherein

- 5 R^{33} is independently selected from H, halogen, CN, C_{1-6} -alkyl, fluoro- C_{1-6} -alkyl, C_{1-4} -alkylene-OH, C_{1-4} -alkylene-O- C_{1-3} -alkyl, C_{1-4} -alkylene-O-fluoro- C_{1-3} -alkyl, OH, O- C_{1-6} -alkyl, O-fluoro- C_{1-6} -alkyl, NH- C_{1-6} -alkyl, NH-fluoro- C_{1-6} -alkyl, C_{3-10} -cycloalkyl,

- wherein alkylene is unsubstituted or substituted with 1 to 3 substituents selected from F and cycloalkyl is unsubstituted or substituted with 1 to 3 substituents independently
10 selected from F, C_{1-3} -alkyl and fluoro- C_{1-3} -alkyl;

R^{34} are independently selected from H, halogen, CN, C_{1-6} -alkyl, fluoro- C_{1-6} -alkyl, C_{1-4} -alkylene-OH, C_{1-4} -alkylene-O- C_{1-3} -alkyl, C_{1-4} -alkylene-O-fluoro- C_{1-3} -alkyl, OH, O- C_{1-6} -alkyl, O-fluoro- C_{1-6} -alkyl, NH- C_{1-6} -alkyl, NH-fluoro- C_{1-6} -alkyl, C_{3-10} -cycloalkyl, C_{0-6} -alkylene- C_{3-10} -heterocycloalkyl, 5-membered heteroaryl, 6-membered heteroaryl, $C(O)N(R^{37})_2$ and $SO_2N(R^{37})_2$,

- 15 wherein alkylene is unsubstituted or substituted with 1 to 3 substituents selected from F and cycloalkyl, heterocycloalkyl and heteroaryl is unsubstituted or substituted with 1 to 3 substituents independently selected from F, C_{1-3} -alkyl, fluoro- C_{1-3} -alkyl, OH, O- C_{1-3} -alkyl, fluoro-O- C_{1-3} -alkyl;

- R^{35} is selected from halogen, C_{1-6} -alkyl, halo- C_{1-6} -alkyl, C_{3-6} -cycloalkyl, C_{3-6} -heterocycloalkyl, 20 oxo, OH, O- C_{1-6} -alkyl and O-halo- C_{1-6} -alkyl;

R^{36} is selected from C_{1-6} -alkyl, fluoro- C_{1-6} -alkyl, $C(O)N(R^{37})_2$, $SO_2N(R^{37})_2$;

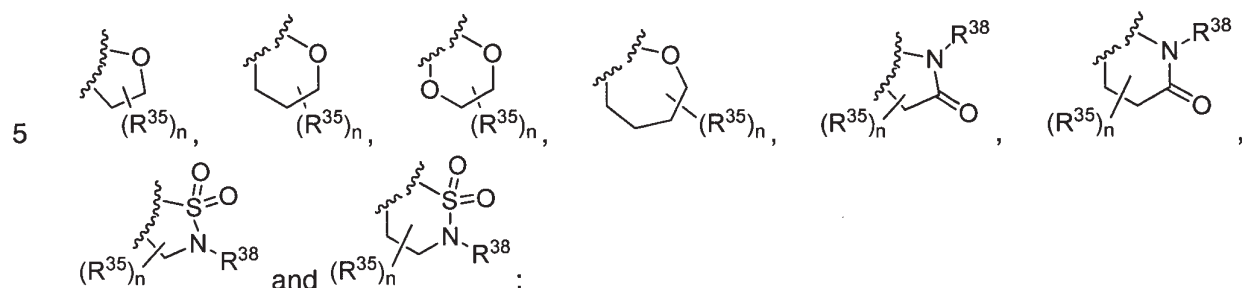
- R^{37} is independently selected from H, C_{1-6} -alkyl, halo- C_{1-6} -alkyl, C_{0-4} -alkylene- C_{3-6} -cycloalkyl, C_{0-4} -alkylene- C_{3-6} -heterocycloalkyl, wherein alkyl and alkylene is unsubstituted or substituted with 1 to 4 substituents selected from halogen, OH, O- C_{1-3} -alkyl, CN, $CONH_2$; and cycloalkyl or heterocycloalkyl is unsubstituted or substituted with 1 to 3 substituents independently
25 selected from F, CN, OH, oxo, C_{1-3} -alkyl and fluoro- C_{1-3} -alkyl;

or wherein two R^{37} when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing 1 or 2

heteroatoms selected from O, S or N, wherein the ring is unsubstituted or substituted with 1 to 4 substituents independently selected from fluoro, OH, oxo, C₁₋₄-alkyl and halo-C₁₋₄-alkyl;

R³⁸ is selected from H, C₁₋₃-alkyl and fluoro-C₁₋₃-alkyl;

X is an annulated saturated heterocycle selected from the group consisting of



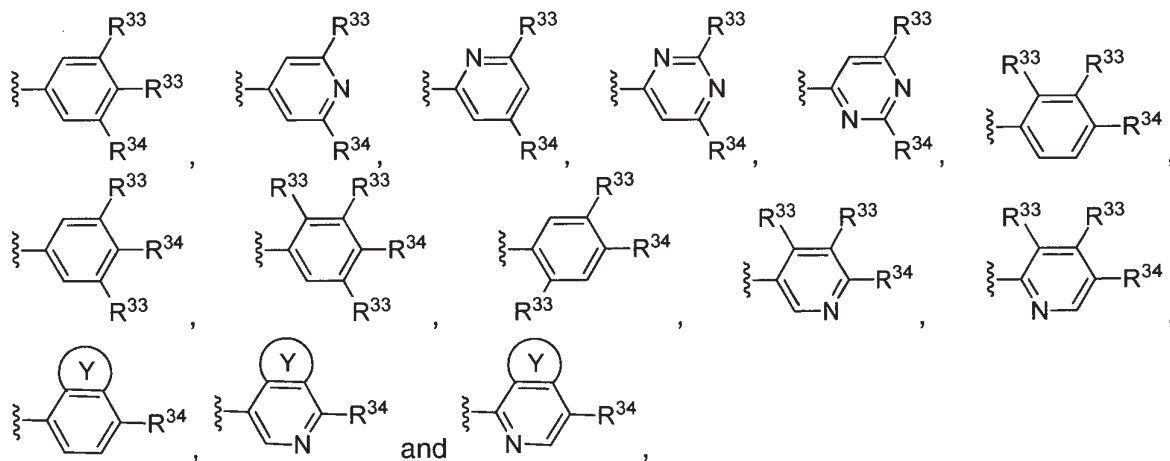
Y is an annulated 5- or 6-membered carbocycle, an annulated 6-membered aryl or an annulated 6-membered heteroaryl containing 1 to 2 nitrogen atoms, wherein the carbocycle, aryl or heteroaryl is unsubstituted or substituted with 1 to 3 substituents selected from halogen, C₁₋₃-alkyl and fluoro-C₁₋₃-alkyl;

10

Z is an annulated 6-membered cycle forming a heteroaryl containing 1 to 2 nitrogen atoms, wherein the heteroaryl is unsubstituted or substituted with 1 to 3 substituents selected from fluoro, C₁₋₃-alkyl and fluoro-C₁₋₃-alkyl;

n is selected from 1 to 4.

15 In a more preferred embodiment in combination with any of the above or below embodiments of the third alternative R³ is selected from



20 wherein

R³³ is independently selected from H, halogen, CN, C₁₋₆-alkyl, fluoro-C₁₋₆-alkyl, C₁₋₄-alkylene-OH, C₁₋₄-alkylene-O-C₁₋₃-alkyl, C₁₋₄-alkylene-O-fluoro-C₁₋₃-alkyl, OH, O-C₁₋₆-alkyl, O-fluoro-C₁₋₆-alkyl, NH-C₁₋₆-alkyl, NH-fluoro-C₁₋₆-alkyl, C₃₋₁₀-cycloalkyl, C(O)N(R³⁷)₂,

wherein alkylene is unsubstituted or substituted with 1 to 3 substituents selected from F and cycloalkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from F, C₁₋₃-alkyl and fluoro-C₁₋₃-alkyl;

- 5 R³⁴ is selected from C₁₋₄-alkylene-OH, C₁₋₄-alkylene-O-C₁₋₃-alkyl, C₁₋₄-alkylene-O-fluoro-C₁₋₃-alkyl, C₃₋₁₀-cycloalkyl, C(O)N(R³⁷)₂, SO₂N(R³⁷)₂,

wherein alkylene is unsubstituted or substituted with 1 to 3 substituents selected from F and cycloalkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from F, C₁₋₃-alkyl and fluoro-C₁₋₃-alkyl;

- 10 R³⁷ is independently selected from H, C₁₋₆-alkyl, halo-C₁₋₆-alkyl, C₀₋₄-alkylene-C₃₋₆-cycloalkyl, C₀₋₄-alkylene-C₃₋₆-heterocycloalkyl,

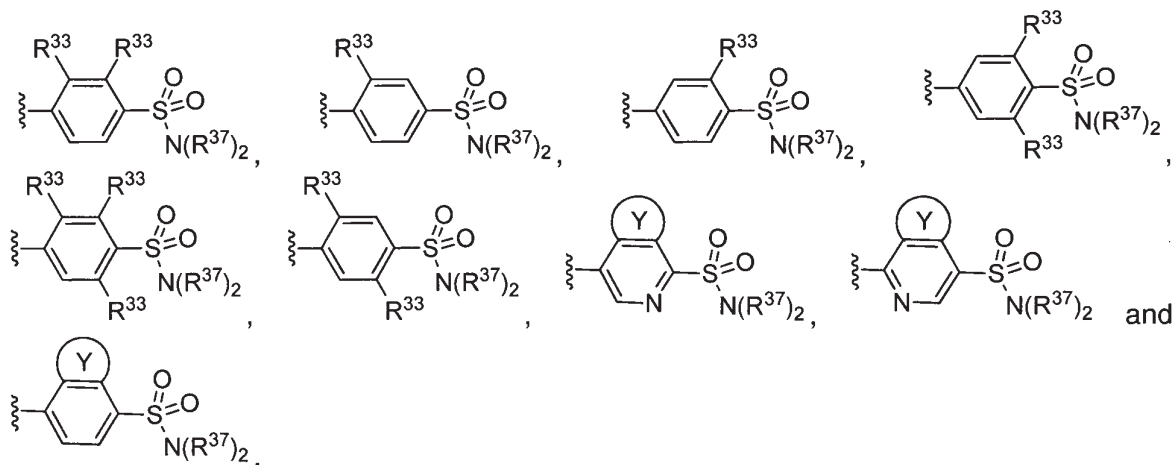
wherein alkyl and alkylene is unsubstituted or substituted with 1 to 4 substituents selected from halogen, OH, O-C₁₋₃-alkyl, CN, CONH₂; and

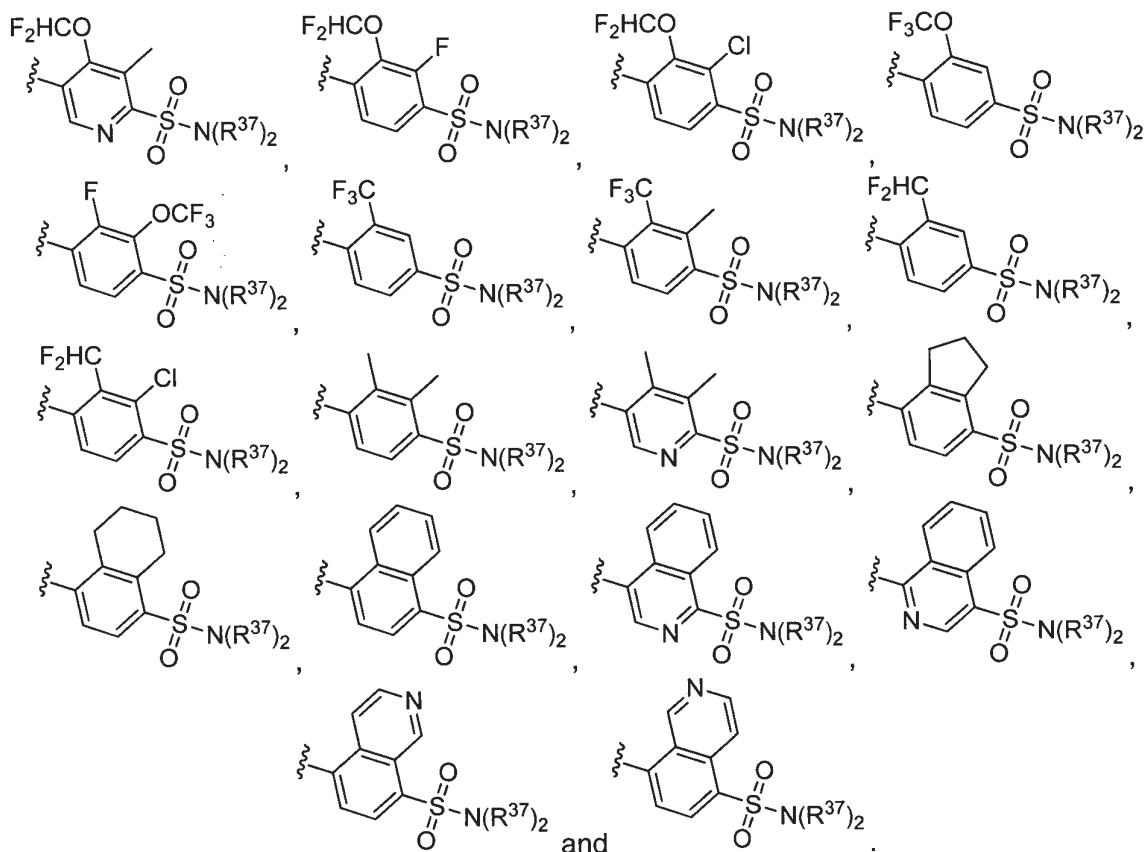
- 15 wherein cycloalkyl or heterocycloalkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from F, CN, OH, oxo, O-C₁₋₃-alkyl, C₁₋₃-alkyl and fluoro-C₁₋₃-alkyl;

or wherein two R³⁷ when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing 1 or 2 heteroatoms selected from O, S or N, wherein the ring is unsubstituted or substituted with 1 to 4 substituents independently selected from fluoro, OH, oxo, C₁₋₄-alkyl and halo-C₁₋₄-alkyl;

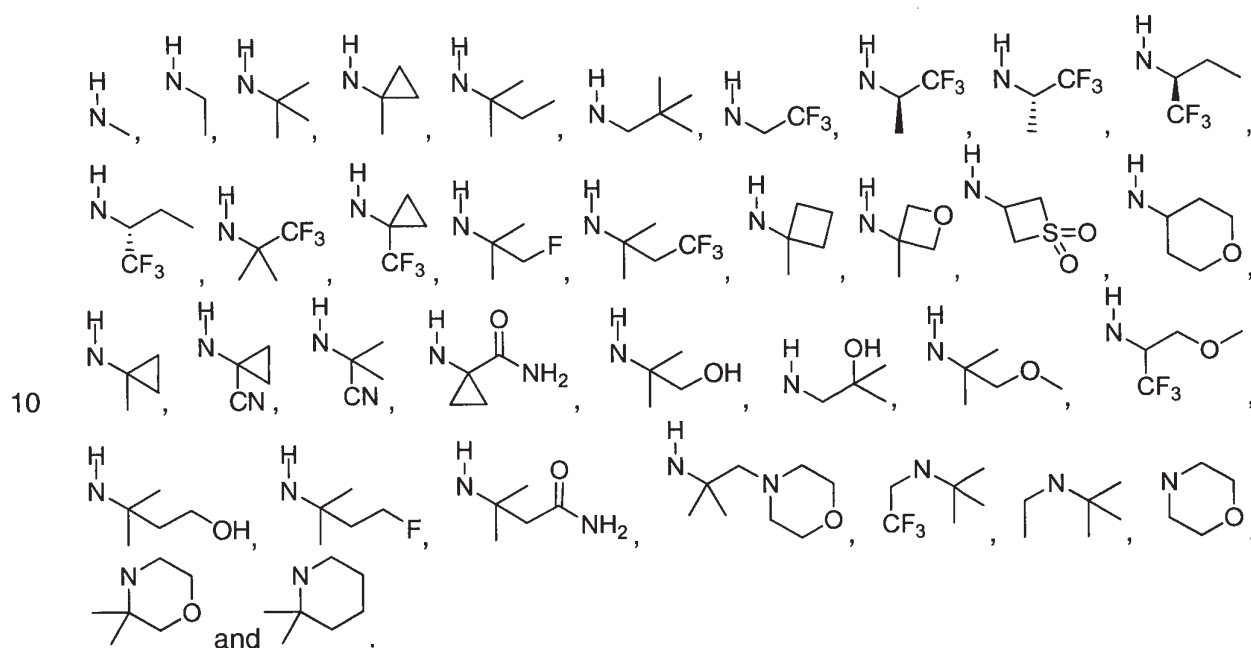
- 20 Y is selected from an annelated 5- or 6-membered carbocycle, an annelated 6-membered aryl or an annelated 6-membered heteroaryl containing 1 to 2 nitrogen atoms, wherein the carbocycle, aryl or heteroaryl is unsubstituted or substituted with 1 to 3 substituents selected from fluoro, methyl or CF₃.

- 25 In an even more preferred embodiment in combination with any of the above or below embodiments of the third alternative R³ is selected from





In another preferred embodiment in combination with any of the above or below embodiments of the third alternative $N(R^{37})_2$ is selected from



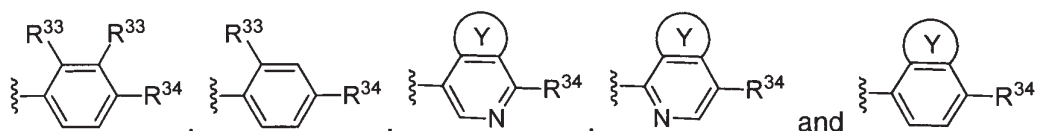
In a more preferred embodiment in combination with any of the above or below embodiments of the third alternative $N(R^{37})_2$ is selected from

R³⁴ is selected from C₁₋₆-alkyl, halo-C₁₋₆-alkyl and C₀₋₆-alkylene-C₃₋₁₀-heterocycloalkyl,

wherein alkyl, alkylene and heterocycloalkyl are unsubstituted or substituted by 1 to 3 substituents independently selected from the group consisting of halogen, C₁₋₆-alkyl, halo-C₁₋₆-alkyl, OH, oxo, N(R³¹)₂, O-C₁₋₆-alkyl, C₃₋₁₀-cycloalkyl, C₃₋₁₀-heterocycloalkyl; and

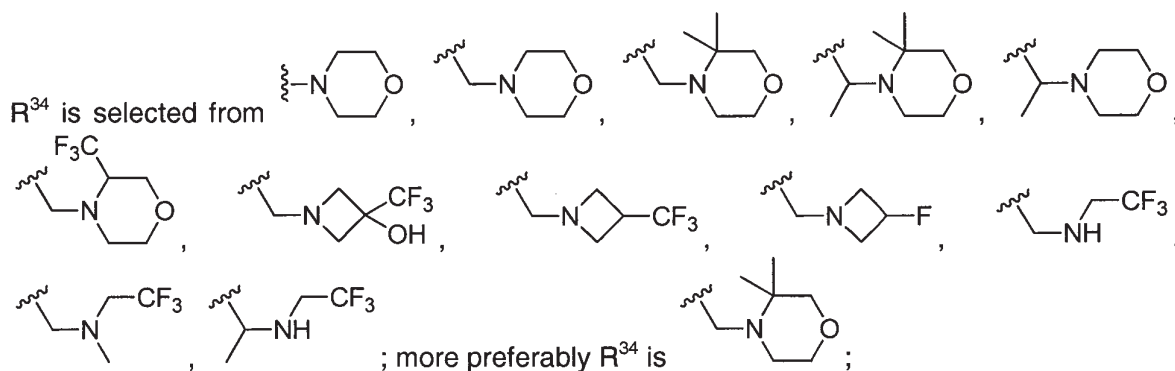
Y is selected from an annelated 5- or 6-membered carbocycle, an annelated 6-membered aryl or an annelated 6-membered heteroaryl containing 1 to 2 nitrogen atoms, wherein the carbocycle, aryl or heteroaryl is unsubstituted or substituted with 1 to 3 substituents selected from fluoro, methyl or CF₃.

10 In more preferred embodiment in combination with any of the above or below embodiments of
the third alternative R³ is selected from



wherein R³³ is independently selected from H, halogen, C₁₋₆-alkyl, fluoro-C₁₋₆-alkyl, C₁₋₄-alkylene-OH, C₁₋₄-alkylene-O-C₁₋₃-alkyl, O-C₁₋₆-alkyl, and O-fluoro-C₁₋₆-alkyl, more preferably

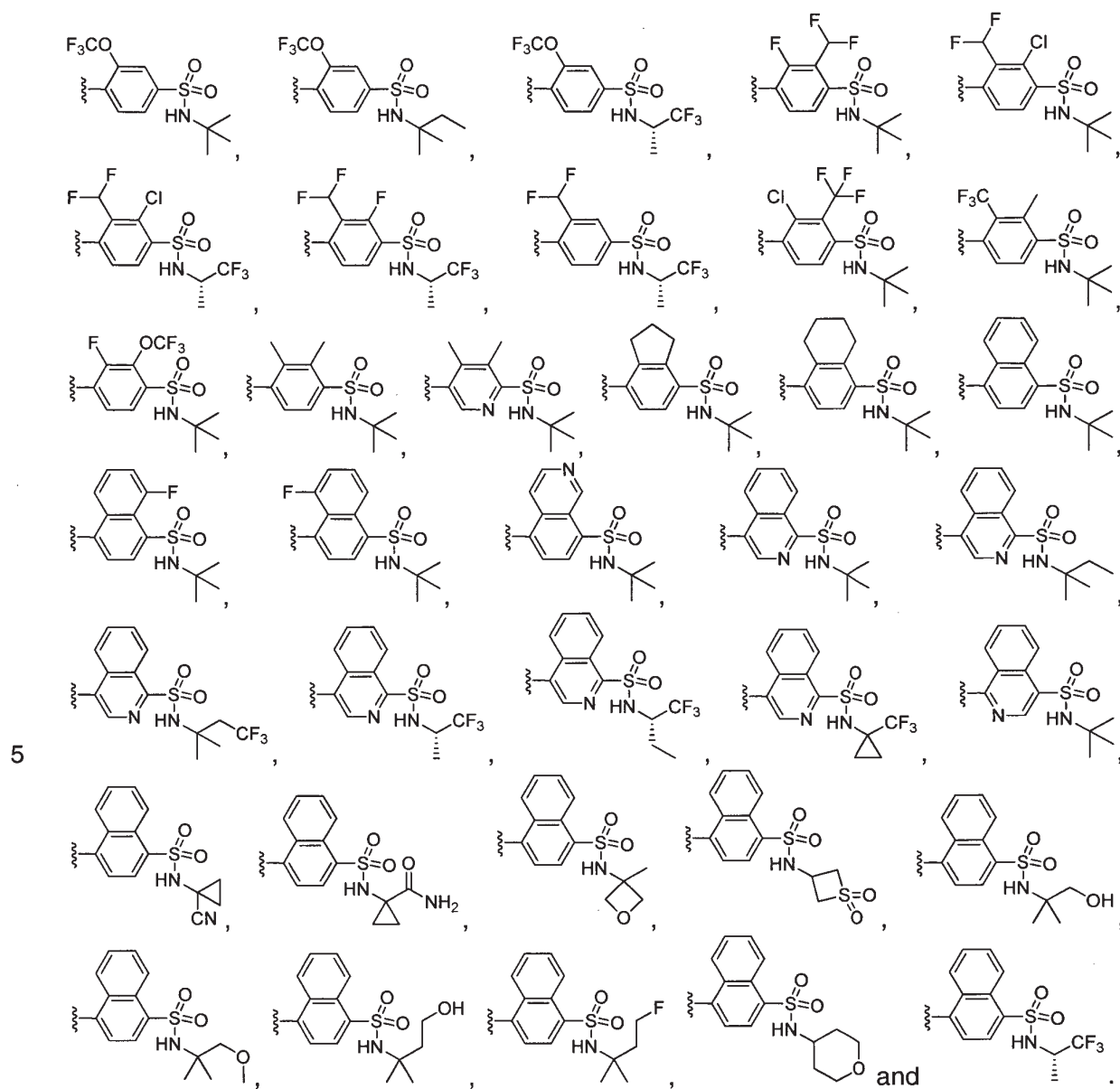
15 R³³ is independently selected from fluoro, chloro, CF₃, CHF₂, OCF₃, OCHF₂, methyl, ^tbutyl and CMe₂OH;



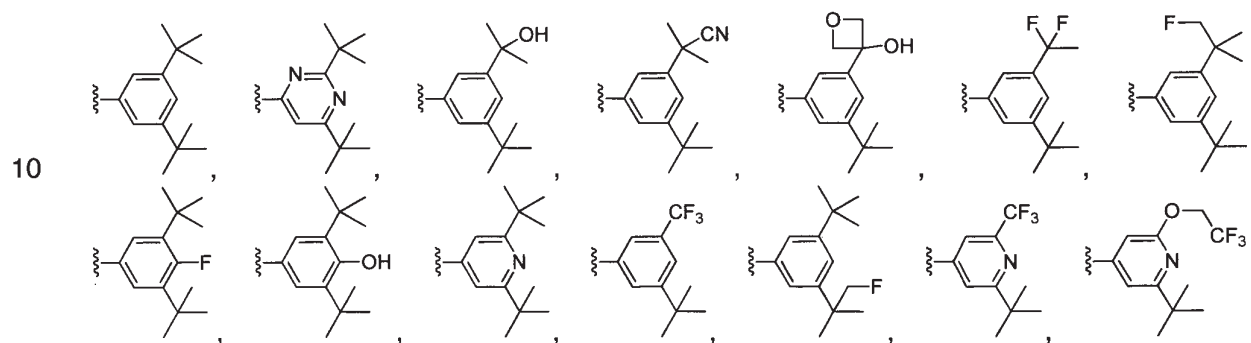
20 Y is selected from an annelated 5- or 6-membered carbocycle, an annelated 6-membered aryl or an annelated 6-membered heteroaryl containing 1 to 2 nitrogen atoms, wherein the carbocycle, aryl or heteroaryl is unsubstituted or substituted with 1 to 3 substituents selected from fluoro, methyl or CF₃.

In an alternative preferred embodiment in combination with any of the above or below
25 embodiments of the third alternative R³ is selected from



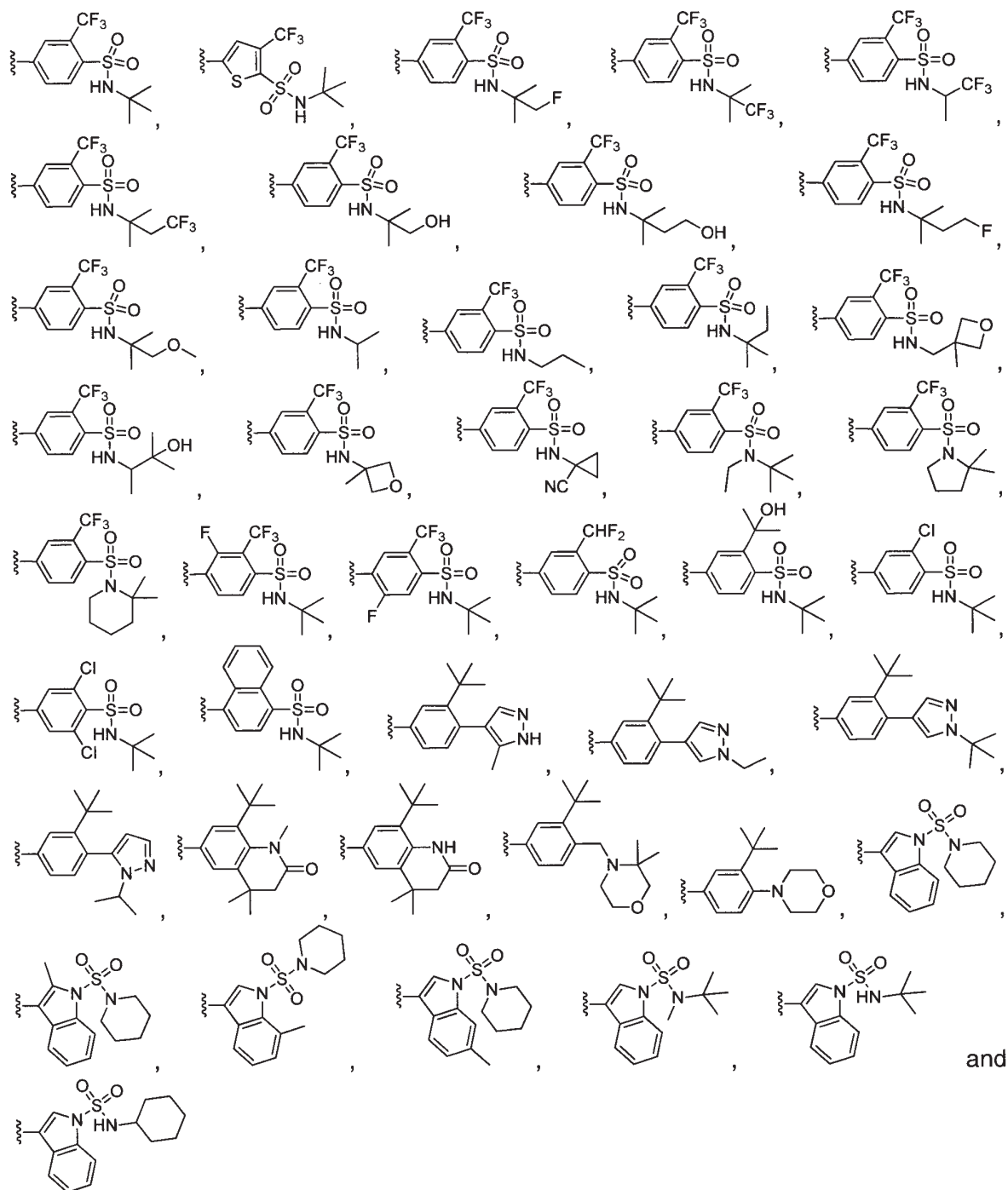


In yet another alternative preferred embodiment in combination with any of the above or below embodiments of the third alternative R^3 is selected from

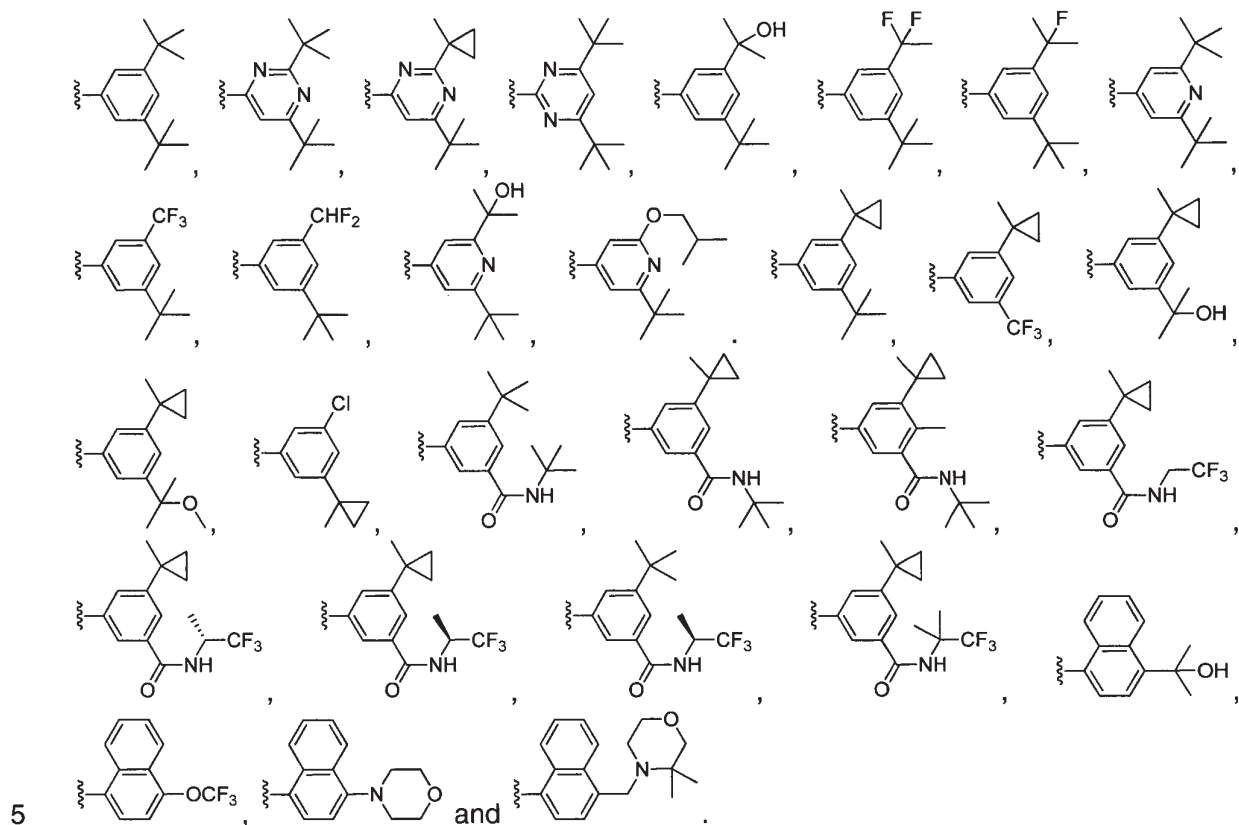




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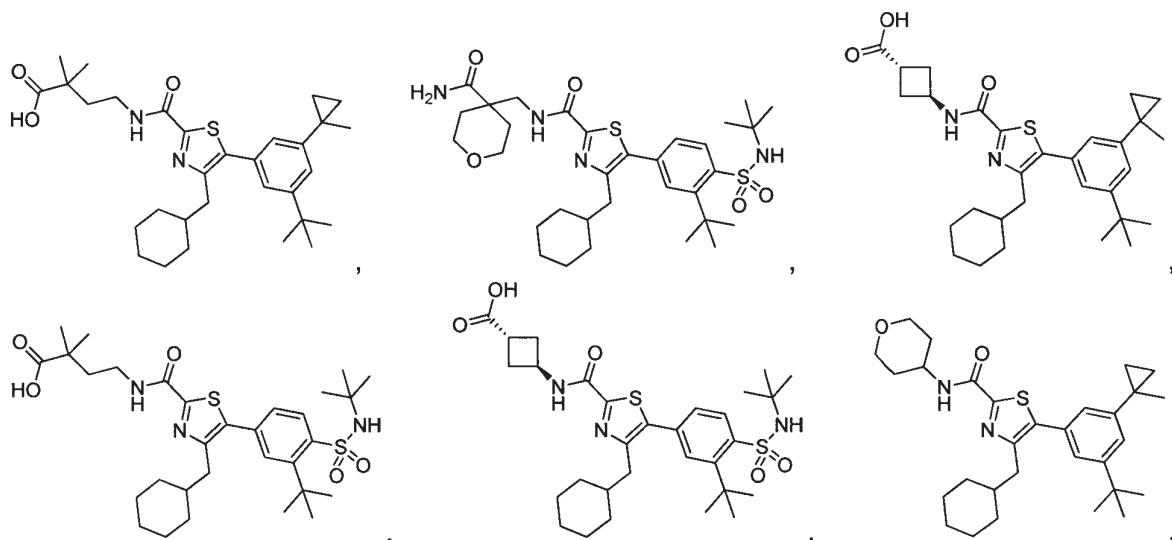


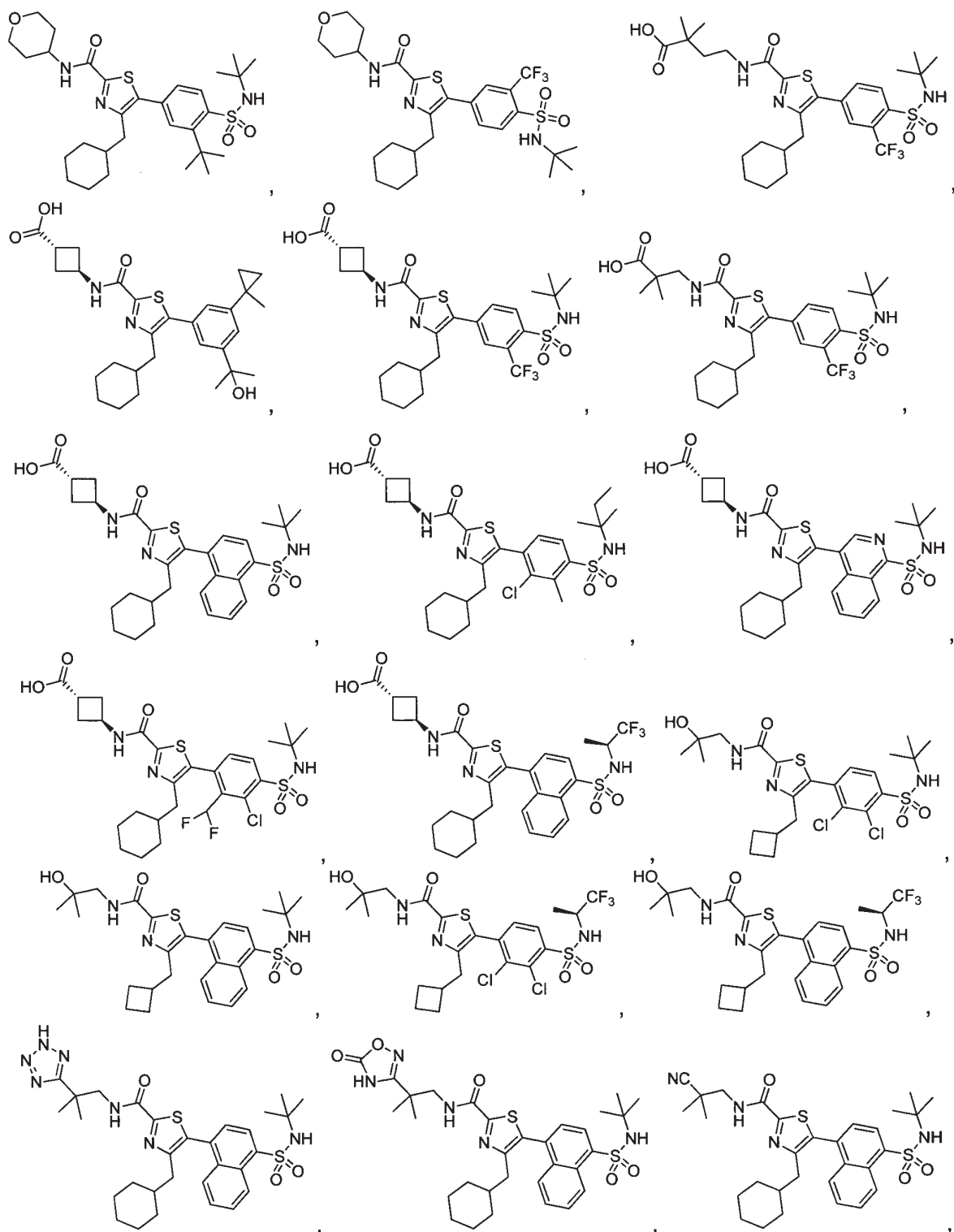
- 10 In a preferred embodiment in combination with any of the above or below embodiments of the third alternative R³ is selected from

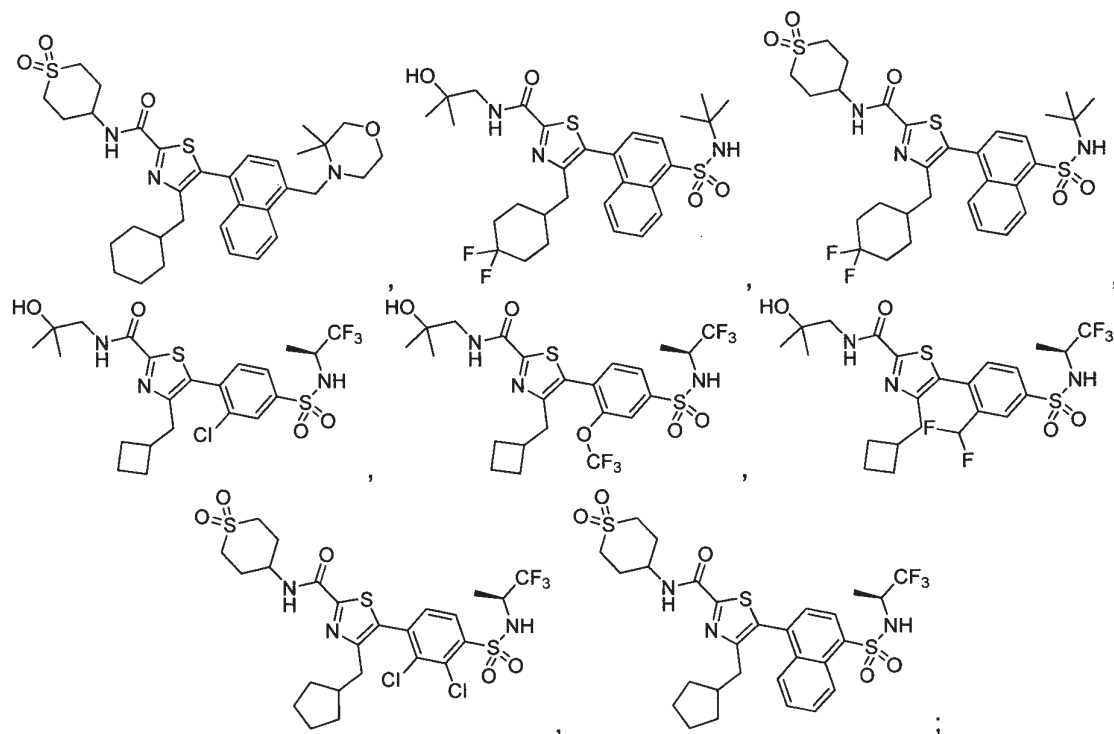


In another preferred embodiment in combination with any of the above or below embodiments of the third alternative the compound is represented by Formula (1).

In yet another preferred embodiment in combination with any of the above or below embodiments of the third alternative, the compound of Formula (1) is selected from the group consisting of







and an enantiomer, diastereomer, tautomer, *N*-oxide, solvate and pharmaceutically acceptable salt thereof.

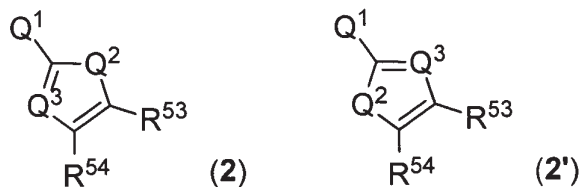
The invention also provides the compound of the third alternative of the invention for use as a medicament.

Also provided is the compound of the third alternative of the invention for use in the treatment or prophylaxis of a disease or disorder associated with the inhibition or activation of the ROR γ receptor.

Also provided is the compound of the third alternative of the invention in treating ROR γ mediated inflammatory and autoimmune diseases. Preferably, the disease is selected from the group consisting of rheumatoid arthritis, ankylosing spondylitis, lupus erythematosus, psoriasis, psoriatic arthritis, atopic eczema, inflammatory bowel diseases such as Crohn's disease, asthma, mucosal leishmaniasis, multiple sclerosis, systemic sclerosis, type 1 diabetes, Kawasaki disease, Hashimoto's thyroiditis, chronic graft-versus-host disease, acute graft-versus-host disease, Celiac Sprue, idiopathic thrombocytopenic thrombotic purpura, myasthenia gravis, Sjorgren's syndrome, scleroderma, ulcerative colitis, epidermal hyperplasia, glomerulonephritis, chronic obstructive pulmonary disease and amyotrophic lateral sclerosis.

Also provided is a pharmaceutical composition comprising the compound of the third alternative of the invention and a pharmaceutically acceptable carrier.

In a fourth alternative the present invention provides a compound according to Formula (2) or Formula (2')



an enantiomer, diastereomer, tautomer, solvate, formulation and pharmaceutically acceptable salt thereof,

wherein

Q^1 is selected from $\text{CO-NR}^{51}\text{R}^{52}$, CO-R^{52} , CO_2R^{51} , $\text{SO}_2\text{-NR}^{51}\text{R}^{52}$, $\text{SO}_2\text{-R}^{52}$, $\text{NR}^{52}\text{CO-R}^{51}$ and $\text{NR}^{52}\text{SO}_2\text{-R}^{51}$;

Q^2 is selected from $-\text{O}-$, $-\text{S}-$, $-\text{CR}^{55}=\text{CR}^{56}-$, $-\text{N}=\text{CR}^{56}-$, $-\text{CR}^{55}=\text{N}-$ and $-\text{N}=\text{N}-$;

10 Q^3 is selected from N and CR^{55} ;

R^{51} and R^{52} are independently selected from H, C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl, C_{0-10} -alkylene- C_{3-10} -cycloalkyl, C_{0-10} -alkylene- C_{3-10} -heterocycloalkyl, C_{0-10} -alkylene-heteroaryl, C_{0-10} -alkylene-aryl, wherein alkyl, alkenyl, alkynyl, alkylene, cycloalkyl, heterocycloalkyl, aryl and heteroaryl is unsubstituted or substituted with 1 to 7 substituents independently selected from
 15 oxo, CN, OR^{61} , O-C_{2-6} -alkylene- OR^{61} , C_{1-6} -alkyl, halo- C_{1-6} -alkyl, halogen, CO_2R^{61} , $\text{CONR}^{61}\text{R}^{62}$, $\text{CONR}^{61}\text{SO}_2\text{R}^{62}$, COR^{61} , SO_xR^{61} , SO_3H , $\text{SO}_2\text{NR}^{61}\text{R}^{62}$, $\text{NR}^{61}\text{COR}^{61}$, $\text{NR}^{61}\text{SO}_2\text{R}^{61}$, $\text{NR}^{61}\text{-CO-NR}^{61}\text{R}^{62}$, $\text{NR}^{61}\text{-SO}_2\text{-NR}^{61}\text{R}^{62}$, C_{3-6} -cycloalkyl, O-C_{3-6} -cycloalkyl, C_{3-6} -heterocycloalkyl, O-C_{3-6} -heterocycloalkyl and $\text{NR}^{61}\text{R}^{62}$;

or R^{51} and R^{52} when taken together with the nitrogen to which they are attached complete a 3-
 20 to 8-membered ring containing carbon atoms and optionally containing 1 or 2 heteroatoms selected from O, S or N, wherein the ring is unsubstituted or substituted with 1 to 4 substituents independently selected from halogen, oxo, CN, OR^{61} , SO_xR^{61} , SO_3H , $\text{NR}^{61}\text{SO}_2\text{R}^{61}$, $\text{SO}_2\text{NR}^{61}\text{R}^{62}$, CO_2R^{61} , $\text{CONR}^{61}\text{R}^{62}$, $\text{CONR}^{61}\text{SO}_2\text{R}^{62}$, COR^{61} , $\text{NR}^{61}\text{-CO-R}^{61}$, $\text{NR}^{61}\text{-CO-NR}^{61}\text{R}^{62}$, $\text{NR}^{61}\text{-SO}_2\text{-NR}^{61}\text{R}^{62}$, $\text{NR}^{61}\text{R}^{62}$, C_{1-6} -alkyl, halo- C_{1-6} -alkyl, hydroxy- C_{1-6} -alkyl, C_{3-6} -cycloalkyl, O-C_{3-6} -cycloalkyl, C_{3-6} -heterocycloalkyl and O-C_{3-6} -heterocycloalkyl;

R^{53} is a 6-10 membered mono- or bicyclic aryl or a 5-14 membered mono-, bi- or tricyclic heteroaryl containing 1 to 5 heteroatoms independently selected from the group consisting of N, O and S,

wherein aryl and heteroaryl are unsubstituted or substituted with 1 to 5 substituents
 30 independently selected from halogen, CN, C_{1-6} -alkyl, C_{1-6} -alkenyl, C_{1-6} -alkynyl, halo- C_{1-6} -alkyl, OH, O-C_{1-6} -alkyl, O-halo- C_{1-6} -alkyl, C_{0-6} -alkylene- C_{3-10} -cycloalkyl, C_{0-6} -alkylene- O-C_{3-10} -cycloalkyl, C_{0-6} -alkylene- C_{3-10} -heterocycloalkyl, C_{0-6} -alkylene- COOR^{81} , C_{0-6} -alkylene- C(O)R^{81} , C_{0-6} -alkylene- $\text{C(O)N(R}^{81})_2$, C_{0-6} -alkylene- $\text{SO}_2\text{-N(R}^{81})_2$, C_{0-6} -alkylene-

SO₂-R⁸¹, C₀₋₆-alkylene-(6-10-membered mono- or bicyclic aryl), C₀₋₆-alkylene-(6-10-membered mono- or bicyclic heteroaryl),

5 wherein alkyl, alkenyl, alkynyl, alkylene, cycloalkyl, heterocycloalkyl and heteroaryl are unsubstituted or substituted by 1 to 3 substituents independently selected from the group consisting of C₁₋₆-alkyl, halo-C₁₋₆-alkyl, halogen, OH, oxo, =N-OR⁸², N(R⁸¹)₂, O-C₁₋₆-alkyl, O-halo-C₁₋₆-alkyl, COOH, CON(R⁸¹)₂, CN, NR⁸¹-COR⁸¹, C₃₋₁₀-cycloalkyl, C₃₋₁₀-heterocycloalkyl, 6-10-membered mono- or bicyclic aryl, 6-10-membered mono- or bicyclic heteroaryl,

10 or wherein two adjacent substituents may complete a 3- to 8-membered saturated or partially unsaturated ring containing carbon atoms and optionally containing 1 to 3 members selected from O, S, SO, SO₂ or NR⁸¹, wherein the ring is unsubstituted or substituted with one to four substituents independently selected from halogen, oxo, =N-OR⁸², OH, O-C₁₋₆-alkyl, O-halo-C₁₋₆-alkyl, C₁₋₆-alkyl, C₃₋₆-cycloalkyl and halo-C₁₋₆-alkyl;

15 R⁵⁴ is selected from C₀₋₆-alkylene-R⁵⁷, C₃-cycloalkyl-R⁵⁷, O-C₀₋₅-alkylene-R⁵⁷, NR⁹¹-C₀₋₅-alkylene-R⁵⁷ and SO_x-C₀₋₅-alkylene-R⁵⁷,

wherein alkylene is optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, OH, oxo, =N-OR⁸², N(R⁸¹)₂, O-C₁₋₆-alkyl, COOH, CON(R⁸¹)₂, CN, NR⁸¹-COR⁸¹, C₃₋₆-cycloalkyl and C₃₋₆-heterocycloalkyl;

R⁵⁵ and R⁵⁶ are independently selected from H, halogen, CN, C₁₋₆-alkyl and O-C₁₋₆-alkyl,

20 wherein alkyl is optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, OH, oxo, O-C₁₋₃-alkyl; O-halo-C₁₋₃-alkyl and C₃₋₆-cycloalkyl;

R⁵⁷ is selected from C₁₋₁₀-alkyl, C₃₋₁₀-cycloalkyl, C₃₋₁₀-heterocycloalkyl, 6-10-membered mono- or bicyclic aryl and 6-10-membered mono- or bicyclic heteroaryl,

25 wherein alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl are unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of halogen, OH, oxo, O-C₁₋₆-alkyl, O-halo-C₁₋₆-alkyl, C₁₋₆-alkyl, halo-C₁₋₆-alkyl, cycloalkyl and heterocycloalkyl;

30 R⁶¹ and R⁸¹ independently selected from H, C₁₋₆-alkyl, C₃₋₁₀-cycloalkyl, C₃₋₁₀-heterocycloalkyl, phenyl, 5-6-membered heteroaryl containing 1 to 4 heteroatoms independently selected from N, O and S

35 wherein alkyl, cycloalkyl and heterocycloalkyl is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of C₁₋₆-alkyl, halo-C₁₋₆-alkyl, OH, O-C₁₋₆-alkyl, O-halo-C₁₋₆-alkyl, phenyl, heteroaryl, halogen, NH₂, NH(C₁₋₆-alkyl), N(C₁₋₆-alkyl)₂, C₃₋₁₀-heterocycloalkyl and C₃₋₁₀-cycloalkyl, SO₂-C₁₋₃-alkyl, oxo, CN,

wherein cycloalkyl and heterocycloalkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of C₁₋₆-alkyl, halo-C₁₋₆-alkyl, OH, O-C₁₋₆-alkyl, O-halo-C₁₋₆-alkyl, phenyl, heteroaryl, halogen, NH₂, NH(C₁₋₆-alkyl), N(C₁₋₆-alkyl)₂ and C₃₋₁₀-cycloalkyl,

5 wherein phenyl and heteroaryl are unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of OH, O-C₁₋₆-alkyl, O-halo-C₁₋₆-alkyl, halogen, C₁₋₆-alkyl, halo-C₁₋₆-alkyl, NH₂, NH(C₁₋₆-alkyl), N(C₁₋₆-alkyl)₂ and C₃₋₁₀-cycloalkyl;

R⁶² and R⁸² are independently selected from H, C₁₋₆-alkyl, halo-C₁₋₆-alkyl and C₃₋₁₀-cycloalkyl;

10 R⁹¹ is selected from H, C₁₋₆-alkyl, C₃₋₆-cycloalkyl and C₃₋₆-heterocycloalkyl,

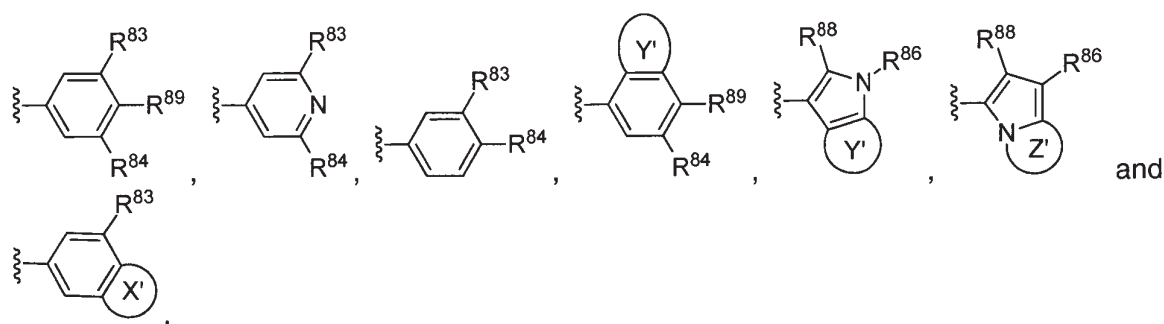
wherein alkyl, cycloalkyl and heterocycloalkyl is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of OH, oxo, CN, halogen, O-C₁₋₆-alkyl, O-halo-C₁₋₆-alkyl, C₃₋₆-heterocycloalkyl and C₃₋₆-cycloalkyl;

x is independently selected from 0, 1 and 2; for use in the treatment or prophylaxis of a
15 disease or disorder associated with the inhibition or activation of the ROR γ receptor; with the proviso that compounds of Formula (2') with Q¹ is NHCO-R⁵¹, Q² is sulfur, Q³ is nitrogen, R⁵³ and R⁵⁷ are optionally substituted aryl and R⁵⁴ is COR⁵⁷ are excluded.

In a preferred embodiment in combination with any of the above or below embodiments of the fourth alternative Q¹ is selected from CO-NR⁵¹R⁵² and NR⁵²CO-R⁵¹; Q² is selected from -O-
20 and -S-; and Q³ is N.

In a further preferred embodiment in combination with any of the above or below embodiments of the fourth alternative R⁵¹ is selected from H, C₁₋₁₀-alkyl, C₀₋₁₀-alkylene-C₃₋₁₀-cycloalkyl, and C₀₋₁₀-alkylene-C₃₋₁₀-heterocycloalkyl, wherein alkyl, alkylene, cycloalkyl and heterocycloalkyl is unsubstituted or substituted with 1 to 7 substituents independently selected from oxo, OR⁶¹,
25 C₁₋₆-alkyl, halo-C₁₋₆-alkyl, halogen, CO₂R⁶¹, CONR⁶¹R⁶², CONR⁶¹SO₂R⁶², COR⁶¹, NR⁶¹COR⁶¹, NR⁶¹SO₂R⁶¹, NR⁶¹-CO-NR⁶¹R⁶², NR⁶¹-SO₂-NR⁶¹R⁶², C₃₋₆-cycloalkyl, O-C₃₋₆-cycloalkyl, C₃₋₆-heterocycloalkyl and O-C₃₋₆-heterocycloalkyl; R⁵² is selected from the group consisting of H, C₁₋₆ alkyl and halo-C₁₋₆ alkyl; or R⁵¹ and R⁵² when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally
30 containing 1 or 2 heteroatoms selected from O, S or N, wherein the ring is unsubstituted or substituted with 1 to 4 substituents independently selected from halogen, oxo, CN, OR⁶¹, SO_xR⁶¹, SO₃H, NR⁶¹SO₂R⁶¹, SO₂NR⁶¹R⁶², CO₂R⁶¹, CONR⁶¹R⁶², CONR⁶¹SO₂R⁶², COR⁶¹, NR⁶¹-CO-R⁶¹, NR⁶¹-CO-NR⁶¹R⁶², NR⁶¹-SO₂-NR⁶¹R⁶², NR⁶¹R⁶², C₁₋₆-alkyl, halo-C₁₋₆-alkyl, hydroxy-C₁₋₆-alkyl, C₃₋₆-cycloalkyl, O-C₃₋₆-cycloalkyl, C₃₋₆-heterocycloalkyl and O-C₃₋₆-heterocycloalkyl.

35 In another preferred embodiment in combination with any of the above or below embodiments of the fourth alternative R⁵³ is selected from



wherein

- R^{83} is selected from halogen, C_{1-6} -alkyl, fluoro- C_{1-6} -alkyl, C_{1-4} -alkylene-OH, C_{1-4} -alkylene-CN, C_{1-4} -alkylene-O- C_{1-3} -alkyl, C_{1-4} -alkylene-O-fluoro- C_{1-3} -alkyl, O- C_{1-6} -alkyl, O-fluoro- C_{1-6} -alkyl, C_{3-10} -cycloalkyl, $C(O)N(R^{87})_2$,

wherein alkylene is unsubstituted or substituted with 1 to 3 substituents selected from F, and cycloalkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from F, C_{1-3} -alkyl and fluoro- C_{1-3} -alkyl;

- R^{84} is selected from C_{1-4} -alkylene-OH, C_{1-4} -alkylene-O- C_{1-3} -alkyl, C_{1-4} -alkylene-O-fluoro- C_{1-3} -alkyl, C_{3-10} -cycloalkyl, $C(O)N(R^{87})_2$, $S(O_2)N(R^{87})_2$,

wherein alkylene is unsubstituted or substituted with 1 to 3 substituents selected from F, and cycloalkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from F, C_{1-3} -alkyl and fluoro- C_{1-3} -alkyl;

- R^{86} is selected from C_{1-6} -alkyl, fluoro- C_{1-6} -alkyl, $C(O)N(R^{87})_2$, $S(O_2)N(R^{87})_2$,

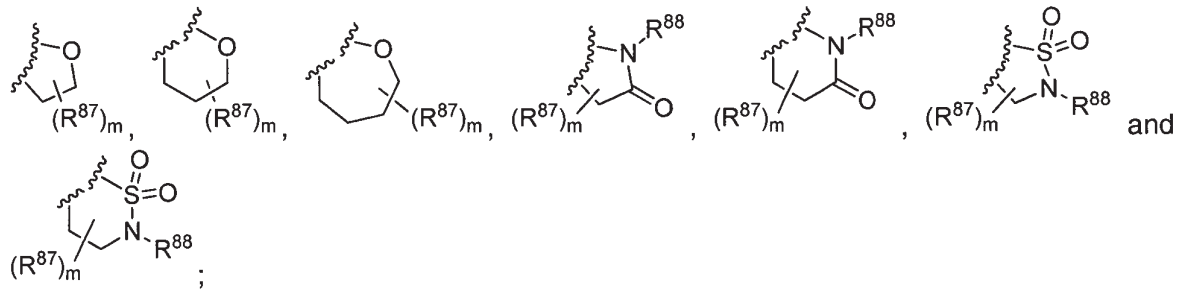
R^{87} is independently selected from H, C_{1-6} -alkyl, fluoro- C_{1-6} -alkyl, C_{0-3} -alkylene- C_{1-6} -cycloalkyl, C_{1-6} -alkylene-OH, C_{1-6} -alkylene-O- C_{1-3} -alkyl, C_{1-6} -alkylene-CN, wherein alkylene and cycloalkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from F, C_{1-3} -alkyl and fluoro- C_{1-3} -alkyl,

- and wherein two R^{87} when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing 1 or 2 heteroatoms selected from O, S or N, wherein the ring is unsubstituted or substituted with 1 to 4 substituents independently selected from fluoro, oxo, C_{1-4} -alkyl and halo- C_{1-4} -alkyl;

R^{88} is selected from H, C_{1-3} -alkyl and fluoro- C_{1-3} -alkyl;

- R^{89} is selected from H, F or OH;

X' is an annelated saturated heterocycle selected from the group consisting of



Y' is an annelated 5- or 6-membered carbocycle, an annelated 6-membered aryl or an annelated 6-membered heteroaryl containing 1 to 2 nitrogen atoms, wherein the carbocycle, aryl or heteroaryl is unsubstituted or substituted with 1 to 3 substituents selected from fluoro, C₁₋₃-alkyl and fluoro-C₁₋₃-alkyl;

Z' is an annelated 6-membered cycle forming a heteroaryl containing 1 to 2 nitrogen atoms, wherein the heteroaryl is unsubstituted or substituted with 1 to 3 substituents selected from fluoro, C₁₋₃-alkyl and fluoro-C₁₋₃-alkyl; and m is selected from 1 to 4.

10 In yet another preferred embodiment in combination with any of the above or below
embodiments of the fourth alternative R⁵⁴ is selected from C₁₋₆-alkylene-R⁵⁷, O-R⁵⁷, and SO₂-
R⁵⁷.

wherein alkylene is optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, OH, oxo, O-C₁₋₆-alkyl, CN and C₃₋₆-cycloalkyl;

15 R⁵⁷ is selected from C₁₋₁₀-alkyl, C₃₋₁₀-cycloalkyl, C₃₋₁₀-heterocycloalkyl, 6-10-membered mono- or bicyclic aryl and 6-10-membered mono- or bicyclic heteroaryl,

wherein alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl are unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of halogen, OH, oxo, O-C₁₋₃-alkyl, O-halo-C₁₋₃-alkyl, C₁₋₃-alkyl, halo-C₁₋₃-alkyl, cycloalkyl and heterocycloalkyl.

In a preferred embodiment in combination with any of the above or below embodiments of the fourth alternative, the disease or disorder associated with the inhibition or activation of the ROR γ receptor is selected from the group consisting of rheumatoid arthritis, ankylosing spondylitis, lupus erythematosus, psoriasis, atopic eczema, inflammatory bowel diseases, Crohn's disease, ulcerative colitis, asthma, multiple sclerosis, type 1 diabetes, amyotrophic lateral sclerosis, Th17 mediated tissue inflammation, or of autoimmune etiology or a skin disease with associated symptoms such as pain, itching or excoriations.

Also provided is a pharmaceutical composition comprising a compound of the present invention and a pharmaceutically acceptable carrier or excipient.

In the context of the present invention "C₁₋₁₀-alkyl" means a saturated alkyl chain having 1 to 10 carbon atoms which may be straight chained or branched. Examples thereof include methyl, ethyl, propyl, isopropyl, *n*-butyl, isobutyl, *tert*-butyl, *n*-pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, nonyl and decyl.

- 5 The term "halo-C₁₋₁₀-alkyl" means that one or more hydrogen atoms in the alkyl chain are replaced by a halogen. A preferred example thereof is CF₃.

"C₂₋₁₀-alkenyl" means an alkyl chain having 1 to 10 carbon atoms which may be straight chained or branched, containing at least one carbon to carbon double bond. Examples thereof include ethenyl, propenyl, decenyl, 2-methylenehexyl and (2*E*,4*E*)-hexa-2,4-dienyl.

- 10 "C₂₋₁₀-alkynyl" means an alkyl chain having 1 to 10 carbon atoms which may be straight chained or branched, containing at least one carbon to carbon triple bond. Examples thereof include ethynyl, propynyl and decynyl.

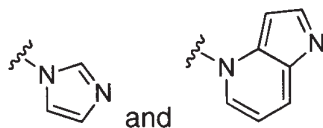
A "C₀₋₁₀-alkylene" means that the respective group is divalent and connects the attached residue with the remaining part of the molecule. Moreover, in the context of the present
15 invention, "C₀-alkylene" is meant to be represent a bond. The same applies to the divalent C₃-cycloalkylene.

- A C₃₋₁₀-cycloalkyl group or C₃₋₁₀-carbocycle means a saturated or partially unsaturated mono-, bi- or multicyclic ring system comprising 3 to 10 carbon atoms. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, bicyclo[2.2.2]octyl, bicyclo[2.2.1]heptyl,
20 adamantyl and pentacyclo[4.2.0.0^{2,5}.0^{3,8}.0^{4,7}]octyl.

- A C₃₋₁₀-heterocycloalkyl group means a saturated or partially unsaturated 3 to 10 membered carbon mono-, bi- or multicyclic ring wherein 1, 2 or 3 carbon atoms are replaced by 1, 2 or 3 heteroatoms, respectively, wherein the heteroatoms are independently selected from N, O, S, SO and SO₂. Examples thereof include epoxidyl, oxetanyl, pyrrolidinyl, tetrahydrofuranyl,
25 piperidinyl, piperazinyl tetrahydropyranyl, 1,4-dioxanyl, morpholinyl, 4-quinuclidinyl, 1,4-dihydropyridinyl and 3,6-dihydro-2*H*-thiopyranyl. The C₃₋₁₀-heterocycloalkyl group can be connected via a carbon or nitrogen atom.

- A 5-14-membered mono-, bi- or tricyclic heteroaromatic ring system (within the application also referred to as heteroaryl) containing up to 4 heteroatoms means a monocyclic
30 heteroaromatic ring such as pyrrolyl, imidazolyl, furanyl, thiophenyl, pyridinyl, pyrimidinyl, pyrazinyl, pyrazolyl, oxazolyl, isoxazolyl, triazolyl, oxadiazolyl and thiadiazolyl. It further means a bi- or tricyclic ring system wherein the heteroatom(s) may be present in one or both rings including the bridgehead atoms. Examples thereof include quinolinyl, isoquinolinyl, quinoxalinyl, benzimidazolyl, benzisoxazolyl, benzodioxanyl, benzofuranyl, benzoxazolyl,
35 indolyl, indolizinyl, pyrazolo[1,5-*a*]pyrimidinyl and dibenzo[*b,d*]furanyl. The nitrogen or sulphur atom of the heteroaryl system may also be optionally oxidized to the corresponding *N*-oxide,

S-oxide or S,S-dioxide. If not stated otherwise, the heteroaryl system can be connected via a carbon or nitrogen atom. Examples for *N*-linked heterocycles are



5 A 6-10-membered mono- or bicyclic aromatic ring system (within the application also referred to as aryl) means an aromatic carbon cycle such as phenyl or naphthalenyl.

The term "*N*-oxide" denotes compounds, where the nitrogen in the heteroaromatic system (preferably pyridinyl) is oxidized. Such compounds can be obtained in a known manner by reacting a compound of the present invention (such as in a pyridinyl group) with H_2O_2 or a peracid in an inert solvent.

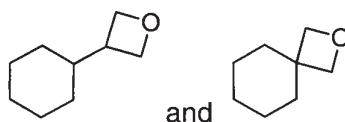
10 Halogen is selected from fluorine, chlorine, bromine and iodine.

Furthermore, the compounds of the present invention are partly subject to tautomerism. For example, if a heteroaromatic group containing a nitrogen atom in the ring is substituted with a hydroxy group on the carbon atom adjacent to the nitrogen atom, the following tautomerism can appear:



15

A C_{3-10} -cycloalkyl or C_{3-10} -heterocycloalkyl group can be connected straight or spirocyclic, e.g. when cyclohexane is substituted with the heterocycloalkyl group oxetane, the following structures are possible:



20 It will be appreciated by the skilled person that when lists of alternative substituents include members which, because of their valency requirements or other reasons, cannot be used to substitute a particular group, the list is intended to be read with the knowledge of the skilled person to include only those members of the list which are suitable for substituting the particular group.

25 The compounds used in the present invention can be in the form of a pharmaceutically acceptable salt or a solvate. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids, including inorganic bases or acids and organic bases or acids. In case the compounds of the present invention contain one or more acidic or basic groups, the invention also comprises their corresponding
30 pharmaceutically or toxicologically acceptable salts, in particular their pharmaceutically

utilizable salts. Thus, the compounds of the present invention which contain acidic groups can be used according to the invention, for example, as alkali metal salts, alkaline earth metal salts or ammonium salts. More precise examples of such salts include sodium salts, potassium salts, calcium salts, magnesium salts or salts with ammonia or organic amines such as, for example, ethylamine, ethanolamine, triethanolamine or amino acids. The compounds of the present invention which contain one or more basic groups, i.e. groups which can be protonated, can be used according to the invention in the form of their addition salts with inorganic or organic acids. Examples of suitable acids include hydrogen chloride, hydrogen bromide, phosphoric acid, sulfuric acid, nitric acid, methanesulfonic acid, p-toluenesulfonic acid, naphthalenedisulfonic acids, oxalic acid, acetic acid, tartaric acid, lactic acid, salicylic acid, benzoic acid, formic acid, propionic acid, pivalic acid, diethylacetic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, malic acid, sulfaminic acid, phenylpropionic acid, gluconic acid, ascorbic acid, isonicotinic acid, citric acid, adipic acid, and other acids known to the person skilled in the art. If the compounds of the present invention simultaneously contain acidic and basic groups in the molecule, the invention also includes, in addition to the salt forms mentioned, inner salts or betaines (zwitterions). The respective salts can be obtained by customary methods which are known to the person skilled in the art like, for example, by contacting these with an organic or inorganic acid or base in a solvent or dispersant, or by anion exchange or cation exchange with other salts. The present invention also includes all salts of the compounds of the present invention which, owing to low physiological compatibility, are not directly suitable for use in pharmaceuticals but which can be used, for example, as intermediates for chemical reactions or for the preparation of pharmaceutically acceptable salts.

In practical use, the compounds used in the present invention can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral (including intravenous). In preparing the compositions for oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols, flavouring agents, preservatives, colouring agents and the like in the case of oral liquid preparations, such as, for example, suspensions, elixirs and solutions; or carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents and the like in the case of oral solid preparations such as, for example, powders, hard and soft capsules and tablets, with the solid oral preparations being preferred over the liquid preparations.

Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be coated by standard aqueous or non-aqueous techniques. Such compositions and preparations should contain at least 0.1 percent of active compound.

The percentage of active compound in these compositions may, of course, be varied and may conveniently be between about 2 percent to about 60 percent of the weight of the unit. The amount of active compound in such therapeutically useful compositions is such that an effective dosage will be obtained. The active compounds can also be administered intranasally as, for example, liquid drops or spray.

The tablets, pills, capsules, and the like may also contain a binder such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose or saccharin. When a dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as a fatty oil.

Various other materials may be present as coatings or to modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar or both. A syrup or elixir may contain, in addition to the active ingredient, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and a flavouring such as cherry or orange flavour.

The compounds used in the present invention may also be administered parenterally. Solutions or suspensions of these active compounds can be prepared in water suitably mixed with a surfactant such as hydroxy-propylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils.

Any suitable route of administration may be employed for providing a mammal, especially a human, with an effective dose of a compound of the present invention. For example, oral, rectal, topical, parenteral (including intravenous), ocular, pulmonary, nasal, and the like may be employed. Dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, creams, ointments, aerosols, and the like. Preferably compounds of the present invention are administered orally.

The effective dosage of active ingredient employed may vary depending on the particular compound employed, the mode of administration, the condition being treated and the severity

of the condition being treated. Such dosage may be ascertained readily by a person skilled in the art.

When treating or preventing ROR γ -mediated conditions for which compounds of Formula (1), (1'), (2), (2'), (100), (100'), (200) and (200') are indicated, generally satisfactory results are obtained when the compounds are administered at a daily dosage of from about 0.1 milligram to about 100 milligram per kilogram of mammal body weight, preferably given as a single daily dose or in divided doses two to six times a day, or in sustained release form. For most large mammals, the total daily dosage is from about 1.0 milligram to about 1000 milligrams, preferably from about 1 milligram to about 50 milligrams. In the case of a 70 kg adult human, the total daily dose will generally be from about 7 milligrams to about 350 milligrams. This dosage regimen may be adjusted to provide the optimal therapeutic response.

The present invention describes modulators, in the following also referred to as ligands, which bind to the ROR γ receptor. Surprisingly, it has been found that compounds of Formula (1), (1'), (2), (2'), (100), (100'), (200) and (200') act as modulators of the ROR γ receptor.

The term "modulator of the ROR γ receptor" includes the inhibition or activation of the ROR γ receptor, wherein the inhibition is preferred.

The ROR γ receptor is considered to be involved in thymocyte development, thus the modulators described herein may be useful in the treatment of inflammatory skin diseases such as atopic eczema and psoriasis. It is further suggested that down-modulation of ROR γ transcriptional activity with a ligand could result in a shift of the immune response towards a Th2 type response which could be beneficial in the treatment of certain allergic inflammatory conditions such as rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease (Crohn's Disease) and multiple sclerosis (Tesmer et. al., *Immunol. Rev.* 2008, 223:97).

The compounds of Formula (1), (1'), (2), (2'), (100), (100'), (200) and (200') show antagonistic activity, with respect to the dose dependent modulation of the constitutive interaction of the ROR γ ligand binding domain with peptides derived from the co-activators such as SRC-1, TRAP 220 or TIF-2.

It has been surprisingly found that the interaction between ROR γ ligand binding domain and the peptides can be determined by a homogenous FRET based ligand-sensing assays. Even more surprising was the identification of compounds of Formula (1), (1'), (2), (2'), (100), (100'), (200) and (200') as ligands for ROR γ .

The identification of high affinity ligands for ROR γ with agonistic and antagonistic properties is the basis to enable experts knowledgeable in the field to establish assays for the identification of novel agonistic and antagonistic ROR γ ligands from libraries of small molecules. The identification of ligands which bind to and modulate the activity of ROR γ 1 and ROR γ 2 is the first mandatory step to develop new small molecule based medicines with a potential to be

developed for the treatment of diseases which are directly or indirectly controlled by the activity of ROR γ 1 or ROR γ 2. Such diseases include but are not restricted to inflammatory diseases, asthma, rheumatoid arthritis, autoimmune diseases or diseases with an autoimmune component such as systemic lupus erythematosus, inflammatory bowel disease (Crohn's disease), ulcerative colitis, inflammatory skin diseases such as atopic eczema or psoriasis, multiple sclerosis or similar diseases.

Another aspect of the invention provides for combination therapy. Thiazoles and related compounds (e.g. a compound of Formula (1), (1'), (2), (2'), (100), (100'), (200) and (200')) or their pharmaceutically acceptable salts may be used in combination with additional therapeutic agents to treat medical disorders, such as medical disorders associated with inappropriate IL-17 pathway activity. Exemplary additional therapeutic agents include, for example, (1) a TNF- α inhibitor; (2) a non-selective COX-1/COX-2 inhibitor; (3) a selective COX-2 inhibitor, such as celecoxib and rofecoxib; (4) other agents for treating inflammatory disease and autoimmune disease including, for example, methotrexate, leflunomide, sulfasalazine, azathioprine, penicillamine, bucillamine, actarit, mizoribine, lobenzarit, hydroxychloroquine, d-penicillamine, aurothiomalate, auranofin, parenteral gold, oral gold, cyclophosphamide, Lymphostat-B, a BAFF/ APRIL inhibitor, CTLA-4-Ig, or a mimetic of CTLA-4-Ig; (5) a leukotriene biosynthesis inhibitor, such as a 5-lipoxygenase (5-LO) inhibitor, or a 5-lipoxygenase activating protein (FLAP) antagonist; (6) a LTD4 receptor antagonist; (7) a phosphodiesterase type IV (PDE-IV) inhibitor, such as cilomilast (Ariflo) or roflumilast; (8) an antihistamine H₁ receptor antagonist; (9) an α 1- and α 2-adrenoceptor agonist; (10) an anticholinergic agent; (11) a β -adrenoceptor agonist; (12) an insulin-like growth factor type I (IGF-1) mimetic; (13) a glucocorticoid; (14) a kinase inhibitor such as an inhibitor of a Janus Kinase (e.g., JAK1 and/or JAK2 and/or JAK3 and/or TYK2), p38 MAPK, Syk or IKK2; (15) a B-cell target biologic such as rituximab; (16) a selective co-stimulation modulator such as abatacept; (17) an interleukin inhibitor or interleukin receptor inhibitor, such as the IL-1 inhibitor anakinra, IL-6 inhibitor tocilizumab and IL12/IL-23 inhibitor ustekimumab; (18) an anti-IL17 antibody, anti-IL21 antibody, or anti-IL22 antibody (19) a S1P1 agonist, such as fingolimod; (20) an interferon, such as interferon beta 1; (21) an integrin inhibitor such as natalizumab; (22) a mTOR inhibitor such as rapamycin, cyclosporin and tacrolimus; (23) a non-steroidal antiinflammatory agent (NSAID), such as propionic acid derivatives (alminoprofen, benoxaprofen, bucloxic acid, carprofen, fenbufen, fenoprofen, fluprofen, flurbiprofen, ibuprofen, indoprofen, ketoprofen, miroprofen, naproxen, oxaprozin, piroprofen, pranoprofen, suprofen, tiaprofenic acid and tioxaprofen), acetic acid derivatives (indomethacin, acetaminophen, alclufenac, clidanac, diclofenac, fenclofenac, fenclozic acid, fentiazac, furofenac, ibufenac, isoxepac, oxpinac, sulindac, tiopinac, tolmetin, zidometacin and zomepirac), fenamic acid derivatives (flufenamic acid, meclofenamic acid, mefenamic acid, niflumic acid and tolfenamic acid), biphenylcarboxylic acid derivatives (diflunisal and flufenisal), oxicams (isoxicam, piroxicam, sudoxicam and tenoxicam), salicylates (acetyl

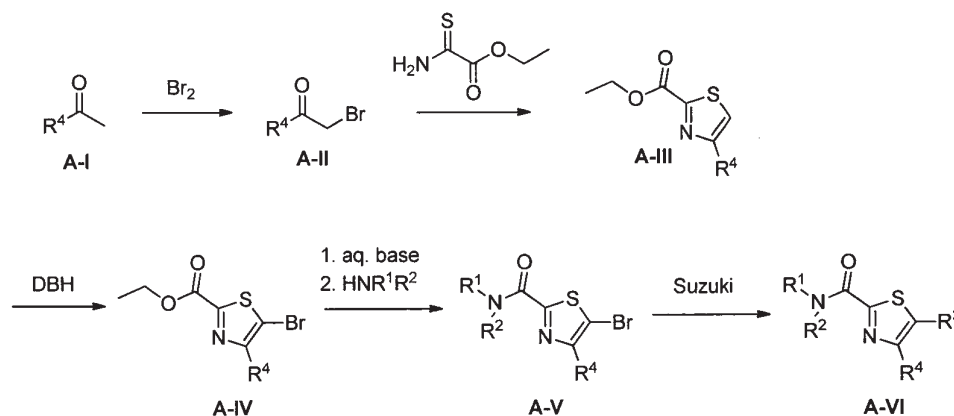
salicylic acid, sulfasalazine) and pyrazolones (apazone, bezpiperylon, feprazone, mofebutazone, oxyphenbutazone, phenylbutazone); (24) a NRF2 pathway activator, such as the fumaric acid derivative, BG-12; and (25) a chemokine or chemokine receptor inhibitor, such as a CCR9 antagonist.

- 5 The amount thiazole or related compound (e.g. a compound of Formula (1), (1'), (2), (2'), (100), 100'), (200) and (200')) and additional therapeutic agent and the relative timing of administration may be selected in order to achieve a desired combined therapeutic effect. For example, when administering a combination therapy to a patient in need of such administration, the therapeutic agents in the combination or a pharmaceutical composition or
10 compositions comprising the therapeutic agents, may be administered in any order such as, for example, sequentially, concurrently, together, simultaneously and the like. Further, for example, a thiazole or related compound may be administered during a time when the additional therapeutic agent(s) exerts its prophylactic or therapeutic effect, or vice versa.

The compounds of the present invention can be prepared by a combination of methods known
15 in the art including the procedures described in Schemes I to V below.

Scheme I depicts the α -bromination of ketone **A-I** ($R^4 = (CR^8R^8)R^{40}$) or ester **A-I** ($R^4 = OR^{40}$) to afford compound **A-II**. Subsequent cyclisation as previously described in US2005/065189 or WO2007/079186 using ethyl 2-amino-2-thioxoacetate furnished thiazole **A-III**, which can be brominated (e.g. with 1,3-dibromo-5,5-dimethylhydantoin) to afford bromide **A-IV**.
20 Saponification using an aqueous base (e.g. 1N NaOH) and coupling of amine HNR^1R^2 affords intermediate **A-V**, which subsequently gives rise to target compound **A-VI** by Pd-catalysed reaction (e.g. Suzuki coupling) using a suitable boronic acid or boronic ester. The thiazolo isomer can be prepared in a similar manner.

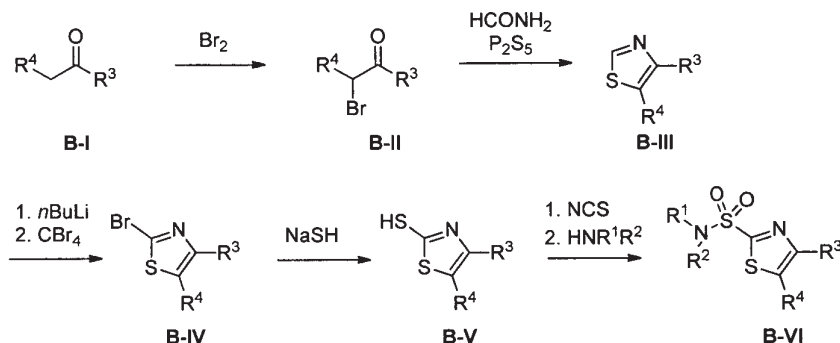
Scheme I



The sulfonamide derivatives can be prepared as shown in Scheme II. Again, α -bromination of a ketone gives intermediate **B-II**, which can be cyclized to thiazole **B-III** by use of formamide and phosphorus sulfide. Incorporation of the sulfonamide moiety can be accomplished via

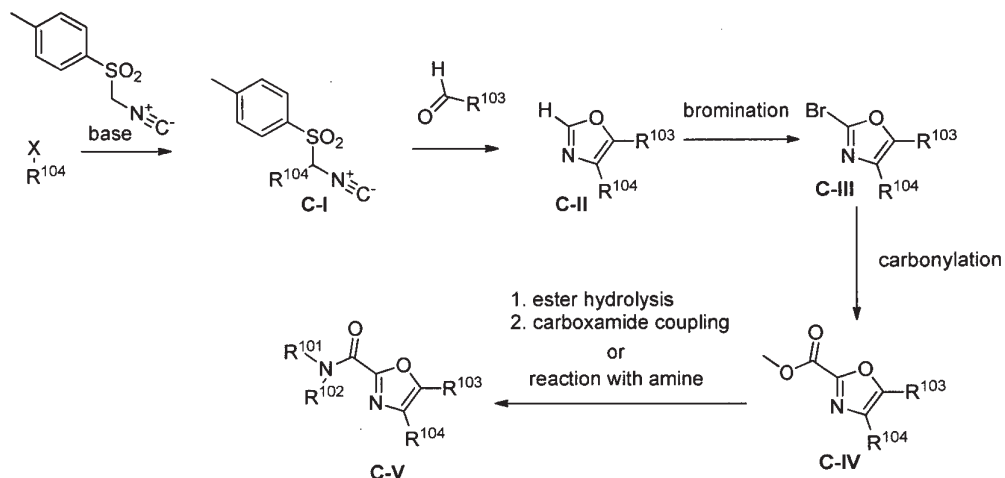
bromination ($\rightarrow$ **B-IV**), Br-SH-exchange ($\rightarrow$ **B-V**) and oxidation of the thiol group with NCS to a sulfonyl chloride moiety and finally reaction with amine HNR^1R^2 to give target compound **B-VI**. An alternative route using a Grignard reagent is described in *Bioorg. Med. Chem.* 2009, 17:1307. The corresponding thiazolo isomer can be prepared in a similar manner.

5 Scheme II



In Scheme III is depicted a synthetic route for oxazoles of the present invention where R^{104} is in the 4-position and R^{103} in the 5-position of the oxazole ring. The synthesis starts with an alkylation of (*p*-tolylsulfonyl)methyl isocyanide (TosMIC) to obtain intermediate **C-I**. A subsequent cylocondensation with aldehyde R^{103}CHO furnishes oxazole intermediates **C-II**. The introduction of a carboxylic ester group at the 2-position of the oxazole ring can be achieved by first bromination (e.g. reaction with NBS) and then Pd-catalysed carbonylation, preferably with a lower alcohol as solvent. The ester can be further transformed into carboxamides by standard methods known in the art.

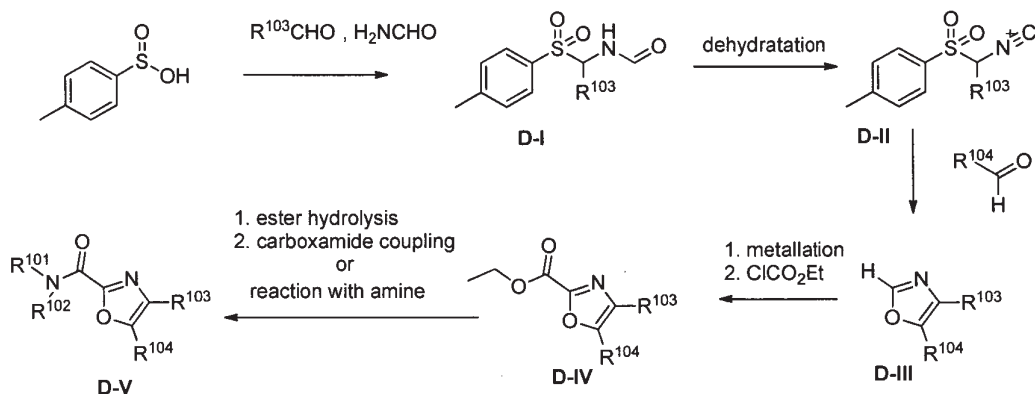
15 Scheme III



In Scheme IV is depicted the synthesis for oxazoles of the present invention where R^{103} is in the 4-position and R^{104} in the 5-position. The aromatic aldehyde R^{103}CHO is reacted with formamide in the presence of TMSCl and then with tosylsulfinic acid to form intermediate **D-I** which is dehydrated to form the substituted TosMIC intermediate **D-II**. After a

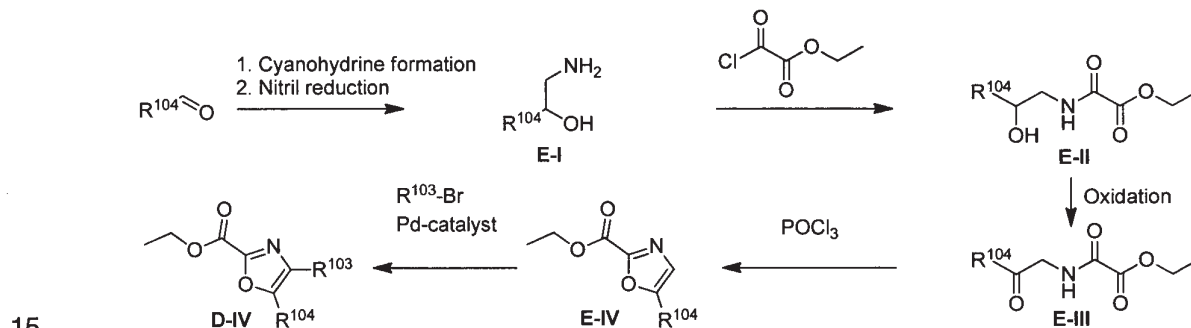
cyclocondensation with $R^{104}CHO$, the 2-position of the oxazole ring can be substituted as depicted in Scheme III. Alternatively the oxazole ring can be metallated and then reacted with ethyl chloroformate to introduce the ester functionality which can be transformed into carboxamides by standard methods known in the art.

5 Scheme IV



Scheme V

An alternative route for the synthesis of oxazoles with R^{103} in the 4-position and R^{104} in the 5-position is depicted in Scheme V. An aldehyde $R^{104}CHO$ can be converted to the aminohydroxy intermediate **E-I** by a sequence of e.g. cyanohydrine formation followed by nitrile reduction. *N*-Acylation of **E-I** with ethyl 2-chloro-2-oxoacetate leads to **E-II** which can be oxidized to the cyclization precursor **E-III**. Treatment of **E-III** with a dehydrating reagent like e.g. $POCl_3$ leads to the formation of the heterocyclic intermediate **E-IV**. Pd catalysed coupling with $R^{103}-Br$ yields intermediate **D-IV**.



For the thiophene and furan derivatives the core decoration can be accomplished in a similar fashion.

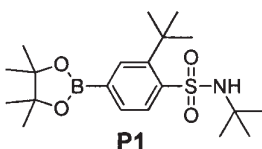
Abbreviations

20	Ac	acetyl
	ACN	acetonitrile
	AIBN	azobisisobutyronitrile

	aq.	aqueous
	B ₂ Pin ₂	4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxaborolane
	m-CPBA	<i>meta</i> -chloroperbenzoic acid
	CC	chromatography on silica gel
5	Cy	cyclohexyl
	DAST	diethylaminosulfur trifluoride
	dba	dibenzylideneacetone
	DBH	1,3-Dibromo-5,5-dimethylhydantoin
	DCM	dichloromethane
10	DIPEA	diisopropylethylamine
	DMA	dimethyl acetamide
	DMF	N,N-dimethylformamide
	dppf	1,1'-bis(diphenylphosphino)ferrocene
	DPPP	1,3-bis(diphenylphosphino)propane
15	DTBPy	2,6-di- <i>tert</i> -butylpyridine
	EA	ethyl acetate
	HATU	O-(7-azabenzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
	MTBE	<i>tert</i> -butylmethylether
20	NBS	N-bromosuccinimide
	NCS	N-chlorosuccinimide
	PCC	pyridinium chlorochromate
	Pin	pinacolato (OCMe ₂ CMe ₂ O)
	PivOH	pivalic acid
25	PE	petroleum ether
	prep.	preparative
	sat.	saturated
	TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxyl
	TFA	trifluoroacetic acid
30	THF	tetrahydrofuran
	TLC	thin layer chromatography

Experimental Section

Preparative Example P1



Step 1: 4-Bromo-2-*tert*-butylaniline (P1a)

To a solution of NBS (218 mg, 1 mmol) in DMF was added a solution of 2-*tert*-butylaniline (149 mg, 1 mmol) in DMF at rt. The reaction mixture was stirred for 4 h at rt, then water (30 mL) was added and the mixture was extracted with EA (150 mL). The organic layer was washed with brine and dried over Na₂SO₄, concentrated and purified by CC (hexane/EA = 3/1) to give compound **P1a** (180 mg, 79%).

Step 2: 4-Bromo-2-*tert*-butylbenzene-1-sulfonyl chloride (P1b)

4-Bromo-2-*tert*-butylaniline **P1a** (20 mmol) was added to a mixture of conc. HCl (11.2 mL) and AcOH (2.24 mL) at -10°C. To this mixture, a solution of NaNO₂ (1.52 g, 22 mmol) in minimum amount of water was added dropwise at -10°C. After stirring for 45 min at -10°C the diazonium salt solution was obtained. SO₂ gas was bubbled into AcOH (22.4 mL) in a three-neck flask until saturation (30 min). Then CuCl (0.49 g, 0.49 mmol) was added and stirring was continued until the mixture turned green. The flask was placed in an ice bath and the diazonium salt solution was added dropwise at 5°C. After the addition was complete, the mixture was stirred overnight at rt and poured into ice water. The solid was collected by filtration to give the compound **P1b** (45%).

Step 3: 4-Bromo-*N*,2-di-*tert*-butylbenzenesulfonamide (P1c)

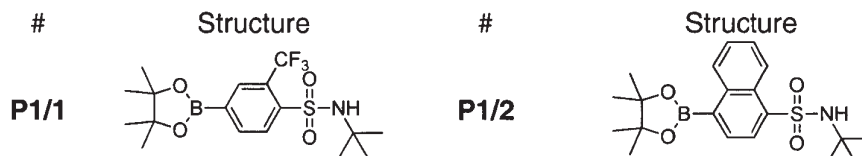
Compound **P1b** (1.0 mmol) and NEt₃ (2.0 mmol) were added into a solution of 2-methylpropan-2-amine (88 mg, 1.2 mmol) in toluene (20 mL). The mixture was stirred for 4 h at reflux, evaporated, poured into water and extracted with EA. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and evaporated to give compound **P1c** as a solid (330 mg, 85%).

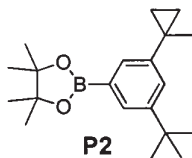
Step 4: *N*,2-Di-*tert*-butyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide (P1)

A flask charged with Pd(dppf)Cl₂ (30 μmol), KOAc (294 mg, 3.0 mmol) and compound **P1c** (279 mg, 1.0 mmol) was flushed with N₂, then 1,4-dioxane (6 mL) and B₂Pin₂ (1.2 mmol) were added. After being stirred at 80°C for an appropriate period, the product was extracted with benzene, washed with water and dried over MgSO₄. Kugelrohr distillation in vacuo gave compound **P1** (200 mg, 50%).

Preparative Example P1/1 to P1/2

Using similar procedures at that described in Preparative Example **P1**, the following compound was prepared:



Preparative Example P2**Step 1: 1-Bromo-3-(*tert*-butyl)-5-(prop-1-en-2-yl)benzene (P2a)**

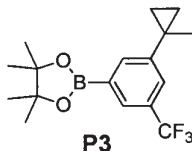
To a solution of 1,3-dibromo-5-(*tert*-butyl)benzene (2.92 g, 10 mmol) in dioxane (20 mL) was added Pd(PPh₃)₄ (3.0 g, 2.6 mmol), prop-1-en-2-ylboronic acid (1.0 g, 12 mmol), K₂CO₃ (2.8 g, 20 mmol) and H₂O (1 mL) under N₂. The resulting mixture was stirred at 90°C overnight, concentrated and purified by CC (hexane) to give compound **P2a** (2.5 g, 100%; 80% by GC/MS) as a liquid.

Step 2: 1-Bromo-3-(*tert*-butyl)-5-(1-methylcyclopropyl)benzene (P2b)

To a solution of Et₂Zn (20 mL of 1M solution in hexanes, 20 mmol) in dry DCM (20 mL) at 0°C was added freshly distilled TFA (1.8 mL, 20 mmol) in DCM (20 mL) over a period of approx. 30 min. The gray mixture was stirred at 0°C for 20 min at which time CH₂I₂ (2.0 mL, 20 mmol) dissolved in DCM (20 mL) was added to the reaction flask by cannulation. The resulting slurry was stirred for 20 min before the addition of compound **P2a** (2.5 g, 10 mmol) dissolved in DCM (15 mL). The slurry was allowed to warm to rt over 30 min, quenched with sat. NH₄Cl (50 mL) and extracted with hexanes. The combined organic layers were dried over MgSO₄. Evaporation and purification by CC (hexane) afforded compound **P2b** (1.6 g, 60%) as a colorless oil.

Step 3: 2-(3-(*tert*-Butyl)-5-(1-methylcyclopropyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (P2)

To a suspension of compound **P2b** (1.6 g, 70 mmol), B₂Pin₂ (3.0 g, 15 mmol), KOAc (2.32 g, 24 mmol) in dioxane (40 mL) was added Pd(dppf)Cl₂ (0.16 g) under N₂. The mixture was heated to 100°C for 16 h, evaporated and purified by CC (PE/EA = 4/1) to afford compound **P2** (1.5 g, 68%) as a white solid.

Preparative Example P3**Step 1: 1-Bromo-3-(prop-1-en-2-yl)-5-(trifluoromethyl)benzene (P3a)**

To a solution of 1,3-dibromo-5-(trifluoromethyl)benzene (3.03 g, 10 mmol) in dioxane (20 mL) was added Pd(PPh₃)₄ (300 mg, 0.26 mmol), prop-1-en-2-ylboronic acid (1.0 g, 12 mmol), K₂CO₃ (2.8 g, 20 mmol) and water (1 mL) under N₂. The mixture was stirred at 90°C overnight, concentrated and purified by CC (hexane) to afford compound **P3a** (1.9 g, 71%) as an oil.

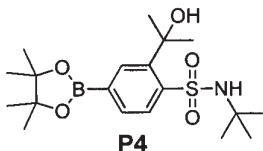
Step 2: 1-Bromo-3-(1-methylcyclopropyl)-5-(trifluoromethyl)benzene (**P3b**)

To a solution of Et₂Zn (4 mL of 1.0 M solution in hexanes, 4 mmol) in dry DCM (4 mL) at 0°C was added freshly distilled TFA (0.36 mL, 4 mmol) in DCM (4 mL) very slowly (ca. 30 min). The grey mixture was stirred at 0°C for 20 min while adding CH₂I₂ (0.4 mL, 4 mmol) in DCM (4 mL), stirred for additional 20 min before compound **P3a** (0.53 g, 2 mmol) dissolved in DCM (3 mL) was added. The slurry was allowed to warm to rt over 30 min, quenched with sat. NH₄Cl (5 mL) and extracted with hexanes. The combined organic layers were dried (MgSO₄), evaporated and purified by CC (hexane) to afford **P3b** (300 mg, 46%) as a colorless oil.

Step 3: 4,4,5,5-Tetramethyl-2-(3-(1-methylcyclopropyl)-5-(trifluoromethyl)phenyl)-1,3,2-dioxaborolane (**P3**)

To a suspension of compound **P3b** (300 mg, 1.0 mmol), B₂Pin₂ (380 mg, 1.5 mmol), KOAc (290 mg, 3 mmol) in dioxane (5 mL) was added Pd(dppf)Cl₂ (20 mg) under N₂. The mixture was heated to 100°C for 16 h, evaporated and purified by CC (PE/EA = 4/1) to give compound **P3** (200 mg, 68%) as a white solid.

Preparative Example P4



Step 1: 2-Amino-5-bromobenzonitrile (**P4a**)

To a solution of 2-aminobenzonitrile (14.9 g, 100 mmol) was added a solution of NBS (17.8 g, 100 mmol) in DMF at rt. The mixture was stirred overnight at rt, then water (30 mL) was added and the mixture was extracted with Et₂O (3 × 250 mL). The organic layer was washed with brine, dried over Na₂SO₄, concentrated and purified by CC to give compound **P4a** (19 g, 83%).

Step 2: 4-Bromo-2-cyanobenzene-1-sulfonyl chloride (**P4b**)

Compound **P4a** (10 g, 51 mmol) was added to a mixture of conc. HCl (28 mL) and AcOH (5.6 mL) at -10°C. Then a solution of NaNO₂ (3.8 g, 55 mmol) in a minimum amount of water was added dropwise at -10°C. After stirring for 45 min at -10°C a diazonium salt solution was obtained. SO₂ gas was bubbled into AcOH (56 mL) until saturation (60 min). Then CuCl₂ (3 g) was added and stirring was continued until the mixture turned green. The flask was placed in an ice bath and the diazonium salt solution was added dropwise at 5°C. After addition was complete, the mixture was stirred overnight at rt and poured into ice water. The solid was collected by filtration to give the crude compound **P4b** (9 g, 71%).

Step 3: 4-Bromo-N-(tert-butyl)-2-cyanobenzenesulfonamide (**P4c**)

To a solution of compound **P4b** (5.0 g, 18 mmol) in pyridine (20 mL) was added 2-methylpropan-2-amine (3.3 g, 45 mmol) and the reaction was purged with N₂, heated at 50°C for 1 h, cooled and concentrated. The residue was purified by CC (DCM/MeOH = 100/1) to give compound **P4c** (3.0 g, 53%) as a yellow solid.

5 Step 4: 2-Acetyl-4-bromo-*N*-(*tert*-butyl)benzenesulfonamide (**P4d**)

A suspension of compound **P4c** (2 g, 6.3 mmol) in THF (20 mL) was added slowly to MeMgBr (6.3 mL, 3M in Et₂O, 19 mmol) and the mixture was heated to reflux for 3 h, placed in an ice bath and 6N HCl (58 mL) was added slowly. The mixture was then heated to reflux, cooled, made alkaline by addition of solid Na₂CO₃ and extracted with EA. The combined organic
10 phases were dried over Na₂SO₄, evaporated and purified by CC (*n*-heptan/EA = 100/0 to 60/40) to give compound **P4d** (0.6 g, 34%).

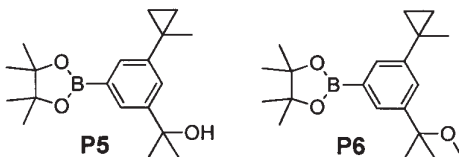
Step 5: 4-Bromo-*N*-(*tert*-butyl)-2-(2-hydroxypropan-2-yl)benzenesulfonamide (**P4e**)

Compound **P4d** (200 mg, 0.60 mmol) was dissolved in THF (15 mL) at 0°C. A 3M solution of MeMgBr in Et₂O (1 mL, 3.0 mmol) was added slowly and the reaction mixture was stirred at rt
15 for 3 h, then another portion of a MeMgBr in Et₂O (1 mL, 3.0 mmol) was added. The mixture was evaporated, diluted with water (20 mL) and extracted with Et₂O. The organic layer was dried over MgSO₄, filtered, evaporated and purified by HPLC (DCM/MeOH = 100/0 to 70/30) to give compound **P4e** (100 mg, 39%; 47% purity).

20 Step 6: *N*-(*tert*-Butyl)-2-(2-hydroxypropan-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide (**P4**)

To a solution of compound **P4e** (200 mg, 0.57 mmol), Pin₂B₂ (290 mg, 1.14 mmol) and KOAc (160 mg, 1.7 mmol) in dioxane (10 mL) at rt under N₂ was added Pd(dppf)Cl₂ (42 mg, 0.05 mmol). The resulting mixture was stirred at rt for 1 h, then heated to 110°C for 2 h, diluted with water (50 mL) and extracted with EA. The combined organic layers were concentrated and
25 purified by CC(PE/EA = 5/1) to give compound **P4** (100 mg, 43%) as a colorless solid.

Preparative Example P5 and Preparative Example P6



Step 1: 3,5-Dibromo-*N*-methoxy-*N*-methylbenzamide (**P5a**)

30 The solution of 3,5-dibromobenzoic acid (26 g, 93 mmol) in SOCl₂ (100 mL) was heated at reflux for 2 h, concentrated, diluted with dry DCM (300 mL) and added slowly to a stirred solution of *N,O*-dimethylhydroxylamine hydrochloride (9.75 g, 100 mmol) and EtN₃ (28 g, 277 mmol) in dry DCM (300 mL) at 0°C. The solution was stirred for 1 h at rt, poured into water and the organic layer was separated. The organic layer was washed with water and brine,

dried over Na₂SO₄, filtered and concentrated to give crude compound **P5a** (28 g, 93%) as an oil.

Step 2: 1-(3,5-Dibromophenyl)ethanone (**P5b**)

To a solution of compound **P5a** (1.0 g, 3.1 mmol) in dry THF (10 mL) was added MeMgCl (3M in Et₂O, 1 mL, 3.0 mmol) dropwise at 0°C and the solution was stirred for 4 h at rt, then quenched with aq. NHCl₄ and extracted with *tert*-butylmethylether. The organic layer was washed with water and brine consecutively, dried over Na₂SO₄, filtered and concentrated to give crude compound **P5b** (0.70 g, 66%) as a yellow oil.

Step 3: 1,3-Dibromo-5-(prop-1-en-2-yl)benzene (**P5c**)

To a stirred solution of PPh₃CH₃Br (5.10 g, 14.4 mmol) in dry THF (50 mL) was added *n*-BuLi (2.5 M in *n*-hexane, 5.76 mL, 14.4 mmol) dropwise at -40°C. After stirring at this temperature for 0.5 h, a solution of compound **P5b** (2.0 g, 7.2 mmol) in dry THF (10 mL) was added dropwise. The resulting solution was allowed to warm to rt and stirred for 1 h, quenched with aq. NHCl₄ and extracted with Et₂O. The organic layer was concentrated and purified by CC (PE) to give compound **P5c** (1.6 g, 80%) as a light yellow oil.

Step 4: 1,3-Dibromo-5-(1-methylcyclopropyl)benzene (**P5d**)

To a solution of compound **P5c** (1.6 g, 5.8 mmol) and Pd(OAc)₂ (350 mg) in THF (20 mL) was added dropwise at 0°C a solution of CH₂N₂ (487 mg, 11.6 mmol) in Et₂O (20 mL) and the mixture was stirred for 1 h at rt. The suspension was filtered and the filtrate was concentrated and purified by CC (PE) to give compound **P5d** (1.4 g, 82%) as a colorless oil.

Step 5: 2-(3-Bromo-5-(1-methylcyclopropyl)phenyl)propan-2-ol (**P5e**)

To a stirred solution of compound **P5d** (0.5 g, 1.7 mmol) in dry THF (5 mL) was added dropwise *n*-BuLi (0.74 mL, 1.87 mmol) at -78°C. After 1 h at this temperature, dry acetone (118 mg, 2.04 mmol) was added dropwise. The solution was allowed to warm to rt and stirred overnight, then quenched with aq. NHCl₄ and extracted with EA. The combined organic layers were concentrated and purified by CC (PE/EA = 20/1) to give compound **P5e** (250 mg, 52%) as a colorless oil.

Step 6: 1-Bromo-3-(2-methoxypropan-2-yl)-5-(1-methylcyclopropyl)benzene (**P5f**)

To a solution of compound **P5e** (1.5 g, 5.6 mmol) in dry THF (10 mL) was added NaH (450 mg, 11.2 mmol) under N₂ and the suspension was stirred for 1 h at rt. Then MeI (2.3 g, 16.8 mmol) was added and the solution was stirred at 70°C in a sealed tube overnight, poured into water and extracted with Et₂O. The organic layer was washed with brine, dried over Na₂SO₄, filtered, concentrated and purified by CC (PE) to give compound **P5f** (1.6 g, 100%) as a colorless oil.

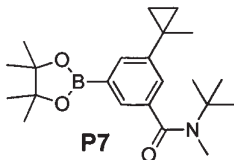
Step 7: 2-(3-(1-Methylcyclopropyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propan-2-ol (**P5**)

Compound **P5** was prepared from compound **P5e** similar as described in Preparative Example 4, Step 6.

Step 8: 2-(3-(2-Methoxypropan-2-yl)-5-(1-methylcyclopropyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**P6**)

- 5 Compound **P6** was prepared from compound **P5f** similar as described in Preparative Example 4, Step 6.

Preparative Example P7



10 Step 1: Methyl 3-bromo-5-(prop-1-en-2-yl)benzoate (**P7a**)

To a solution of methyl 3-bromo-5-iodobenzoate (3.40 g, 10 mmol) in dioxane (20 mL) was added Pd(PPh₃)₄ (300 mg, 0.26 mmol), prop-1-en-2-yl boronic acid (1.0 g, 12 mmol), K₂CO₃ (2.8 g, 20 mmol) and H₂O (1 mL) under N₂ atmosphere. The mixture was stirred overnight at 90°C. Then the mixture was concentrated and purified by CC (PE/EA = 6/1) to afford
15 compound **P7a** (1.9 g, 71%) as a solid.

Step 2: Methyl 3-bromo-5-(1-methylcyclopropyl)benzoate (**P7b**)

- To a solution of Et₂Zn (4 mL of 1.0M solution in hexanes, 4.0 mmol) in dry DCM (4 mL) at 0°C was added freshly distilled TFA (0.36 mL, 4.0 mmol) in DCM (4 mL) very slowly (ca. 30 min). The gray mixture was stirred at 0°C for 20 min at which time diodomethene (0.4 mL, 4.0
20 mmol) dissolved in DCM (4 mL) was introduced by cannulation. The resulting slurry was stirred for 20 min before the addition of compound **P7a** (0.53 g, 2.0 mmol) dissolved in DCM (3 mL). The slurry allowed to warm to rt over 30 min. Progress of the reaction was monitored by TLC. When deemed complete, the reaction was quenched by the addition of sat. aq. NH₄Cl (5 mL) and the layers were separated. The aq. layer was extracted with hexane (2 x) and
25 dried over MgSO₄. Evaporation and purification by CC (PE/EA = 7/1) afforded compound **P7b** (300 mg, 46%) as a clear colorless oil.

Step 3: 3-Bromo-5-(1-methylcyclopropyl)benzoic acid (**P7c**)

- Compound **P7b** (270 mg, 1.0 mmol) and LiOH (50 mg, 2.0 mmol) were mixed in THF (3 mL) and H₂O (3 mL). The mixture was stirred for 10 h, then the pH was adjusted to pH 3 with aq.
30 HCl and extracted with EA (3 x 10 mL). The organic layer was dried and concentrated to afford the crude product **P7c** (250 mg, 100%).

Step 4: 3-Bromo-N-(tert-butyl)-N-methyl-5-(1-methylcyclopropyl)benzamide (**P7d**)

To a solution of compound **P7c** (250 mg, 1.0 mmol) in DMF (5 mL) was added HATU (380 mg, 1.0 mmol) and Et₃N (202 mg, 2.0 mmol) and the mixture was stirred overnight. After

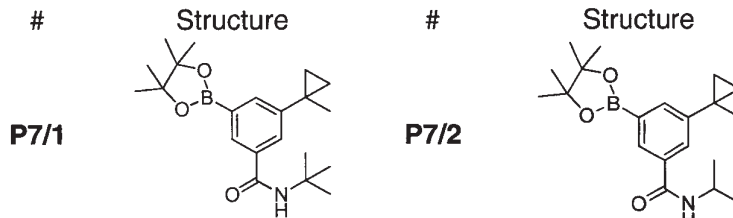
removal of the solvents the crude product was purified with prep. HPLC to afford compound **P7d** (300 mg, 95%).

Step 5: *N*-(*tert*-Butyl)-*N*-methyl-3-(1-methylcyclopropyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (**P7**)

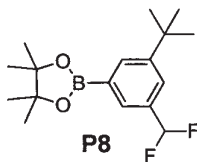
- 5 To a suspension of compound **P7d** (323 mg, 1.0 mmol), B_2Pin_2 (380 mg, 1.5 mmol), KOAc (290 mg, 3.0 mmol) in dioxane (5 mL) was added $Pd(dppf)Cl_2$ (20 mg) under N_2 atmosphere. The mixture was heated to 100°C for 16 h. The mixture was purified by CC (PE/EA = 4/1) to afford compound **P7** (200 mg, 68%) as a white solid.

10 Preparative Example P7/1 to P7/2

Using similar procedures at that described in Preparative Example **P7**, the following compounds were prepared:



Preparative Example P8



15

Step 1: 3-Bromo-5-(*tert*-butyl)benzaldehyde (**P8a**)

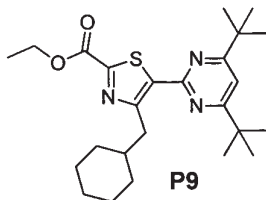
- To a solution of 1,3-dibromo-5-(*tert*-butyl)benzene (55 g, 190 mmol) in dry THF (500 mL) was added *n*-BuLi (2.5M in hexane, 88 mL, 220 mmol) at -78°C under N_2 and the solution was stirred for 1 h at this temperature. Then DMF (20.8 g, 285 mmol) was added slowly and the solution was stirred for 3 h at -78°C, warmed to rt, quenched with sat. NH_4Cl , extracted with EA. The organic layer was washed with water and brine, dried over Na_2SO_4 , filtered, concentrated and purified by CC (PE) to give compound **P8a** (40 g, 82%) as a colorless oil.
- 20

Step 2: 1-Bromo-3-(*tert*-butyl)-5-(difluoromethyl)benzene (**P8b**)

- A solution of compound **P8a** (256 mg, 1.0 mmol) and DAST (158 mg, 2.0 mmol) in DCM (5 mL) was reacted under microwave condition (70°C) for 15 min, washed with sat. $NaHCO_3$, water and brine consecutively, dried over Na_2SO_4 , filtered and concentrated to give a residue. This reaction was repeated ten times and the combined residues were purified by CC (PE) to give compound **P8b** (2.2 g, 82%) as a colorless oil.
- 25

Step 3: 2-(3-(*tert*-Butyl)-5-(difluoromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**P8**)

Compound **P8** was prepared from compound **P8b** similar as described in Preparative Example 4, Step 6.

5 Preparative Example P9Step 1: 4,6-Di-*tert*-butyl-2-chloropyrimidine (**P9a**)

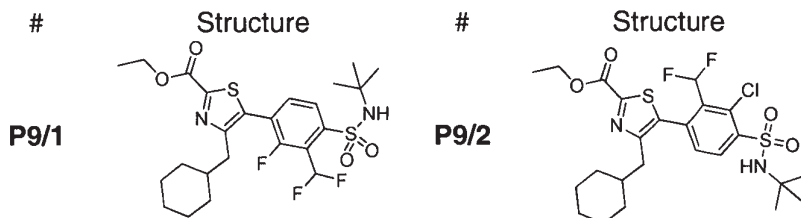
A mixture of 2,4,6-trichloropyrimidine (46 mg, 250 μ mol) and CuI (3 mg, 12 μ mol) in dry THF (10 mL) was cooled to -20°C and purged with N_2 for 10 min. Then a *tert*-BuMgCl solution (2M in THF, 64 mg, 0.55 mmol) was added dropwise at a rate such that the reaction solution did not exceed 0°C . After the addition, the solution was stirred at rt for 24 h, diluted with *tert*-BuOMe and washed with a sat. NH_4Cl solution and then brine, dried (Na_2SO_4), concentrated and purified by CC (PE/EA = 100/1) to give compound **P9a** (45 mg, 80%) as yellow solid.

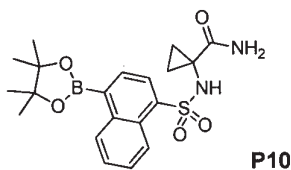
Step 2: Ethyl 4-(cyclohexylmethyl)-5-(4,6-di-*tert*-butylpyrimidin-2-yl)thiazole-2-carboxylate (**P9**)

The solution of **P9a** (45 mg, 0.2 mmol), methyl 4-(cyclohexylmethyl)thiazole-2-carboxylate (50 mg, 0.2 mmol), K_2CO_3 (46 mg, 0.33 mmol), $\text{Pd}(\text{OAc})_2$ (2 mg, 4 μ mol), $\text{PCy}_3 \cdot \text{HBF}_4$ (4 mg, 8 μ mol) and PivOH (6 mg, 0.06 mmol) in a solution of DMA (2 mL) was heated under Ar at 100°C overnight, cooled to rt, partitioned between EA and water and separated. The organic phase was washed with water and brine, dried over Na_2SO_4 , filtered, concentrated and purified by CC (PE/EA = 10/1 to 5/1) to give compound **P9** (57 mg, 65%) as a white solid.

Preparative Example P9/1 to P9/2

Using similar procedures at that described in Preparative Example **P9**, the following compounds were prepared:

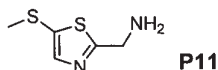


Preparative Example P10**Step 1: 1-(4-Bromonaphthalene-1-sulfonamido)cyclopropanecarboxamide (P10a)**

The solution of 4-bromo-*N*-(1-cyanocyclopropyl)naphthalene-1-sulfonamide (200 mg, 0.57 mmol), 2N NaOH (0.6 mL, 1.20 mmol) and 30% aq. H₂O₂ (0.5 mL) in MeOH (3 mL) was heated at 60°C for 3 h, cooled and extracted with Et₂O twice. The combined organic layers were washed with water and brine, dried over Na₂SO₄, filtered and concentrated to give compound **P10a** (188 mg, 89%) as a white solid.

Step 2: 1-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalene-1-sulfonamido)cyclopropanecarboxamide (P10)

The solution of compound **P10a** (188 mg, 0.51 mmol), (Bpin)₂ (153 mg, 0.60 mmol), KOAc (196 mg, 2.0 mmol) and Pd(dppf)Cl₂ (20 mg) in dioxane (5 mL) was heated for 16 h at 95°C under N₂, cooled, filtered, diluted with water and extracted with EA twice. The combined organic layers were washed with water and brine, dried over Na₂SO₄, filtered, concentrated and purified by (PE/EA = 10/1) to give compound **P10** (60 mg, 28%) as a white solid.

Preparative Example P11**Step 1: 5-Bromo-*N*-(*tert*-butyl)thiazole-2-carboxamide (P11a)**

A solution of 5-bromothiazole-2-carboxylic acid (2.70 g, 13.0 mmol), HATU (5.71 g, 15.0 mmol) and *tert*-butylamine (4.1 mL, 39.0 mmol) in dry THF (30 mL) was stirred overnight under Ar. The resulting solution was partitioned between EA and sat. Na₂CO₃. The organic layer was washed with 1N HCl and brine, dried over Na₂SO₄, filtered, concentrated and purified by CC (PE/EA = 4/1) to give compound **P11a** (3.42 g, 100%) as a yellow solid.

Step 2: *N*-(*tert*-Butyl)-5-(methylthio)thiazole-2-carboxamide (P11b)

To a solution of compound **P11a** (3.42 g, 13.0 mmol) in dry THF (40 mL) was added *n*-BuLi (2.5M in hexane, 10.4 mL, 26.0 mmol) at -78°C under Ar and the solution was stirred for 2 h at -78°C. Then Me₂S (2.4 g, 26.0 mmol) was added at -78°C and the solution was stirred at rt for 2 h, quenched by water and extracted with EA twice. The combined organic layers were dried over Na₂SO₄, filtered, concentrated and purified by CC (PE/EA = 5/1) to give compound **P11b** (2.50 g, 90%) as a brown solid.

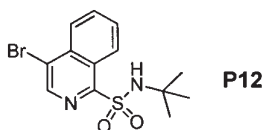
Step 3: 5-(Methylthio)thiazole-2-carboxamide (P11c)

To a solution of compound **P11b** (2.50 g, 10.9 mmol) in dry DCM (15 mL) was added TFA (15 mL) at 0°C and the solution was stirred at rt overnight, concentrated and diluted with DCM. The solution was washed with 1N NaOH twice and brine, dried over Na₂SO₄, filtered and concentrated to give compound **P11c** (1.77 g, 93%) as a yellow solid.

5 Step 4: (5-(Methylthio)thiazol-2-yl)methanamine (**P11**)

A solution of compound **P11c** (1.77 g, 10.2 mmol) in dry THF (20 mL) was added a solution of LiAlH₄ in THF (1M, 20.0 mL, 20.0 mmol) under stirring and the suspension was further stirred at 8°C for 3 h, cooled to 0°C and quenched slowly by addition of H₂O, 15% aq. NaOH and H₂O. The suspension was stirred until all LiAlH₄ was neutralized and a white precipitate was
10 formed, filtered and the precipitate was washed with Et₂O. The combined organic layers were dried over Na₂SO₄, filtered, concentrated and purified by prep-HPLC to give compound **P11** (410 mg, 25%) as a brown oil.

Preparative Example P12



15

Step 1: 4-Bromoisquinolin-1-ol (**P12a**)

To a solution of isoquinolin-1-ol (5.0 g, 34.5 mmol) in DCM (100 mL) was added a solution of Br₂ (6.0 g, 37.7 mmol) in DCM (20 mL) and the mixture was stirred for 4 h. The formed solid was collected by filtration, washed with DCM and re-crystallized from Et₂O to give compound
20 **P12a** (5.0 g, 62%) as a yellow solid.

Step 2: 4-Bromoisquinoline-1-thiol (**P12b**)

A mixture of compound **P12a** (1.0 g, 4.40 mmol), pyridine (0.3 mL) and Lawesson's reagent (3.5 g, 8.00 mmol) in toluene (20 mL) was stirred under reflux for 2 h, cooled to 40°C and the precipitated crystals were collected by filtration and dried in vacuum to give compound **P12b**
25 (600 mg, 56%) as pale yellow crystal.

Step 3: 4-Bromoisquinoline-1-sulfonyl chloride (**P12c**)

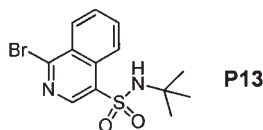
To a solution of compound **P12b** (3.0 g, 12.4 mmol) in a mixture of MeCN (30 mL), AcOH (10 mL) and water (5 mL) was added NCS (4.7 g, 36.0 mmol) and the solution was allowed to warm to 50°C and stirred for overnight before being partitioned between brine and EA. The
30 organic layer was dried over Na₂SO₄, filtered, concentrated and purified by CC (PE/EA = 10/1) to give compound **P12c** (1.1 g, 29%) as a yellow powder.

Step 4: 4-Bromo-N-(tert-butyl)isoquinoline-1-sulfonamide (**P12**)

To a solution of *t*-BuNH₂ (731 mg, 10.0 mmol) in dry DCM (10 mL) was added a solution of compound **P12c** (1.1 g, 3.59 mmol) in dry DCM (15 mL) at 0°C and the solution was stirred at

rt for 3 h and quenched by water. The organic layer was washed with water and brine, dried over Na₂SO₄, filtered, concentrated and purified by CC (PE/EA = 6/1) to give compound **P12** (800 mg, 65%) as a yellow solid.

5 Preparative Example P13



Step 1: 4-Nitroisoquinolin-1-ol (**P13a**)

To a hot solution of isoquinolin-1-ol (10.0 g, 69.0 mmol) in a mixture of AcOH (40 mL) and water (10 mL) was added nitric acid (13 mL, 207 mmol) over 1 h at 65°C (maintained the reaction temperature between 68-70°C) and the solution was stirred at 65°C for 3 h, cooled to rt and diluted with water. The formed solid was collected by filtration and dried in vacuum to give compound **P13a** (8.0 g, 61%) as a yellow solid.

Step 2: 4-Aminoisoquinolin-1-ol (**P13b**)

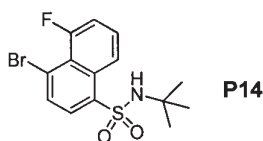
To a solution of compound **P13a** (8.0 g, 42.1 mmol) and NH₄Cl (5.35 g, 100 mmol) in EtOH (100 mL) was added Fe dust (4.48 g, 80.0 mmol) at rt and the suspension was stirred at 70°C for 3 h and filtered through a celite pad. The filtrate was concentrated, diluted with EA, washed with water and brine, dried over Na₂SO₄ and concentrated to give compound **P13b** (6.1 g, 90%) as a brown solid.

Step 3: 1-Bromoisoquinolin-4-amine (**P13c**)

A solution of compound **P13b** (6.1 g, 38.1 mmol) and PBr₃ (28.7 g, 100 mmol) was stirred at 135°C for overnight, cooled to rt, diluted with water, adjusted to pH = 8 with Na₂CO₃ (solid) and extracted with EA (3x). The combined organic layers were washed with sat. NaHCO₃ and brine, dried over Na₂SO₄, filtered, concentrated and purified by CC (PE/EA = 1/1) to give compound **P13c** (4.4 g, 52%) as a pale yellow solid.

Step 4: 1-Bromo-N-(tert-butyl)isoquinoline-4-sulfonamide (**P13**)

To a solution of compound **P13c** (3.0 g, 13.5 mmol), HOAc (50 mL) and a solution of HBr in AcOH (48%, 10 mL) in MeCN (50 mL) was added a solution of NaNO₂ (1.12 g, 16.2 mmol) in water (20 mL) at 0°C. After stirring 20 min, SO₂ gas was bubbled in over 20 min, keeping the reaction temperature <0°C. A solution of CuCl₂·2H₂O (1.67 g, 8.1 mmol) in water (10 mL) was added and the solution was stirred for 3 h at rt, concentrated and dissolved in DCM (15 mL). To this solution was added *tert*-BuNH₂ (1.9 g, 26 mmol) and the solution was stirred at rt for overnight. The resulting suspension was filtered and the filtrate was diluted with water. The organic layer was washed with brine, dried over Na₂SO₄, filtered, concentrated and purified by CC (PE/EA = 8/1) to give crude compound **P13** (300 mg, 6.5%) with 10% of chloride determined by LCMS as a white solid.

Preparative Example P14**Step 1: 5-Nitronaphthalen-1-amine (P14a)**

A solution of sodium sulfide (31.7 g, 330 mmol) and sodium bicarbonate in water (70 mL) was heated to 70°C and the a suspension of 1,5-dinitronaphthalene (20 g, 91.6 mmol) in methanol (300 mL) was added dropwise at reflux. The resultant mixture was stirred for 5 min, cooled to 0°C, quenched with ice and stirred for further 10 min followed by acidification with conc. HCl. The resulting mixture was stirred for 30 min, then washed with EA twice. The aq. layer was basified with aq. ammonia and extracted with EA twice. The combined organic layers were washed with water twice and brine twice consecutively, dried over Na₂SO₄, filtrated and concentrated to give compound **P14a** (12.0 g, 71%) as a brown solid.

Step 2: 1-Fluoro-5-nitronaphthalene (P14b)

To a suspension of compound **P14a** (12 g, 63.8 mmol) in a mixture of water/conc. HCl (1/1, 100 mL) was added NaNO₂ (6.60 g, 95.7 mmol) portionwise at -5°C and the mixture was stirred for 15 min at -5°C. Then a 60% w/w hexafluorophosphoric acid solution (60 mL) was added. The brown precipitate was filtered and washed with cold water and Et₂O and then dried in vacuum. The resulting solid was suspended in toluene and heated to 110°C for 2 h, cooled to rt, concentrated and purified by CC (PE) to give compound **P14b** (4.50 g, 37%) as a yellow solid.

Step 3: 5-Fluoronaphthalen-1-amine (P14c)

A solution of compound **P14b** (19.1 g, 100 mmol) in EtOH (500 mL, containing 50 mL 12N HCl) was heated to reflux and Fe powder (16.8 g, 300 mmol) was added in small portions and heating was continued for 2 h. The resulting mixture was cooled to rt and neutralized with 1N NaOH. The aq. layer was extracted with DCM (3x). The combined organic layers were washed with water and brine, dried over MgSO₄, filtered, concentrated and purified by CC (PE/EA = 3/1) to give compound **P14c** (11.6 g, 72%) as a yellow solid.

Step 4: 4-Bromo-5-fluoronaphthalen-1-amine (P14d)

To a solution of compound **P14c** (7.0 g, 43.4 mmol) in THF (100 mL) at -78°C was added NBS (7.73 g, 43.4 mmol) and the solution was stirred for 1 h at -78°C, diluted with water and extracted with EA twice. The combined organic layers was dried over Na₂SO₄, filtered, concentrated and purified by CC (PE/EA = 4/1) to give compound **P14d** (6.5 g, 62%) as an off-white solid.

Step 5: 4-Bromo-5-fluoronaphthalene-1-sulfonyl chloride (P14e)

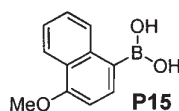
To a solution of compound **P14d** (7.1 g, 29.6 mmol), HOAc (50 mL) and a solution of HBr in AcOH (48%, 100 mL) in MeCN (230 mL) was added a solution of NaNO₂ (2.45 g, 35.5 mmol)

in water (50 mL) at 0°C. After stirring 20 min, SO₂ gas was bubbled in over 1 h, keeping the reaction temperature <0°C. A solution of CuCl₂·2H₂O (3.02 g, 17.8 mmol) in water (10 mL) was added and the solution was stirred for 3 h at rt, concentrated and purified by CC (PE/EA = 30/1) to give compound **P14e** (5.4 g, 56%) as a pale yellow oil.

5 Step 6: 4-Bromo-*N*-(*tert*-butyl)-5-fluoronaphthalene-1-sulfonamide (**P14**)

To a solution of compound **P14e** (3.0 g, 9.27 mmol) in pyridine (15 mL) was added *tert*-BuNH₂ (2.0 g, 27.3 mmol) and the solution was stirred at rt for overnight, concentrated and purified by CC (PE/EA = 30/1) to give compound **P14** (1.71 g, 51%) as a white solid.

10 Preparative Example P15

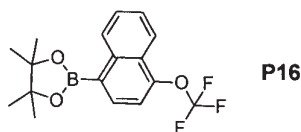


(4-Methoxynaphthalen-1-yl)boronic acid (**P15**)

15 A mixture of 1-bromo-4-methoxynaphthalene (2.0 g, 8.44 mmol) in Et₂O (10 mL) was cooled down to -70°C under N₂ and then *n*-BuLi in hexane (3.37 mL, 8.44 mmol) was added dropwise. The solution was stirred under N₂ for 2 h, then warmed to rt and triisopropyl borate (1.74 g, 9.28 mmol) was added. The mixture was stirred for 16 h under N₂. Then 2M HCl (10 mL) and Et₂O (10 mL) was added to the mixture which was washed by brine till it turned neutral. The organic layer was dried over Na₂SO₄, filtered, concentrated and the residue was washed with EA to give compound **P15** (500 mg, 29%) as a colorless solid.

20

Preparative Example P16



Step 1: 4-Bromonaphthalen-1-ol (**P16a**)

25 A solution of naphthalen-1-ol (35.0 g, 243 mmol) in ACN (300 mL) was cooled to 0°C. Then NBS (42.7 g, 243 mmol) in ACN (500 mL) was added dropwise and the mixture was stirred for 1 h, concentrated and dissolved in DCM. The solution was washed with brine, dried over Na₂SO₄, filtered, concentrated and washed with PE to give compound **P16a** (30.0 g, 55%) as an off-white solid.

Step 2: 1-Bromo-4-(bromodifluoromethoxy)naphthalene (**P16b**)

30 NaH (60%, 1.26 g, 31.5 mmol) was added to a solution of compound **P16a** (2.0 g, 10.5 mmol) in DMF (20 mL) in a 75 mL seal tube slowly under ice-bath cooling. After stirring for 10 min, *t*-BuOK (1.3 g, 11.6 mmol) and CF₂Br₂ (8.8 g, 42.0 mmol) were added slowly to the mixture. The sealed tube was quickly closed and heated to 70°C overnight. The resulting mixture was

poured into water and extracted with EA twice. The combined organic layers were washed with water (3x) and brine consecutively, dried over Na₂SO₄, filtered, concentrated and purified by CC (PE) to give compound **P16b** (1.6 g, 43%) as a colorless oil.

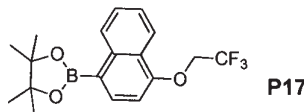
Step 3: 1-Bromo-4-(trifluoromethoxy)naphthalene (P16c)

- 5 A solution of compound **P16b** (3.5 g, 10.0 mmol) in DCM (70 mL) was cooled to –78°C under N₂, then AgBF₄ (4.3 g, 22.0 mmol) was added and the solution was warmed to rt slowly and stirred overnight. NaHCO₃ solution was added to the mixture until pH > 8. Then the resulting suspension was filtered and the filtrate was extracted with DCM twice. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated to give compound
- 10 **P16c** (3.0 g, quant.) as a brown oil.

Step 4: 4,4,5,5-Tetramethyl-2-(4-(trifluoromethoxy)naphthalen-1-yl)-1,3,2-dioxaborolane (P16)

- A mixture of compound **P16c** (1.0 g, 3.45 mmol), Pin₂B₂ (1.75 g, 6.9 mmol), AcOK (1.0 g, 10.4 mmol) and Pd(dppf)Cl₂·CH₂Cl₂ (282 mg, 0.35 mmol) in 1,4-dioxane (20 mL) was bubbled with N₂ for 10 min and the mixture was stirred at 80°C for 16 h under N₂, cooled to rt and diluted
- 15 with EA and filtered. The filtrate was concentrated and purified by CC (PE) to give compound **P16** (0.90 g, 77%) as an off-white solid.

Preparative Example P17

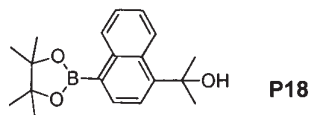


- 20 **Step 1: 1-Bromo-4-(2,2,2-trifluoroethoxy)naphthalene (P17a)**

A mixture of 4-bromonaphthalen-1-ol (5.00 g, 22.4 mmol), 1,1,1-Trifluoro-2-iodoethane (5.65 g, 26.9 mmol) and Cs₂CO₃ (15 g, 46.1 mmol) in DMF (150 mL) was stirred at 100°C for 16 h, cooled to rt, diluted with EA and then filtered. The filtrate was concentrated and purified by CC (PE) to give compound **P17a** (2.8 g, 41%) as a colorless solid.

- 25 **Step 2: 4,4,5,5-Tetramethyl-2-(4-(2,2,2-trifluoroethoxy)naphthalen-1-yl)-1,3,2-dioxaborolane (P17)**

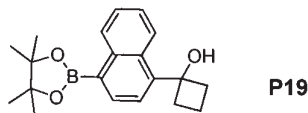
- A mixture of compound **P17a** (500 mg, 1.64 mmol), B₂Pin₂ (835 mg, 3.29 mmol) and KOAc (483 mg, 4.93 mmol) in dioxane (30 mL) was bubbled with N₂ for 10 min, then Pd(dppf)Cl₂·CH₂Cl₂ (134 mg, 0.164 mmol) was added and the mixture was stirred at 80°C for
- 30 16 h under N₂, diluted with EA, filtered, concentrated and purified by CC (EA/PE = 1/20) to give compound **P17** (180 mg, 31%) as a colorless solid.

Preparative Example P18**Step 1: 2-(4-Bromonaphthalen-1-yl)propan-2-ol (P18a)**

To a solution of 1,4-dibromonaphthalene (2.0 g, 7.0 mmol) in dry Et₂O (50 mL) was added *n*-BuLi (2.5M in hexanes, 3.1 mL, 7.7 mmol) at 0°C and the solution was stirred for 20 min. Then acetone (488 mg, 8.4 mmol) was added and the solution was warmed to rt and stirred at this temperature for 1 h, quenched with water and extracted with Et₂O (3x). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered, concentrated and purified by CC (PE/EA = 10/1) to give compound **P18a** (1.2 g, 65%) as an off- white solid.

Step 2: 2-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)propan-2-ol (P18)

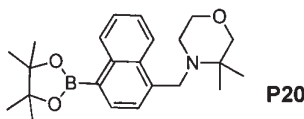
A solution of compound **P18a** (600 mg, 2.3 mmol), B₂Pin₂ (690 mg, 2.7 mmol), KOAc (450 mg, 4.6 mmol) and Pd(dppf)Cl₂ (150 mg, 0.2 mmol) in dioxane (10 mL) was heated overnight at 85°C under N₂, cooled to rt, filtered and the filtrate diluted with water. The aqueous layer was extracted with EA twice. The combined organic layers were washed with water and brine, dried over Na₂SO₄, filtered, concentrated and purified by CC (PE/EA = 20/1) to give compound **P18** (600 mg, 83%) as a colorless solid.

Preparative Example P19**Step 1: 3-(4-Bromonaphthalen-1-yl)oxetan-3-ol (P19a)**

To a solution of 1,4-dibromonaphthalene (2.0 g, 7.0 mmol) in dry Et₂O (50 mL) was added *n*-BuLi (2.5M in hexanes, 3.1 mL, 7.7 mmol) at 0°C and the solution was stirred for 20 min. Then oxetan-3-one (604 mg, 8.4 mmol) was added and the solution was warmed to rt and stirred at this temperature for 1 h, quenched with water and extracted with Et₂O (3x). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered, concentrated and purified by CC (PE/EA = 5/1) to give compound **P19a** (1.20 g, 61%) as an off- white solid.

Step 2: 3-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)oxetan-3-ol (P19)

The solution of compound **P19a** (500 mg, 1.8 mmol), B₂Pin₂ (559 mg, 2.2 mmol), KOAc (353 mg, 3.6 mmol) and Pd(dppf)Cl₂ (145 mg, 0.2 mmol) in dioxane (10 mL) was heated overnight at 85°C under N₂, cooled to rt, filtered and the filtrate was diluted with water. The aqueous layer was extracted with EA twice. The combined organic layers were washed with water and brine, dried over Na₂SO₄, filtered, concentrated and purified by CC (PE/EA = 20/1) to give compound **P19** (110 mg, 15%) as a colorless solid.

Preparative Example P20**Step 1: 4-Bromo-1-naphthaldehyde (P20a)**

To a solution of 1,4-dibromonaphthalene (2.0 g, 7.0 mmol) in dry Et₂O (50 mL) was added *n*-BuLi (2.5M in hexanes, 3.1 mL, 7.7 mmol) at 0°C and the solution was stirred for 20 min. Then DMF (1.62 mL, 21 mmol) was added and the solution was warmed to rt and stirred at this temperature for 1 h, quenched with water and extracted with Et₂O (3x). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered, concentrated and purified by CC (PE/EA = 50/1) to give compound **P20a** (1.02 g, 62%) as an off- white solid.

Step 2: (4-Bromonaphthalen-1-yl)methyl methanesulfonate (P20b)

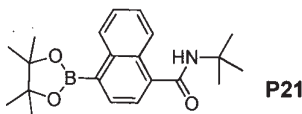
To a solution of compound **P20a** (1.02 g, 4.3 mmol) in MeOH (10 mL) was added NaBH₄ (378 mg, 10 mmol) slowly and the suspension was stirred at rt for 1 h, was quenched with sat. NH₄Cl, concentrated and diluted with EA and water. The organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated to give a residue. To this residue was added DCM (10 mL), NEt₃ (1.01 g, 10 mmol) and MsCl (1.15 g, 10 mmol) and the mixture was stirred for 1 h, quenched with water and the organic layer was dried over Na₂SO₄, filtered and concentrated to give crude compound **P20b** (700 mg, 52%) as a colorless oil.

Step 3: 4-((4-Bromonaphthalen-1-yl)methyl)-3,3-dimethylmorpholine (P20c)

A suspension of compound **P20b** (700 mg, 2.2 mmol), 3,3-dimethyl-morpholine (512 mg, 4.4 mmol) and K₂CO₃ (828 mg, 6.0 mmol) in ACN (10 mL) was refluxed overnight, cooled to rt, filtered, concentrated and purified by CC (PE/EA = 5/1) to give compound **P20c** (460 mg, 54% over two steps) as a colorless solid.

Step 4: 3,3-Dimethyl-4-((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)methyl)morpholine (P20)

A solution of compound **P20c** (460 mg, 1.38 mmol), B₂Pin₂ (953 mg, 3.75 mmol), KOAc (368 mg, 3.75 mmol) and Pd(dppf)Cl₂ (51 mg, 0.06 mmol) in dioxane (10 mL) was heated overnight at 90°C under N₂, cooled to rt, filtered and the filtrate was diluted with water. The aqueous layer was extracted with EA twice. The combined organic layers were washed with water and brine, dried over Na₂SO₄, filtered, concentrated and purified by CC (PE/EA = 5/1) to give compound **P20** (110 mg, 21%) as a colorless solid.

Preparative Example P21

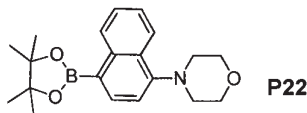
Step 1: 4-Bromo-*N*-(*tert*-butyl)-1-naphthamide (P21a)

A mixture of 4-bromo-1-naphthoic acid (4.0 g, 16 mmol) in thionyl chloride (20 mL) was heated under reflux for 2 h, cooled to rt and concentrated to give the acid chloride. The crude intermediate was dissolved in dry DCM (40 mL) and treated with *t*-BuNH₂ (2.92 g, 40 mmol), and the mixture was stirred at rt for 20 h and quenched with 1M HCl. The organic layer was washed with 1M HCl and brine, dried over Na₂SO₄, concentrated and purified by CC (PE/EA = 8/1) to give compound **P21a** (3.8 g, 78%) as a colorless solid.

Step 2: *N*-(*tert*-Butyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-naphthamide (P21)

The solution of compound **P21a** (1.5 g, 5.0 mmol), B₂Pin₂ (1.5 g, 6.0 mmol), KOAc (980 mg, 10.0 mmol) and Pd(dppf)Cl₂ (366 mg, 0.5 mmol) in dioxane (15 mL) was heated overnight at 90°C under N₂, cooled to rt, filtered and the filtrate was diluted with water. The aqueous layer was extracted with EA twice. The combined organic layers were washed with water and brine, dried over Na₂SO₄, filtered, concentrated and purified by CC (PE/EA = 10/1) to give compound **P21** (1.7 g, 96%) as a colorless solid.

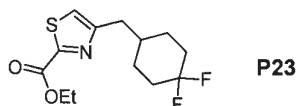
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Preparative Example P22Step 1: 4-(4-Bromonaphthalen-1-yl)morpholine (P22a)

To a solution of 4-bromonaphthalen-1-amine (2.0 g, 9.0 mmol) in DMF (20 mL) was added 1-bromo-2-(2-bromoethoxy)ethane (1.43 mL, 9.0 mmol) and potassium carbonate (2.76 g, 20 mmol). The mixture was heated at 100°C for 48 h, cooled to rt, diluted with water and extracted with EA (3x). The combined organic layers were washed with water and brine, dried over Na₂SO₄, filtered, concentrated and purified by CC (PE/EA = 4/1) to give compound **P22a** (900 mg, 34%) as a yellow solid.

Step 2: 4-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)morpholine (P22)

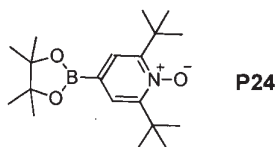
A solution of compound **P22a** (900 mg, 3.1 mmol), B₂Pin₂ (945 mg, 3.7 mmol), KOAc (608 mg, 6.2 mmol) and Pd(dppf)Cl₂ (220 mg, 0.3 mmol) in dioxane (10 mL) was heated overnight at 90°C under N₂, cooled to rt, filtered and the filtrate was diluted with water. The aqueous layer was extracted with EA twice. The combined organic layers were washed with water and brine, dried over Na₂SO₄, filtered, concentrated and purified by CC (PE/EA = 4/1) to give compound **P22** (770 mg, 73%) as a colorless solid.

Preparative Example P23**Step 1: 1-Bromo-3-(4,4-difluorocyclohexyl)propan-2-one (P23a)**

2-(4,4-Difluorocyclohexyl)acetic acid (4.0 g, 22.5 mmol) in SOCl_2 (50 mL) was refluxed for 2h and concentrated. The brown oil was dissolved in ACN (50 mL) and cooled to 0°C . TMSCHN_2 (1N, 34 mmol) was added dropwise and the mixture was stirred at rt for 2h. It was cooled to 0°C again, and HBr in HOAc (3 mL) was added dropwise. The mixture was stirred at rt overnight. H_2O (100 mL) and EA (100 mL) was added. The aq. phase was extracted with EA (80 mL x 2), the combined organic phases were washed with brine and concentrated. The residue was purified by CC (PE/EA = 25/1) to afford compound **P23a** (2.51 g, 44%) as a colorless oil.

Step 2: Ethyl 4-((4,4-difluorocyclohexyl)methyl)thiazole-2-carboxylate (P23)

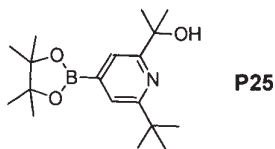
A mixture of compound **P23a** (2.51 g, 9.9 mmol) and ethyl 2-amino-2-thioxoacetate (1.45 g, 10.9 mmol) in ethanol (50 mL) was stirred at 90°C overnight. After concentration to dryness the residue was purified by CC (PE/EA = 15:1) to give compound **P23** (1.6 g, 65%) as a brown solid.

Preparative Example P24**Step 1: 2,6-Di-tert-butylpyridine 1-oxide (P24a)**

To a solution of 2,6-di-tert-butylpyridine (6.00 g, 31.4 mmol) in EA (100 mL) was added *m*-CPBA (16.5 g, 95.6 mmol) and the solution was refluxed for overnight, washed with sat. NaHCO_3 and sat. $\text{Na}_2\text{S}_2\text{O}_3$ consecutively, dried over Na_2SO_4 , filtered, concentrated and purified by CC (PE/EA = 30/1) to give compound **P24a** (186 mg, 3%) as a white solid.

Step 2: 2,6-Di-tert-butyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine 1-oxide (P24)

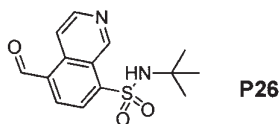
A solution of compound **P24a** (118 mg, 570 μmol), $[\text{Ir}(\text{COD})(\text{OMe})_2]$ (13 mg, 20 μmol), DTBPy (11 mg, 40 μmol) and $(\text{BPin})_2$ (174 mg, 680 μmol) in dry THF (5 mL) was refluxed for 16 h, concentrated and purified by CC (PE/EA = 30/1) to give compound **P24** (98 mg, 52%) as a white solid.

Preparative Example P25**Step 1: 2-(6-(*tert*-Butyl)pyridin-2-yl)propan-2-ol (P25a)**

A solution of 1-(6-(*tert*-butyl)pyridin-2-yl)ethanone (3.20 g, 18.1 mmol) in THF (20 mL) was cooled to -78°C and CH_3MgBr in THF (1M, 3.6 mL, 3.6 mol) was added dropwise. The mixture was stirred at -78°C and allowed to warm to rt for 3 h, quenched with aq. saturated NH_4Cl , extracted with EA (3x) and then the combined organic layers were dried over Na_2SO_4 . The solvent was filtered, concentrated and purified by CC (PE/EA = 5/1) to give compound **P25a** (3.1 g, 89%) as an oil.

Step 2: 2-(6-(*tert*-Butyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)propan-2-ol (P25)

A solution of compound **P25a** (1.00 g, 5.18 mmol), $[\text{Ir}(\text{COD})(\text{OMe})_2]$ (100 mg, 0.16 mmol), DTBPy (83 mg, 0.31 mmol) and $(\text{BPin})_2$ (1.58 g, 6.2 mmol) in THF (10 mL) was stirred at 80°C overnight, concentrated and purified by CC (PE/EA = 10/1 to 1/1) to give compound **P25** (0.9 g, 54%) as a slight yellow solid.

Preparative Example P26**Step 1: 5-Bromoisquinoline-8-sulfonic acid (P26a)**

A solution of 5-bromoisquinoline (50 g, 250 mmol) in fuming sulphuric acid (500 mL) was heated to 200°C and stirred for 4 h. After cooling to rt the mixture was poured into 2500 mL ice water. A white solid was obtained by filtration, washed with water and acetone and dried in vacuum to give compound **P26a** (59 g, 90%) as a white solid.

Step 2: 5-Bromo-N-(*tert*-butyl)isoquinoline-8-sulfonamide (P26b)

A solution of **P26a** (28 g, 100 mmol) and DMF (4 mL) in SOCl_2 (300 mL) was heated to reflux for 5 h. The excess of SOCl_2 was removed under reduced pressure. A solution of *tert*-butylamine (37 g, 500 mmol) in DCM (100 mL) was added dropwise to a solution of the crude residue in 150 mL DCM at 0°C . The reaction mixture was stirred for 2 h at rt, quenched with water and extracted with DCM. The organic layer was concentrated to dryness to give a yellow solid, which was washed with Et_2O and dried in vacuum to give compound **P26b** (22g, 63%) as a yellow solid.

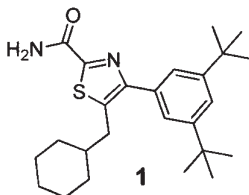
Step 3: N-(*tert*-Butyl)-5-formylisoquinoline-8-sulfonamide (P26)

A solution of *n*-butyllithium (46 mL, 114 mmol) in hexane was added dropwise to a solution of **P26b** (15 g, 52 mmol) in THF/Et₂O (200 mL/200 mL) at -78°C. Then the reaction was stirred for 30 min at this temperature. A solution of DMF (4 mL) in THF was added slowly to the reaction mixture at -78°C and stirring was continued for 3 h. The reaction was quenched with a solution of NH₄Cl and extracted with EA. The organic layer was washed with brine, dried with Na₂SO₄, concentrated and purified by CC (PE/E = 6/1) to give compound **P26** (5.5 g, 36%) as a yellow solid.

Additional Preparative Examples

- 10 The synthesis of additional Preparative Examples (e.g. boronic esters) is described in WO2012/139775 and in PCT/EP2012/004977.

Example 1



15 Step 1: 3-Cyclohexyl-1-(3,5-di-*tert*-butylphenyl)propan-1-one (**1a**)

A solution of 1,3-di-*tert*-butylbenzene (4.36 g, 22.9 mmol) in dry CH₂Cl₂ (20 mL) was sequentially treated at 0°C with 3-cyclohexylpropanoyl chloride (4.00 g, 22.9 mmol) and AlCl₃ (3.35 g, 25.2 mmol) and the solution was stirred at 0°C for 2 h. The resulting solution was poured into 0.1N HCl and the organic layer was separated. The aq. phase was extracted with EA. The combined organic layers were washed with sat. NaHCO₃ and brine consecutively, dried over Na₂SO₄, filtered, concentrated and purified by CC (DCM/PE = 1/6) to give compound **1a** (2.3 g, 30%) as a light yellow oil.

25 Step 2: 2-Bromo-3-cyclohexyl-1-(3,5-di-*tert*-butylphenyl)propan-1-one (**1b**)

To a solution of compound **1a** (2.0 g, 6.02 mmol) in AcOH (20 mL) was added Br₂ (0.96 g, 6.02 mmol) at 0°C and the solution was stirred at rt for 1 h. The resulting solution was poured into sat. Na₂SO₃ and extracted with EA twice. The combined organic layers were washed with water and brine consecutively, dried over Na₂SO₄, filtered, concentrated and purified by CC (DCM/PE = 1/8) to give compound **1b** (2.2 g, 89%) as a colorless oil.

Step 3: Ethyl 5-(cyclohexylmethyl)-4-(3,5-di-*tert*-butylphenyl)thiazole-2-carboxylate (**1c**)

30 The solution of compound **1b** (0.47 g, 1.2 mmol) and ethyl thiooxamate (0.24 g, 1.8 mmol) in *n*-BuOH (10 mL) was heated at reflux for 16 h. After concentration under reduced pressure, the residue was dissolved in a mixture of water and EA and the organic layer was separated. The aq. layer was extracted with EA twice. The combined organic layers were washed with

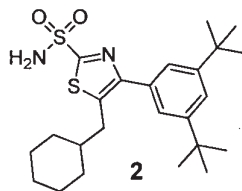
water and brine consecutively, dried over Na₂SO₄, filtered, concentrated and purified by CC (DCM/PE = 1/5) to give compound **1c** (0.2 g, 38%) as a yellow oil.

Step 4: 5-(Cyclohexylmethyl)-4-(3,5-di-*tert*-butylphenyl)thiazole-2-carboxamide (**1**)

5 To a solution of compound **1c** (0.15 g, 0.34 mmol) in methanol (5 mL) was bubbled NH₃ and the solution was heated at reflux for 16 h. After concentration under reduced pressure, the residue was purified by CC (EA/PE = 1/6) to give compound **1** (100 mg, 71%) as a white solid. ¹H-NMR (CDCl₃, 300 MHz) δ: 0.92-0.97 (2H, m), 1.14-1.28 (4H, m), 1.37 (18H, s), 1.57-1.80 (5H, m), 2.80 (2H, d, J = 7.2 Hz), 5.53 (1H, br s), 7.17 (1H, br s), 7.37 (2H, d, J = 2.1 Hz), 7.46 (1H, t, J = 1.8 Hz). MS 413.4 (M+1).

10

Example 2



Step 1: 5-(Cyclohexylmethyl)-4-(3,5-di-*tert*-butylphenyl)thiazole (**2a**)

15 To a solution of compound **1b** (1.70 g, 4.14 mmol) in 1,4-dioxane (15 mL) was added formamide (0.37 g, 8.3 mmol) and phosphorus pentasulfide (0.37 g, 1.67 mmol) and the solution was heated at reflux for 16 h. 2N HCl was added and the solution was refluxed for another 1 h. After concentration under reduced pressure, the residue was dissolved in dilute 2N NaOH and the solution was extracted with EA twice. The combined organic layers were washed with water and sat. Na₂CO₃, dried over Na₂SO₄, filtered, concentrated and purified by
20 CC (DCM/PE = 1/3) to give compound **2a** (0.9 g, 59%) as a colorless sticky oil.

Step 2: 2-Bromo-5-(cyclohexylmethyl)-4-(3,5-di-*tert*-butylphenyl)thiazole (**2b**)

To a solution of compound **2a** (0.30 g, 0.90 mmol) in dry THF (5 mL) was added a solution of *n*-BuLi (2.5M in *n*-hexane, 0.4 mL, 1.0 mmol) at -78°C and the solution was stirred for 30 min. CBr₄ (0.33 g, 1.0 mmol) in dry THF (1 mL) was added at -78°C and the solution was stirred at
25 rt for 1 h. The resulting solution was quenched with sat. NH₄Cl and extracted with EA twice. The combined organic layers were washed with water and brine consecutively, dried over Na₂SO₄, filtered, concentrated and purified by CC (DCM/PE = 1/4) to give compound **2b** (0.36 g, 86%) as a white solid.

Step 3: 5-(Cyclohexylmethyl)-4-(3,5-di-*tert*-butylphenyl)thiazole-2-thiol (**2c**)

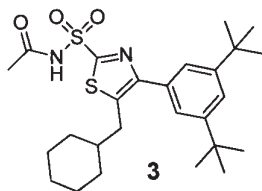
30 To a solution of compound **2b** (0.35 g, 0.78 mmol) in EtOH (5 mL) was added NaSH (87 mg, 1.6 mmol) and the solution was heated at reflux for 24 h. After concentration under reduced pressure, the residue was dissolved in a mixture of water and EA and the organic layer was separated. The aq. layer was extracted with EA twice. The combined organic layers were

washed with water and brine consecutively, dried over Na₂SO₄, filtered, concentrated and purified by CC (EA/PE = 1/4) to give compound **2c** (80 mg, 26%) as a white solid.

Step 4: 5-(Cyclohexylmethyl)-4-(3,5-di-*tert*-butylphenyl)thiazole-2-sulfonamide (**2**)

To a solution of compound **2c** (45 mg, 0.11 mmol) in CH₂Cl₂ (5 mL) was added NCS (58 mg, 0.44 mmol) and the solution was stirred at rt for 2 h. Water was added and the solution was extracted with CH₂Cl₂ twice. The combined organic layers were washed with sat. NaHCO₃ and brine consecutively, dried over Na₂SO₄, filtered and concentrated. The residue was dissolved in a mixture of acetone (3 mL) and NH₄OH (5 mL) and the solution was stirred for 30 min. The organic layer was removed under reduced pressure and the aq. layer was extracted with EA twice. The combined organic layers were washed with water and brine consecutively, dried over Na₂SO₄, filtered, concentrated and purified by CC (EA/PE = 1/4) to give compound **2** (27 mg, 55%) as a white solid. ¹H-NMR (CDCl₃, 300 MHz) δ: 0.85-0.96 (2H, m), 1.16-1.25 (4H, m), 1.35 (18H, s), 1.60-1.76 (5H, m), 2.80 (2H, d, J = 6.9 Hz), 5.29 (2H, br s), 7.34 (2H, d, J = 1.8 Hz), 7.46 (1H, t, J = 2.1 Hz). MS 449.4 (M+1).

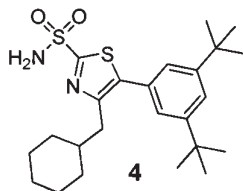
Example 3



N-((5-(Cyclohexylmethyl)-4-(3,5-di-*tert*-butylphenyl)thiazol-2-yl)sulfonyl)acetamide (**3**)

To a solution of compound **2** (20 mg, 45 μmol) in CH₂Cl₂ (2 mL) was added NEt₃ (50 μL) and Ac₂O (50 μL) and the solution was stirred at rt for 1 h. Water was added to quench the reaction and the organic layer was separated. The aq. phase was extracted with DCM twice. The combined organic layers were washed with water and brine consecutively, dried over Na₂SO₄, filtered, concentrated and purified by CC (EA/PE = 1/3) to give compound **3** (18 mg, 81%) as a white solid. ¹H-NMR (CDCl₃, 300 MHz) δ: 0.94-0.97 (2H, m), 1.17-1.28 (4H, m), 1.36 (18H, s), 1.67-1.79 (5H, m), 1.86 (3H, s), 2.76 (2H, d, J = 6.9 Hz), 7.30 (2H, d, J = 1.8 Hz), 7.50 (1H, t, J = 1.8 Hz). MS 491.4 (M+1).

Example 4



Step 1: 1-Allyl-3,5-di-*tert*-butylbenzene (**4a**)

To a solution of (3,5-di-*tert*-butylphenyl)boronic acid (12.0 g, 52.0 mmol) in dry toluene (300 mL) was added K₂CO₃ (27.6 g, 200 mmol), Pd₂(dba)₃ (2.0 g) and 3-bromoprop-1-ene (6.2 g, 52 mmol) by injection under nitrogen atmosphere and the suspension was stirred at reflux overnight, then cooled to rt and filtered. The filtrate was concentrated and purified by CC (PE) to give product **4a** (7.3 g, 62%) as a light yellow oil.

Step 2: 2-(3,5-Di-*tert*-butylbenzyl)oxirane (**4b**)

To a solution of compound **4a** (7.3 g, 32 mmol) in CH₂Cl₂ (70 mL) was added *m*-CPBA (6.6 g, 38 mmol) at rt and the solution was stirred for 2 h, quenched with aq. Na₂S₂O₃ and the organic layer was separated, washed with water and brine consecutively, dried over Na₂SO₄, filtered, concentrated and CC (PE) to give compound **4b** (6.0 g, 76%) as a colorless oil.

Step 3: 1-Cyclohexyl-3-(3,5-di-*tert*-butylphenyl)propan-2-ol (**4c**)

To a solution of CuBr (150 mg) and cyclohexylmagnesium chloride (2M in Et₂O, 15 mL, 30 mmol) was added a solution of compound **4b** (6.0 g, 24.4 mmol) in dry THF (10 mL) slowly at -30°C and the solution was stirred at rt for 30 min, then quenched with sat. NH₄Cl and extracted with MTBE (3x). The combined organic layers were concentrated to give crude compound **4c** (6.5 g, 82%) as a yellow oil.

Step 4: 1-Cyclohexyl-3-(3,5-di-*tert*-butylphenyl)propan-2-one (**4d**)

A solution of H₅IO₆ (5.5 g 24 mmol) in ACN (100 mL) was stirred vigorously at rt for 15 min. After cooling to 0°C, compound **4c** (6.5 g, 20 mmol) was added, followed by the addition of PCC (10.3 g, 48 mmol) in CAN (20 mL) and the solution was stirred for 2 h at 0°C, diluted with MTBE and passed on a pad of silica gel. The collected solution was concentrated to give the crude compound **4d** (6.0 g, 91%) as a brown oil.

Step 5: 1-Bromo-3-cyclohexyl-1-(3,5-di-*tert*-butylphenyl)propan-2-one (**4e**)

To a solution of compound **4d** (6.0 g, 18.3 mmol) in CCl₄ (100 mL) was added a solution of Br₂ (1M in CH₂Cl₂, 2.93 g, 18.3 mmol) at -15°C and the solution was stirred at 0°C for 1 h, then poured into sat. Na₂SO₃ and extracted with EA twice. The combined organic layers were washed with water and brine consecutively, dried over Na₂SO₄, filtered, concentrated and purified by CC (PE) to give compound **4e** (6.5 g, 87%) as a colorless oil.

Step 6: 4-(Cyclohexylmethyl)-5-(3,5-di-*tert*-butylphenyl)thiazol-2-amine (**4f**)

To a solution of compound **4e** (6.5 g, 16 mmol) in EtOH (150 mL) was added thiourea (4.9 g, 64 mmol) and the solution was heated at 80°C for 4 h, cooled to rt and a solution of sat. NaHCO₃ was added. The formed solid was collected by filtration and dried in vacuo to give compound **4f** (6.0 g, 98%) as a light yellow solid.

Step 7: 2-Bromo-4-(cyclohexylmethyl)-5-(3,5-di-*tert*-butylphenyl)thiazole (**4g**)

The solution of CuBr₂ (4.05 g, 18 mmol) and *tert*-butyl nitrite (2.1g, 19 mmol) in ACN (75 mL) was heated at reflux until gas evolution stopped. Compound **4f** (5.7 g, 15 mmol) was added and the solution was heated at reflux until gas evolution stopped again, then diluted with EA

and washed repeatedly with sat. Na_2CO_3 . The organic layer was dried over MgSO_4 , filtered, concentrated and purified by CC (DCM/PE = 2/1) to give compound **4g** (4.4 g, 67%) as a light yellow solid.

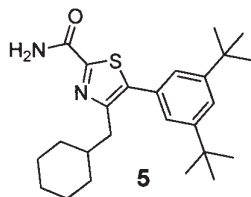
Step 8: 4-(Cyclohexylmethyl)-5-(3,5-di-*tert*-butylphenyl)thiazole-2-thiol (**4h**)

- 5 To a solution of compound **4g** (4.2 g, 9.4 mmol) in EtOH (150 mL) was added NaSH (2.1 g, 38 mmol) and thiourea (2.9 g, 38 mmol) and the solution was heated at reflux for 24 h. After concentration, the residue was diluted with water and extracted with EA twice. The combined organic layers were washed with water and brine consecutively, dried over Na_2SO_4 , filtered, concentrated and purified by CC (EA/PE = 1/9) to give compound **4h** (1.8 g, 48%) as a white solid.

Step 9: 4-(Cyclohexylmethyl)-5-(3,5-di-*tert*-butylphenyl)thiazole-2-sulfonamide (**4**)

- To a solution of compound **4h** (150 mg, 0.38 mmol) in CH_2Cl_2 (15 mL) was added NCS (200 mg, 1.5 mmol) and the solution was stirred at rt for 1. Water was added to quench the reaction and the solution was extracted with CH_2Cl_2 . The organic layer washed with sat. NaHCO_3 and brine consecutively, dried over Na_2SO_4 , filtered and concentrated. The residue was taken up in acetone (10 mL) and NH_4OH (10 mL) and the solution was stirred for 15 min, concentrated and extracted with EA twice. The combined organic layers were washed with water and brine consecutively, dried over Na_2SO_4 , filtered, concentrated and purified by CC (EA/PE = 1/4) to give compound **4** (70 mg, 41%) as a white solid. $^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ : 0.87-0.96 (2H, m), 1.12-1.25 (3H, m), 1.35 (18H, s), 1.63-1.74 (5H, m), 1.78-1.85 (1H, m), 2.67 (2H, d, J = 7.2 Hz), 5.39 (2H, s), 7.23 (2H, d, J = 2.0 Hz), 7.49 (1H, t, J = 2.0 Hz). MS 449.1 ($M+1$).

Example 5



- 25 Step 1: 2-(3,5-Di-*tert*-butylphenyl)acetonitrile (**5a**)

- A solution of 1,3-di-*tert*-butyl-5-methylbenzene (25 g, 12.3 mmol), NBS (24 g, 13.5 mmol), AIBN (50 mg, 0.31 mmol) in CCl_4 (250 mL) was heated at reflux for 12 h. The resulting solution was cooled to rt and placed in the refrigerator overnight. The formed solid was filtered and the filtrate was concentrated under reduced pressure. The residue was dissolved in DMF (200 mL) and NaCN (9.0 g, 18.4 mmol) was added. The solution was stirred at 50°C for 16 h, poured into water and extracted with EA twice. The combined organic layers were washed with water and brine consecutively, dried over Na_2SO_4 , filtered, concentrated and purified by CC (PE) to give compound **5a** (16.9 g, 60%) as a colorless oil.

Step 2: 2-(3,5-Di-*tert*-butylphenyl)acetic acid (**5b**)

To a solution of compound **5a** (16.9 g, 73.8 mmol) in a mixture of THF (130 mL) and EtOH (80 mL) was added aq. KOH solution (40 wt%, 80 mL) and the solution was vigorously stirred at 100°C for 6 d, cooled to rt and acidified with 2N aq. HCl to pH=3. The suspension was
5 extracted with EA three times. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered, concentrated and purified by CC (EA/PE = 1/6) to give compound **5b** (6.4 g, 35%) as a white solid.

Step 3: 2-(3,5-Di-*tert*-butylphenyl)-*N*-methoxy-*N*-methylacetamide (**5c**)

A solution of compound **5b** (6.4 g, 25.7 mmol) in SOCl₂ (5 mL) was heated at reflux for 1 h, concentrated under reduced pressure and diluted in dry CH₂Cl₂ (40 mL). This solution was
10 slowly added to a solution of *N,O*-dimethylhydroxylamine hydrochloride (2.52 g, 25.7 mmol) and DIEA (9.9 g, 77 mmol) in dry CH₂Cl₂ (30 mL) at 0°C and the solution was stirred at rt overnight, quenched with water and extracted with EA twice. The combined organic layers were washed with 1N aq. HCl, sat. Na₂CO₃ and brine consecutively, dried over Na₂SO₄,
15 filtered, concentrated and purified by CC (EA/PE = 1/6) to give compound **5c** (5.1 g, 68%) as a white solid.

Step 4: 1-Cyclohexyl-3-(3,5-di-*tert*-butylphenyl)propan-2-one (**5d**)

To a solution of compound **5c** (2.5 g, 8.6 mmol) in dry THF (20 mL) was added a solution of cyclohexanyl magnesium bromide (0.57 M in Et₂O, 15 mL, 8.6 mmol) at 0°C and the solution
20 was stirred at rt for 3 h, quenched with sat. NH₄Cl and extracted with EA twice. The combined organic layers were washed with water and brine consecutively, dried over Na₂SO₄, filtered, concentrated and purified by CC (DCM/PE = 1/6) to give compound **5d** (187 mg, 7%) as a colorless sticky oil.

Step 5: 1-Bromo-3-cyclohexyl-1-(3,5-di-*tert*-butylphenyl)propan-2-one (**5e**)

To a solution of compound **5d** (687 mg, 2.10 mmol) in AcOH (5 mL) was added a solution of Br₂ (335 mg, 2.1 mmol) in AcOH (1 mL) slowly at 0°C and the solution was stirred at rt for 30 min, poured into sat. Na₂SO₃ and extracted with EA. The combined organic layers were washed with water and brine consecutively, dried over Na₂SO₄, filtered, concentrated and purified by CC (DCM/PE = 1/8) to give compound **5e** (0.50 g, 59%) as a yellow oil.

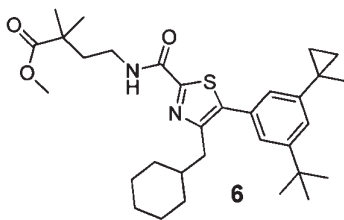
30 Step 6: Ethyl 4-(cyclohexylmethyl)-5-(3,5-di-*tert*-butylphenyl)thiazole-2-carboxylate (**5f**)

The solution of compound **5e** (84 mg, 0.2 mmol) and ethyl thiooxamate (55 mg, 0.41 mmol) in *n*-BuOH (5 mL) was heated at reflux for 2 h and then concentrated under reduced pressure. The residue was dissolved in a mixture of water and EA and the organic layer was separated, washed with water and brine consecutively, dried over Na₂SO₄, filtered, concentrated and
35 purified by CC (DCM/PE = 1/5) to give compound **5f** (60 mg, 67%) as a light yellow sticky oil.

Step 7: 4-(Cyclohexylmethyl)-5-(3,5-di-*tert*-butylphenyl)thiazole-2-carboxamide (**5**)

To a solution of compound **5f** (60 mg, 0.14 mmol) in MeOH (10 mL) was bubbled NH₃ and the solution was heated at 90°C for 16 h and concentrated under reduced pressure. The residue was purified by CC (EA/PE = 1/6) to give **5** (30 mg, 52%) as a white solid. ¹H-NMR (400 MHz, CDCl₃) δ: 0.87-1.00 (2H, m), 1.15-1.25 (4H, m), 1.35 (18H, s), 1.61-1.72 (5H, m), 1.79-1.84 (1H, m), 2.66 (2H, d, J = 6.8 Hz), 5.61 (1H, br s), 7.16 (1H, br s), 7.25 (2H, d, J = 2.0 Hz), 7.46 (1H, t, J = 2.0 Hz). MS 413.2 (M+1).

Example 6



10 Step 1: 1-Bromo-3-cyclohexylpropan-2-one (**6a**)

To an ice-cooled solution of 1-cyclohexylpropan-2-one (19.6 g, 140 mmol) in MeOH (150 mL) was added Br₂ (22.4 g, 140 mmol) in a single portion and the reaction temperature was kept below 15°C until the red color of the solution turned colorless. H₂O was added and the solution was extracted with Et₂O (3x). The combined organic layers were combined, washed with 10% aq. K₂CO₃ (3x), dried over Na₂SO₄, filtered and concentrated to give crude compound **6a** (22 g) as a yellowish liquid.

Step 2: Ethyl 4-(cyclohexylmethyl)thiazole-2-carboxylate (**6b**)

A solution of compound **6a** (20 g, 92 mmol) and ethylthioxamate (14.6 g, 110 mmol) in EtOH (300 mL) was heated at 80°C for 6 h, then cooled to 0°C, diluted with water and EA and then neutralized to pH=7 using NH₄OH. The aq. layer was extracted with EA (3x). The combined organic layers were dried over Na₂SO₄, filtered, concentrated and purified by CC (PE/EA = 20/1) to give compound **6b** (14.5 g, 63% over two steps) as a yellow oil.

Step 3: Ethyl 5-bromo-4-(cyclohexylmethyl)thiazole-2-carboxylate (**6c**)

To a solution of compound **6b** (14.5 g, 57.3 mmol) in CH₂Cl₂ (300 mL) was added TFA (3.26 g, 28.6 mmol) and DBH (8.17 g, 28.6 mmol) and the solution was stirred for 15 h at rt. A saturated solution of sodium hydrosulfite was then added. The organic phase was neutralized (pH = 7) with 2M Na₂CO₃ solution and then washed with water, dried over MgSO₄, filtered, concentrated and purified by CC (PE/EA = 10/1 to 5/1) to give compound **6c** (12.1 g, 64%) as a white solid.

30 Step 4: Ethyl 5-(3-(*tert*-butyl)-5-(1-methylcyclopropyl)phenyl)-4-(cyclohexylmethyl)thiazole-2-carboxylate (**6d**)

A solution of compound **6c** (2.0 g, 6.0 mmol), 2-(3-(*tert*-butyl)-5-(1-methylcyclopropyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.3 g, 7.2 mmol), Na₂CO₃ (2.5 g, 24 mmol) and

Pd(dppf)Cl₂ (438 mg, 0.6 mmol) in toluene (30 mL), EtOH (15 mL) and water (15 mL) was heated at 70°C for 15 h before cooled to rt. The resulting solution was partitioned between EA and water and the layers were separated. The organic phase was washed with water and brine, dried over Na₂SO₄, filtered, concentrated and purified by CC (PE/EA = 10/1 to 5/1) to give compound **6d** (1.5 g, 57%) as a white solid.

Step 5: 5-(3-(*tert*-Butyl)-5-(1-methylcyclopropyl)phenyl)-4-(cyclohexylmethyl)thiazole-2-carboxylic acid (**6e**)

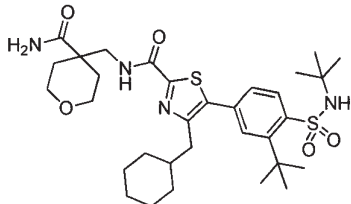
To a solution of compound **6d** (1.5 g, 3.4 mmol) in a solution of MeOH (50 mL) and H₂O (10 mL) was added KOH (765 mg, 13.6 mmol) and then the solution was stirred for 4 h at 90°C, then concentrated and diluted with H₂O. 1N HCl solution was added to adjust pH to 5, which was then extracted with DCM. The organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated to give compound **6e** (1.2 g, 86%) as a white solid.

Step 6: Methyl 4-(5-(3-(*tert*-butyl)-5-(1-methylcyclopropyl)phenyl)-4-(cyclohexylmethyl)thiazole-2-carboxamido)-2,2-dimethylbutanoate (**6**)

To a solution of compound **6e** (300 mg, 0.73 mmol) in DMF (3 mL) was added HATU (416 mg, 1.09 mmol), DIEA (283 mg, 2.2 mmol) and methyl 4-amino-2,2-dimethylbutanoate hydrochloride (125 mg, 0.87 mmol) and the solution was stirred for 20 min, then H₂O and EA was added. The organic layer was washed with brine, dried over Na₂SO₄, filtered, concentrated and purified by CC (PE/EA = 5/1) to give compound **8** (300 mg, 76%) as white powder. ¹H-NMR (300 MHz, CDCl₃) δ: 7.29 (s, 1H), 7.22 (s, 1H), 7.10 (s, 1H), 3.68 (s, 3H), 3.48 (dd, J = 4.5 Hz, J = 11.4 Hz, 2H), 2.60-2.63 (m, 2H), 1.92-1.96 (m, 2H), 1.80-1.84 (m, 1H), 1.62-1.70 (m, 7H), 1.43 (s, 3H), 1.34 (s, 9H), 1.27 (s, 6H), 1.14-1.25 (m, 3H), 0.87-0.96 (m, 3H), 0.75-0.78 (m, 2H). MS 539.4 (M+1)⁺.

Example 6/1 to 6/64

The following Examples were prepared similar as in Example 6. Due to some extent of decarboxylation upon storage it is preferred not to neutralize the reaction mixture in Step 6e above but to use the potassium salt for the amide coupling.

#	Structure	Analytical data
6/1		¹ H-NMR (400 MHz, CDCl ₃) δ: 8.22 (d, J = 7.6 Hz, 1H), 7.64-7.67 (m, 2H), 7.32-7.35 (m, 1H), 5.93 (br s, 1H), 5.65 (br s, 1H), 4.66 (s, 1H), 3.86 (br s, 2H), 3.72-3.76 (m, 4H), 2.65 (d, J = 5.2 Hz, 2H), 1.89-2.00 (m, 2H), 1.69-1.78 (m, 3H), 1.62 (s, 15H), 1.34 (s, 9H), 1.07-1.28 (m, 3H), 0.85-0.91 (m, 2H). MS 633.3 (M+1) ⁺

#	Structure	Analytical data
6/2		$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 7.58-7.61 (m, 1H), 7.30 (s, 1H), 7.22 (s, 1H), 7.09 (s, 1H), 5.91 (br s, 1H), 5.53 (br s, 1H), 3.86-3.92 (m, 2H), 3.68-3.74 (m, 4H), 2.63 (d, J = 6.8 Hz, 2H), 1.99-2.03 (m, 2H), 1.58-1.83 (m, 9H), 1.43 (s, 3H), 1.34 (s, 9H), 1.10-1.27 (m, 3H), 0.87-0.93 (m, 3H), 0.75-0.77 (m, 2H). MS 552.3 ($\text{M}+1$) $^+$
6/3		$^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ : 0.52-0.70 (m, 2H), 0.90-1.40 (m, 12H), 1.45-1.71 (m, 8H), 1.74-1.83 (m, 2H), 2.00-2.08 (m, 2H), 2.29-2.34 (m, 2H), 3.69-3.81 (m, 4H), 3.87-3.94 (m, 2H), 4.72 (s, 1H), 4.69 (s, 1H), 5.54 (br s, 1H), 5.93 (br s, 1H), 7.49-7.60 (m, 2H), 7.68-7.73 (s, 3H), 8.34 (d, J = 7.5 Hz, 1H), 8.68 (d, J = 8.7 Hz, 1H). MS 627.3 ($\text{M}+1$) $^+$
6/4		$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 0.60-0.69 (m, 2H), 0.88-1.02 (m, 1H), 1.06-1.15 (m, 2H), 1.22 (s, 9H), 1.36 (s, 6H), 1.43-1.72 (m, 6H), 2.20 (br s, 1H), 2.35 (br s, 1H), 3.53 (d, J = 6.8 Hz, 2H), 4.70 (s, 1H), 7.52 (d, J = 7.6 Hz, 1H), 7.56-7.60 (m, 1H), 7.69-7.75 (m, 3H), 8.35 (d, J = 7.6 Hz, 1H), 8.69 (d, J = 8.8 Hz, 1H). MS 558.2 ($\text{M}+1$) $^+$
6/5		$^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ : 0.63-0.71 (m, 2H), 0.88-1.12 (m, 3H), 1.22 (s, 9H), 1.47-1.70 (m, 6H), 2.18-2.21 (m, 4H), 2.35-2.36 (m, 2H), 2.89-2.95 (m, 2H), 3.44-3.55 (m, 2H), 3.59 (d, J = 6.0 Hz, 2H), 4.69 (s, 1H), 7.50 (d, J = 7.5 Hz, 1H), 7.55-7.60 (m, 1H), 7.68-7.77 (m, 3H), 8.36 (d, J = 7.5 Hz, 1H), 8.70 (d, J = 8.4 Hz, 1H). MS 648.2 ($\text{M}+1$) $^+$
6/6		$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 0.60-0.69 (m, 2H), 0.96-1.20 (m, 3H), 1.22 (s, 9H), 1.36 (s, 6H), 1.48-1.70 (m, 6H), 2.32-2.42 (m, 4H), 2.46-2.51 (m, 2H), 3.15-3.20 (m, 4H), 4.26-4.30 (m, 1H), 4.63 (s, 1H), 7.27-7.31 (m, 1H), 7.51 (d, J = 7.6 Hz, 1H), 7.55-7.59 (m, 1H), 7.71 (d, J = 8.0 Hz, 1H), 8.35 (d, J = 7.6 Hz, 1H), 8.69 (d, J = 8.4 Hz, 1H). MS 615.8 ($\text{M}-1$) $^-$
6/7		$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 0.70-0.72 (m, 2H), 0.98-1.26 (m, 3H), 1.22 (s, 9H), 1.50-1.56 (m, 6H), 1.89 (t, J = 5.4 Hz, 2H), 2.33-2.37 (m, 2H), 3.68-3.73 (m, 4H), 4.01 (s, 2H), 4.49 (s, 2H), 4.62 (s, 1H), 7.50 (d, J = 7.8 Hz, 1H), 7.55-7.59 (m, 1H), 7.71-7.74 (m, 2H), 8.35 (d, J = 7.8 Hz, 1H), 8.68 (d, J = 8.1 Hz, 1H). MS 596.3 ($\text{M}+1$) $^+$
6/8		$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 0.61-0.65 (m, 2H), 1.03-1.12 (m, 3H), 1.21 (s, 9H), 1.45-1.66 (m, 6H), 1.89-1.91 (m, 6H), 1.97-2.17 (m, 6H), 2.31 (br s, 2H), 4.65 (s, 1H), 7.07 (s, 1H), 7.49 (d, J = 7.8 Hz, 1H), 7.55-7.58 (m, 1H), 7.70-7.73 (m, 2H), 8.34 (d, J = 7.8 Hz, 1H), 8.67 (d, J = 8.4 Hz, 1H). MS 638.3 ($\text{M}+1$) $^+$

#	Structure	Analytical data
6/9		$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 7.58 (d, 1H, $J = 7.6$ Hz), 7.14 (s, 1H), 4.86-4.79 (m, 1H), 3.37 (d, 2H, $J = 7.6$ Hz), 3.22-3.17 (m, 1H), 2.85-2.79 (m, 2H), 2.55-2.47 (m, 2H), 1.92-1.68 (m, 6H), 1.37 (s, 18H), 1.30-1.06 (m, 5H). MS 513.3 ($\text{M}+1$) $^+$
6/10		$^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ : 0.64-0.72 (m, 2H), 0.95-1.20 (m, 3H), 1.22 (s, 9H), 1.26 (s, 3H), 1.37 (s, 3H), 1.51-1.53 (m, 3H), 1.57-1.75 (m, 4H), 2.34 (br s, 2H), 2.62-2.71 (m, 1H), 3.58-3.65 (m, 2H), 4.10-4.16 (m, 1H), 4.44-4.50 (m, 1H), 4.62 (s, 1H), 7.40-7.45 (m, 2H), 7.51 (d, $J = 7.5$ Hz, 1H), 7.56-7.61 (m, 1H), 7.70-7.71 (m, 2H), 8.35 (d, $J = 7.8$ Hz, 1H), 8.69 (d, $J = 11.4$ Hz, 1H). MS 612.3 ($\text{M}+1$) $^+$
6/11		$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 0.60-0.69 (m, 2H), 0.96-1.02 (m, 1H), 1.06-1.15 (m, 2H), 1.22 (s, 9H), 1.49-1.59 (m, 5H), 1.63-1.77 (m, 3H), 2.06 (dd, $J = 12.8$ Hz, 2H), 2.35 (br s, 2H), 3.57 (td, $J = 11.2$ Hz, 1.6 Hz, 2H), 4.03-4.06 (m, 2H), 4.18-4.26 (m, 1H), 4.68-4.69 (m, 1H), 7.21 (d, $J = 8.0$ Hz, 1H), 7.51 (d, $J = 7.6$ Hz, 1H), 7.55-7.59 (m, 1H), 7.69-7.74 (m, 2H), 8.35 (d, $J = 7.6$ Hz, 1H), 8.69 (d, $J = 8.4$ Hz, 1H). MS 570.2 ($\text{M}+1$) $^+$
6/12		$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 0.48-1.04 (m, 2H), 0.95-1.12 (m, 3H), 1.24-1.33 (m, 4H), 1.47-1.55 (m, 2H), 1.64-1.78 (m, 4H), 2.02-2.10 (br s, 2H), 3.49-3.60 (m, 2H), 3.99-4.07 (m, 3H), 4.19-4.24 (m, 1H), 7.20-7.23 (m, 1H), 7.51-7.61 (m, 2H), 7.71-7.76 (m, 2H), 8.33 (d, $J = 7.5$ Hz, 1H), 8.65 (d, $J = 8.4$ Hz, 1H). MS 610.2 ($\text{M}+1$) $^+$
6/13		$^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ : 0.70-0.74 (m, 2H), 0.98-1.18 (m, 2H), 1.22 (s, 9H), 1.55-1.65 (m, 6H), 2.35 (d, $J = 5.4$ Hz, 2H), 2.55-2.58 (m, 4H), 2.67 (t, $J = 6.0$ Hz, 2H), 3.61 (q, $J = 6.0$ Hz, 2H), 3.77 (t, $J = 4.8$ Hz, 4H), 4.66 (s, 1H), 7.51 (d, $J = 7.5$ Hz, 1H), 7.56-7.59 (m, 1H), 7.68-7.75 (m, 3H), 8.35 (d, $J = 7.2$ Hz, 1H), 8.69 (d, $J = 8.7$ Hz, 1H). MS 599.3 ($\text{M}+1$) $^+$
6/14		$^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ : 0.63-0.66 (m, 2H), 0.88-1.18 (m, 2H), 1.22 (s, 9H), 1.48-1.53 (m, 7H), 2.34-2.35 (m, 2H), 3.44-3.50 (m, 2H), 3.56-3.62 (m, 2H), 4.64 (s, 1H), 5.45-5.47 (m, 1H), 7.50 (d, $J = 7.5$ Hz, 1H), 7.56-7.59 (m, 1H), 7.69-7.73 (m, 3H), 8.35 (d, $J = 7.5$ Hz, 1H), 8.68 (d, $J = 8.7$ Hz, 1H). MS 558.2 ($\text{M}+1$) $^+$
6/15		$^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ : 0.63-0.67 (m, 2H), 0.96-1.13 (m, 2H), 1.22 (s, 9H), 1.49-1.59 (m, 6H), 1.68-1.77 (m, 4H), 2.10-2.13 (m, 1H), 2.36 (br s, 2H), 2.71-3.02 (m, 6H), 3.46-3.51 (m, 1H), 4.16-4.19 (m, 1H), 4.67 (s, 1H), 7.44 (d, $J = 7.5$ Hz, 1H), 7.51 (d, $J = 7.5$ Hz, 1H), 7.54-7.59 (m, 1H), 7.68-7.75 (m, 2H), 8.35 (d, $J = 7.5$ Hz, 1H), 8.69 (d, $J = 8.7$ Hz, 1H). MS 595.3 ($\text{M}+1$) $^+$

#	Structure	Analytical data
6/16		$^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ : 0.59-0.65 (m, 2H), 0.98-1.16 (m, 3H), 1.21 (s, 9H), 1.45-1.69 (m, 3H), 2.32-2.44 (m, 3H), 2.74-2.81 (m, 1H), 3.45-3.48 (m, 3H), 3.78-3.97 (m, 6H), 4.52 (br s, 2H), 4.79 (s, 1H), 7.50 (d, $J = 7.2$ Hz, 1H), 7.56-7.59 (m, 1H), 7.68-7.73 (m, 2H), 8.21-8.23 (m, 1H), 8.34 (d, $J = 7.8$ Hz, 1H), 8.68 (d, $J = 8.1$ Hz, 1H). MS 569.3 ($\text{M}+1$) $^+$
6/17		$^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ : 0.62-0.66 (m, 2H), 0.95-1.12 (m, 3H), 1.22 (s, 9H), 1.47-1.56 (m, 4H), 2.33 (br s, 2H), 2.58 (s, 6H), 4.74 (s, 1H), 7.51 (d, $J = 7.5$ Hz, 1H), 7.57-7.59 (m, 1H), 7.71 (t, $J = 7.8$ Hz, 1H), 8.35 (d, $J = 7.5$ Hz, 1H), 8.69 (d, $J = 8.4$ Hz, 1H). MS 596.2 ($\text{M}+1$) $^+$
6/18		$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 7.98 (d, 1H, $J = 8.0$ Hz), 7.71-7.55 (m, 3H), 4.60 (s, 1H), 3.51 (d, 2H, $J = 6.4$ Hz), 2.53 (d, 2H, $J = 7.2$ Hz), 1.77-1.56 (m, 6H), 1.34 (s, 6H), 1.29 (s, 9H), 1.26-1.06 (m, 3H), 0.83-0.78 (m, 2H). MS 576.3 ($\text{M}+1$) $^+$
6/19		$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 8.31 (d, 1H, $J = 8.0$ Hz), 7.68 (t, 1H, $J = 6.0$ Hz), 7.36 (d, 1H, $J = 8.0$ Hz), 6.88 (t, 1H, $J = 5.3$ Hz), 5.05 (s, 1H), 3.51 (br s, 2H), 2.48-2.24 (m, 2H), 1.76-1.44 (m, 6H), 1.35 (s, 6H), 1.28-1.20 (m, 13H), 0.82-0.74 (m, 2H). MS 592.2 ($\text{M}+1$) $^+$
6/20		$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 0.74-0.82 (m, 2H), 1.12-1.20 (m, 3H), 1.28 (s, 9H), 1.51-1.74 (m, 5H), 2.41 (d, $J = 7.2$ Hz, 2H), 3.02-3.05 (m, 4H), 3.87-3.90 (m, 4H), 5.06 (s, 1H), 7.37 (d, $J = 8.1$ Hz, 1H), 8.03 (s, 1H), 8.12 (d, $J = 8.1$ Hz, 1H). MS 589.2 [$\text{M}+1$] $^+$
6/21		$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 0.74-0.78 (m, 2H), 1.11-1.19 (m, 3H), 1.28 (s, 9H), 1.52-1.70 (m, 6H), 2.40 (d, $J = 6.9$ Hz, 2H), 3.27-3.30 (m, 4H), 3.61-3.65 (m, 4H), 5.09 (s, 1H), 7.36 (d, $J = 8.4$ Hz, 1H), 8.13 (d, $J = 8.4$ Hz, 1H), 8.42 (s, 1H). MS 637.1 [$\text{M}+1$] $^+$
6/22		$^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ : 0.80-0.89 (m, 2H), 1.05-1.19 (m, 3H), 1.26 (s, 9H), 1.61-1.66 (m, 6H), 1.69 (s, 7H), 1.73-1.78 (m, 1H), 2.02 (dd, $J = 12.3$ Hz, 3.2 Hz, 2H), 2.63 (d, $J = 7.2$ Hz, 2H), 3.54 (td, $J = 11.6$ Hz, 1.8 Hz, 2H), 4.00-4.04 (m, 2H), 4.14-4.20 (m, 1H), 7.15 (d, $J = 8.4$ Hz, 1H), 7.35-7.39 (m, 2H), 8.21-8.24 (m, 1H). MS 578.3 ($\text{M}+1$) $^+$
6/23		$^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ : 0.83-0.89 (m, 2H), 1.12-1.27 (m, 3H), 1.28 (s, 11H), 1.33 (s, 6H), 1.61-1.67 (m, 5H), 1.70 (s, 6H), 2.64 (d, $J = 7.2$ Hz, 2H), 3.50 (d, $J = 6.6$ Hz, 2H), 7.37-7.40 (m, 2H), 7.64-7.66 (m, 1H), 8.24 (d, $J = 9.0$ Hz, 1H). MS 566.3 ($\text{M}+1$) $^+$

#	Structure	Analytical data
6/24		$^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ : 0.83-0.89 (m, 2H), 1.12-1.27 (m, 3H), 1.27 (s, 11H), 1.54-1.67 (m, 4H), 1.70 (s, 6H), 1.73-1.83 (m, 1H), 2.64 (d, $J = 7.2$ Hz, 2H), 3.42-3.58 (m, 4H), 4.38-4.39 (m, 1H), 5.39-5.47 (m, 1H), 6.23-6.24 (m, 1H), 7.27-7.39 (m, 2H), 7.60-7.64 (m, 1H), 8.22-8.25 (m, 1H). MS 566.2 ($\text{M}+1$) $^+$
6/25		$^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ : 0.83-0.89 (m, 2H), 1.12-1.27 (m, 3H), 1.28 (s, 11H), 1.58-1.66 (m, 3H), 1.70 (s, 7H), 1.73-1.79 (m, 1H), 2.52-2.55 (m, 4H), 2.62-2.66 (m, 4H), 3.55-3.60 (m, 2H), 3.73-3.76 (m, 4H), 4.40 (s, 1H), 6.24 (s, 1H), 7.37-7.40 (m, 2H), 7.68-7.70 (m, 1H), 8.24 (d, $J = 8.7$ Hz, 1H). MS 607.3 ($\text{M}+1$) $^+$
6/26		$^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ : 0.83-0.89 (m, 2H), 1.12-1.27 (m, 3H), 1.28 (s, 10H), 1.59-1.68 (m, 5H), 1.70 (s, 6H), 1.73-1.81 (m, 1H), 2.31-2.48 (m, 5H), 2.63-2.65 (m, 2H), 3.14-3.18 (m, 4H), 4.24-4.26 (m, 1H), 7.22 (d, $J = 8.4$ Hz, 1H), 7.36-7.39 (m, 2H), 8.23-8.26 (m, 1H). MS 626.3 ($\text{M}+1$) $^+$
6/27		$^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ : 0.82-0.90 (m, 2H), 1.06-1.23 (m, 3H), 1.27 (s, 12H), 1.60-1.64 (m, 3H), 1.70-1.80 (m, 11H), 2.63 (d, $J = 6.9$ Hz, 2H), 3.53 (d, $J = 6.3$ Hz, 2H), 3.78-3.81 (m, 5H), 7.36-7.38 (m, 2H), 7.61-7.65 (m, 1H), 8.22-8.25 (m, 1H). MS 608.3 ($\text{M}+1$) $^+$
6/28		$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 0.63-0.74 (m, 2H), 0.97-1.26 (m, 3H), 1.38 (s, 9H), 1.51-1.59 (m, 5H), 1.70-1.87 (m, 1H), 2.40 (d, $J = 7.2$ Hz, 2H), 2.50-2.60 (m, 2H), 2.82-2.90 (m, 2H), 3.20-3.26 (m, 1H), 4.81-4.89 (m, 1H), 5.30 (s, 1H), 7.54 (d, $J = 7.8$ Hz, 1H), 7.70-7.82 (m, 3H), 8.46 (s, 1H), 9.08-9.11 (m, 1H). MS 585.2 [$\text{M}+1$] $^+$
6/29		$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 0.73-0.77 (m, 2H), 1.11-1.19 (m, 3H), 1.28 (s, 9H), 1.33 (s, 6H), 1.53-1.61 (m, 2H), 1.71-1.76 (m, 3H), 2.40 (d, $J = 6.9$ Hz, 2H), 3.50 (d, $J = 6.3$ Hz, 2H), 5.09 (s, 1H), 5.07 (s, 1H), 7.38 (d, $J = 8.1$ Hz, 1H), 7.63-7.66 (m, 1H), 8.13 (d, $J = 8.1$ Hz, 1H). MS 576.2 [$\text{M}+1$] $^+$
6/30		$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 0.74-0.82 (m, 2H), 1.04-1.23 (m, 5H), 1.25 (s, 9H), 1.53-1.73 (m, 4H), 2.40 (d, $J = 6.9$ Hz, 2H), 3.42-3.47 (m, 2H), 3.56 (t, $J = 9.6$ Hz, 2H), 5.07 (s, 1H), 5.42 (q, $J = 8.7$ Hz, 1H), 7.37 (d, $J = 8.1$ Hz, 1H), 7.66 (d, $J = 8.4$ Hz, 1H), 8.12 (d, $J = 8.1$ Hz, 1H). MS 576.1 ($\text{M}+1$) $^+$
6/31		$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 0.68-0.80 (m, 4H), 0.87-0.94 (m, 2H), 1.03-1.18 (m, 3H), 1.27 (s, 9H), 1.51-1.74 (m, 5H), 2.38 (d, $J = 7.2$ Hz, 2H), 2.87-2.94 (m, 1H), 5.07 (s, 1H), 7.30 (d, $J = 3.0$ Hz, 1H), 7.37 (d, $J = 8.4$ Hz, 1H), 8.12 (d, $J = 8.4$ Hz, 1H). MS 544.2 ($\text{M}+1$) $^+$

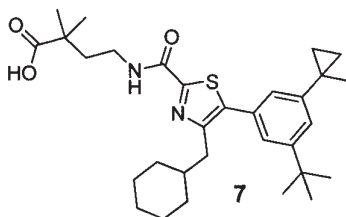
#	Structure	Analytical data
6/32		$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 0.77-0.81 (m, 2H), 1.13-1.23 (m, 3H), 1.28 (s, 9H), 1.57-1.63 (m, 7H), 2.40 (d, $J = 6.9$ Hz, 2H), 3.44-3.49 (m, 4H), 4.26 (s, 2H), 4.77 (s, 2H), 5.06 (s, 1H), 5.42 (q, $J = 8.7$ Hz, 1H), 7.36 (d, $J = 8.1$ Hz, 1H), 8.11 (d, $J = 8.1$ Hz, 1H). MS 602.1 ($\text{M}+1$) $^+$
6/33		$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 0.77-0.81 (m, 2H), 1.20-1.26 (m, 3H), 1.28 (s, 9H), 1.54-1.63 (m, 7H), 2.40 (d, $J = 7.2$ Hz, 2H), 4.39 (s, 2H), 4.87-4.89 (m, 6H), 5.06 (s, 1H), 7.36 (d, $J = 8.1$ Hz, 1H), 8.11 (d, $J = 8.1$ Hz, 1H). MS 586.1 ($\text{M}+1$) $^+$
6/34		$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 0.75-0.83 (m, 2H), 1.06-1.21 (m, 3H), 1.28 (s, 9H), 1.54-1.78 (m, 5H), 2.42 (d, $J = 7.2$ Hz, 2H), 4.72 (t, $J = 6.6$ Hz, 2H), 5.00-5.07 (m, 3H), 5.22-5.30 (m, 1H), 7.38 (d, $J = 8.4$ Hz, 1H), 7.75 (d, $J = 7.8$ Hz, 1H), 8.13 (d, $J = 8.1$ Hz, 1H). MS 560.1 ($\text{M}+1$) $^+$
6/35		$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : -0.02-0.04 (m, 2H), 0.40-0.46 (m, 2H), 0.93-1.02 (m, 1H), 1.28 (s, 9H), 2.27-2.48 (m, 6H), 3.15-3.18 (m, 4H), 4.21-4.27 (m, 1H), 5.07 (s, 1H), 7.26-7.27 (m, 1H), 7.40 (d, $J = 8.1$ Hz, 1H), 8.13 (d, $J = 8.1$ Hz, 1H). MS 594.1 [$\text{M}+1$] $^+$
6/36		$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 0.72-0.80 (m, 2H), 1.06-1.16 (m, 3H), 1.28 (s, 9H), 1.51-1.75 (m, 9H), 2.15-2.21 (m, 2H), 2.41 (d, $J = 7.2$ Hz, 2H), 3.60-3.67 (m, 2H), 3.76 (d, $J = 6.9$ Hz, 2H), 3.88-3.95 (m, 2H), 5.10 (s, 1H), 7.37 (d, $J = 8.1$ Hz, 1H), 7.78 (t, $J = 6.9$ Hz, 1H), 8.13 (d, $J = 8.1$ Hz, 1H). MS 646.2 [$\text{M}+1$] $^+$
6/37		$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 0.72-0.88 (m, 2H), 1.06-1.16 (m, 3H), 1.28 (s, 9H), 1.51-1.75 (m, 6H), 2.36-2.47 (m, 2H), 3.06-3.11 (m, 1H), 4.05-4.11 (m, 1H), 4.23-4.30 (m, 1H), 4.53-4.59 (m, 1H), 4.74-4.80 (m, 1H), 5.09 (s, 1H), 7.37 (t, $J = 8.1$ Hz, 1H), 8.11 (d, $J = 8.1$ Hz, 1H). MS 630.2 [$\text{M}+1$] $^+$
6/38		$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 0.73-0.1 (m, 2H), 1.09-1.20 (m, 3H), 1.28 (s, 9H), 1.52-1.72 (m, 4H), 2.40 (d, $J = 7.5$ Hz, 2H), 2.56 (s, 6H), 5.10 (s, 1H), 7.38 (d, $J = 8.1$ Hz, 1H), 7.67 (s, 1H), 8.13 (d, $J = 8.4$ Hz, 1H). MS 614.2 [$\text{M}+1$] $^+$
6/39		$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 0.73-0.81 (m, 2H), 1.06-1.24 (m, 3H), 1.27 (s, 9H), 1.31 (s, 6H), 1.52-1.74 (m, 6H), 1.94-1.99 (m, 2H), 2.40 (d, $J = 7.2$ Hz, 2H), 3.49-3.57 (m, 2H), 5.12 (s, 1H), 7.38 (d, $J = 8.1$ Hz, 1H), 7.46 (t, $J = 8.4$ Hz, 1H), 8.12 (d, $J = 8.1$ Hz, 1H). MS 618.2 [$\text{M}+1$] $^+$

#	Structure	Analytical data
6/40		$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 0.73-0.77 (m, 2H), 1.10-1.18 (m, 3H), 1.28 (s, 9H), 1.52-1.61 (m, 6H), 2.40 (d, $J = 6.9$ Hz, 2H), 2.47 (s, 3H), 4.91 (d, $J = 6.0$ Hz, 2H), 5.12 (s, 1H), 7.37 (d, $J = 8.1$ Hz, 1H), 7.62 (s, 1H), 7.96 (t, 1H), 8.12 (d, $J = 8.4$ Hz, 1H). MS 647.1 $[\text{M}+1]^+$
6/41		$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 0.74-0.82 (m, 2H), 1.05-1.25 (m, 3H), 1.28 (s, 9H), 1.55-1.80 (m, 5H), 2.41 (d, $J = 7.5$ Hz, 2H), 2.59-2.70 (m, 2H), 2.81-2.91 (m, 5H), 3.54-3.64 (m, 1H), 4.67-4.76 (m, 1H), 5.07 (s, 1H), 7.38 (d, $J = 7.8$ Hz, 1H), 7.58 (d, $J = 8.7$ Hz, 1H), 8.12 (d, $J = 8.4$ Hz, 1H). MS 636.5 $(\text{M}+1)^+$
6/42		$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 0.75-0.82 (m, 2H), 1.09-1.19 (m, 3H), 1.28 (s, 9H), 1.53-1.72 (m, 5H), 2.40 (d, $J = 7.2$ Hz, 2H), 2.76-2.84 (m, 2H), 2.89 (s, 3H), 2.96-3.06 (m, 2H), 3.81-3.87 (m, 1H), 4.69-4.74 (m, 1H), 5.07 (s, 1H), 7.38 (d, $J = 8.1$ Hz, 1H), 7.48 (d, $J = 6.9$ Hz, 1H), 8.13 (d, $J = 8.1$ Hz, 1H). MS 636.5 $(\text{M}+1)^+$
6/43		$^1\text{H-NMR}$ (300 MHz, DMSO-d_6) δ : 0.66-0.74 (m, 2H), 1.00-1.10 (m, 3H), 1.13 (s, 9H), 1.21 (s, 2H), 1.46-1.49 (m, 5H), 1.62-1.66 (m, 1H), 2.02-2.07 (m, 2H), 2.16-2.28 (m, 2H), 2.42 (d, $J = 6.9$ Hz, 2H), 3.05-3.09 (m, 2H), 4.17-4.21 (m, 1H), 7.66 (d, $J = 8.4$ Hz, 1H), 8.02 (s, 1H), 8.08 (d, $J = 8.4$ Hz, 1H), 9.00 (d, $J = 8.1$ Hz, 1H). MS 636.1 $(\text{M}+1)^+$
6/44		$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 0.77-0.82 (m, 2H), 1.07-1.18 (m, 3H), 1.28 (s, 9H), 1.50-1.59 (m, 1H), 1.73-1.76 (m, 4H), 1.87 (br s, 1H), 1.97 (d, $J = 9.3$ Hz, 2H), 2.42 (d, $J = 6.6$ Hz, 2H), 3.30-3.33 (m, 1H), 3.87-3.92 (m, 1H), 4.04-4.09 (m, 1H), 4.35-4.40 (m, 1H), 4.74-4.78 (m, 3H), 5.08 (s, 1H), 7.39 (d, $J = 10.5$ Hz, 1H), 8.12 (d, $J = 7.8$ Hz, 1H). MS 586.2 $(\text{M}+1)^+$
6/45		$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 0.77-0.85 (m, 2H), 1.10-1.20 (m, 3H), 1.28 (s, 9H), 1.54-1.65 (m, 5H), 2.40-2.46 (m, 6H), 3.05-3.08 (m, 4H), 4.03 (s, 2H), 4.51 (s, 2H), 5.08 (s, 1H), 7.37 (d, $J = 8.1$ Hz, 1H), 8.12 (d, $J = 8.1$ Hz, 1H). MS 662.4 $(\text{M}+1)^+$
6/46		$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 0.65-0.69 (m, 2H), 1.05-1.12 (m, 3H), 1.22 (s, 9H), 1.47-1.52 (m, 5H), 1.60-1.75 (m, 1H), 2.28-2.36 (m, 2H), 4.44 (s, 4H), 4.50 (s, 2H), 4.63 (s, 1H), 5.03 (s, 2H), 7.50-7.59 (m, 2H), 7.68-7.71 (m, 2H), 8.35 (d, $J = 7.2$ Hz, 1H), 8.68 (d, $J = 8.4$ Hz, 1H). MS 616.2 $[\text{M}+1]^+$
6/47		$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : -0.17 to -0.12 (m, 2H), 0.29-0.35 (m, 2H), 0.90-0.95 (m, 1H), 1.31 (d, $J = 7.2$ Hz, 3H), 2.35-2.51 (m, 6H), 3.17-3.20 (m, 4H), 3.97-4.05 (m, 1H), 4.27-4.32 (m, 1H), 5.03 (d, $J = 9.9$ Hz, 1H), 7.33 (d, $J = 8.1$ Hz, 1H), 7.55 (d, $J = 7.5$ Hz, 1H), 7.57-7.63 (m, 1H), 7.72-7.77 (m, 2H), 8.32 (d, $J = 7.8$ Hz, 1H), 8.65 (d, $J = 8.4$ Hz, 1H). MS 616.2 $[\text{M}+1]^+$

#	Structure	Analytical data
6/48		$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : -0.17 to -0.12 (m, 2H), 0.28-0.34 (m, 2H), 0.90-0.96 (m, 1H), 1.30 (d, J = 6.9 Hz, 3H), 1.35 (s, 6H), 2.18 (s, 1H), 2.38 (d, J = 6.9 Hz, 2H), 3.53 (d, J = 6.3 Hz, 2H), 3.97-4.05 (m, 1H), 5.12 (d, J = 9.6 Hz, 1H), 7.55 (d, J = 7.8 Hz, 1H), 7.60-7.62 (m, 1H), 7.70-7.79 (m, 3H), 8.32 (d, J = 7.5 Hz, 1H), 8.65 (d, J = 8.7 Hz, 1H). MS 556.2 $[\text{M}+1]^+$
6/49		$^1\text{H-NMR}$ (400 MHz, CD_3OD) δ : 0.57-0.65 (m, 2H), 1.04 (m, 12H), 1.36-1.45 (m, 8H), 1.58-1.60 (m, 1H), 1.85-1.97 (m, 1H), 2.26-2.43 (m, 2H), 3.37-4.67 (m, 4H), 7.53-7.56 (m, 2H), 7.63-7.67 (m, 2H), 8.23 (d, J = 7.2 Hz, 1H), 8.73 (d, J = 9.2 Hz, 1H). MS 598.3 $[\text{M}+1]^+$
6/50		$^1\text{H-NMR}$ (400 MHz, CD_3OD) δ : 0.65-0.81 (m, 2H), 0.96-1.12 (m, 3H), 1.14 (s, 9H), 1.28 (s, 6H), 1.52-1.56 (m, 5H), 1.65-1.72 (m, 1H), 1.82-1.98 (m, 1H), 2.04-2.16 (m, 1H), 2.39 (br s, 2H), 2.57-2.68 (m, 1H), 3.47-3.61 (m, 1H), 3.84-4.03 (m, 2H), 4.46-4.59 (m, 1H), 7.61-7.65 (m, 2H), 7.73-7.76 (m, 2H), 8.33 (d, J = 7.6 Hz, 1H), 8.83 (d, J = 8.4 Hz, 1H). MS 626.3 $[\text{M}+1]^+$
6/51		$^1\text{H-NMR}$ (400 MHz, CD_3OD) δ : 0.53-0.58 (m, 2H), 1.06-1.13 (m, 12H), 1.48-1.85 (m, 7H), 1.96-2.08 (m, 4H), 2.33-2.41 (m, 3H), 2.92-2.96 (m, 1H), 4.43-4.47 (m, 1H), 7.62-7.75 (m, 4H), 8.32 (d, J = 6.0 Hz, 1H), 8.83 (d, J = 8.4 Hz, 1H). MS 598.3 $(\text{M}+1)^+$
6/52		$^1\text{H-NMR}$ (400 MHz, CD_3OD) δ : 0.67-0.76 (m, 4H), 0.78-0.82 (m, 2H), 1.09-1.11 (m, 3H), 1.25 (s, 9H), 1.33 (s, 3H), 1.50-1.56 (m, 6H), 1.68-1.70 (m, 2H), 1.92-1.95 (m, 2H), 2.57 (d, J = 7.2 Hz, 2H), 2.94 (s, 2H), 3.48-3.80 (m, 3H), 3.94-3.98 (m, 2H), 4.52-4.62 (br s, 0.3 H), 5.26-5.28 (br s, 0.7 H), 7.04 (s, 1H), 7.16 (s, 1H), 7.28 (s, 1H). MS 509.4 $(\text{M}+1)$
6/53		$^1\text{H-NMR}$ (400 MHz, d_6 -DMSO) δ : 8.80(d, 1H, J = 8.4 Hz), 8.25 (d, 1H, J = 7.6 Hz), 7.93 (s, 1H), 7.79-7.60 (m, 4H), 4.35 (s, 2H), 3.70 (s, 2H), 2.44 (s, 4H), 2.33 (s, 2H), 2.23 (s, 3H), 1.57 (s, 1H), 1.45-1.43 (m, 5H), 1.10-0.91 (m, 12H), 0.67-0.62 (m, 2H). MS 569.2 $(\text{M}+1)^+$
6/54		$^1\text{H-NMR}$ (400 MHz, d_6 -DMSO) δ : 9.42 (s, 1H), 8.81 (d, 1H, J = 8.8 Hz), 8.27 (d, 1H, J = 7.6 Hz), 7.95 (s, 1H), 7.80-7.69 (m, 4H), 5.36 (s, 2H), 4.43-4.41 (m, 1H), 4.09-4.07 (m, 2H), 3.70-3.60 (m, 2H), 3.39-3.33 (m, 2H), 1.59-1.55 (m, 1H), 1.45-1.43 (m, 5H), 1.28 (s, 6H), 1.08-0.93 (m, 12H), 0.67-0.58 (m, 2H). MS 637.3 $(\text{M}+1)^+$
6/55		$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 0.65-0.74 (m, 2H), 0.98-1.14 (m, 3H), 1.22 (s, 9H), 1.48-1.65 (m, 5H), 1.81 (m, 1H), 2.36 (m, 2H), 3.22 (m, 2H), 3.31 (m, 2H), 4.33 (m, 2H), 4.81 (m, 1H), 5.00 (m, 2H), 7.50-7.60 (m, 2H), 7.70-7.83 (m, 2H), 8.36 (d, J = 7.6 Hz, 1H), 8.71 (d, J = 8.8 Hz, 1H). MS 604.3 $(\text{M}+1)^+$

#	Structure	Analytical data
6/56		$^1\text{H-NMR}$ (400 MHz, CD_3OD) δ : 0.52-0.60 (m, 2H), 0.85-1.03 (m, 12H), 1.37-1.39 (m, 5H), 1.50-1.55 (m, 1H), 1.71-1.83 (m, 2H), 2.16-2.20 (m, 4H), 2.87-2.94 (m, 4H), 3.34-3.42 (m, 2H), 4.68 (d, $J = 12.4$ Hz, 1H), 5.61 (d, $J = 11.6$ Hz, 1H), 7.44-7.52 (m, 2H), 7.60-7.66 (m, 2H), 8.20-8.22 (m, 1H), 8.71-8.78 (m, 1H). MS 632.3 ($\text{M}+1$) $^+$
6/57		$^1\text{H-NMR}$ (400 MHz, CD_3OD) δ : 0.70-0.75 (m, 2H), 1.00-1.16 (m, 12H), 1.52-1.54 (m, 5H), 1.67-1.71 (m, 1H), 2.40 (s, 2H), 3.08 (s, 3H), 4.41-4.60 (m, 3H), 5.03-5.15 (m, 2H), 7.58-7.65 (m, 2H), 7.72-7.88 (m, 2H), 8.35 (d, $J = 7.6$ Hz, 1H), 8.85 (d, $J = 8.8$ Hz, 1H). MS 604.3 ($\text{M}+1$) $^+$
6/58		$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 8.69 (d, $J = 8.4$ Hz, 1H), 8.36 (d, $J = 7.6$ Hz, 1H), 7.75-7.69 (m, 3H), 7.61-7.57 (m, 1H), 7.52 (d, $J = 7.2$ Hz, 1H), 4.66 (s, 1H), 3.67 (m, 2H), 2.39 (m, 2H), 1.95 (m, 2H), 1.72-1.69 (m, 1H), 1.56-1.48 (m, 11H), 1.24-0.96 (m, 12H), 0.69-0.60 (m, 2H). MS 567.2 ($\text{M}+1$) $^+$
6/59		$^1\text{H-NMR}$ (400 MHz, DMSO-d_6) δ : 8.86 (m, 1H), 8.80 (d, $J = 8.8$ Hz, 1H), 8.25 (d, $J = 6.8$ Hz, 1H), 7.94 (m, 1H), 7.78-7.67 (m, 4H), 3.59 (m, 2H), 2.41-2.33 (m, 2H), 1.60-1.31 (m, 12H), 1.07-0.95 (m, 12H), 0.58-0.55 (m, 2H). MS 610.2 ($\text{M}+1$) $^+$
6/60		$^1\text{H-NMR}$ (400 MHz, DMSO-d_6) δ : 8.94 (m, 1H), 8.80 (d, $J = 8.8$ Hz, 1H), 8.25 (d, $J = 7.6$ Hz, 1H), 7.94 (s, 1H), 3.49 (m, 2H), 2.36-2.31 (m, 2H), 1.60 (m, 1H), 1.50-1.40 (m, 5H), 1.25 (s, 6H), 1.07-0.88 (m, 12H), 0.60-0.51 (m, 2H). MS 626.2 ($\text{M}+1$) $^+$
6/61		$^1\text{H-NMR}$ (400 MHz, DMSO-d_6) δ : 12.25 (br s, 1H), 8.93 (d, $J = 8.4$ Hz, 1H), 7.77 (m, 2H), 7.49 (m, 1H), 4.88 (m, 1H), 3.47 (m, 2H), 2.64 (m, 2H), 1.80 (m, 1H), 1.61-1.58 (m, 5H), 1.44 (s, 3H), 1.38 (d, $J = 6.8$ Hz, 3H), 1.23 (s, 6H), 1.16-1.09 (m, 3H), 0.97-0.84 (m, 6H). MS 634.2 ($\text{M}+1$) $^+$
6/62		$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 7.88 (m, 1H), 7.70 (m, 1H), 7.55 (m, 1H), 7.42 (m, 1H), 6.16 (d, $J = 8.8$ Hz, 1H), 4.96 (m, 1H), 3.86 (d, $J = 7.2$ Hz, 2H), 2.58 (d, $J = 6.8$ Hz, 2H), 1.78-1.59 (m, 12H), 1.46-1.45 (m, 6H), 1.20-1.11 (m, 3H), 0.94-0.83 (m, 6H). MS 618.2 ($\text{M}+1$) $^+$
6/63		$^1\text{H NMR}$ (DMSO-d_6 , 300 MHz) δ : 0.70-0.77 (m, 2H), 1.04-1.08 (m, 3H), 1.17 (s, 9H), 1.46-1.56 (m, 5H), 1.66-1.72 (m, 1H), 2.04-2.11 (m, 2H), 2.21 (s, 3H), 2.22-2.27 (m, 2H), 2.37 (d, $J = 6.9$ Hz, 2H), 3.06-3.10 (m, 2H), 3.39-3.40 (m, 2H), 4.19-4.22 (m, 1H), 7.61 (s, 1H), 8.02 (s, 1H), 8.99 (d, $J = 11.6$ Hz, 1H). MS 650.2 ($\text{M}+1$) $^+$

#	Structure	Analytical data
6/64		$^1\text{H-NMR}$ (400 MHz, DMSO-d_6) δ : 8.80 (d, J = 8.8 Hz, 1H), 8.31 (m, 1H), 8.26 (d, J = 8.4 Hz, 1H), 7.94 (s, 1H), 7.79-7.65 (m, 4H), 7.35 (s, 1H), 7.09 (s, 1H), 3.41 (d, J = 6.4 Hz, 2H), 2.42-2.33 (m, 2H), 1.60-1.42 (m, 6H), 1.16 (s, 6H), 1.07-0.88 (m, 12H), 0.62-0.54 (m, 2H). MS 585.2 ($\text{M}+1$) $^+$.

Example 7

4-(5-(3-(*tert*-Butyl)-5-(1-methylcyclopropyl)phenyl)-4-(cyclohexylmethyl)thiazole-2-carboxamido)-2,2-dimethylbutanoic acid (7)

To a solution of compound **6** (300 mg, 0.55 mmol) in a solution of MeOH (10 mL) and H_2O (2 mL) was added KOH (125 mg, 2.23 mmol) and the solution was stirred for 4 h at 50°C , concentrated under reduced pressure, diluted with H_2O and adjusted to pH = 5 with 1N HCl. The solution was extracted with DCM and the organic layer was washed with brine, dried over Na_2SO_4 , filtered, concentrated and purified by prep-HPLC to give compound **7** (40 mg, 14%) as a white solid. $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 7.44 (t, 1H), 7.29 (s, 1H), 7.21 (s, 1H), 7.09 (s, 1H), 3.50-3.56 (m, 2H), 2.63 (d, J = 5.7 Hz, 2H), 1.95-1.99 (m, 2H), 1.77-1.81 (m, 1H), 1.62-1.68 (m, 5H), 1.43 (s, 3H), 1.33 (s, 9H), 1.31 (s, 6H), 1.13-1.29 (m, 3H), 0.87-0.93 (m, 3H), 0.75-0.78 (m, 2H). MS 525.3 ($\text{M}+1$) $^+$.

Example 7/1 to 7/27

The following Examples were prepared similar as in Example 7:

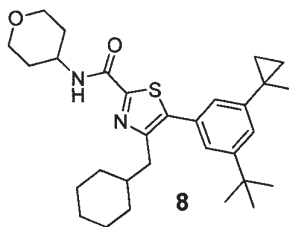
#	Structure	Analytical data
7/1		$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 8.19 (d, J = 8.4 Hz, 1H), 7.67 (d, J = 1.5 Hz, 1H), 7.52-7.48 (t, J = 5.7 Hz, 1H), 7.30 (dd, J = 9.6, 1.5 Hz, 1H), 4.69 (s, 1H), 3.50-3.57 (m, 2H), 2.63 (2H, d, J = 6.9 Hz), 1.95-2.00 (m, 2H), 1.74-1.78 (m, 1H), 1.66-1.61 (m, 5H), 1.62 (s, 9H), 1.33 (s, 9H), 1.08-1.25 (m, 3H), 0.83-0.94 (m, 2H). MS 606.3 ($\text{M}+1$) $^+$
7/2		$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 8.23 (d, J = 8.4 Hz, 1H), 7.68 (d, J = 1.5 Hz, 1H), 7.49 (d, J = 8.1 Hz, 1H), 7.36 (dd, J = 8.1, 1.5 Hz, 1H), 4.79-4.88 (m, 1H), 4.64 (s, 1H), 3.16-3.25 (m, 1H), 2.78-2.88 (m, 2H), 2.67 (d, J = 7.2 Hz, 2H), 2.48-2.57 (m, 2H), 1.77-1.84 (m, 1H), 1.62-1.67 (m, 5H), 1.64 (s, 9H), 1.34 (s, 9H), 1.07-1.28 (m, 3H), 0.85-0.92 (m, 2H). MS 590.3 ($\text{M}+1$) $^+$

#	Structure	Analytical data
7/3		$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 7.55 (d, $J = 6.9$ Hz, 1H), 7.31 (s, 1H), 7.23 (s, 1H), 7.11 (s, 1H), 4.80-4.86 (m, 1H), 3.18-3.21 (br s, 1H), 2.80-2.83 (m, 2H), 2.65 (d, $J = 6.9$ Hz, 2H), 2.51-2.53 (m, 2H), 1.79-1.84 (m, 1H), 1.67-1.70 (m, 5H), 1.44 (s, 3H), 1.35 (s, 9H), 1.07-1.29 (m, 3H), 0.87-0.93 (m, 4H), 0.75-0.77 (m, 2H). MS 509.3 ($\text{M}+1$) $^+$
7/4		$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 0.74-0.81 (m, 2H), 0.85-0.90 (m, 3H), 1.12-1.21 (m, 3H), 1.29 (s, 6H), 1.54-1.63 (m, 8H), 2.47-2.57 (m, 2H), 2.78 (s, 3H), 2.80-2.87 (m, 2H), 3.16-3.24 (m, 1H), 4.50 (s, 1H), 4.80-4.83 (m, 1H), 7.28 (d, $J = 8.4$ Hz, 1H), 7.50 (d, $J = 8.4$ Hz, 1H), 8.05 (d, $J = 8.4$ Hz, 1H). MS 596.2 [$\text{M}+1$] $^+$
7/5		$^1\text{H-NMR}$ (DMSO-d_6 , 300 MHz) δ : 0.81-0.89 (m, 2H), 1.09-1.17 (m, 3H), 1.34 (s, 9H), 1.52-1.60 (m, 5H), 1.79-1.85 (m, 1H), 2.39-2.47 (m, 3H), 2.53-2.57 (m, 1H), 2.66 (d, $J = 7.2$ Hz, 2H), 3.20-3.33 (m, 2H), 4.54-4.63 (m, 1H), 7.09 (t, $J = 25.8$ Hz, 1H), 7.47 (s, 1H), 7.65 (d, $J = 1.2$ Hz, 1H), 9.07 (d, $J = 8.1$ Hz, 1H). MS 505.3 ($\text{M}+1$) $^+$
7/6		$^1\text{H-NMR}$ (400 MHz, CD_3OD) δ : 0.77-0.78 (m, 2H), 0.80-0.82 (m, 2H), 0.86-0.87 (m, 2H), 1.11-1.23 (m, 3H), 1.38 (s, 3H), 1.54-1.56 (m, 5H), 1.75-1.77 (m, 1H), 2.39-2.47 (m, 2H), 2.51-2.60 (m, 4H), 2.98-2.99 (m, 1H), 4.00 (q, $J = 9.2$ Hz, 2H), 4.61-4.65 (m, 1H), 7.43 (d, $J = 0.8$ Hz, 1H), 7.64 (d, $J = 1.6$ Hz, 1H), 7.72 (d, $J = 1.6$ Hz, 1H). MS 578.3 [$\text{M}+1$] $^+$
7/7		$^1\text{H-NMR}$ (300 MHz, CD_3OD) δ : 0.78-0.84 (m, 2H), 1.06-1.15 (m, 2H), 1.22 (s, 9H), 1.54-1.57 (m, 6H), 1.72-1.77 (m, 1H), 2.48-2.67 (m, 6H), 3.05-3.10 (m, 1H), 4.70-4.83 (m, 1H), 7.56 (d, $J = 8.4$ Hz, 1H), 8.16 (d, $J = 8.4$ Hz, 1H). MS 602.1 [$\text{M}+1$] $^+$
7/8		$^1\text{H-NMR}$ (300 MHz, CD_3OD) δ : 0.73-0.84 (m, 2H), 1.13-1.26 (m, 10H), 1.49-1.61 (m, 6H), 1.67-1.84 (m, 5H), 2.37-2.64 (m, 9H), 3.09 (br s, 1H), 3.26-3.30 (m, 2H), 4.71-4.76 (m, 1H), 7.22 (d, $J = 7.8$ Hz, 1H), 7.92-7.95 (d, $J = 7.8$ Hz, 1H). MS 588.2 [$\text{M}+1$] $^+$
7/9		$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 0.60-0.69 (m, 2H), 0.96-1.02 (m, 1H), 1.06-1.15 (m, 2H), 1.22 (s, 9H), 1.49-1.59 (m, 5H), 1.63-1.77 (m, 3H), 2.06 (dd, $J = 9.6$ Hz, 2.8 Hz, 2H), 2.35 (br s, 2H), 3.57 (td, $J = 11.2$ Hz, 1.6 Hz, 1H), 4.03-4.06 (m, 2H), 4.18-4.26 (m, 1H), 4.65-4.72 (m, 1H), 7.21 (d, $J = 8.0$ Hz, 1H), 7.51 (d, $J = 7.6$ Hz, 1H), 7.55-7.59 (m, 1H), 7.69-7.74 (m, 2H), 8.35 (d, $J = 7.6$ Hz, 1H), 8.69 (d, $J = 8.4$ Hz, 1H). MS 584.2 [$\text{M}+1$] $^+$

#	Structure	Analytical data
7/10		$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 0.52-1.04 (m, 2H), 0.75-1.17 (m, 3H), 1.25-1.31 (m, 4H), 1.47-1.70 (m, 6H), 2.32-2.34 (m, 2H), 2.50-2.60 (m, 2H), 2.81-2.89 (m, 2H), 3.18-3.26 (m, 1H), 3.97-4.05 (m, 1H), 4.81-4.89 (m, 1H), 4.98 (d, J = 9.6 Hz, 1H), 7.51-7.62 (m, 3H), 7.72-7.76 (m, 2H), 8.33 (d, J = 7.5 Hz, 1H), 8.65 (d, J = 8.1 Hz, 1H). MS 624.2 [M+] $^{+}$
7/11		$^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ : 0.82-0.91 (m, 2H), 0.97 (d, J = 6.8 Hz, 6H), 1.06-1.23 (m, 3H), 1.32 (s, 9H), 1.52-1.59 (m, 5H), 1.78-1.86 (m, 1H), 2.05-2.08 (m, 1H), 2.39-2.44 (m, 2H), 2.52-2.55 (m, 2H), 2.70 (d, J = 6.8 Hz, 2H), 2.92-2.96 (m, 1H), 4.11 (d, J = 6.8 Hz, 2H), 4.55-4.61 (m, 1H), 6.68 (s, 1H), 7.01 (s, 1H), 9.11 (d, J = 8.4 Hz, 1H), 12.24 (s, 1H). MS 528.3 (M+) $^{+}$
7/12		$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 8.36 (d, 1H, J = 8.4 Hz), 7.60 (d, 1H, J = 8.4 Hz), 7.46 (d, 1H, J = 7.6 Hz), 4.86-4.80 (m, 2H), 3.19 (t, 1H, J = 4.8 Hz), 2.85-2.80 (m, 2H), 2.56-2.48 (m, 2H), 2.38 (d, 2H, J = 6.8 Hz), 1.75-1.54 (m, 6H), 1.31 (s, 9H), 1.27-1.05 (m, 3H), 0.81-0.72 (m, 2H). MS 636.2 (M+) $^{+}$
7/13		$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 8.06 (d, 1H, J = 7.0 Hz), 7.48-7.45 (m, 1H), 7.32 (d, 1H, J = 8.4 Hz), 6.06 (t, 1H, J = 7.4 Hz), 4.84-4.78 (m, 1H), 4.52 (s, 1H), 3.24-3.19 (m, 1H), 2.86-2.79 (m, 2H), 2.67-2.49 (m, 7H), 1.79-1.53 (m, 6H), 1.27-1.05 (m, 12H), 0.83-0.73 (m, 2H). MS 614.2 (M+) $^{+}$
7/14		$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 8.29 (d, 1H, J = 8.4 Hz), 7.49 (d, 1H, J = 8.0 Hz), 7.25 (d, 1H, J = 8.0 Hz), 4.85-4.78 (m, 1H), 4.66 (s, 1H), 3.23-3.18 (m, 1H), 2.86-2.79 (m, 5H), 2.56-2.47 (m, 3H), 2.21-2.15 (m, 1H), 1.74-1.59 (m, 5H), 1.46-1.43 (m, 1H), 1.29-1.12 (m, 12H), 0.88-0.60 (m, 2H). MS 616.2 (M+) $^{+}$
7/15		$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 7.97 (d, 1H, J = 8.4 Hz), 7.71-7.50 (m, 3H), 4.85-4.79 (m, 1H), 4.69 (s, 1H), 3.23-3.19 (m, 1H), 2.86-2.80 (m, 2H), 2.56-2.47 (m, 4H), 1.77-1.55 (m, 6H), 1.26 (s, 9H), 1.24-0.74 (m, 5H). MS 602.2 (M+) $^{+}$
7/16		$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 8.31 (d, 1H, J = 8.0 Hz), 7.48 (d, 1H, J = 8.0 Hz), 7.35 (d, 1H, J = 8.4 Hz), 6.87 (t, 1H, J = 5.3 Hz), 5.08 (s, 1H), 4.85-4.79 (m, 1H), 3.23-3.17 (m, 1H), 2.84-2.79 (m, 2H), 2.54-2.21 (m, 4H), 1.74-1.49 (m, 6H), 1.26-0.65 (m, 14H). MS 618.2 (M+) $^{+}$

#	Structure	Analytical data
7/17		$^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ : 0.84-0.88 (m, 2H), 1.13-1.26 (m, 3H), 1.28 (s, 12H), 1.60-1.64 (m, 5H), 1.70 (s, 6H), 1.74-1.77 (m, 1H), 2.48-2.53 (m, 2H), 2.64 (d, $J = 7.2$ Hz, 2H), 2.78-2.87 (m, 2H), 3.18-3.20 (m, 1H), 4.80-4.83 (m, 1H), 7.37-7.39 (m, 2H), 7.47 (d, $J = 7.8$ Hz, 1H), 8.24 (d, $J = 8.7$ Hz, 1H). MS 592.3 ($[\text{M}+1]^+$)
7/18		$^1\text{H-NMR}$ (DMSO-d_6 , 300 MHz) δ : 0.88-0.95 (m, 2H), 1.18-1.35 (m, 3H), 1.39 (s, 9H), 1.55-1.67 (m, 5H), 1.95 (t, $J = 18.3$ Hz, 3H), 2.37-2.47 (m, 2H), 2.60-2.69 (m, 4H), 3.00-3.02 (m, 1H), 4.66-4.71 (m, 1H), 7.40 (s, 1H), 7.56 (s, 1H), 7.61 (s, 1H). MS 519.3 ($[\text{M}+1]^+$)
7/19		$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 0.87-0.94 (m, 2H), 1.15-1.26 (m, 3H), 1.33 (s, 9H), 1.45 (d, $J = 6.9$ Hz, 3H), 1.64-1.67 (m, 4H), 1.70-1.88 (m, 1H), 2.47-2.54 (m, 2H), 2.60 (d, $J = 6.9$ Hz, 2H), 2.76-2.83 (m, 2H), 3.15-3.22 (m, 1H), 4.78-4.81 (m, 1H), 4.95-4.98 (m, 1H), 6.51 (d, $J = 9.6$ Hz, 1H), 7.53-7.58 (m, 3H), 7.89 (s, 1H). MS 594.3 ($[\text{M}+1]^+$)
7/20		$^1\text{H-NMR}$ (400 MHz, DMSO-d_6) δ : 0.62-0.65 (m, 2H), 0.96 (m, 1H), 1.03-1.11 (m, 2H), 1.47-1.50 (m, 5H), 1.74-1.76 (m, 1H), 2.32-2.41 (m, 4H), 2.55-2.58 (m, 2H), 2.96 (m, 1H), 4.04 (s, 3H), 4.60-4.62 (m, 1H), 7.09 (d, $J = 7.6$ Hz, 1H), 7.47-7.57 (m, 4H), 8.24-8.27 (m, 1H), 9.14 (d, $J = 8.4$ Hz, 1H), 12.27 (s, 1H). MS 479 ($[\text{M}+1]^+$)
7/21		$^1\text{H-NMR}$ (400 MHz, CD_3OD) δ : 0.63-0.73 (m, 2H), 0.99-1.17 (m, 3H), 1.53-1.55 (m, 5H), 1.75-1.79 (m, 1H), 2.41 (m, 2H), 2.51-2.59 (m, 2H), 2.63-2.69 (m, 2H), 3.08-3.12 (m, 1H), 4.75 (m, 1H), 7.56 (m, 2H), 7.61-7.72 (m, 3H), 8.21 (d, $J = 8.4$ Hz, 1H). MS 533 ($[\text{M}+1]^+$)
7/22		$^1\text{H-NMR}$ (400 MHz, CD_3OD) δ : 0.69-0.75 (m, 2H), 1.06-1.17 (m, 3H), 1.56-1.62 (m, 5H), 1.79 (m, 1H), 2.44 (m, 2H), 2.56-2.61 (m, 2H), 2.65-2.71 (m, 2H), 3.14-3.15 (m, 1H), 4.76-4.90 (m, 3H), 7.14 (d, $J = 8.4$ Hz, 1H), 7.47-7.48 (d, $J = 7.6$ Hz, 1H), 7.59-7.63 (m, 3H), 8.34 (d, $J = 7.6$ Hz, 1H). MS 547.2 ($[\text{M}+1]^+$)
7/23		$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 0.62-0.77 (m, 2H), 0.96-1.26 (m, 3H), 1.51 (s, 3H), 1.54-1.57 (m, 2H), 1.69-1.81 (m, 1H), 1.92 (s, 6H), 2.03 (s, 1H), 2.32-2.51 (m, 6H), 3.15-3.21 (m, 4H), 4.23-4.33 (m, 1H), 7.27-7.65 (m, 6H), 8.95 (d, $J = 8.4$ Hz, 1H). MS 541.3 ($[\text{M}+1]^+$)
7/24		$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 0.64-0.76 (m, 2H), 0.98-1.18 (m, 3H), 1.52-1.54 (m, 3H), 1.58-1.61 (m, 2H), 1.71-1.79 (m, 1H), 2.33-2.52 (m, 6H), 2.77 (s, 1H), 3.17-3.20 (m, 4H), 4.24-4.33 (m, 1H), 5.20 (d, $J = 6.9$ Hz, 1H), 5.38 (d, $J = 6.9$ Hz, 1H), 7.31 (d, $J = 7.8$ Hz, 1H), 7.44-7.62 (m, 4H), 7.67 (d, $J = 8.4$ Hz, 1H), 7.82 (d, $J =$

#	Structure	Analytical data
		8.4 Hz, 1H). MS 555.2 [M+1] ⁺
7/25		¹ H-NMR (300 MHz, CDCl ₃) δ: 0.65-0.70 (m, 2H), 1.11-1.17 (m, 3H), 1.50-1.61 (m, 14H), 1.71-1.79 (m, 1H), 2.33-2.48 (m, 6H), 3.16-3.20 (m, 4H), 4.26-4.30 (m, 1H), 5.85 (s, 1H), 7.26-7.31 (m, 1H), 7.41 (d, J = 7.2 Hz, 1H), 7.49-7.562 (m, 1H), 7.58-7.63 (m, 3H), 8.30-8.34 (m, 1H). MS 582.2 [M+1] ⁺
7/26		¹ H-NMR (300 MHz, CDCl ₃) δ: 0.65-0.74 (m, 2H), 1.00-1.16 (m, 3H), 1.28 (s, 6H), 1.52-1.58 (m, 5H), 1.71-1.79 (m, 1H), 2.33-2.51 (m, 8H), 3.16-3.19 (m, 4H), 3.47 (s, 2H), 3.66-3.69 (m, 2H), 4.06 (s, 2H), 4.27-4.29 (m, 1H), 7.29-7.68 (m, 6H), 8.36 (d, J = 8.4 Hz, 1H). MS 610.3 [M+1] ⁺
7/27		¹ H-NMR (300 MHz, CDCl ₃) δ: 0.65-0.74 (m, 2H), 1.00-1.16 (m, 3H), 1.50-1.51 (m, 3H), 1.54-1.59 (m, 2H), 1.71-1.79 (m, 1H), 2.37-2.51 (m, 6H), 3.16-3.20 (m, 8H), 4.00-4.03 (m, 4H), 4.27-4.29 (m, 1H), 7.12 (d, J = 7.8 Hz, 1H), 7.26-7.29 (m, 1H), 7.37 (d, J = 7.8 Hz, 1H), 7.45-7.57 (m, 3H), 8.28 (d, J = 8.4 Hz, 1H). MS 568.2 [M+1] ⁺

Example 8

Step 1: 5-Bromo-4-(cyclohexylmethyl)-N-(tetrahydro-2H-pyran-4-yl)thiazole-2-carboxamide (8a)

5

To a solution of **6c** (0.20 g, 0.60 mmol) in toluene (0.6 mL) was added tetrahydro-2H-pyran-4-amine (182 mg, 1.8 mmol) and the resulting solution was heated at 130°C for 15 h. The reaction mixture was then cooled to rt and purified by CC (PE/EA = 10/1 to 5/1) to afford compound **8a** (0.21 g, 91%) as a white solid.

Step 2: 5-(3-(tert-Butyl)-5-(1-methylcyclopropyl)phenyl)-4-(cyclohexylmethyl)-N-(tetrahydro-2H-pyran-4-yl)thiazole-2-carboxamide (8)

10

Compound **8a** (210 mg, 540 μmol), 2-(3-(tert-butyl)-5-(1-methylcyclopropyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (180 mg, 560 μmol), Na₂CO₃ (180 mg, 1.69 mmol), Pd(dppf)Cl₂·CH₂Cl₂ (44 mg, 54 μmol) in toluene (3 mL), EtOH (1.5 mL) and water (1.5 mL) were heated at 70°C for 15 h before cooled to rt. The mixture was partitioned between EA (10

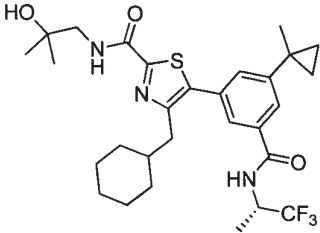
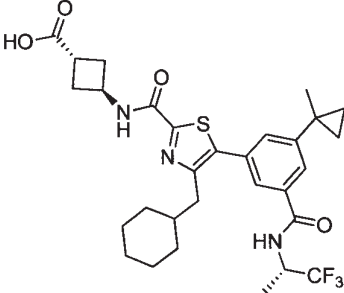
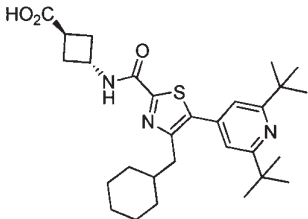
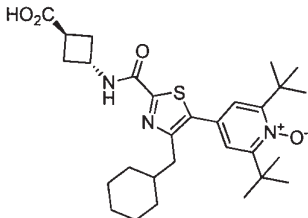
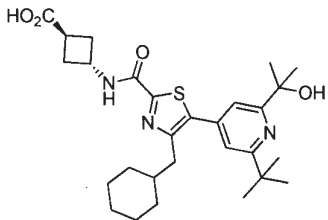
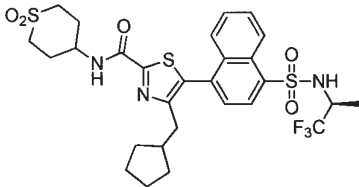
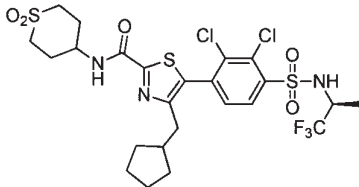
15

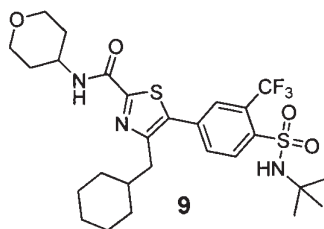
mL) and water (10 mL) and the layers were separated. The organic phase was washed with water and brine, dried over Na₂SO₄, concentrated and purified by CC (PE/EA = 10/1 to 5/1) to give compound **8** (189 mg, 75%). ¹H-NMR (400 MHz, CDCl₃) δ: 7.30 (s, 1H), 7.22 (s, 1H), 7.13 (d, J = 8.1 Hz, 1H), 7.10 (s, 1H), 4.15-4.21 (m, 1H), 4.02 (d, J = 8.8 Hz, 2H), 3.52-3.57 (m, 2H), 2.64 (d, J = 7.1 Hz, 2H), 2.01-2.04 (m, 2H), 1.79-1.83 (m, 1H), 1.63-1.72 (m, 7H), 1.43 (s, 3H), 1.34 (s, 9H), 1.01-1.25 (m, 3H), 0.87-0.95 (m, 4H), 0.76-0.79 (m, 2H). MS 495.3 (M+1)⁺.

Example 8/1 to 8/12

10 The following Example was prepared similar as in Example **8**:

#	Structure	Analytical data
8/1		¹ H-NMR (400 MHz, CDCl ₃) δ: 8.22 (d, J = 8.3 Hz, 1H), 7.67 (d, J = 1.7 Hz, 1H), 7.35 (dd, J = 8.3 Hz, J = 1.7 Hz, 1H), 7.12 (d, J = 7.1 Hz, 1H), 4.46 (s, 1H), 4.17-4.20 (m, 1H), 4.02-4.04 (m, 2H), 3.53-3.57 (m, 2H), 2.66 (d, J = 7.2 Hz, 2H), 2.01-2.04 (m, 2H), 1.76-1.81 (m, 1H), 1.62-1.72 (m, 7H), 1.62 (s, 9H), 1.33 (s, 9H), 1.07-1.25 (m, 3H), 0.85-0.92 (m, 2H). MS 606.3 (M+1) ⁺
8/2		¹ H-NMR (300 MHz, CDCl ₃) δ: 0.59-0.71 (m, 2H), 0.94-1.19 (m, 3H), 1.22 (s, 11H), 1.48-1.58 (m, 4H), 1.65-1.74 (m, 2H), 2.34-2.35 (m, 2H), 4.71 (s, 1H), 5.67 (br s, 1H), 7.25 (br s, 1H), 7.51-7.60 (m, 2H), 7.69-7.74 (m, 2H), 8.35 (d, J = 7.5 Hz, 1H), 8.70 (d, J = 8.7 Hz, 1H). MS 486.2 [M+1] ⁺
8/3		¹ H-NMR (300 MHz, CDCl ₃) δ: 0.63-0.80 (m, 4H), 0.88-1.30 (m, 5H), 1.35 (s, 6H), 1.37-1.56 (m, 6H), 2.32-2.36 (m, 2H), 3.53 (d, J = 6.6 Hz, 2H), 5.60-5.63 (m, 1H), 5.87 (s, 1H), 6.89-6.91 (m, 1H), 7.55-7.63 (m, 2H), 7.69-7.80 (m, 3H), 8.34 (d, J = 7.8 Hz, 1H), 8.58 (d, J = 8.4 Hz, 1H). MS 585.2 [M+1] ⁺
8/4		¹ H-NMR (300 MHz, CDCl ₃) δ: 0.63-0.68 (m, 2H), 0.86-0.90 (m, 2H), 1.09-1.13 (m, 3H), 1.13-1.14 (m, 2H), 1.27 (s, 6H), 1.29-1.52 (m, 5H), 1.60-1.70 (m, 1H), 2.16 (s, 1H), 2.34-2.36 (m, 2H), 3.51-3.54 (m, 2H), 5.58-5.63 (m, 1H), 7.60 (d, J = 7.2 Hz, 2H), 7.64-7.80 (m, 3H), 8.46 (d, J = 7.5 Hz, 1H), 8.67 (d, J = 8.7 Hz, 1H). MS 567.2 [M+1] ⁺
8/5		¹ H-NMR (300 MHz, CDCl ₃) δ: 0.64-0.72 (m, 2H), 0.98-1.15 (m, 3H), 1.36 (s, 6H), 1.49-1.61 (m, 8H), 1.68-1.75 (m, 1H), 2.13 (s, 1H), 2.35-2.37 (m, 2H), 3.53 (d, J = 6.6 Hz, 2H), 4.34 (d, J = 6.6 Hz, 2H), 4.72 (d, J = 6.6 Hz, 2H), 5.20 (s, 1H), 7.54 (d, J = 7.5 Hz, 1H), 7.58-7.78 (m, 4H), 8.33 (d, J = 7.5 Hz, 1H), 8.68 (d, J = 8.7 Hz, 1H). MS 572.2 [M+1] ⁺

#	Structure	Analytical data
8/6		$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 0.75-0.88 (m, 2H), 0.89-1.01 (m, 2H), 1.05-1.30 (m, 5H), 1.32 (s, 6H), 1.42-1.46 (m, 6H), 1.59-1.83 (m, 6H), 2.19 (s, 1H), 2.60 (d, $J = 10.5$ Hz, 2H), 2.60 (d, $J = 6.3$ Hz, 2H), 4.91-4.99 (m, 1H), 4.94-4.99 (m, 1H), 6.11 (d, $J = 9.9$ Hz, 1H), 7.25-7.26 (m, 1H), 7.44-7.45 (m, 1H), 7.60-7.64 (m, 1H), 7.68-7.69 (m, 1H). MS 566.3 $[\text{M}+1]^+$
8/7		$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 0.75-0.88 (m, 2H), 0.89-1.01 (m, 2H), 1.05-1.30 (m, 5H), 1.46 (s, 6H), 1.59-1.83 (m, 6H), 2.45-2.56 (m, 2H), 2.60 (d, $J = 6.9$ Hz, 2H), 2.77-2.85 (m, 2H), 3.15-3.22 (m, 1H), 4.77-4.82 (m, 1H), 4.94-4.99 (m, 1H), 6.25 (d, $J = 9.6$ Hz, 1H), 7.43 (s, 1H), 7.48 (d, $J = 7.8$ Hz, 2H), 7.55 (s, 1H), 7.69 (s, 1H). MS 592.3 $[\text{M}+1]^+$
8/8		$^1\text{H-NMR}$ (400 MHz, DMSO-d_6) δ : 0.89-0.94 (m, 2H), 1.12-1.23 (m, 3H), 1.34 (s, 18H), 1.58-1.67 (m, 5H), 1.75-1.86 (m, 1H), 2.39-2.44 (m, 2H), 2.48-2.55 (m, 2H), 2.70 (d, $J = 7.2$ Hz, 2H), 2.92-2.97 (m, 1H), 4.56-4.60 (m, 1H), 7.26 (s, 2H), 9.11 (d, $J = 8.0$ Hz, 1H), 12.25 (s, 1H). MS 512.4 $(\text{M}+1)^+$
8/9		$^1\text{H-NMR}$ (400 MHz, DMSO-d_6) δ : 0.94-0.97 (m, 2H), 1.14-1.19 (m, 3H), 1.47 (s, 18H), 1.50-1.55 (m, 5H), 1.61-1.65 (m, 1H), 2.39-2.43 (m, 2H), 2.47-2.50 (m, 2H), 2.70 (d, $J = 7.2$ Hz, 2H), 2.92-2.96 (m, 1H), 4.57-4.59 (m, 1H), 7.37 (s, 2H), 9.11 (d, $J = 8.0$ Hz, 1H), 12.21 (br s, 1H). MS 528.3 $(\text{M}+1)^+$
8/10		$^1\text{H-NMR}$ (400 MHz, CD_3OD) δ : 0.95-1.01 (m, 2H), 1.20-1.30 (m, 3H), 1.46 (s, 9H), 1.62 (s, 6H), 1.68-1.70 (m, 5H), 1.91-1.92 (m, 1H), 2.52-2.69 (m, 4H), 2.80 (d, $J = 7.2$ Hz, 2H), 3.09-3.12 (m, 1H), 4.76 (t, $J = 8.0$ Hz, 1H), 7.48 (s, 1H), 7.65 (s, 1H). MS 514.3 $(\text{M}+1)^+$
8/11		MS 644.1.3 $(\text{M}+1)^+$
8/12		MS 662.0 $(\text{M}+1)^+$

Example 9**Step 1: 5-Bromo-4-(cyclohexylmethyl)thiazole-2-carboxylic acid (9a)**

To a solution of compound **6c** (72 mg, 0.23 mmol) in EtOH (2 mL) was added 4N NaOH (1 mL). The mixture was stirred at rt overnight, evaporated and the residue was adjusted pH<2 with 4N HCl, extracted with EA (3 x) and the combined organic layer was washed with brine and dried over Na₂SO₄. After filtration, the filtrate was evaporated to give compound **9a** (60 mg, 87%) as a white solid.

Step 2: 5-Bromo-4-(cyclohexylmethyl)thiazole-2-carbonyl chloride (9b)

Oxalyl dichloride (48 mg, 0.38 mmol) was added to a mixture of compound **9a** (57 mg, 0.19 mmol) in DCM (5 mL) of at 0°C. After stirred for 80 min at rt the mixture was evaporated to give compound **9b** (55 mg, 91%) as a yellow oil.

Step 3: 5-Bromo-4-(cyclohexylmethyl)-N-(tetrahydro-2H-pyran-4-yl)thiazole-2-carboxamide (9c)

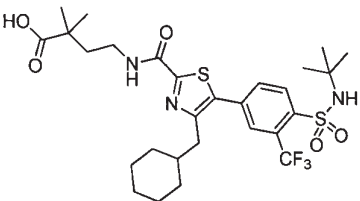
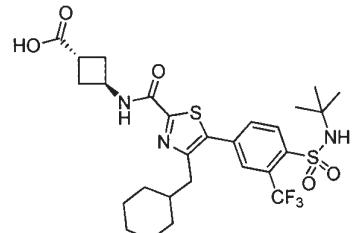
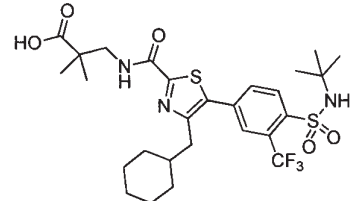
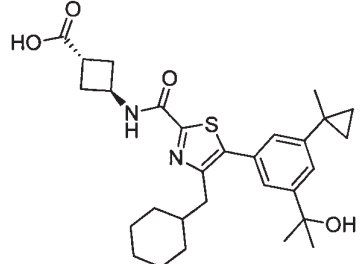
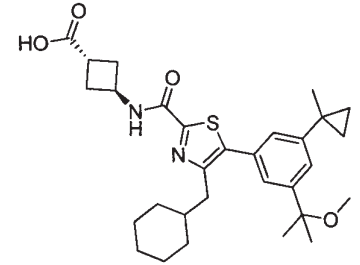
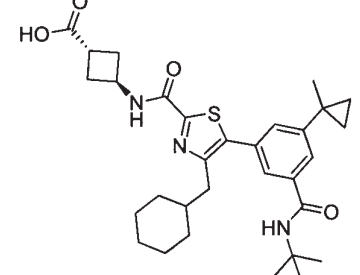
To a solution of compound **9b** (50 mg, 0.16 mmol) in DCM (2.5 mL) was added TEA (33 mg, 0.32 mmol) and tetrahydro-2H-pyran-4-amine (20 mg, 0.19 mmol). The mixture was stirred overnight, quenched with water and extracted with EA. The organic layer was separated and washed with brine, dried over Na₂SO₄, filtered and evaporated to give compound **9c** (51 mg, 85%) as a yellow solid.

Step 4: 5-(4-(N-(tert-Butyl)sulfonyl)-3-(trifluoromethyl)phenyl)-4-(cyclohexylmethyl)-N-(tetrahydro-2H-pyran-4-yl)thiazole-2-carboxamide (9)

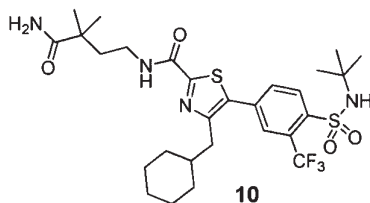
A suspension of compound **9c** (46 mg, 0.12 mmol), Na₂CO₃ (32 mg, 0.32 mmol), *N*-(tert-butyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trifluoromethyl)benzenesulfonamide (59 mg, 0.14 mmol), Pd(dppf)Cl₂ (30 mg) in DMF/H₂O (10:1, 10 mL) was heated overnight under N₂ at 90°C, cooled, concentrated and extracted with EA. The organic layer was washed with brine, dried over MgSO₄, filtered, evaporated and purified by prep-HPLC to give compound **9** (41 mg, 59%) as a white solid. ¹H-NMR (400 MHz, DMSO-d₆) δ: 8.78 (d, 1H, J = 8.4 Hz), 8.30 (d, 1H, J = 8.4 Hz), 8.20 (dd, 1H, J = 8.4, J = 1.6 Hz), 7.95-7.98 (m, 2H), 3.99-4.04 (m, 1H), 3.87-3.90 (m, 2H), 3.34-3.41 (m, 2H), 2.68 (d, 2H, J = 6.8 Hz), 1.71-1.80 (m, 5H), 1.52-1.55 (m, 5H), 1.19 (s, 9H), 1.03-1.16 (m, 3H), 0.76-0.84 (m, 2H). MS 488.2 (M+1)⁺.

Example 9/1 to 9/11

The following Examples were prepared similar as in Example 9:

#	Structure	Analytical data
9/1		$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 8.36 (d, 1H, $J = 8.4$ Hz), 7.87 (d, 1H, $J = 1.2$ Hz), 7.71 (dd, 1H, $J = 8.4$, $J = 1.8$ Hz), 7.39 (t, 1H, $J = 6.0$ Hz), 4.75 (s, 1H), 3.51-3.57 (m, 2H), 2.63 (d, 2H, $J = 6.8$ Hz), 1.95-2.01 (m, 2H), 1.77-1.81 (m, 1H), 1.62-1.68 (m, 5H), 1.32 (s, 5H), 1.29 (s, 9H), 1.10-1.26 (m, 3H), 0.83-0.92 (m, 2H). MS 618.2 ($\text{M}+1$) $^+$
9/2		$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 8.37 (d, 1H, $J = 8.4$ Hz), 7.88 (s, 1H), 7.72 (dd, 1H, $J = 8.0$, $J = 1.6$ Hz), 7.45 (d, 1H, $J = 7.6$ Hz), 4.78-4.84 (m, 1H), 4.73 (s, 1H), 3.21-3.24 (m, 1H), 2.79-2.83 (m, 2H), 2.65 (d, 2H), 2.51-2.56 (m, 2H), 1.62-1.68 (m, 6 H), 1.29 (s, 9H), 1.11-1.26 (m, 3H), 0.84-0.93 (m, 2H). MS 602.2 ($\text{M}+1$) $^+$
9/3		$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 8.35 (d, 1H, $J = 8.4$ Hz), 7.87 (s, 1H), 7.68-7.76 (m, 2H), 4.72 (s, 1H), 3.63 (d, 2H, $J = 6.4$ Hz), 2.64 (d, 2H, $J = 7.2$ Hz), 1.44-1.64 (m, 6H), 1.34 (s, 6H), 1.29 (s, 9H), 1.09-1.25 (m, 3H), 0.83-0.92 (m, 2H). MS 604.2 ($\text{M}+1$) $^+$
9/4		$^1\text{H-NMR}$ (400 MHz, CD_3OD) δ : 0.77-0.80 (m, 2H), 0.88-0.95 (m, 4H), 1.12-1.23 (m, 3H), 1.43 (s, 3H), 1.54 (s, 6H), 1.64-1.67 (m, 5H), 1.79-1.89 (m, 1H), 2.48-2.56 (m, 2H), 2.61-2.70 (m, 4H), 3.05-3.13 (m, 1H), 4.68-4.76 (m, 1H), 7.18 (t, $J = 2.0$ Hz, 1H), 7.36 (t, $J = 2.0$ Hz, 1H), 7.36 (t, $J = 2.0$ Hz, 1H). MS 511.3 ($\text{M}+1$) $^+$
9/5		$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 0.78-0.80 (m, 2H), 0.86-0.94 (m, 4H), 1.10-1.23 (m, 3H), 1.44 (s, 3H), 1.54 (s, 6H), 1.64-1.68 (m, 5H), 1.74-1.85 (m, 1H), 2.50-2.52 (m, 2H), 2.65 (d, $J = 7.2$ Hz, 2H), 2.80-2.84 (m, 2H), 3.11 (s, 3H), 3.15-3.23 (m, 1H), 4.77-4.87 (m, 1H), 7.16 (t, $J = 1.6$ Hz, 1H), 7.25 (t, $J = 1.6$ Hz, 1H), 7.30 (d, $J = 1.6$ Hz, 1H), 7.50 (d, $J = 8.0$ Hz, 1H). MS 525.3 ($\text{M}+1$) $^+$
9/6		$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 7.66 (t, $J = 1.6$ Hz, 1H), 7.45-7.38 (m, 2H), 7.38 (d, $J = 1.6$ Hz, 1H), 5.89 (s, 1H), 4.83-4.77 (m, 1H), 3.24-3.18 (m, 1H), 2.85-2.80 (m, 2H), 2.58 (d, 2H, $J = 6.4$ Hz), 2.55-2.47 (m, 2H), 1.82-1.52 (m, 6H), 1.49 (m, 9H), 1.44 (s, 3H), 1.27-1.12 (m, 3H), 0.93-0.88 (m, 6H). MS 552.3 ($\text{M}+1$) $^+$

#	Structure	Analytical data
9/7		$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 7.85 (t, $J = 1.6$ Hz, 1H), 7.52 (t, $J = 1.6$ Hz, 1H), 7.46-7.44 (m, 2H), 5.90 (s, 1H), 4.84-4.78 (m, 1H), 3.21-3.18 (m, 1H), 2.86-2.80 (m, 2H), 2.62 (d, 2H, $J = 6.4$ Hz), 2.55-2.48 (m, 2H), 1.83-1.66 (m, 6H), 1.49 (s, 9H), 1.37 (s, 9H), 1.34-1.09 (m, 3H), 0.94-0.86 (m, 2H). MS 554.3 ($\text{M}+1$) $^+$
9/8		$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 7.50 (s, 1H), 7.43-7.44 (m, 3H), 4.78-4.84 (m, 1H), 3.19-3.23 (m, 1H), 2.82-2.85 (m, 2H), 2.60 (d, 2H), 2.50-2.56 (m, 2H), 1.79-1.84 (m, 1H), 1.63-1.68 (m, 5H), 1.46 (s, 3H), 1.11-1.28 (m, 3H), 0.85-0.94 (m, 6H). MS 521.2 ($\text{M}+1$) $^+$
9/9		$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 7.42 (m, 1H), 7.24 (s, 1H), 7.18 (s, 1H), 7.13 (s, 1H), 4.81-4.75 (m, 1H), 3.21-3.18 (m, 1H), 2.84-2.80 (m, 2H), 2.62 (d, $J = 5.6$ Hz, 2H), 2.55-2.47 (m, 2H), 1.81-1.78 (m, 1H), 1.66-1.55 (m, 5H), 1.42 (s, 3H), 1.31-1.17 (m, 3H), 0.90-0.78 (m, 6H). MS 487.2 ($\text{M}+1$) $^+$
9/10		$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 0.77-0.80 (m, 2H), 0.83-0.93 (m, 4H), 1.12-1.25 (m, 4H), 1.43 (s, 3H), 1.60 (s, 6H), 1.64-1.66 (m, 5H), 1.69-1.83 (m, 1H), 2.46-2.53 (m, 2H), 2.64 (d, $J = 7.2$ Hz, 2H), 2.74-2.82 (m, 2H), 2.95-3.02 (m, 1H), 4.62-4.69 (m, 1H), 7.16 (t, $J = 1.6$ Hz, 1H), 7.30 (t, $J = 1.6$ Hz, 1H), 7.43 (t, $J = 1.6$ Hz, 1H), 8.00 (d, $J = 8.0$ Hz, 1H). MS 511.3 ($\text{M}+1$) $^+$
9/11		$^1\text{H-NMR}$ (400 MHz, CD_3OD) δ : 0.76-0.84 (m, 2H), 1.06-1.20 (m, 4H), 1.23 (s, 9H), 1.55-1.62 (m, 5H), 1.76-1.80 (m, 1H), 2.12-2.20 (m, 2H), 2.51-2.58 (m, 4H), 2.64-2.69 (m, 2H), 2.83-2.87 (m, 2H), 3.08-3.13 (m, 1H), 3.48-3.54 (m, 1H), 4.73-4.78 (m, 1H), 7.33 (d, $J = 8.0$ Hz, 1H), 7.83 (d, $J = 8.4$ Hz, 1H). MS 574.3 [$\text{M}+1$] $^+$

Example 10

N-(4-Amino-3,3-dimethyl-4-oxobutyl)-5-(4-(*N*-(*tert*-butyl)sulfamoyl)-3-(trifluoromethyl)phenyl)-4-(cyclohexylmethyl)thiazole-2-carboxamide (**10**)

To a solution of compound **9/1** (90 mg, 0.15 mmol) in dry DMF (2 mL) was added HATU (86 mg, 0.23 mmol) and DIPEA (48 mg, 0.38 mmol). The mixture was stirred for 60 min and then NH_4Cl (10 mg, 0.18 mmol) was added. The reaction mixture was stirred overnight, quenched with water and extracted with EA. The organic layer was washed with brine, dried over Na_2SO_4 , filtered, evaporated and purified by prep-HPLC to give compound **10** (17 mg, 19%) as a white solid. $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 8.36 (d, 1H, $J = 8.0$ Hz), 7.88 (s, 1H), 7.71 (dd, 2H, $J = 8.0$, $J = 1.6$ Hz), 7.46 (t, 1H, $J = 5.6$ Hz), 6.10 (br s, 1H), 5.28 (br s, 1H), 4.72 (s, 1H), 3.49-3.55 (m, 2H), 2.63 (d, 2H, $J = 6.8$ Hz), 1.93-2.00 (m, 2H), 1.79-1.82 (m, 1H), 1.62-1.65 (m, 5H), 1.29 (m, 15H), 1.10-1.25 (m, 3H), 0.88-0.93 (m, 2 H). MS 617.3 ($\text{M}+1$) $^+$.

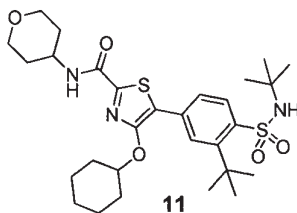
10

Example 10/1 to 10/4

The following Examples were prepared from the corresponding acids via amide coupling similar as described in Example 10:

#	Structure	Analytical data
10/1		$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 8.36 (d, 1H, $J = 8.0$ Hz), 7.87 (s, 1H), 7.71 (dd, 1H, $J = 8.4$, $J = 1.6$ Hz), 7.46 (t, $J = 6.0$ Hz, 1H), 6.02 (br s, 1H), 4.71 (s, 1H), 3.46-3.51 (m, 1H), 2.78 (d, 3H, $J = 4.8$ Hz), 2.63 (d, 2H, $J = 7.2$ Hz), 1.92-1.96 (m, 2H), 1.81-1.84 (m, 1H), 1.50-1.67 (m, 5H), 1.28-1.10 (m, 18H), 0.86-0.93 (m, 2H). MS 631.3 ($\text{M}+1$) $^+$
10/2		$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 0.83-0.92 (m, 6H), 1.09-1.27 (m, 3H), 1.36-1.41 (m, 2H), 1.44 (s, 3H), 1.62-1.79 (m, 8H), 2.32-2.47 (m, 4H), 2.61 (d, $J = 6.9$ Hz, 2H), 3.14-3.18 (m, 4H), 4.20-4.26 (m, 1H), 6.86 (s, 1H), 7.22-7.23 (m, 1H), 7.44 (s, 1H), 7.55 (s, 1H), 7.68 (s, 1H). MS Found: 595.7 ($\text{M}+1$) $^+$
10/3		$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 0.83-0.92 (m, 6H), 1.12-1.27 (m, 3H), 1.43 (s, 3H), 1.56 (s, 6H), 1.61-1.80 (m, 6H), 1.89-1.93 (m, 3H), 2.30-2.48 (m, 4H), 2.62 (d, $J = 6.9$ Hz, 2H), 3.14-3.19 (m, 4H), 3.94-3.98 (m, 2H), 4.23-4.27 (m, 1H), 7.23 (d, $J = 8.4$ Hz, 1H), 7.49 (s, 1H), 7.53 (t, $J = 1.8$ Hz, 1H), 7.70 (t, $J = 1.8$ Hz, 1H). MS 616.3 ($\text{M}+1$) $^+$
10/4		$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 0.84-0.91 (m, 6H), 1.09-1.32 (m, 4H), 1.45 (s, 3H), 1.77 (s, 5H), 2.29-2.49 (m, 4H), 2.62 (d, $J = 6.9$ Hz, 2H), 3.14-3.15 (m, 4H), 4.23-4.25 (m, 1H), 4.59 (d, $J = 6.3$ Hz, 2H), 4.86 (d, $J = 6.3$ Hz, 2H), 6.47 (s, 1H), 7.22 (s, 1H), 7.41 (s, 1H), 7.54 (s, 1H), 7.68 (s, 1H). MS 600.3 ($\text{M}+1$) $^+$

15 **Example 11**



Step 1: Cyclohexyl 2-bromoacetate (11a)

If one were to treat cyclohexyl acetate with Br₂ in MeOH, compound **11a** can be obtained.

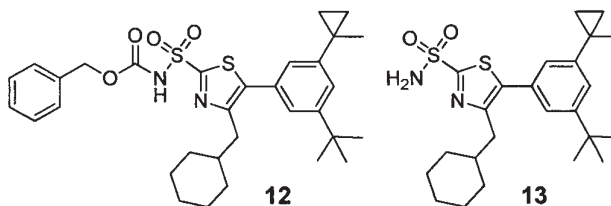
Step 2: Ethyl 4-(cyclohexyloxy)thiazole-2-carboxylate (11b)

- 5 If one were to treat compound **11a** with ethyl 2-amino-2-thioxoacetate in ethanol similar as described in Example 6, Step 2, compound **11b** can be obtained.

Step 3: 5-(3-(*tert*-Butyl)-4-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-4-(cyclohexyloxy)-*N*-(tetrahydro-2*H*-pyran-4-yl)thiazole-2-carboxamide (11)

- 10 If one were to treat compound **11b** similar as described in Example 6, Step 3 to 6, compound **11** can be obtained.

Example 12



Step 1: 4-(Cyclohexylmethyl)thiazol-2-amine (12a)

- 15 A solution of 1-bromo-3-cyclohexylpropan-2-one (2.8 g, 12.8 mmol) and thiourea (1.07 g, 14.1 mmol) in EtOH (20 mL) was refluxed for 4 h, concentrated and portioned between DCM and sat. NaHCO₃. The organic layer was washed with brine, dried over Na₂SO₄, filtered, concentrated and purified by CC (PE/EA = 3/1) to give compound **12a** (1.1 g, 44%) as a yellow solid.

20 **Step 2: 5-Bromo-4-(cyclohexylmethyl)thiazol-2-amine (12b)**

To a solution of compound **12a** (1.0 g, 5.1 mmol) in MeCN (10 mL) was added NBS (1.1 g, 6.1 mmol) and the solution was stirred overnight at rt, diluted with sat. NaHCO₃ and extracted with EA. The organic layer was washed water and brine consecutively, dried over Na₂SO₄, filtered and concentrated to give crude compound **12b** (1.14 g, 81%) as a pale yellow solid.

25 **Step 3: 2,5-Dibromo-4-(cyclohexylmethyl)thiazole (12c)**

To a solution of compound **12b** (1.14 g, 4.1 mmol) in MeCN (15 mL) was added CuBr₂ (1.37 g, 6.1 mmol) and isoamyl nitrite (900 mg, 7.65 mmol) at 0°C and the solution was stirred at this temperature for 1 h, concentrated and diluted with water. The aq. phase was extracted

with EA and the organic layer was washed with water and brine consecutively, dried over Na₂SO₄, filtered, concentrated and purified by CC (PE/EA = 5/1) to give compound **12c** (800 mg, 57%) as a brown-red oil.

Step 4: 5-Bromo-4-(cyclohexylmethyl)thiazole-2-sulfonamide (**12d**)

- 5 The solution of compound **12c** (3.1 g, 9.14 mmol), BnSH (1.7 g, 13.7 mmol) and K₂CO₃ (2.52 g, 18.3 mmol) in DMF (30 mL) was stirred at 60°C for 2 h, cooled to rt, diluted with water and extracted with EA (3 x). The combined organic layers were washed with water (3 x) and brine twice consecutively, dried over Na₂SO₄, filtered and concentrated to give a residue. To this residue was added CCl₄ (15 mL) and water (1.5 mL) and the solution was stirred for 1 min. Cl₂
- 10 was bubbled through the system for 30 min. The organic layer was separated, washed with water, dried over Na₂SO₄, filtered and concentrated to give a residue. This residue was dissolved in THF (10 mL) and then 20% aq. NH₄OH (5 mL) was added. The solution was stirred at rt overnight, concentrated and extracted with EA. The organic layer was separated, washed with water, dried over Na₂SO₄, filtered, concentrated and purified by CC (PE/EA =
- 15 2/1) to give compound **12d** (1.3 g, 42%) as a brown solid.

Step 5: Benzyl (5-bromo-4-(cyclohexylmethyl)thiazol-2-yl)sulfonylcarbamate (**12e**)

- To a solution of compound **12d** (550 mg, 2.0 mmol) and NEt₃ (404 mg, 7.0 mmol) and DIPEA (3.09 g, 4.0 mmol) in THF (10 mL) was added Cbz-Cl (525 mg, 3.0 mmol) at 0°C under nitrogen and the solution was stirred at rt for 3 h, poured into water and extracted with EA
- 20 twice. The combined organic layers were washed with water and brine consecutively, dried over Na₂SO₄, filtered, concentrated and purified by CC (PE/EA = 3/1) to give compound **12e** (230 mg, 28%) as a yellow solid.

Step 6: Benzyl (5-(3-(*tert*-butyl)-5-(1-methylcyclopropyl)phenyl)-4-(cyclohexylmethyl)thiazol-2-yl)sulfonylcarbamate (**12**)

- 25 A solution of compound **12e** (400 mg, 0.98 mmol), compound **P2** (458 mg, 1.46 mmol), K₂CO₃ (552 mg, 4.0 mmol) and Pd(PPh₃)Cl₂ (40 mg) in a mixture of EtOH (3 mL), toluene (6 mL) and water (3 mL) was stirred at 90°C overnight under nitrogen, concentrated, poured into water and extracted with EA. The organic layer was washed with water and brine consecutively, dried over Na₂SO₄, filtered, concentrated and purified by CC (PE/EA = 1/1) to give compound
- 30 **12** (200 mg, 35%) as a white solid. ¹H-NMR (CDCl₃, 400 MHz) δ: 0.78-0.80 (m, 2H), 0.84-0.90 (m, 4H), 1.11-1.15 (m, 3H), 1.24-1.27 (m, 1H), 1.31 (s, 9H), 1.47 (s, 3H), 1.58-1.61 (m, 5H), 1.66-1.73 (m, 1H), 2.59 (d, J = 6.8 Hz, 2H), 5.00 (s, 2H), 7.06 (s, 1H), 7.23 (s, 1H), 7.28-7.33 (m, 6H). MS 581.3 (M+1)⁺.

Step 6: 5-(3-(*tert*-Butyl)-5-(1-methylcyclopropyl)phenyl)-4-(cyclohexylmethyl)thiazole-2-sulfonamide (**13**)

- 35 The solution of compound **12** (130 mg, 0.22 mmol) and 10% Pd/C (50% wet, 15 mg) in MeOH (5 mL) was stirred overnight at rt under H₂ atmosphere, concentrated and purified by prep-HPLC to give compound **13** (25 mg, 25%) as a white solid. ¹H-NMR (300 MHz, CDCl₃) δ: 7.33

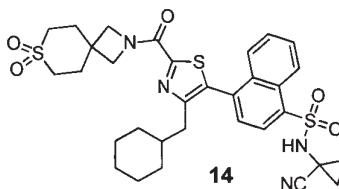
(t, 1H, J = 1.7 Hz), 7.21 (t, 1H, J = 1.7 Hz), 7.09 (t, 1H, J = 1.7 Hz), 5.56 (s, 2H), 2.66 (d, 2H, J = 6.9 Hz), 1.76-1.81 (m, 1H), 1.63-1.68 (m, 5H), 1.43 (s, 3H), 1.34 (s, 9H), 1.13-1.22 (m, 3H), 0.76-0.96 (m, 6H). MS 447.1 (M+1)⁺.

5 Example 13/1 to 13/3

The following Examples were prepared similar as in Example 12:

#	Structure	Analytical data
13/1		¹ H-NMR (300 MHz, CDCl ₃) δ: 8.24 (d, 1H, J = 8.1 Hz), 7.67 (d, 1H, J = 0.9 Hz), 7.32 (d, 1H, J = 7.5 Hz), 5.40 (s, 2H), 4.64 (s, 1H), 2.68 (d, 2H, J = 6.9 Hz), 1.79-1.82 (m, 1H), 1.59-1.64 (m, 14H), 1.34 (s, 9H), 1.13-1.26 (m, 3H), 0.81-0.92 (m, 2 H). MS 528.2 (M+1) ⁺
13/2		¹ H-NMR (CDCl ₃ , 400 MHz) δ: 0.86-0.92 (m, 2H), 1.09-1.15 (m, 3H), 1.18-1.29 (m, 10H), 1.64-1.67 (m, 5H), 1.75-1.85 (m, 1H), 2.66 (d, J = 6.8 Hz, 2H), 4.75 (s, 1H), 5.35 (s, 2H), 7.72 (d, J = 8.4 Hz, 1H), 7.87 (s, 1H), 8.39 (d, J = 8.4 Hz, 1H). MS 540.2 (M+1) ⁺
13/3		¹ H-NMR (300 MHz, CDCl ₃) δ: 0.62-0.66 (m, 2H), 0.90-1.03 (m, 3H), 1.23 (s, 9H), 1.44-1.55 (m, 6H), 2.38 (br s, 2H), 4.68 (s, 1H), 5.30 (br s, 1H), 7.52 (d, J = 7.5 Hz, 1H), 7.61-7.63 (m, 1H), 7.70-7.76 (m, 2H), 8.36 (d, J = 7.5 Hz, 1H), 8.70 (d, J = 8.7 Hz, 1H). MS 522.2 [M+1] ⁺

Example 14



10 Step 1: Benzyl(naphthalen-1-yl)sulfane (14a)

To a suspension of naphthalene-1-thiol (40 g, 0.25 mol) and K₂CO₃ (138 g, 1.00 mol) in DMF (150 mL) was added BnBr (85.5 g, 0.50 mol) and the suspension was stirred at 45°C overnight, cooled to rt, filtered and the filtrate was washed with EA. The combined organic phase was concentrated and purified by CC (PE) to give compound **14a** (59 g, 94%) as a yellow solid.

15

Step 2: Benzyl(4-bromonaphthalen-1-yl)sulfane (14b)

To a solution of compound **14a** (59 g, 236 mmol) in CCl₄ (500 mL) was added NBS (160 g, 1.00 mol) at -78°C and the solution was stirred at this temperature for 1 h, quenched with water and stirred at rt for 1 h. The organic layer was washed with water and brine, dried over Na₂SO₄, filtered, concentrated and purified by CC (PE) to give crude compound **14b** (18 g, 23%) as a pale red solid.

20

Step 3: Ethyl 5-(4-(benzylthio)naphthalen-1-yl)-4-(cyclohexylmethyl)thiazole-2-carboxylate (14c)

The solution of compound **14b** (2.34 g, 7.10 mmol), ethyl 4-(cyclohexylmethyl)thiazole-2-carboxylate (1.80 g, 7.10 mmol), KOAc (1.39 g, 14.2 mmol), PPh₃ (2.05 g, 7.80 mmol) and Pd(OAc)₂ (160 mg, 0.71 mmol) in a solution of DMF (30 mL) was heated at 110°C overnight, cooled to rt, diluted with EA and water. The organic phase was washed with water and brine, dried over Na₂SO₄, filtered, concentrated and purified by CC (PE/EA = 10/1) to give compound **14c** (1.40 g, 39%) as a white solid.

Step 4: Ethyl 5-(4-(chlorosulfonyl)naphthalen-1-yl)-4-(cyclohexylmethyl)thiazole-2-carboxylate (14d)

To an ice cold solution of compound **14c** (1.40 g, 2.79 mmol) in AcOH (15 mL) was added a solution of Cl₂ in AcOH (~1M, 10 mL, 10 mmol) and the solution was allowed to warm to rt and stirred for overnight, quenched with water and extracted with Et₂O twice. The combined organic layers were washed with water and brine, dried over Na₂SO₄, filtered, concentrated and purified by CC (PE/EA = 10/1) to give compound **14d** (550 mg, 41%) as a light yellow oil.

Step 5: Ethyl 5-(4-(N-(1-cyanocyclopropyl)sulfamoyl)naphthalen-1-yl)-4-(cyclohexylmethyl)thiazole-2-carboxylate (14e)

The solution of compound **14d** (150 mg, 0.314 mmol) and DIEA (129 mg, 1.00 mmol) in dry DCM (2 mL) was added 1-aminocyclopropanecarbonitrile (33 mg, 0.40 mmol) at 0°C and the solution was stirred at this temperature overnight, washed with water and brine, dried over Na₂SO₄, filtered, concentrated and purified by CC (PE/EA = 6/1) to give compound **14e** (101 mg, 61%) as a white solid.

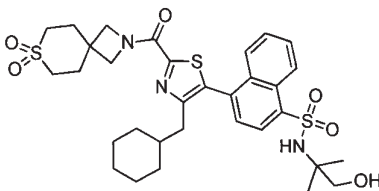
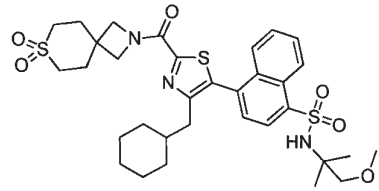
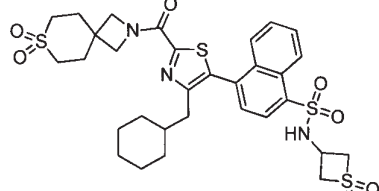
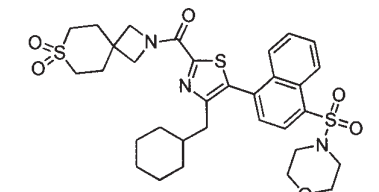
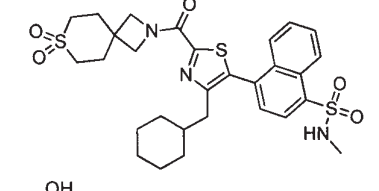
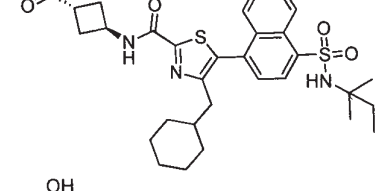
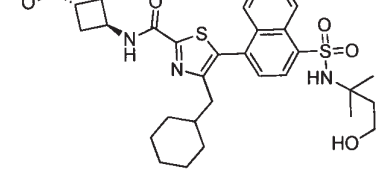
Step 6: N-(1-Cyanocyclopropyl)-4-(4-(cyclohexylmethyl)-2-(7,7-dioxido-7-thia-2-azaspiro[3.5]nonane-2-carbonyl)thiazol-5-yl)naphthalene-1-sulfonamide (14)

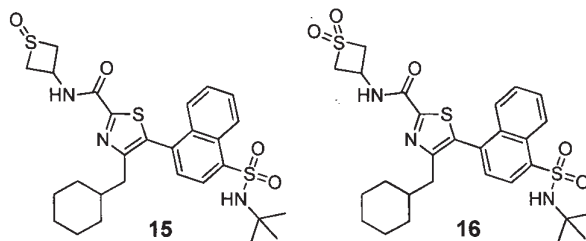
Compound **14e** was saponified and then coupled with the appropriate amine 7-thia-2-azaspiro[3.5] nonane 7,7-dioxide to give compound **14** (27%) as a white solid. ¹H-NMR (CDCl₃, 300 MHz) δ: 0.68-0.74 (m, 2H), 0.98-1.21 (m, 3H), 1.25 (s, 2H), 1.38 (s, 2H), 1.48-1.56 (m, 6H), 2.34-2.36 (m, 2H), 2.46 (s, 4H), 3.08 (br s, 4H), 4.06 (s, 2H), 4.55 (s, 2H), 5.65 (s, 1H), 7.60 (t, J = 7.8 Hz, 2H), 7.76 (t, J = 8.4 Hz, 2H), 8.45 (d, J = 7.8 Hz, 1H), 8.68 (d, J = 8.4 Hz, 1H). MS 653.2 (M+1)⁺.

Example 14/1 to 14/7

The following Examples were prepared similar as in Example **14**:

#	Structure	Analytical data
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#	Structure	Analytical data
14/1		$^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ : 0.59-0.74 (m, 2H), 0.97-1.07 (m, 3H), 1.20 (s, 6H), 1.38 (s, 2H), 1.53-1.68 (m, 6H), 2.32-2.36 (m, 2H), 2.46-2.47 (m, 4H), 3.07-3.09 (m, 4H), 3.47 (s, 2H), 4.06 (s, 2H), 4.55 (s, 2H), 5.05 (s, 1H), 7.51 (d, $J = 7.5$ Hz, 1H), 7.55-7.61 (m, 1H), 7.70-7.74 (m, 2H), 8.35 (d, $J = 7.5$ Hz, 1H), 8.71 (d, $J = 5.7$ Hz, 1H). MS 660.2 ($\text{M}+1$) $^+$
14/2		$^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ : 0.68-0.71 (m, 2H), 1.03-1.10 (m, 3H), 1.18 (s, 6H), 1.26 (s, 2H), 1.51-1.52 (m, 3H), 1.55-1.58 (m, 1H), 2.33-2.36 (m, 2H), 2.44-2.48 (m, 4H), 3.05 (s, 2H), 3.06-3.10 (m, 4H), 3.15 (s, 3H), 4.05 (s, 2H), 4.55 (s, 2H), 5.23 (s, 1H), 7.49 (d, $J = 5.7$ Hz, 1H), 7.51-7.56 (m, 1H), 7.68-7.72 (m, 2H), 8.34 (d, $J = 7.8$ Hz, 1H), 8.69 (d, $J = 5.7$ Hz, 1H). MS 674.2 ($\text{M}+1$) $^+$
14/3		$^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ : 0.68-0.71 (m, 2H), 1.03-1.10 (m, 3H), 1.13 (s, 2H), 1.51-1.52 (m, 3H), 1.58-1.71 (m, 1H), 2.33-2.36 (m, 2H), 2.45-2.49 (m, 4H), 3.07-3.11 (m, 2H), 3.84-3.89 (m, 2H), 4.07 (s, 2H), 4.22-4.36 (m, 3H), 4.55 (s, 2H), 5.68-5.72 (m, 1H), 7.53 (d, $J = 7.5$ Hz, 1H), 7.59-7.64 (m, 1H), 7.73-7.77 (m, 2H), 8.31 (d, $J = 7.5$ Hz, 1H), 8.67 (d, $J = 8.4$ Hz, 1H). MS 692.2 ($\text{M}+1$) $^+$
14/4		$^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ : 0.67-0.72 (m, 2H), 1.05-1.08 (m, 3H), 1.16-1.25 (m, 2H), 1.57-1.69 (m, 4H), 2.35-2.37 (m, 2H), 2.45-2.49 (m, 4H), 3.07-3.10 (m, 4H), 3.23-3.26 (m, 4H), 3.72-3.75 (m, 4H), 4.06 (s, 2H), 4.55 (s, 2H), 7.52 (d, $J = 7.5$ Hz, 1H), 7.56-7.62 (m, 1H), 7.68-7.72 (m, 2H), 8.24 (d, $J = 7.5$ Hz, 1H), 8.85 (d, $J = 7.8$ Hz, 1H). MS 658.2 ($\text{M}+1$) $^+$
14/5		$^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ : 0.67-0.72 (m, 2H), 1.05-1.08 (m, 3H), 1.16-1.25 (m, 2H), 1.51-1.60 (m, 4H), 2.35-2.37 (m, 2H), 2.46-2.47 (m, 4H), 2.68-2.70 (m, 3H), 3.06-3.09 (m, 4H), 4.06 (s, 2H), 4.55 (s, 2H), 4.65-4.68 (m, 1H), 7.50-7.58 (m, 2H), 7.69-7.73 (m, 2H), 8.29 (d, $J = 7.2$ Hz, 1H), 8.75 (d, $J = 8.7$ Hz, 1H). MS 602.2 ($\text{M}+1$) $^+$
14/6		$^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ : 0.57-0.69 (m, 2H), 0.76 (t, $J = 7.2$ Hz, 3H), 0.95-1.09 (m, 3H), 1.15 (s, 6H), 1.47-1.73 (m, 8H), 2.29-2.38 (m, 2H), 2.50-2.61 (m, 2H), 2.82-2.90 (m, 2H), 3.18-3.28 (m, 1H), 4.67 (s, 1H), 4.82-4.90 (m, 1H), 7.51 (d, $J = 7.5$ Hz, 1H), 7.55-7.60 (m, 2H), 7.69-7.74 (m, 2H), 8.35 (d, $J = 7.8$ Hz, 1H), 8.69 (d, $J = 9.0$ Hz, 1H). MS 598.3 ($\text{M}+1$) $^+$
14/7		$^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ : 0.59-0.70 (m, 2H), 1.00-1.13 (m, 3H), 1.25 (s, 6H), 1.48-1.57 (m, 5H), 1.71-1.75 (m, 3H), 2.35 (br s, 2H), 2.50-2.60 (m, 2H), 2.82-2.88 (m, 2H), 3.19-3.26 (m, 1H), 3.85 (t, $J = 5.7$ Hz, 1H), 4.82-4.89 (m, 1H), 6.23 (s, 1H), 7.49-7.59 (m, 3H), 7.68-7.73 (m, 2H), 8.35 (d, $J = 7.5$ Hz, 1H), 8.69 (d, $J = 8.7$ Hz, 1H). MS 614.3 ($\text{M}+1$) $^+$

Example 15 and Example 16

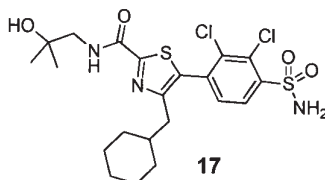
To a solution of compound **6/14** (250 mg, 0.45 mmol) in DCM (10 mL) was added *m*-CPBA (102 mg, 0.50 mmol) and the solution was stirred at rt for 30 min, quenched with aq. Na₂SO₃ and extracted with EA (3x). The combined organic layers were washed with water and brine, dried over Na₂SO₄, filtered, concentrated and purified by prep-HPLC to give compound **15** (35 mg, 14%) as a white solid and compound **16** (33 mg, 12%) as a white solid. For compound **15**: ¹H-NMR (CDCl₃, 300 MHz) δ: 0.64-0.68 (m, 2H), 0.92-1.18 (m, 2H), 1.25 (s, 9H), 1.48-1.53 (m, 7H), 2.36 (br s, 2H), 3.40 (td, J = 3.0 Hz, 9.6 Hz, 2H), 4.23 (td, J = 3.0 Hz, 7.8 Hz, 2H), 4.64 (s, 1H), 7.51 (d, J = 7.8 Hz, 1H), 7.57-7.60 (m, 1H), 7.65-7.74 (m, 3H), 8.35 (d, J = 7.5 Hz, 1H), 8.69 (d, J = 8.4 Hz, 1H). MS 574.2 [M+1]⁺. For compound **16**: ¹H-NMR (CDCl₃, 300 MHz) δ: 0.62-0.66 (m, 2H), 0.88-1.14 (m, 2H), 1.22 (s, 9H), 1.46-1.52 (m, 7H), 2.34 (br s, 2H), 4.22-4.28 (m, 2H), 4.61-4.70 (m, 4H), 4.91-4.93 (m, 1H), 7.51 (d, J = 7.5 Hz, 1H), 7.58-7.60 (m, 1H), 7.68-7.74 (m, 2H), 7.83 (d, J = 6.9 Hz, 1H), 8.36 (d, J = 7.5 Hz, 1H), 8.69 (d, J = 8.4 Hz, 1H). MS 590.2 [M+1]⁺.

Example 15/1 to 15/9

The following Examples were prepared similar as in Example **15**:

#	Structure	Analytical data
15/1	Isomer 1	¹ H-NMR (CDCl ₃ , 300 MHz) δ: 0.82-0.86 (m, 2H), 1.12-1.20 (m, 3H), 1.27 (s, 10H), 1.58-1.67 (m, 5H), 1.70 (s, 6H), 1.73-1.77 (m, 1H), 2.63 (d, J = 7.5 Hz, 2H), 3.54-3.62 (m, 2H), 4.38-4.39 (m, 1H), 5.33-5.35 (m, 1H), 6.25-6.26 (m, 1H), 7.36-7.39 (m, 2H), 7.57 (d, J = 6.6 Hz, 1H), 8.25 (d, J = 9.0 Hz, 1H). MS 582.2 (M+1) ⁺
15/2	Isomer 2	¹ H-NMR (CDCl ₃ , 300 MHz) δ: 0.85-0.89 (m, 2H), 1.16-1.25 (m, 3H), 1.28 (s, 9H), 1.58-1.64 (m, 5H), 1.70 (s, 6H), 1.75-1.81 (m, 1H), 2.65 (d, J = 7.2 Hz, 2H), 3.33-3.42 (m, 2H), 4.18-4.25 (m, 2H), 4.38-4.40 (m, 1H), 4.61-4.64 (m, 1H), 6.25-6.26 (m, 1H), 7.36-7.39 (m, 2H), 7.59 (d, J = 8.1 Hz, 1H), 8.23-8.26 (m, 1H). MS 582.2 (M+1) ⁺
15/3		¹ H-NMR (CDCl ₃ , 300 MHz) δ: 0.84-0.87 (m, 2H), 1.14-1.25 (m, 3H), 1.27 (s, 12H), 1.59-1.64 (m, 5H), 1.70 (s, 6H), 1.74-1.80 (m, 1H), 2.65 (d, J = 7.2 Hz, 2H), 4.19-4.25 (m, 2H), 4.60-4.67 (m, 1H), 4.88-4.90 (m, 1H), 7.36-7.39 (m, 1H), 7.78 (d, J = 7.2 Hz, 1H), 8.25 (d, J = 9.0 Hz, 1H). MS 598.2 (M+1) ⁺

#	Structure	Analytical data
15/4		$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 0.65-0.83 (m, 2H), 1.04-1.25 (m, 3H), 1.28 (s, 9H), 1.53-1.55 (m, 4H), 1.71-1.77 (m, 1H), 2.42 (d, $J = 7.2$ Hz, 2H), 4.19-4.25 (m, 2H), 4.59-4.69 (m, 2H), 4.87-4.91 (m, 1H), 5.07 (s, 1H), 7.38 (d, $J = 8.1$ Hz, 1H), 7.77 (d, $J = 9.3$ Hz, 1H), 8.14 (d, $J = 8.1$ Hz, 1H). MS 608.1 ($\text{M}+1$) $^+$
15/5		$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 0.76-0.83 (m, 2H), 1.06-1.26 (m, 3H), 1.28 (s, 9H), 1.54-1.63 (m, 4H), 1.71-1.76 (m, 1H), 2.23-2.27 (m, 2H), 2.42 (d, $J = 7.5$ Hz, 2H), 3.40-3.48 (m, 2H), 4.19-4.25 (m, 2H), 4.63-4.66 (m, 1H), 5.11 (s, 1H), 7.37 (d, $J = 8.4$ Hz, 1H), 7.68 (d, $J = 7.8$ Hz, 1H), 8.13 (d, $J = 8.4$ Hz, 1H). MS 592.1 ($\text{M}+1$) $^+$
15/6		$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 0.77-0.83 (m, 2H), 1.10-1.20 (m, 3H), 1.28 (s, 9H), 1.53-1.77 (m, 5H), 2.40 (d, $J = 6.9$ Hz, 2H), 4.43 (s, 4H), 4.48 (s, 2H), 4.99 (s, 2H), 5.08 (s, 1H), 7.37 (d, $J = 6.3$ Hz, 1H), 8.12 (d, $J = 6.0$ Hz, 1H). MS 634.1 ($\text{M}+1$) $^+$
15/7		$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 0.75-0.79 (m, 2H), 1.15-1.19 (m, 3H), 1.28 (s, 9H), 1.52-1.63 (m, 6H), 2.42 (d, $J = 6.9$ Hz, 2H), 3.22 (s, 3H), 5.00 (d, $J = 6.6$ Hz, 2H), 5.07 (s, 1H), 7.39 (d, $J = 8.4$ Hz, 1H), 8.00-8.03 (m, 1H), 8.14 (d, $J = 8.4$ Hz, 1H), 8.25 (s, 1H). MS 679.1 [$\text{M}+1$] $^+$
15/8		$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 0.63-0.71 (m, 2H), 1.00-1.13 (m, 3H), 1.23 (s, 9H), 1.48-1.58 (m, 5H), 2.34 (br s, 1H), 3.02-3.07 (m, 1H), 3.80 (t, $J = 6.6$ Hz, 2H), 3.98-4.05 (m, 2H), 4.24-4.32 (m, 2H), 4.63 (s, 1H), 7.51 (d, $J = 7.8$ Hz, 1H), 7.58-7.63 (m, 2H), 7.70-7.73 (m, 2H), 8.36 (d, $J = 7.5$ Hz, 1H), 8.69 (d, $J = 8.1$ Hz, 1H). MS 604.2 [$\text{M}+1$] $^+$
15/9		$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 8.68 (d, 1H, $J = 8.8$ Hz), 8.34 (d, 1H, $J = 7.6$ Hz), 7.73-7.69 (m, 2H), 7.58-7.49 (m, 2H), 4.63 (s, 1H), 4.51 (s, 2H), 4.02-4.01 (m, 2H), 3.06-3.03 (m, 2H), 2.83-2.73 (m, 2H), 2.65-2.59 (m, 2H), 2.38-2.35 (m, 2H), 2.08-2.04 (m, 2H), 1.65-1.57 (m, 6H), 1.22 (s, 9H), 1.19-1.03 (m, 3H), 0.74-0.65 (m, 2H). MS 628.2 ($\text{M}+1$) $^+$

Example 17

5 4-(Cyclohexylmethyl)-5-(2,3-dichloro-4-sulfamoylphenyl)-N-(2-hydroxy-2-methylpropyl)thiazole-2-carboxamide (17)

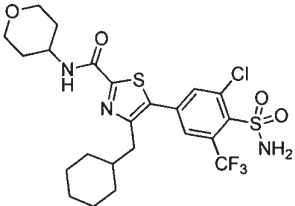
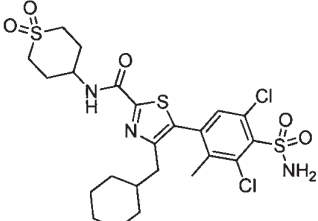
A solution of compound **6/29** (260 mg, 0.45 mmol) in TFA (2 mL) was stirred for 2 h at 55°C, concentrated, diluted with EA, washed with brine, dried over Na_2SO_4 , filtered, concentrated

and purified by prep-HPLC to give compound **17** (90 mg, 39%) as a white solid. ¹H-NMR (300 MHz, CDCl₃) δ: 0.71-0.83 (m, 2H), 1.04-1.30 (m, 3H), 1.33 (s, 6H), 1.55-1.80 (m, 8H), 2.00 (s, 1H), 2.41 (d, J = 6.9 Hz, 2H), 3.49 (d, J = 6.9 Hz, 2H), 5.38 (s, 2H), 7.39 (d, J = 8.4 Hz, 1H), 7.65 (t, J = 6.3 Hz, 1H), 8.11 (d, J = 8.1 Hz, 1H). MS 520.1 (M+1)⁺.

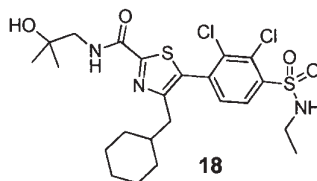
5

Example 17/1 to 17/2

The following Examples were prepared similar as in Example 17:

#	Structure	Analytical data
17/1		$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 0.86-0.97 (m, 2H), 1.13-1.30 (m, 3H), 1.57-1.82 (m, 7H), 1.84-1.87 (m, 1H), 2.00-2.06 (m, 2H), 2.64 (d, $J = 7.2$ Hz, 2H), 3.51-3.59 (m, 2H), 4.01-4.06 (m, 2H), 4.13-4.22 (m, 1H), 5.51-5.53 (m, 2H), 7.10-7.13 (m, 1H), 7.80 (s, 1H), 7.87 (s, 1H). MS 566.1 ($\text{M}+1$) $^+$
17/2		$^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ : 0.74-0.86 (m, 2H), 1.13-1.25 (m, 3H), 1.53-1.74 (m, 6H), 2.26 (s, 3H), 2.35-2.47 (m, 6H), 3.15-3.17 (m, 4H), 4.24-4.28 (m, 1H), 5.58 (s, 2H), 7.22 (d, $J = 11.2$ Hz, 1H), 7.36 (s, 1H). MS 594.1 ($\text{M}+1$) $^+$

Example 18

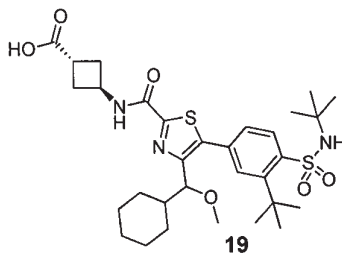


4-(Cyclohexylmethyl)-5-(2,3-dichloro-4-(*N*-ethylsulfamoyl)phenyl)-*N*-(2-hydroxy-2-methylpropyl)thiazole-2-carboxamide (18)

The solution of compound **17** (40 mg, 0.07 mmol) and aq. CH₃CHO (0.5 mL) in MeOH (5 mL) was stirred for 10 min at rt. Then NaBH₃CN (50 mg, 0.7 mmol) was added and the solution was stirred for 3 d at rt, diluted with DCM, washed with brine, dried over Na₂SO₄, filtered, concentrated and purified by prep-HPLC to give compound **18** (26 mg, 62%) as a white solid. ¹H-NMR (300 MHz, CD₃OD) δ: 0.74-0.84 (m, 2H), 1.06-1.20 (m, 5H), 1.26 (s, 6H), 1.56-1.60 (m, 4H), 1.77 (br s, 1H), 2.49 (d, J = 6.9 Hz, 2H), 3.00 (q, J = 6.9 Hz, 2H), 3.31 (s, 1H), 3.42 (s, 2H), 7.57 (t, J = 8.1 Hz, 1H), 8.11 (d, J = 7.8 Hz, 1H). MS 548.2 (M+1)⁺.

20

Example 19



Step 1: 2-Cyclohexyl-2-methoxyacetic acid (19a**)**

To a solution of NaH (21.4 g, 357 mmol) in dry THF (360 mL) was added cyclohexanecarbaldehyde (20 g, 179 mmol) and CHCl_3 (42.6 g, 536 mmol) at 0°C under N_2 and the solution was stirred at this temperature for 3 h. Then a solution of NaOH (50 g, 1.25 mol) in MeOH (214 mL) was added and the solution was stirred at 65°C for 3 h, quenched with water and extracted with Et_2O . The aq. layer was adjusted pH to 1 with conc. HCl and extracted with Et_2O twice. The combined organic layers were washed with water and brine, dried over Na_2SO_4 , filtered and concentrated to give crude compound **19a** (12.9 g, 42%) as a brown oil.

Step 2: 2-Cyclohexyl-*N*,2-dimethoxy-*N*-methylacetamide (19b**)**

A solution of crude compound **19a** (12.9 g, 75.0 mmol) in dry DMF (300 mL) was cooled with an ice bath and HATU (28.5 g, 75.0 mmol) was added. After being stirred at rt for 30 min, DIEA (29.0 g, 225 mmol) and *N,O*-dimethylhydroxylamine hydrochloride (8.80 g, 90 mmol) were added and the mixture was stirred at rt for 2 h, quenched with water and extracted with EA twice. The combined organic layers were washed with water (3x) and brine, dried over Na_2SO_4 , filtered, concentrated and purified by CCI (PE/EA = 9/1) to give compound **19b** (8.4 g, 52%) as a pale yellow liquid.

Step 3: 1-Cyclohexyl-1-methoxypropan-2-one (19c**)**

To a solution of compound **19b** (8.40 g, 39.1 mmol) in dry THF (100 mL) was added MeMgBr (3M in Et_2O , 30 mL, 90 mol) under ice cooling and the solution was stirred at rt for 3 h, quenched carefully with saturated aq. NH_4Cl . The organic phase was separated and concentrated, diluted with EA, washed with water and brine, dried over Na_2SO_4 , filtered, concentrated and purified by CC (PE/EA = 40/1) to give compound **19c** (6.1 g, 92%) as a pale yellow oil.

Step 4: 3-Bromo-1-cyclohexyl-1-methoxypropan-2-one (19d**)**

To an ice-cooled solution of compound **19c** (6.1 g, 35.9 mmol) in MeOH (60 mL) was added Br_2 (5.74 g, 35.9 mmol) in a single portion and the reaction temperature was kept below 15°C until the red color of the solution turned colorless. H_2O was added and the solution was extracted with in Et_2O (3x). The combined organic layers were washed with 10% aq. K_2CO_3 (3x), dried over Na_2SO_4 , filtered and concentrated to give compound **19d** (8.5 g, 95%) as a yellowish liquid.

Step 5: Ethyl 4-(cyclohexyl(methoxy)methyl)thiazole-2-carboxylate (**19e**)

A solution of compound **19d** (8.5 g, 34.1 mmol) and ethylthioxamate (5.05 g, 38.0 mmol) in EtOH (100 mL) was heated at 80°C for 6 h and then cooled to 0°C. The resulting solution was diluted with water and EA and then neutralized to pH = 7 using NH₄OH. The aq. layer was
5 extracted with EA (3x). The combined organic layers were dried over Na₂SO₄, filtered, concentrated and purified by CC (PE/EA = 40/1) to give compound **19e** (5.4 g, 56%) as a pale yellow oil.

Step 6: Ethyl 5-(3-(*tert*-butyl)-4-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-4-(cyclohexyl(methoxy)methyl)thiazole-2-carboxylate (**19f**)

10 A solution of compound **19e** (2.2 g, 7.78 mmol), 4-bromo-*N*,2-di-*tert*-butylbenzenesulfonamide (3.24 g, 9.32 mmol), Pd(OAc)₂ (200 mg) and PPh₃ (2.24 g, 8.54 mmol) in DMF (80 mL) was bubbled with N₂ for 5 min and then stirred at 170°C for 3 h and then 130°C overnight, cooled, diluted with water and extracted with EA. The organic layer was washed with brine, dried over Na₂SO₄, filtered, concentrated and purified by CC (PE/EA = 15/1) and then prep-HPLC to give
15 compound **19f** (280 mg, 6.5%) as a pale yellow solid.

Step 7: Potassium 5-(3-(*tert*-butyl)-4-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-4-(cyclohexyl(methoxy)methyl)thiazole-2-carboxylate (**19g**)

The solution of compound **19f** (280 mg, 0.51 mmol) and KOH (84 mg, 1.50 mmol) in MeOH (5 mL) was stirred at rt for 1 h and concentrated to give crude compound **19g** (350 mg) as a
20 white solid.

Step 8: *trans*-Methyl 3-(5-(3-(*tert*-butyl)-4-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-4-(cyclohexyl(methoxy)methyl)thiazole-2-carboxamido)cyclobutanecarboxylate (**19h**)

The solution of compound **19g** (250 mg, 0.364 mmol), *trans* methyl 3-aminocyclobutanecarboxylate hydrochloride (93 mg, 0.56 mmol), DIEA (867 mg, 6.72 mmol) and HATU
25 (213 mg, 0.56 mmol) in DMF (5 mL) was stirred overnight at rt, diluted with water and extracted with EA (3x). The combined organic layers were washed with water (3x) and brine consecutively, dried over Na₂SO₄, filtered, concentrated and purified by CC (PE/EA = 6/1) to give compound **19h** (91 mg, 39%) as a yellow solid.

Step 9: *trans*-3-(5-(3-(*tert*-Butyl)-4-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-4-(cyclohexyl(methoxy)methyl)thiazole-2-carboxamido)cyclobutanecarboxylic acid (**19**)

30 To a solution of compound **19h** (91 mg, 0.14 mmol) in a mixture of THF/MeOH/water (2 mL/2 mL/1 mL) was added LiOH·H₂O (11 mg, 0.26 mmol) and the solution was stirred at rt for 2 h, diluted with water and extracted with EA. The aq. layer was adjusted with 1N HCl to pH = 2 and then extracted with DCM. The combined organic phase was washed with brine, dried over
35 Na₂SO₄, filtered, concentrated and purified by prep-HPLC to give compound **19** (45 mg, 52%) as a white solid. ¹H-NMR (400 MHz, CDCl₃) δ: 0.75-1.02 (m, 2H), 1.10-1.31 (m, 4H), 1.34 (s, 9H), 1.60-1.68 (m, 11H), 1.73-1.78 (m, 1H), 1.92-2.00 (m, 1H), 2.18 (d, J = 12.8 Hz, 1H), 2.47-2.55 (m, 2H), 2.77-2.83 (m, 2H), 3.15 (s, 3H), 3.17-3.22 (m, 1H), 3.94 (d, J = 9.2 Hz, 1H), 4.60

(s, 1H), 4.78-4.84 (m, 1H), 7.35 (dd, J = 8.0 Hz, 2.0 Hz, 1H), 7.59 (d, J = 7.6 Hz, 1H), 7.68 (d, J = 2.0 Hz, 1H), 8.25 (d, J = 8.0 Hz, 1H). MS 620.2 [M+1]⁺.

Example 19/1 to 19/14

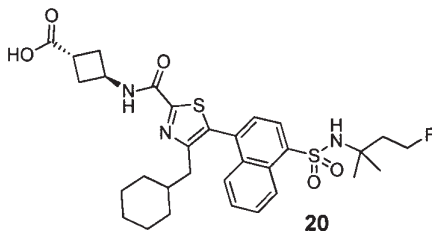
5 The following Examples were prepared similar as in Example 19:

#	Structure	Analytical data
19/1		¹ H-NMR (400 MHz, CDCl ₃) δ: 0.75-1.01 (m, 2H), 1.10-1.31 (m, 4H), 1.34 (s, 9H), 1.62 (s, 9H), 1.65-1.78 (m, 5H), 1.92-2.02 (m, 3H), 2.18 (d, J = 14.0 Hz, 1H), 3.14 (s, 3H), 3.53 (td, J = 11.6 Hz, 2.0 Hz, 2H), 3.93 (d, J = 9.2 Hz, 1H), 4.03 (d, J = 11.6 Hz, 2H), 4.08-4.20 (m, 1H), 7.24 (d, J = 8.4 Hz, 1H), 7.35 (dd, J = 8.4 Hz, 1.6 Hz, 1H), 7.69 (d, J = 1.6 Hz, 1H), 8.25 (d, J = 8.4 Hz, 1H). MS 606.3 [M+1] ⁺
19/2		¹ H-NMR (300 MHz, CDCl ₃) δ: 0.75-0.79 (m, 2H), 0.80-0.85 (m, 2H), 1.00-1.29 (m, 6H), 1.34 (s, 9H), 1.41 (s, 3H), 1.54-1.78 (m, 3H), 1.93-2.00 (m, 1H), 2.16-2.21 (m, 1H), 2.46-2.56 (m, 2H), 2.76-2.84 (m, 2H), 3.14 (s, 3H), 3.16-3.22 (m, 1H), 3.93 (d, J = 9.3 Hz, 1H), 4.77-4.84 (m, 1H), 7.05-7.06 (m, 1H), 7.18-7.19 (m, 1H), 7.32-7.33 (m, 1H), 7.57 (d, J = 8.1 Hz, 1H). MS 539.3 [M+1] ⁺
19/3		¹ H-NMR (300 MHz, CDCl ₃) δ: 0.75-0.79 (m, 2H), 0.80-0.85 (m, 2H), 1.00-1.29 (m, 5H), 1.33 (s, 9H), 1.44 (s, 3H), 1.57 (s, 1H), 1.60-1.76 (m, 5H), 1.93-2.03 (m, 3H), 2.15-2.21 (m, 3H), 2.21 (d, J = 12.6 Hz, 1H), 3.12 (s, 3H), 3.48-3.57 (m, 2H), 3.91 (d, J = 9.0 Hz, 1H), 4.01-4.04 (m, 2H), 4.12-4.20 (m, 1H), 7.04-7.06 (m, 1H), 7.18-7.19 (m, 1H), 7.22-7.24 (m, 1H), 7.27-7.33 (m, 1H). MS 525.3 [M+1] ⁺
19/4		¹ H-NMR (300 MHz, CDCl ₃) δ: 0.75-0.78 (m, 2H), 0.91-0.96 (m, 3H), 1.29 (s, 9H), 1.62-1.91 (m, 5H), 2.13 (d, J = 9.9 Hz, 1H), 2.45-2.55 (m, 2H), 2.78-2.83 (m, 3H), 3.19 (s, 3H), 3.59 (d, J = 9.0 Hz, 1H), 4.79-4.82 (m, 1H), 5.08 (s, 1H), 7.39 (d, J = 8.1 Hz, 1H), 7.57 (d, J = 7.2 Hz, 1H), 8.15 (d, J = 8.1 Hz, 1H). MS 632.1 [M+1] ⁺
19/5		¹ H-NMR (300 MHz, CDCl ₃) δ: 0.65-0.73 (m, 2H), 1.00-1.14 (m, 3H), 1.27 (s, 9H), 1.35 (s, 6H), 1.40 (s, 9H), 1.48-1.63 (m, 3H), 1.70-1.75 (m, 1H), 2.17 (s, 1H), 2.39 (d, J = 7.2 Hz, 2H), 3.53 (d, J = 6.6 Hz, 2H), 5.27 (s, 1H), 7.68-7.81 (m, 4H), 8.46 (s, 1H), 9.06-9.10 (m, 1H). MS 559.2 [M+1] ⁺
19/6		¹ H-NMR (300 MHz, CDCl ₃) δ: 0.60-0.65 (m, 2H), 1.00-1.14 (m, 3H), 1.28 (s, 9H), 1.35 (s, 6H), 1.49-1.59 (m, 3H), 2.50 (d, J = 7.2 Hz, 2H), 3.53 (d, J = 6.3 Hz, 2H), 4.75 (s, 1H), 7.68-7.73 (m, 2H), 7.89-7.95 (m, 1H), 8.01 (d, J = 8.4 Hz, 1H), 8.66 (d, J = 8.4 Hz, 1H), 9.26 (s, 1H). MS 559.3 [M+1] ⁺

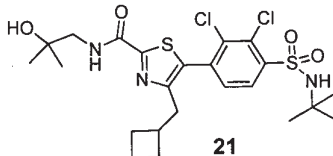
#	Structure	Analytical data
19/7		$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 7.47 (d, 1H, $J = 8.0$ Hz), 7.39 (d, 1H, $J = 1.6$ Hz), 7.17 (d, 1H, $J = 1.6$ Hz), 5.58 (s, 1H), 4.78-4.83 (m, 1H), 3.16-3.22 (m, 1H), 2.79-2.85 (m, 2H), 2.62 (d, 2H, $J = 7.2$ Hz), 2.47-2.53 (m, 5H), 1.66-1.82 (m, 6H), 1.48 (s, 9H), 1.32 (s, 3H), 1.11-1.27 (m, 3H), 0.86-0.90 (m, 2H), 0.78 (s, 4H). MS 566.3 ($\text{M}+1$) $^+$
19/8		$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ : 0.46-0.53 (m, 2H), 0.85-0.96 (m, 3H), 1.24 (s, 9H), 1.27-1.33 (m, 9H), 1.47-1.74 (m, 6H), 2.26-2.36 (m, 3H), 3.52 (d, $J = 6.3$ Hz, 2H), 5.17 (d, $J = 8.4$ Hz, 1H), 7.39-7.59 (m, 4H), 7.71 (t, $J = 6.3$ Hz, 1H), 8.54 (d, $J = 7.8$ Hz, 1H). MS 576.2 [$\text{M}+1$] $^+$
19/9		$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ : 0.62-0.71 (m, 2H), 0.90-1.19 (m, 3H), 1.22 (s, 9H), 1.34 (s, 6H), 1.53-1.54 (m, 4H), 1.61-1.70 (m, 1H), 2.16-2.27 (m, 2H), 2.41-2.47 (m, 1H), 3.51 (d, $J = 6.6$ Hz, 2H), 4.61 (s, 1H), 7.14-7.21 (m, 1H), 7.51-7.54 (m, 1H), 7.66-7.77 (m, 2H), 8.34-8.38 (m, 1H), 8.75-8.79 (m, 1H). MS 602.2 [$\text{M}+1$] $^+$
19/10		$^1\text{H-NMR}$ (400 MHz, CD_3OD): δ : 0.74-0.82 (m, 2H), 1.07-1.19 (m, 3H), 1.24 (s, 9H), 1.53-1.60 (m, 5H), 1.73-1.78 (m, 1H), 2.47-2.66 (m, 6H), 3.04-3.10 (m, 1H), 4.69-4.77 (m, 1H), 7.61 (dd, $J = 8.0$ Hz, 6.4 Hz, 1H), 7.93 (d, $J = 8.0$ Hz, 1H). MS 634.2 [$\text{M}-1$] $^-$
19/11		$^1\text{H-NMR}$ (400 MHz, CD_3OD): δ : 0.78-0.87 (m, 2H), 1.10-1.26 (m, 3H), 1.32 (s, 9H), 1.59-1.62 (m, 5H), 1.77-1.81 (m, 1H), 2.51-2.59 (m, 4H), 2.2.63-2.69 (m, 2H), 3.08-3.13 (m, 1H), 4.73-4.77 (m, 1H), 7.75 (s, 1H), 8.24 (s, 1H). MS 600.2 [$\text{M}-1$] $^-$
19/12		$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ : 7.48 (d, 1H, $J = 8.0$ Hz), 7.24 (s, 1H), 4.82-4.80 (m, 1H), 3.19-3.18 (m, 1H), 3.07 (d, 2H, $J = 7.2$ Hz), 2.85-2.78 (m, 2H), 2.54-2.46 (m, 2H), 1.85-1.68 (m, 6H), 1.58 (s, 3H), 1.42-1.40 (m, 2H), 1.33 (s, 9H), 1.29-1.05 (m, 5H), 0.90-0.88 (m, 2H). MS 511.3 ($\text{M}+1$) $^+$
19/13		$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ : 7.51 (d, 1H, $J = 8.0$ Hz), 7.29 (s, 1H), 4.85-4.79 (m, 1H), 3.22-3.17 (m, 1H), 3.11 (d, 2H, $J = 7.2$ Hz), 2.86-2.79 (m, 2H), 2.55-2.47 (m, 2H), 1.87-1.85 (m, 1H), 1.72-1.69 (m, 5H), 1.42 (s, 9H), 1.40 (s, 9H), 1.36-1.06 (m, 5H). MS 513.3 ($\text{M}+1$) $^+$
19/14		$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ : 0.62-0.71 (m, 2H), 0.90-1.19 (m, 3H), 1.21 (s, 9H), 1.34 (s, 6H), 1.47-1.57 (m, 4H), 1.61-1.70 (m, 1H), 2.15-2.27 (m, 1H), 2.42-2.60 (m, 3H), 2.80-2.89 (m, 2H), 3.40-3.51 (m, 1H), 4.73 (s, 1H), 4.80-4.88 (m, 1H), 7.14-7.21 (m, 1H), 7.51-7.57 (m, 2H), 7.72-7.77 (m, 2H), 8.34-8.38 (m, 1H), 8.76-8.80 (m, 1H). MS 576.3 [$\text{M}+1$] $^+$

Example 20

trans-3-(4-(Cyclohexylmethyl)-5-(4-(*N*-(4-fluoro-2-methylbutan-2-yl)sulfamoyl)naphthalen-1-yl)thiazole-2-carboxamido)cyclobutanecarboxylic acid (**20**)



- 5 To a solution of compound **14/7** (200 mg, 0.33 mmol) in DCM (6 mL) was added DAST (161 mg, 1.00 mmol) at 0°C and the solution was stirred at rt overnight, washed with water and extracted with CH₂Cl₂. The organic layer was dried with MgSO₄, filtered, concentrated and purified by CC (DCM/MeOH = 10/1) to give compound **20** (170 mg, 84%) as a white solid. ¹H-NMR (CDCl₃, 300 MHz) δ: 0.58-0.69 (m, 2H), 0.95-1.13 (m, 3H), 1.23-1.25 (m, 6H), 1.48-1.72 (m, 6H), 1.91-2.04 (m, 2H), 2.34 (br s, 2H), 2.50-2.60 (m, 2H), 2.82-2.89 (m, 2H), 3.19-3.25 (m, 1H), 4.45-6.64 (m, 2H), 4.82-4.90 (m, 1H), 5.07 (d, J = 3.0 Hz, 1H), 7.50-7.60 (m, 3H), 7.70-7.74 (m, 2H), 8.33 (d, J = 7.8 Hz, 1H), 8.66 (d, J = 9.3 Hz, 1H). MS 616.3 (M+1)⁺.

Example 21

15

5-(4-(*N*-(*tert*-butyl)sulfamoyl)-2,3-dichlorophenyl)-4-(cyclobutylmethyl)-*N*-(2-hydroxy-2-methylpropyl)thiazole-2-carboxamide (**21**)

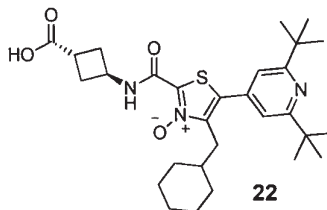
- A solution of 4-(cyclobutylmethyl)-*N*-(2-hydroxy-2-methylpropyl)thiazole-2-carboxamide (27 mg, 0.1 mmol, prepared using similar procedures as described above), 4-bromo-*N*-(*tert*-butyl)-2,3-dichlorobenzenesulfonamide (36 mg, 0.1 mmol), K₂CO₃ (21 mg, 0.15 mmol), Pd(OAc)₂ (1 mg, 2 μmol), PCy₃·HBF₄ (2 mg, 4 μmol) and PivOH (4 mg, 0.03 mmol) in a solution of DMA (2 mL) was heated under argon at 100°C overnight, cooled to rt, partitioned between EA and water, and the layers were separated. The organic phase was washed with water and brine, dried over Na₂SO₄, filtered, concentrated and purified by CC (PE/EA = 10/1 to 5/1) to give compound **21** as a white solid (33 mg, 64%). ¹H-NMR (400 MHz, CDCl₃) δ: 8.13 (d, 1H, J = 8.4 Hz), 7.65 (s, 1H), 7.39 (d, 1H, J = 8.0 Hz), 5.06 (s, 1H), 3.50 (d, 2H, J = 6.4 Hz), 2.63 (s, 3H), 1.98-1.94 (m, 2H), 1.81-1.71 (m, 2H), 1.58-1.53 (m, 2H), 1.31 (s, 6H), 1.30 (s, 9H). MS 548.2 (M+1)⁺.

Example 21/1 to 21/25

The following examples were prepared according to Example 21.

#	Structure	Analytical data
21/1		¹ H-NMR (400 MHz, CDCl ₃) δ: 8.13 (d, 1H, J = 8.4 Hz), 7.62 (t, 1H, J = 6.4 Hz), 7.43 (d, 1H, J = 8.4 Hz), 6.50-6.13 (m, 1H), 5.02 (s, 1H), 3.49 (d, 2H, J = 6.0 Hz), 2.73-2.65 (m, 3H), 2.02-1.95 (m, 2H), 1.85-1.52 (m, 4H), 1.33 (s, 6H), 1.27 (s, 9H). MS 579.6 (M+1) ⁺
21/2		¹ H-NMR (400 MHz, CDCl ₃) δ: 8.69 (d, 1H, J = 8.8 Hz), 8.35 (d, 1H, J = 7.6 Hz), 7.72 (t, 3H, J = 8.0 Hz), 7.59 (t, 1H, J = 7.6 Hz), 7.52 (d, 1H, J = 7.6 Hz), 4.66 (s, 1H), 3.53 (d, 2H, J = 6.4 Hz), 2.61-2.56 (m, 3H), 1.90-1.42 (m, 6H), 1.36 (s, 6H), 1.23 (s, 9H). MS 529.7 (M+1) ⁺
21/3		¹ H-NMR (400 MHz, CDCl ₃) δ: 8.12 (d, 1H, J = 8.0 Hz), 7.52 (d, 1H, J = 7.6 Hz), 7.42 (d, 1H, J = 8.4 Hz), 6.48-6.11 (m, 1H), 5.64 (s, 1H), 4.84 (d, 1H, J = 8.0 Hz), 3.20-3.14 (m, 1H), 2.81-2.77 (m, 2H), 2.54-2.48 (m, 4H), 1.78-1.53 (m, 6H), 1.27-0.76 (m, 14H). MS 634.2 (M+1) ⁺
21/4		¹ H-NMR (400 MHz, CDCl ₃) δ: 8.13 (d, 1H, J = 8.4 Hz), 7.67 (t, 1H, J = 6.0 Hz), 7.43 (d, 1H, J = 8.4 Hz), 6.50-6.13 (m, 1H), 3.51 (d, 2H, J = 6.4 Hz), 2.51-2.49 (m, 2H), 1.78-1.54 (m, 6H), 1.34 (s, 6H), 1.29 (s, 9H), 1.27-1.06 (m, 3H), 0.83-0.77 (m, 2H). MS 608.2 (M+1) ⁺
21/5		¹ H-NMR (400 MHz, CDCl ₃) δ: 8.28 (s, 1H), 8.11 (d, 1H, J = 6.4 Hz), 7.34 (d, 1H, J = 8.0 Hz), 7.56 (d, 1H, J = 8.0 Hz), 4.85 (m, 1H), 4.77 (s, 1H), 3.20 (m, 1H), 2.79 (m, 2H), 2.49 (m, 4H), 1.75 (m, 1H), 1.62-1.41 (m, 5H), 1.31-1.15 (m, 12H), 0.75 (m, 2H). MS 602.2 (M+H) ⁺
21/6		¹ H-NMR (400 MHz, CDCl ₃) δ: 8.02 (s, 1H), 7.83 (d, 1H, J = 6.8 Hz), 7.44 (m, 2H), 4.80 (m, 1H), 4.59 (s, 1H), 3.20 (m, 1H), 2.80 (m, 2H), 2.51 (m, 4H), 1.74-1.51 (m, 6H), 1.31-1.04 (m, 12H), 0.71 (m, 2H). MS 568.2 (M+H) ⁺
21/7		¹ H-NMR (400 MHz, DMSO-d ₆) δ: 12.25 (s, 1H), 9.19 (d, 1H, J = 8.0 Hz), 7.95 (m, 3H), 7.84 (d, 1H, J = 8.0 Hz), 4.58 (m, 1H), 2.95 (m, 1H), 2.55 (m, 4H), 2.43 (m, 2H), 1.71 (m, 1H), 1.49 (m, 5H), 1.12-1.00 (m, 12H), 0.70 (m, 2H). MS 618.2 (M+H) ⁺
21/8		¹ H-NMR (400 MHz, DMSO-d ₆) δ: 8.23 (m, 1H), 7.98-7.82 (m, 4H), 4.72 (s, 1H), 3.29 (m, 2H), 2.56-2.49 (m, 2H), 1.68 (m, 1H), 1.56-1.45 (m, 5H), 1.20-1.01 (m, 18H), 0.73 (m, 2H). MS 592.2 (M+H) ⁺

#	Structure	Analytical data
21/9		¹ H-NMR (400 MHz, CDCl ₃) δ: 8.70 (d, 1H, J = 8.8 Hz), 8.34 (d, 1H, J = 7.2 Hz), 7.73 (m, 2H), 7.59 (m, 1H), 7.52 (d, 1H, J = 7.6 Hz), 4.65 (d, 1H, J = 8.0 Hz), 4.56 (s, 2H), 4.07 (s, 2H), 3.83 (m, 2H), 3.43 (m, 1H), 3.32 (m, 2H), 3.08 (m, 4H), 2.46 (m, 4H), 2.35 (m, 2H), 1.68 (m, 3H), 1.48 (m, 7H), 1.07 (m, 3H), 0.69 (m, 2H). MS 672.2 (M+H) ⁺
21/10		¹ H-NMR (400 MHz, CDCl ₃) δ: 8.15 (d, 1H, J = 8.0 Hz), 7.34 (d, 1H, J = 8.0 Hz), 5.69 (m, 1H), 5.60 (m, 1H), 4.51 (s, 2H), 4.03 (s, 2H), 3.05 (m, 4H), 2.43 (m, 6H), 1.72 (m, 3H), 1.46 (m, 6H), 1.31 (s, 9H), 1.11 (m, 3H), 1.82 (m, 2H). MS 672.2 (M+H) ⁺
21/11		¹ H-NMR (400 MHz, DMSO-d ₆) δ: 8.82 (d, J = 8.8 Hz, 1H), 8.31-8.26 (m, 2H), 7.93 (s, 1H), 7.79-7.66 (m, 4H), 4.74 (s, 1H), 3.32 (d, J = 4.0 Hz, 2H), 2.35-2.45 (m, 2H), 1.81-1.54 (m, 7H), 1.15 (s, 6H), 1.07 (s, 9H), 0.91-0.82 (m, 2H). MS 594.3 (M+1) ⁺
21/12		¹ H-NMR (400 MHz, DMSO-d ₆) δ: 9.05 (d, J = 8 Hz, 1H), 8.82 (d, J = 8.8 Hz, 1H), 8.27 (d, J = 7.6 Hz, 1H), 7.93 (s, 1H), 7.79-7.66 (m, 4H), 4.27-4.24 (m, 1H), 3.41-3.32 (m, 2H), 3.13 (d, J = 12.4 Hz, 2H), 2.40-2.23 (m, 4H), 2.12 (d, J = 11.6 Hz, 2H), 1.80-1.53 (m, 7H), 1.07 (s, 9H), 0.85-0.82 (m, 2H). MS 654.3 (M+1) ⁺
21/13		¹ H-NMR (400 MHz, DMSO-d ₆) δ: 10.19 (s, 1H), 8.65 (d, 1H, J = 6.0 Hz), 8.46 (d, 1H, J = 8.0 Hz), 7.96 (d, 1H, J = 7.6 Hz), 7.69 (d, 1H, J = 6.0 Hz), 4.30 (m, 1H), 3.95 (m, 2H), 3.16 (m, 2H), 2.46-2.34 (m, 6H), 1.73 (m, 1H), 1.54 (m, 5H), 1.28 (s, 9H), 1.06 (m, 3H), 0.68 (m, 2H). MS 619.3 (M+1) ⁺
21/14		¹ H-NMR (400 MHz, DMSO-d ₆) δ: 8.98 (d, 1H, J = 8.4 Hz), 8.11 (d, 1H, J = 8.0 Hz), 7.97 (m, 1H), 7.68 (d, 1H, J = 8.4 Hz), 4.21 (m, 1H), 3.38 (m, 2H), 3.10 (m, 2H), 2.60 (m, 3H), 2.21 (m, 2H), 2.08 (m, 2H), 1.89 (m, 2H), 1.66 (m, 2H), 1.44 (m, 2H), 1.16 (s, 9H). MS 608.2 (M+H) ⁺
21/15		¹ H-NMR (400 MHz, DMSO-d ₆) δ: 12.25 (s, 1H), 9.16 (d, 1H, J = 8.0 Hz), 8.11 (d, 1H, J = 8.4 Hz), 8.04 (s, 1H), 7.69 (d, 1H, J = 8.4 Hz), 4.57 (m, 1H), 2.95 (m, 1H), 2.62 (m, 3H), 2.47-2.42 (m, 4H), 1.89 (m, 2H), 1.67 (m, 2H), 1.44 (m, 2H), 1.16 (s, 9H). MS 574.1 (M+H) ⁺
21/16		¹ H-NMR (400 MHz, DMSO-d ₆) δ: 9.01 (d, 1H, J = 8.4 Hz), 8.81 (d, 1H, J = 8.8 Hz), 8.26 (d, 1H, J = 7.6 Hz), 7.94 (s, 1H), 7.74 (m, 4H), 4.25 (m, 1H), 3.40 (m, 2H), 3.10 (m, 2H), 2.67 (m, 3H), 2.29 (m, 2H), 2.11 (m, 2H), 1.80 (m, 2H), 1.53 (m, 2H), 1.26 (m, 2H), 1.09 (s, 9H). MS 590.2 (M+H) ⁺

Example 22

Step 1: 4-(Cyclohexylmethyl)-5-(2,6-di-*tert*-butylpyridin-4-yl)-2-(((*trans*)-3-(methoxycarbonyl)-cyclobutyl)carbamoyl)thiazole 3-oxide (**22a**)

- 5 To a solution of (*trans*)-methyl 3-(4-(cyclohexylmethyl)-5-(2,6-di-*tert*-butylpyridin-4-yl)thiazole-2-carboxamido)cyclobutanecarboxylate (60 mg, 0.11 mmol) in DCM (2 mL) was added *m*-CPBA (35 mg, 0.17 mmol) and the solution was stirred at rt overnight, washed with sat. NaHCO₃ and sat. aq. NaS₂O₃ consecutively, dried over Na₂SO₄, filtered, concentrated and purified by CC (PE/EA = 3/1) to give compound **22a** (38 mg, 62%) as a pale yellow solid.

- 10 Step 2: 2-(((*trans*)-3-Carboxycyclobutyl)carbamoyl)-4-(cyclohexylmethyl)-5-(2,6-di-*tert*-butylpyridin-4-yl)thiazole 3-oxide (**22**)

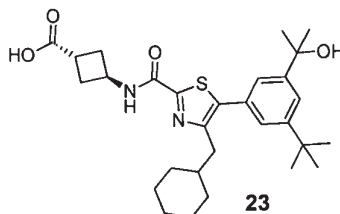
- A solution of compound **22a** (36 mg, 0.066 mmol) and LiOH•H₂O (6 mg, 0.1 mmol) in a mixture of MeOH (2 mL) and H₂O (1 mL) was stirred at rt overnight, diluted with aq. HCl to adjust the pH to ca. 5 and extracted with EA. The organic layer was washed with water and
15 brine, dried over Na₂SO₄, filtered, concentrated and purified by CC (DCM/MeOH = 10/1) to give compound **22** (22 mg, 63%) as a white solid. ¹H-NMR (400 MHz, DMSO-d₆) δ: 0.83-0.89 (m, 2H), 1.04-1.06 (m, 3H), 1.35 (s, 18H), 1.52-1.55 (m, 5H), 1.75-1.78 (m, 1H), 2.40-2.45 (m, 2H), 2.50-2.53 (m, 2H), 2.76 (d, J = 7.2 Hz, 2H), 2.98-3.01 (m, 1H), 4.59-4.61 (m, 1H), 7.37 (s, 2H), 10.56 (d, J = 7.6 Hz, 1H), 12.32 (s, 1H). MS 528.3 (M+1)⁺.

20

Example 22/1 to 22/2

The following examples were prepared similar to Example 22.

#	Structure	Analytical data
22/1		¹ H-NMR (400 MHz, DMSO-d ₆) δ: 0.44-0.51 (m, 2H), 0.81-0.92 (m, 6H), 1.06 (s, 9H), 1.45 (s, 3H), 1.22-1.28 (m, 1H), 1.38-1.40 (m, 5H), 1.55-1.60 (m, 1H), 2.40-2.45 (m, 2H), 3.00-3.04 (m, 1H), 4.60-4.66 (m, 1H), 7.69 (t, J = 7.6 Hz, 1H), 7.77-7.82 (m, 2H), 7.90 (d, J = 8.4 Hz, 1H), 8.00 (s, 1H), 8.29 (d, J = 7.6 Hz, 1H), 8.81 (d, J = 8.8 Hz, 1H), 10.68 (d, J = 7.6 Hz, 1H), 12.34 (m, 1H). MS 600.3 (M+1) ⁺
22/2		¹ H-NMR (300 MHz, CDCl ₃) δ: 0.79-0.95 (m, 6H), 1.11-1.26 (m, 4H), 1.35 (s, 9H), 1.45 (s, 3H), 1.62-1.65 (m, 5H), 1.89-1.91 (m, 1H), 2.45-2.57 (m, 2H), 2.76-2.87 (m, 4H), 3.17-3.23 (m, 1H), 4.80-4.88 (m, 1H), 7.14 (s, 1H), 7.26 (s, 1H), 7.39 (s, 1H), 10.76 (d, J = 6.0 Hz, 1H). MS 525.3 (M+1) ⁺

Example 23

Step 1: (*trans*)-Methyl 3-(5-(3-acetyl-5-(*tert*-butyl)phenyl)-4-(cyclohexylmethyl)thiazole-2-carboxamido)cyclobutanecarboxylate (**23a**)

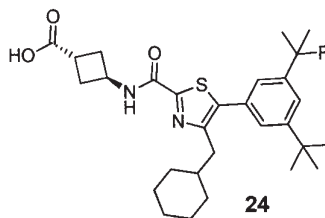
A mixture of (*trans*)-methyl 3-(5-bromo-4-(cyclohexylmethyl)thiazole-2-carboxamido)cyclobutanecarboxylate (415 mg, 1.00 mmol), 1-(3-(*tert*-butyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethanone (362 mg, 1.20 mmol) and K₂CO₃ (500 mg, 3.62 mmol) in dry DMF (10 mL) was purged with N₂ for 10 min. Pd(dppf)Cl₂ (50 mg) was added and degassing with N₂ was continued for 10 min. The mixture was stirred at 100 °C for 14 h under N₂, cooled to rt, concentrated and purified by CC (PE/EA = 5/1) to give compound **23a** (465 mg, 91%) as a white solid.

Step 2: (*trans*)-Methyl 3-(5-(3-(*tert*-butyl)-5-(2-hydroxypropan-2-yl)phenyl)-4-(cyclohexylmethyl)-thiazole-2-carboxamido)cyclobutanecarboxylate (**23b**)

To a solution of compound **23a** (465 mg, 0.91 mmol) in dry THF (10 mL) was added MeMgBr (3M in Et₂O, 0.30 mL, 0.90 mmol) at 0°C under N₂ and the solution was stirred at rt for 2.5 h, quenched with sat. NH₄Cl and extracted with EA. The organic layer was washed with water and brine, dried over Na₂SO₄, filtered, concentrated and purified by CC (PE/EA = 5/1) to give compound **23b** (240 mg, 50%) as a white solid.

Step 3: (*trans*)-3-(5-(3-(*tert*-Butyl)-5-(2-hydroxypropan-2-yl)phenyl)-4-(cyclohexylmethyl)-thiazole-2-carboxamido)cyclobutanecarboxylic acid (**23**)

To a solution of compound **23b** (50 mg, 0.095 mmol) in a mixture of THF (4 mL) and water (1 mL) was added LiOH•H₂O (40 mg, 0.95 mmol), and the resulting mixture was stirred at rt overnight, pH-adjusted to pH = 5~6 with 1N HCl and extracted with EA. The organic layer was washed with brine, dried over Na₂SO₄, filtered, concentrated and purified by prep-HPLC to give compound **23** (20 mg, 41%) as a white solid. ¹H-NMR (300 MHz, CD₃OD) δ: 0.89-0.96 (m, 2H), 1.12-1.32 (m, 3H), 1.37 (s, 9H), 1.51 (s, 6H), 1.56-1.66 (m, 5H), 1.82-1.88 (m, 1H), 2.51-2.71 (m, 6H), 3.05-3.11 (m, 1H), 4.71-4.74 (m, 1H), 7.32 (s, 1H), 7.36 (s, 1H), 7.64 (s, 1H), 8.78 (d, J = 8.1 Hz, 1H). MS 513.3 (M+1)⁺.

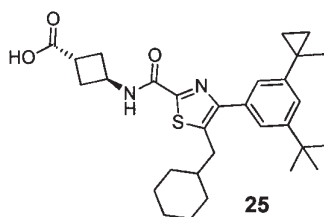
Example 24

Step 1: (trans)-Methyl 3-(5-(3-(tert-butyl)-5-(2-fluoropropan-2-yl)phenyl)-4-(cyclohexylmethyl)-thiazole-2-carboxamido)cyclobutanecarboxylate (24a)

- 5 To a solution of compound **23b** (180 mg, 0.34 mmol) in dry DCM (5 mL) was added DAST (165 mg, 1.03 mmol) at 0°C under N₂ and the solution was stirred at this temperature for 15 h, quenched with water and extracted with EA. The organic layer was washed with water and brine, dried over Na₂SO₄, filtered, concentrated and purified by prep-TLC (PE/EA = 5/1) to give compound **24a** (90 mg, 50%) as a white solid.

- 10 Step 2: (trans)-3-(5-(3-(tert-Butyl)-5-(2-fluoropropan-2-yl)phenyl)-4-(cyclohexylmethyl)thiazole-2-carboxamido)cyclobutanecarboxylic acid (24)

- A similar procedure as described for Example **23** was applied to afford compound **24** (50 mg, 52%) as a white solid. ¹H-NMR (300 MHz, CD₃OD) δ: 0.89-0.96 (m, 2H), 1.12-1.32 (m, 3H), 1.37 (s, 9H), 1.58-1.70 (m, 8H), 1.72 (s, 3H), 1.81-1.88 (m, 1H), 2.47-2.70 (m, 6H), 3.04-3.12 (m, 1H), 4.70-4.75 (m, 1H), 7.27 (t, J = 1.5 Hz, 1H), 7.38 (t, J = 1.5 Hz, 1H), 7.51 (t, J = 1.5 Hz, 1H), 8.78 (d, J = 8.1 Hz, 1H). MS 515.3 (M+1)⁺.

Example 25

- 20 Step 1: 2,4-Dibromothiazole-5-carbaldehyde (25a)

- To a solution of LDA (1M in THF, 183 mL, 183 mmol) was added a solution of 2,4-dibromothiazole (37 g, 154 mmol) in dry THF (500 mL) at -78°C under N₂ and the solution was stirred under this condition for 40 min. Then DMF (13 g, 178 mmol) was added slowly at this temperature and the solution was stirred for another 1 h, warmed to rt, quenched with sat. NH₄Cl and extracted with EA twice. The combined organic layers were washed with water and brine, dried over Na₂SO₄, filtered, concentrated and purified by CC (PE/EA = 15/1) to give compound **25a** (14.5 g, 35%) as a yellow solid.

Step 2: Cyclohexyl(2,4-dibromothiazol-5-yl)methanol (25b)

To a solution of compound **25a** (11.2 g, 41.7 mmol) in dry THF (150 mL) was added a solution of cyclohexylmagnesium chloride (1M in THF, 45 mL, 45.0 mol) at -78°C and the solution was stirred at this temperature for 1 h, warmed to rt, quenched with water and extracted with EA twice. The combined organic layers were washed with water and brine, dried over Na_2SO_4 ,
5 filtered, concentrated and purified by CC (PE/EA = 20/1) to give compound **25b** (5.4 g, 37%) as a pale yellow solid.

Step 3: 2,4-Dibromo-5-(cyclohexylmethyl)thiazole (**25c**)

To a solution of compound **25b** (5.4 g, 15.3 mmol) in DCM (50 mL) was added Et_3SiH (17.7 g, 153 mmol) and TFA (684 mg, 30.6 mmol) and the solution was stirred at rt for overnight and
10 quenched with water. The organic layer was washed with water and brine, dried over Na_2SO_4 , filtered, concentrated and purified by CC (PE/EA = 30/1) to give compound **25c** (2.91 g, 56%) as a white solid.

Step 4: Ethyl 4-bromo-5-(cyclohexylmethyl)thiazole-2-carboxylate (**25d**)

To a solution of compound **25c** (6.50 g, 19.1 mmol) in dry THF (60 mL) was added a solution
15 of *n*-BuLi (2.5M in THF, 8.0 mL, 20.0 mmol) at -78°C under N_2 and the solution was stirred at this temperature for 1 h. Then ethylchloroformate (2.36 g, 25.0 mmol) was added and the solution was stirred at -78°C for another 1 h, quenched with water and extracted with EA twice. The combined organic layers were washed with water and brine, dried over Na_2SO_4 , filtered, concentrated and purified by CC (PE/EA = 30/1) to give compound **25d** (2.54 g, 40%)
20 as a light yellow oil.

Step 5: Ethyl 4-(3-(*tert*-butyl)-5-(1-methylcyclopropyl)phenyl)-5-(cyclohexylmethyl)thiazole-2-carboxylate (**25e**)

The suspension of compound **25d** (500 mg, 1.50 mmol), K_2CO_3 (690 mg, 5.00 mmol), 2-(3-(*tert*-butyl)-5-(1-methylcyclopropyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (471 mg, 1.50 mmol) and $\text{Pd}(\text{dppf})\text{Cl}_2$ (150 mg) in DMF (10 mL) was stirred at 100°C for overnight,
25 cooled to rt, concentrated and purified by CC (PE/EA = 15/1) to give compound **25e** (299 mg, 45%) as a white solid.

Step 6: Potassium 4-(3-(*tert*-butyl)-5-(1-methylcyclopropyl)phenyl)-5-(cyclohexylmethyl)thiazole-2-carboxylate (**25f**)

30 To a solution of compound **25e** (299 mg, 0.68 mmol) in MeOH (3.0 mL) was added KOH (50.4 mg, 0.90 mmol) and the solution was stirred at rt for overnight and concentrated to give crude compound **25f** (305 mg) as a yellow solid.

Step 7: *trans*-3-(4-(3-(*tert*-Butyl)-5-(1-methylcyclopropyl)phenyl)-5-(cyclohexylmethyl)thiazole-2-carboxamido)cyclobutanecarboxylic acid (**25**)

35 The solution of compound **25f** (305 mg, 0.68 mmol), *trans*-3-amino-cyclobutane carboxylic acid hydrochloride (106 mg, 0.70 mmol), HATU (285 mg, 0.75 mmol) and DIEA (257 mg, 2.00 mmol) in DMF (5 mL) was stirred at rt for 30 min, diluted with water and extracted by EA (3x).

The combined organic layers were washed by water (3x) and brine consecutively, dried over Na_2SO_4 , filtered, concentrated and purified by prep-HPLC and then prep-TLC to give compound **25** (37 mg, 11%) as a white solid. $^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ : 0.75-0.78 (m, 2H), 0.85-0.87 (m, 2H), 0.97-1.16 (m, 2H), 1.20-1.30 (m, 4H), 1.34 (s, 9H), 1.43 (s, 3H), 1.71-1.87 (m, 6H), 2.55-2.57 (m, 2H), 2.85-2.90 (m, 4H), 4.48-4.49 (m, 1H), 5.83 (d, $J = 9.0$ Hz, 1H), 7.24 (s, 1H), 7.33 (s, 1H), 7.41 (s, 1H). MS 509.3 ($\text{M}+1$) $^+$.

Example 25/1 to 25/2

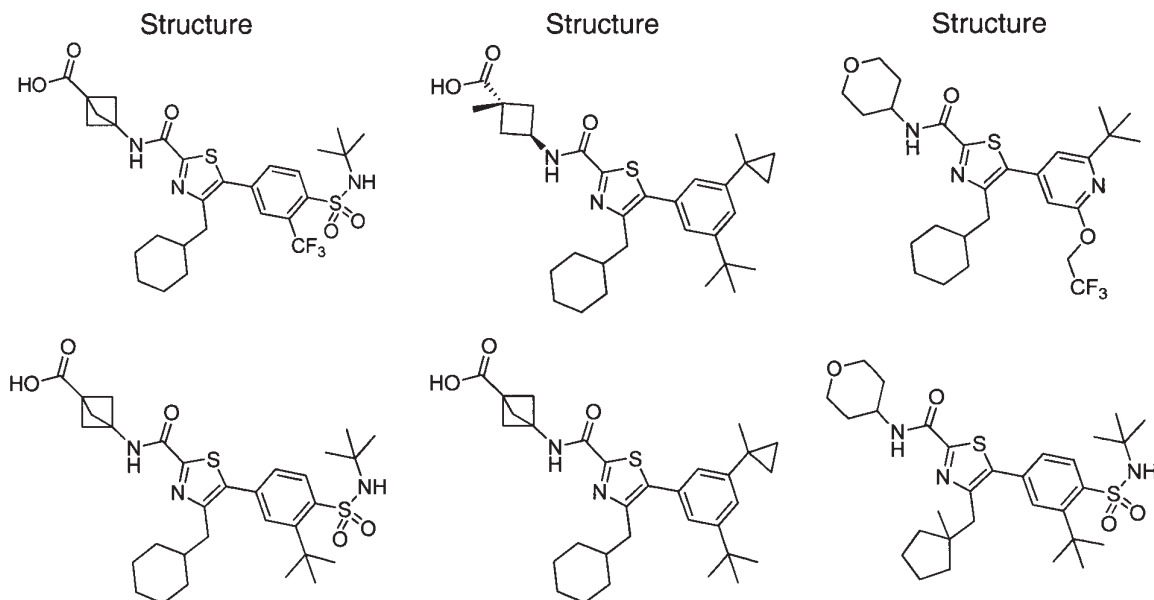
The following examples were prepared similar to Example **25**.

#	Structure	Analytical data
25/1		$^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ : 0.63-0.66 (m, 2H), 0.98-1.20 (m, 3H), 1.22 (s, 9H), 1.48-1.67 (m, 6H), 2.37 (br s, 2H), 2.53-2.57 (m, 2H), 2.84-2.86 (m, 2H), 3.20-3.21 (m, 2H), 4.67 (s, 1H), 4.81-4.83 (m, 1H), 7.48-7.51 (m, 3H), 7.70-7.75 (m, 1H), 8.36 (d, $J = 10.8$ Hz, 1H), 8.69 (d, $J = 8.4$ Hz, 1H). MS 584.2 ($\text{M}+1$) $^+$
25/2		$^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ : 1.00-1.05 (m, 2H), 1.10-1.20 (m, 3H), 1.27 (s, 9H), 1.46-1.56 (m, 2H), 1.60-1.90 (m, 6H), 1.95-2.09 (m, 2H), 2.39-2.46 (m, 2H), 2.79-2.82 (m, 2H), 2.96 (d, $J = 7.8$ Hz, 2H), 3.81-3.82 (m, 1H), 4.78 (s, 1H), 5.13 (d, $J = 7.8$ Hz, 2H), 7.61-7.83 (m, 4H), 8.42 (d, $J = 7.8$ Hz, 1H), 8.75 (d, $J = 8.4$ Hz, 1H). MS 618.2 ($\text{M}+1$) $^+$

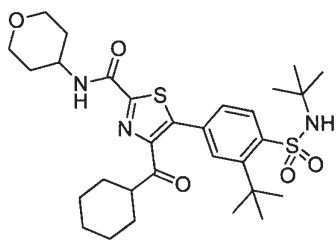
10

Additional Examples

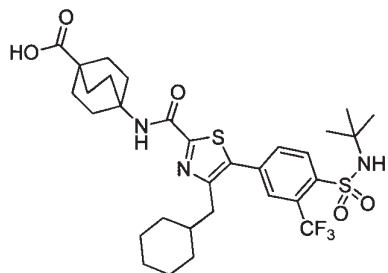
The following compounds can be prepared in the same manner by using the procedures as described above:



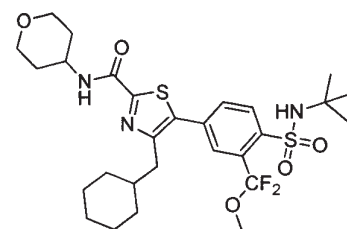
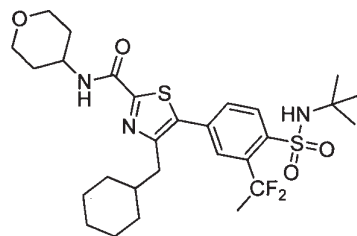
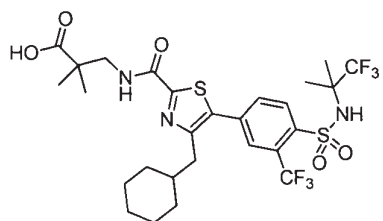
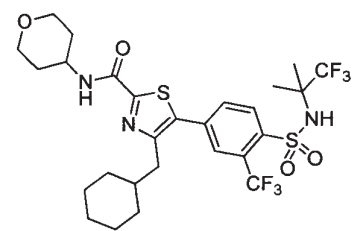
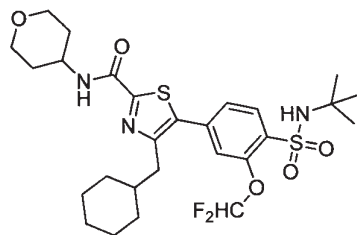
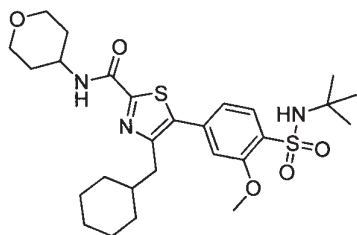
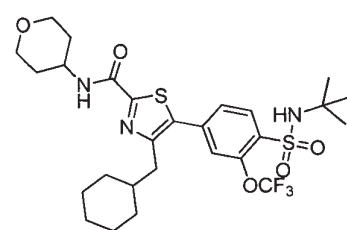
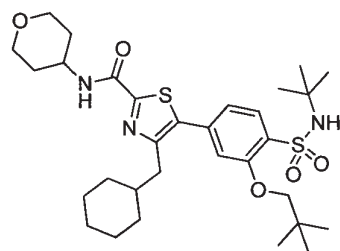
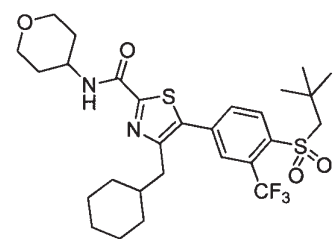
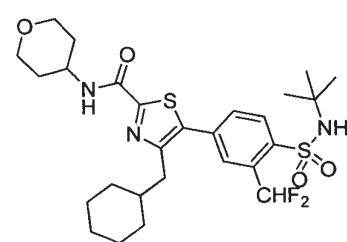
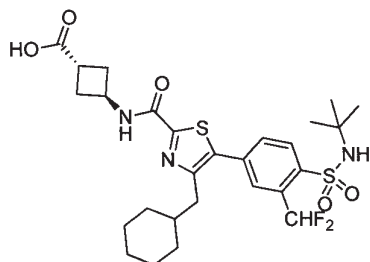
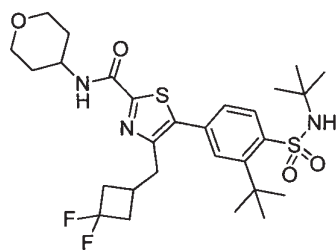
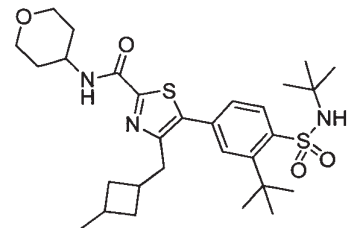
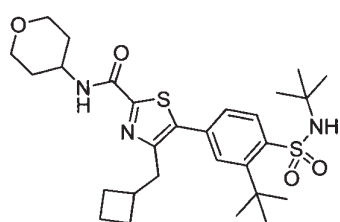
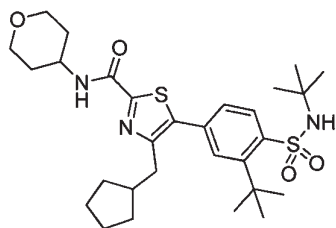
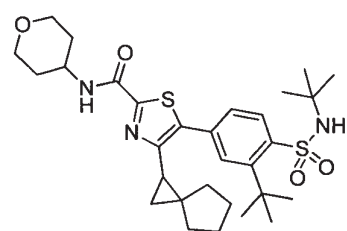
Structure



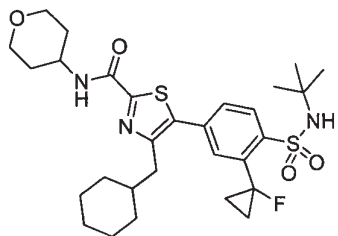
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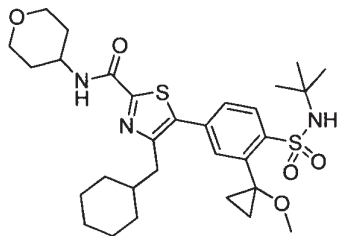
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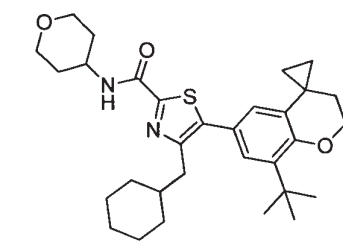
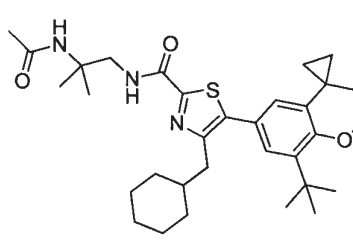
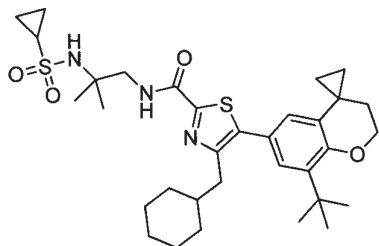
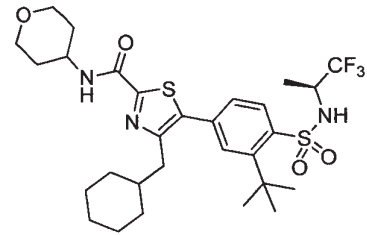
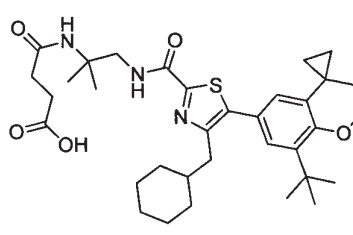
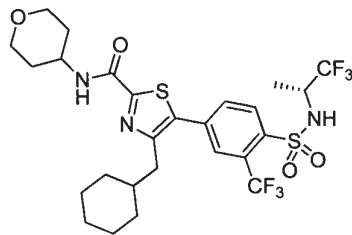
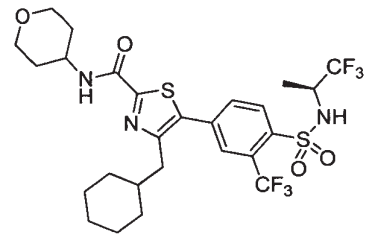
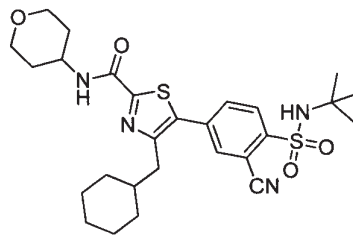
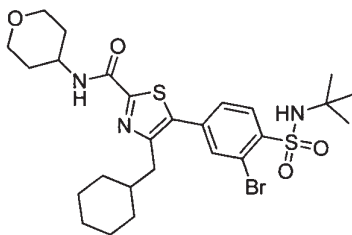
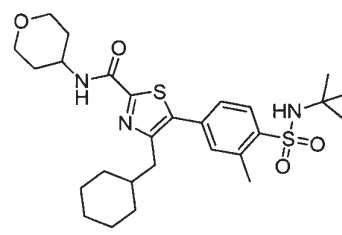
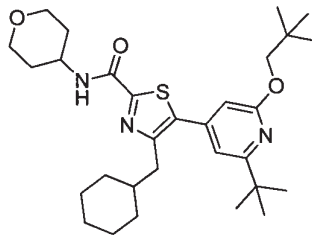
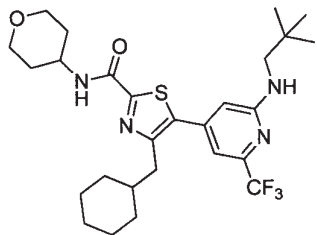
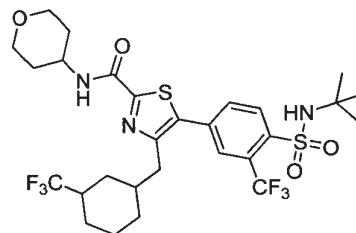
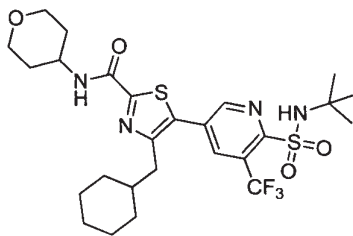
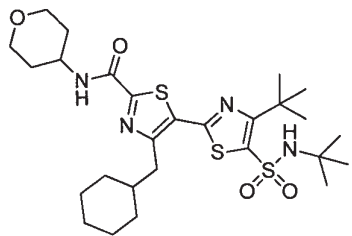
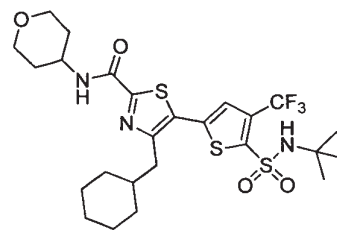
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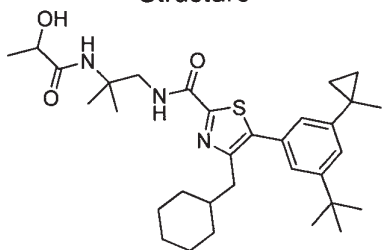
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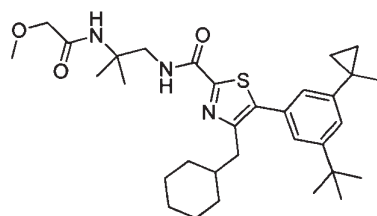
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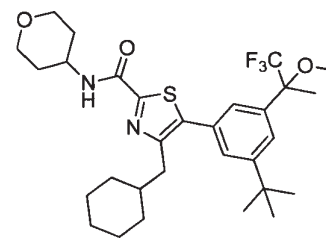
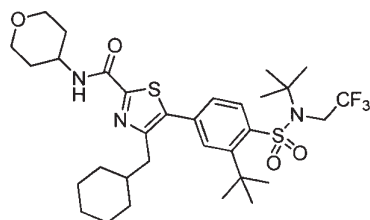
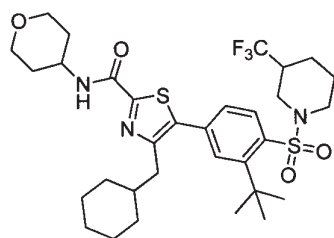
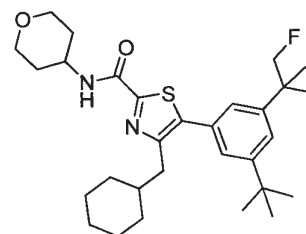
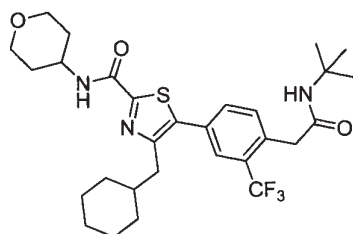
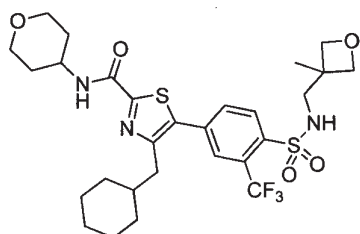
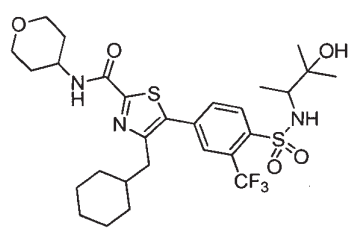
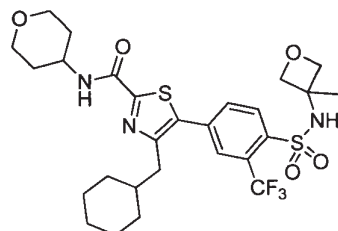
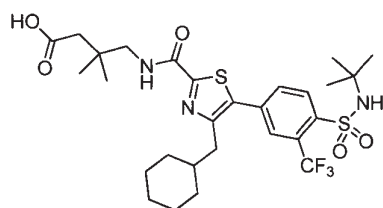
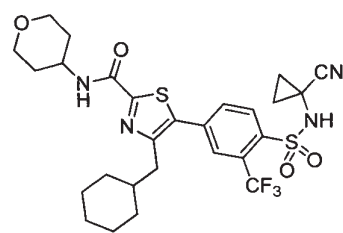
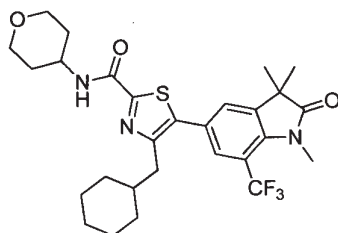
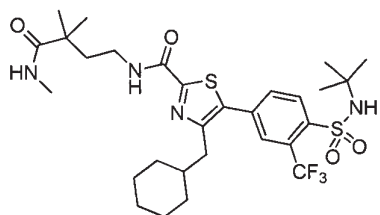
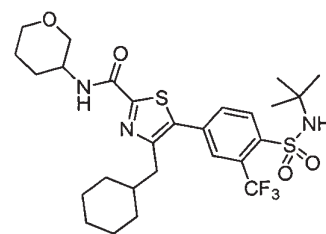
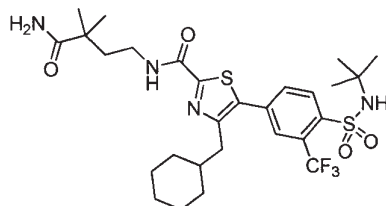
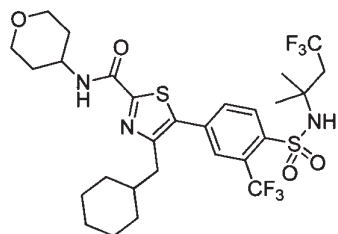
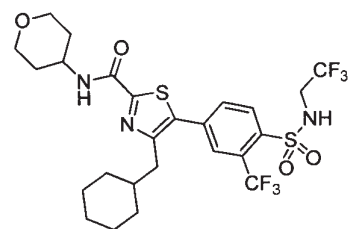
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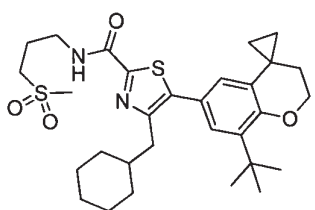
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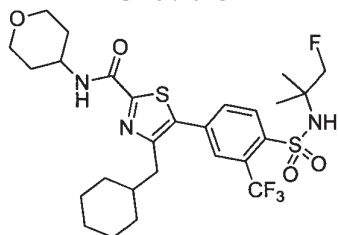
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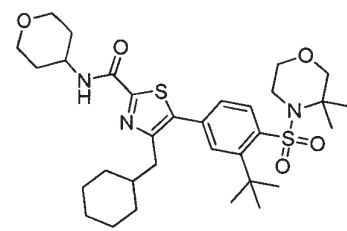
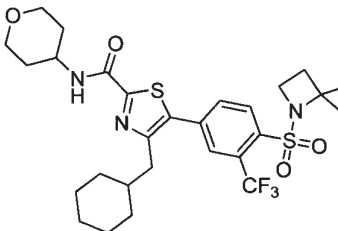
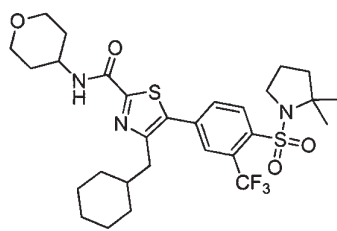
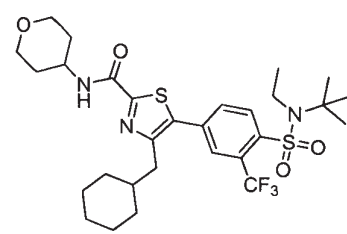
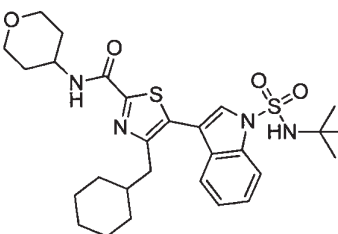
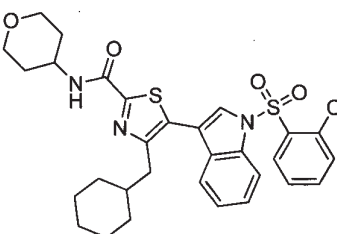
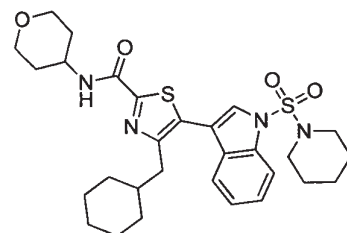
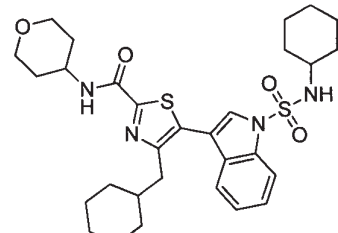
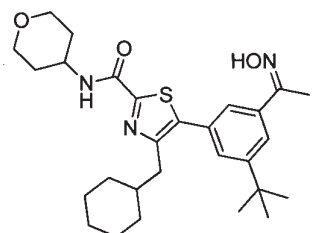
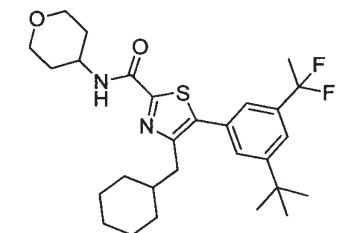
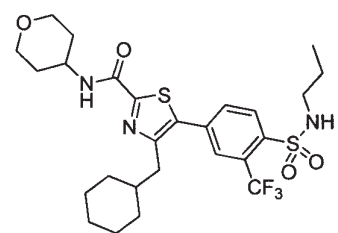
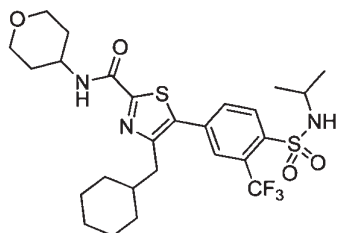
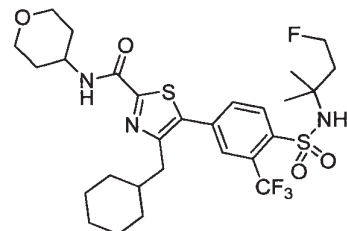
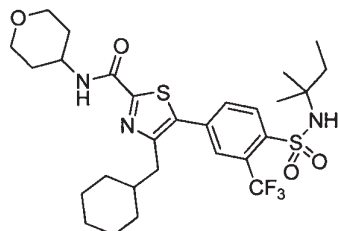
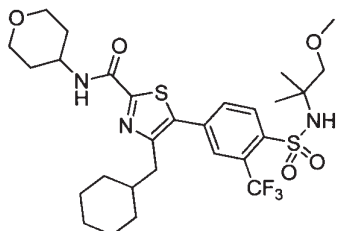
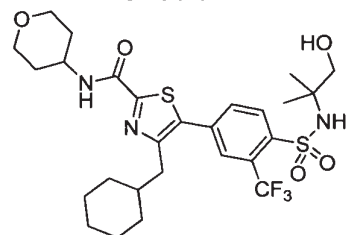
Structure



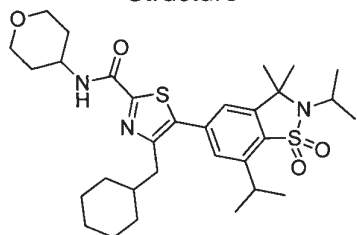
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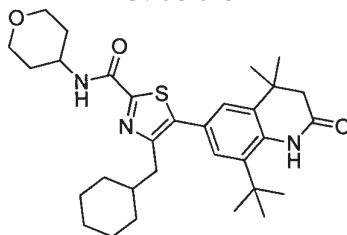
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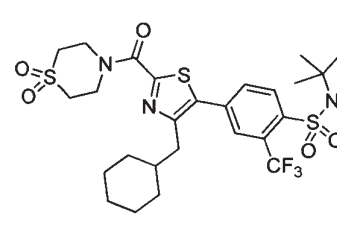
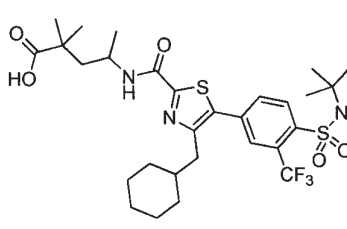
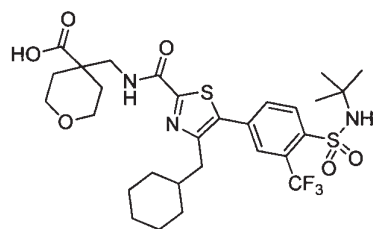
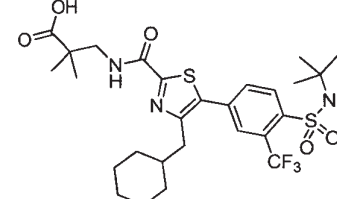
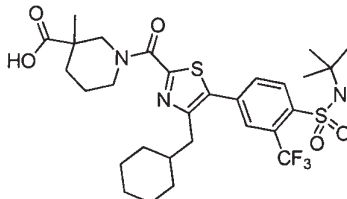
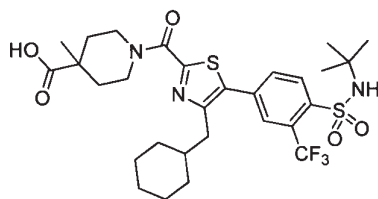
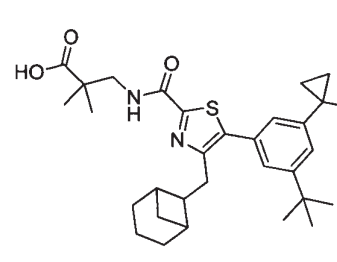
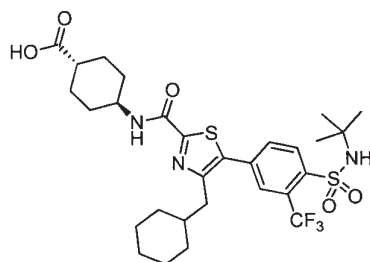
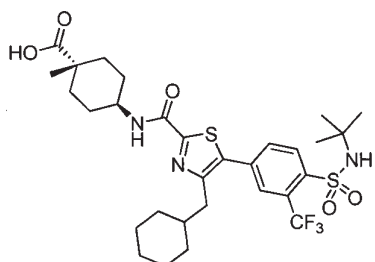
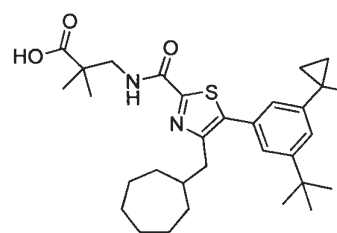
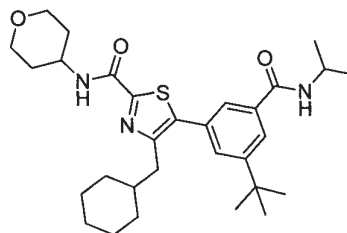
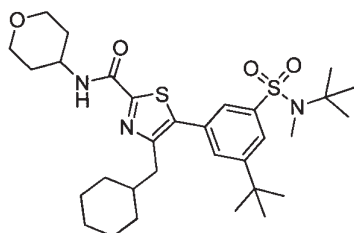
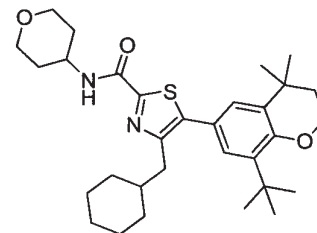
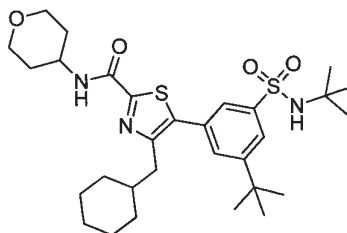
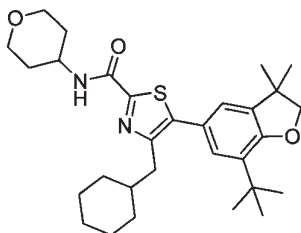
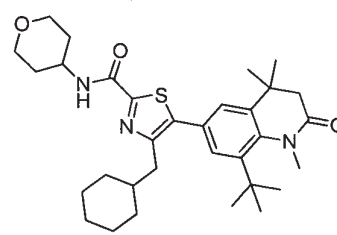
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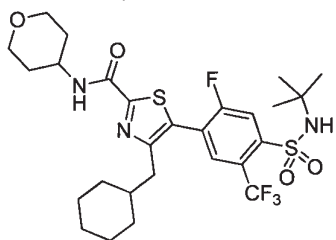
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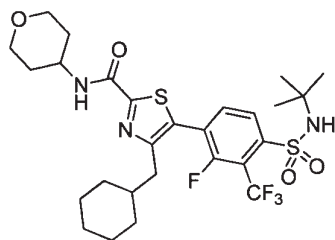
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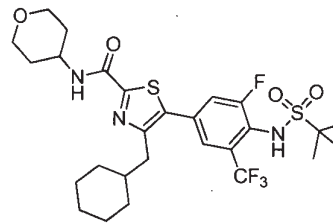
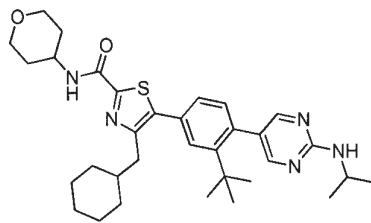
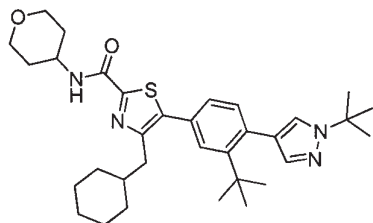
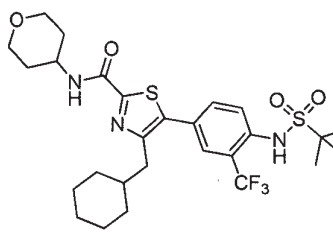
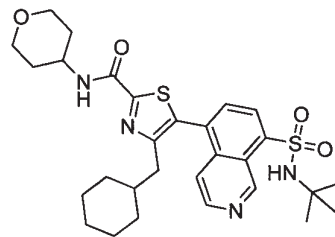
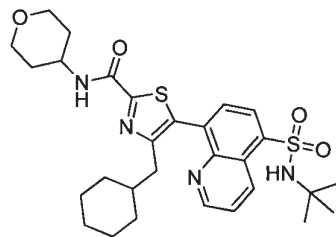
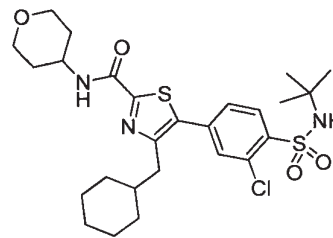
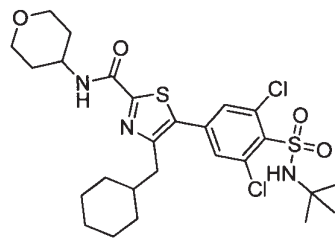
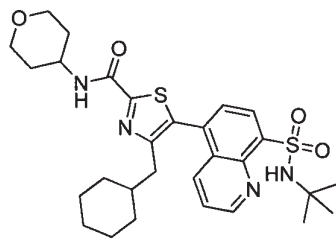
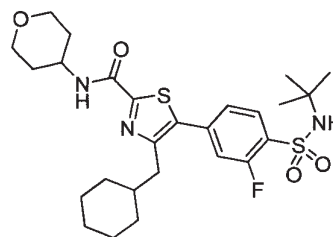
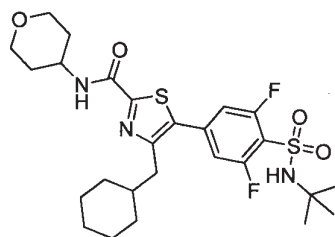
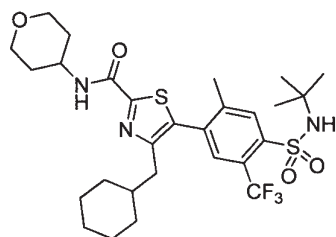
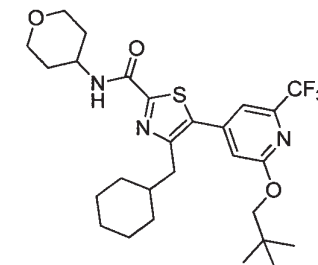
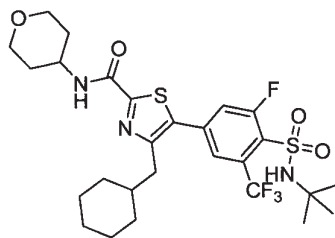
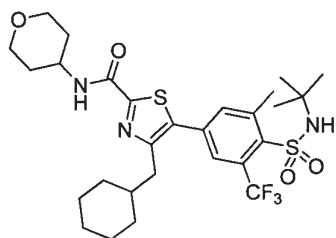
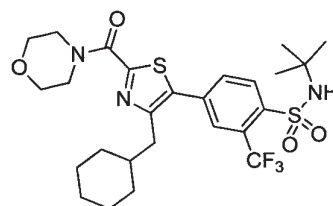
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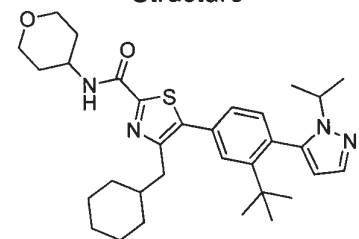
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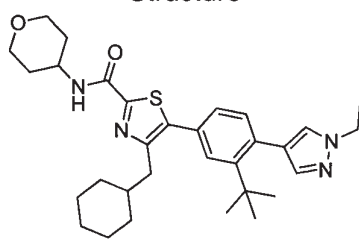
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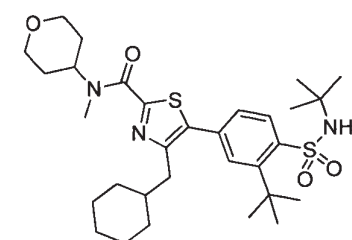
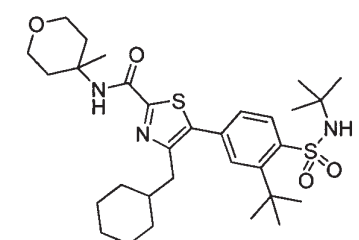
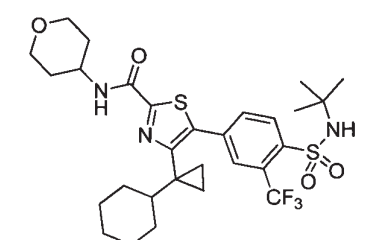
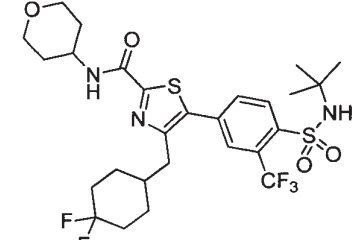
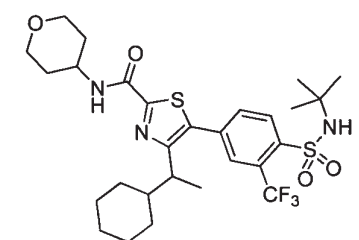
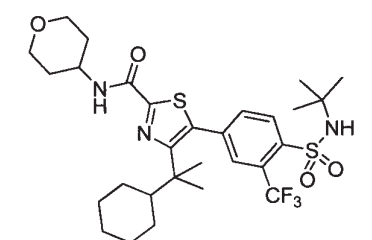
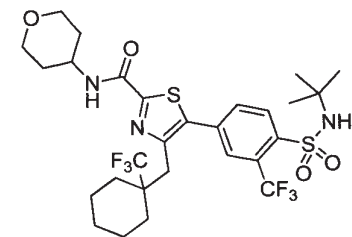
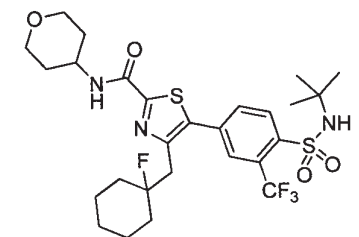
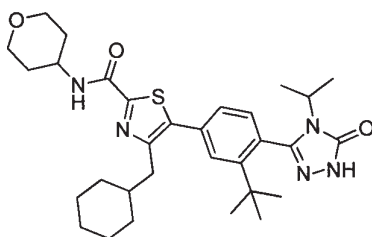
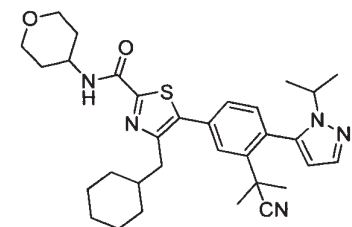
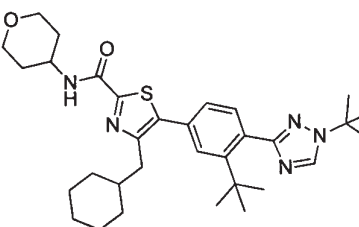
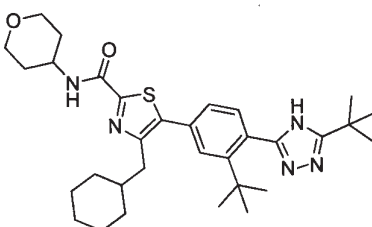
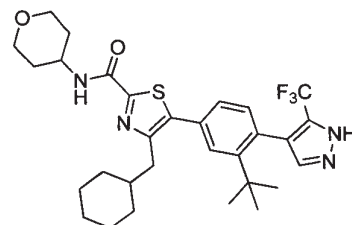
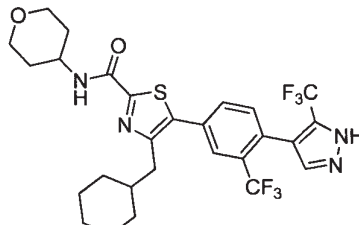
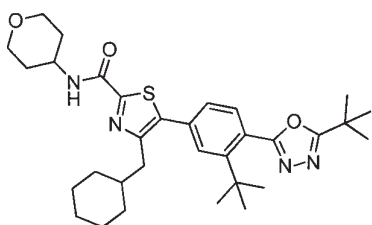
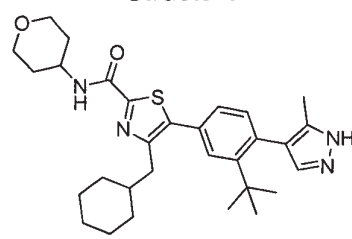
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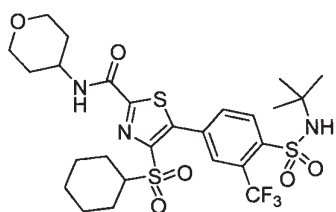
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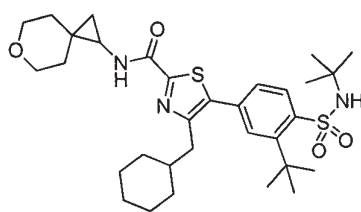
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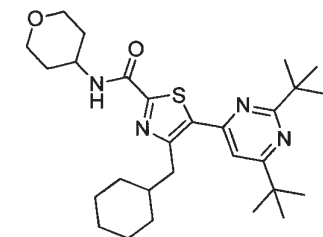
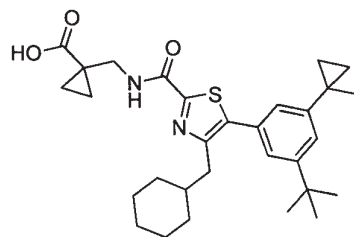
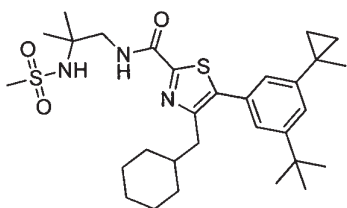
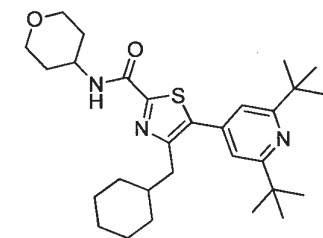
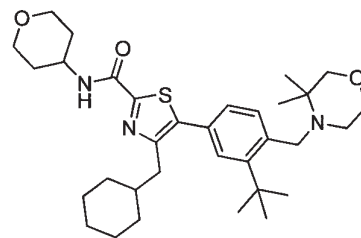
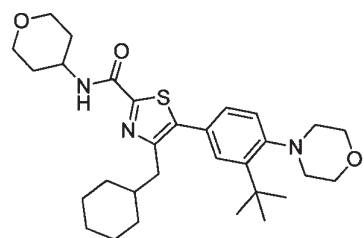
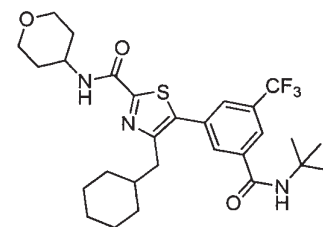
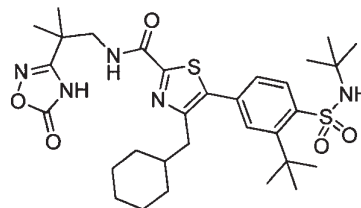
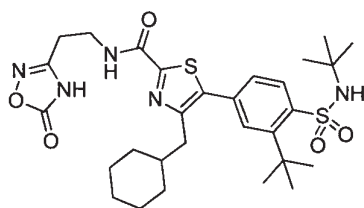
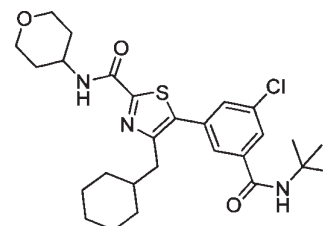
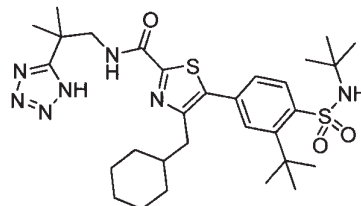
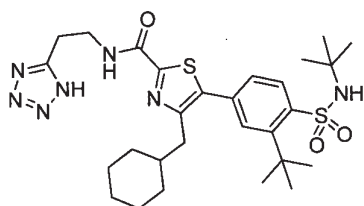
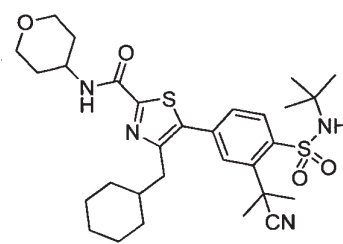
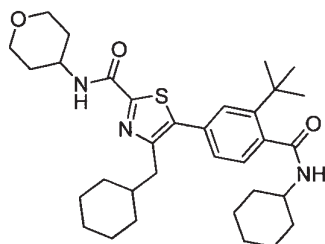
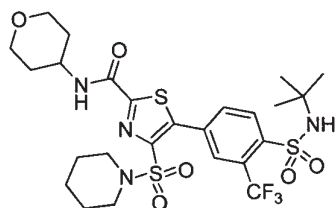
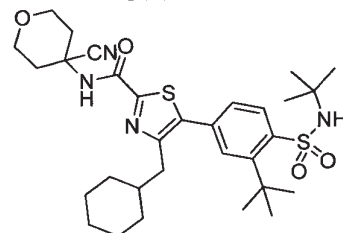
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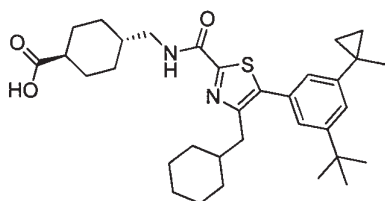
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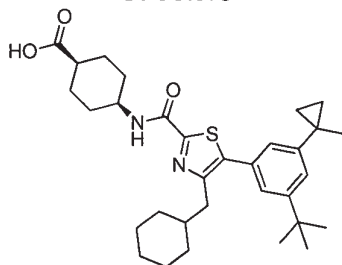
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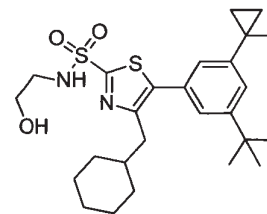
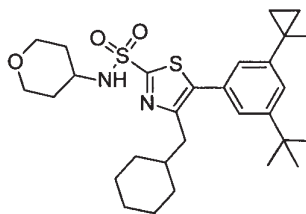
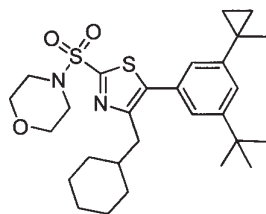
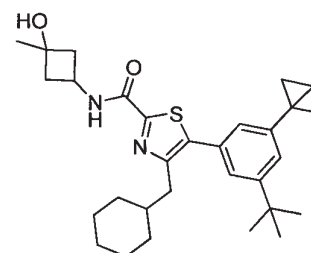
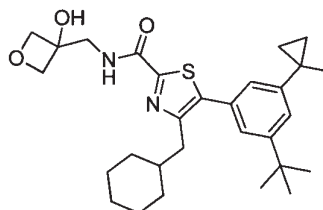
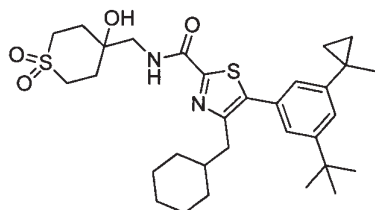
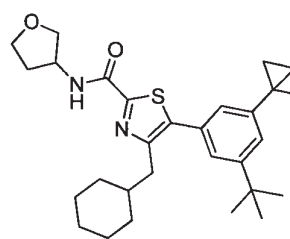
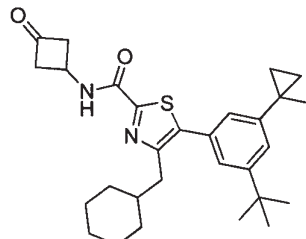
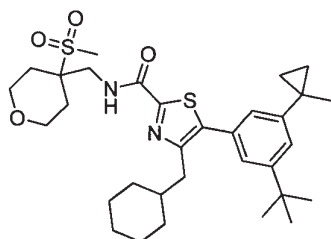
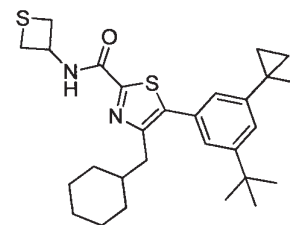
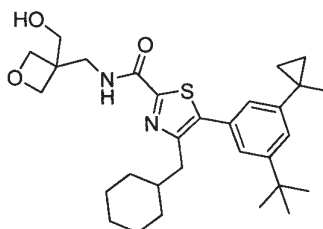
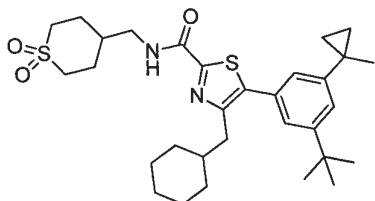
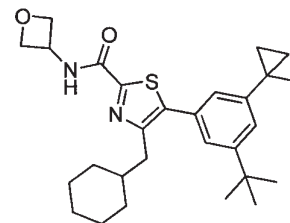
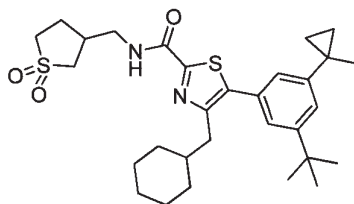
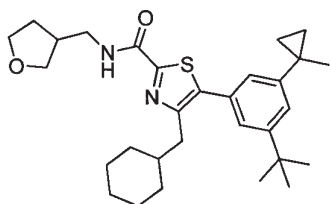
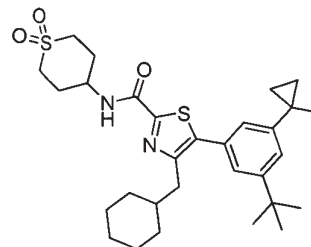
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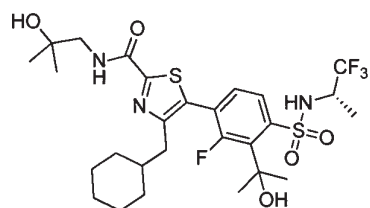
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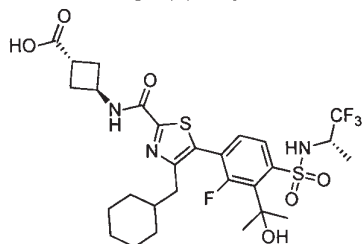
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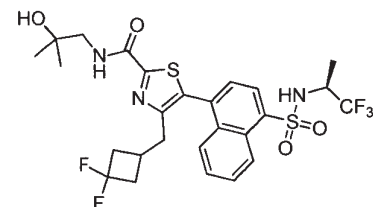
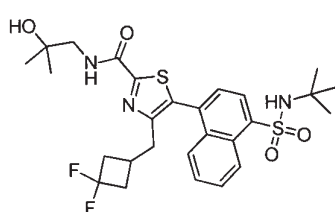
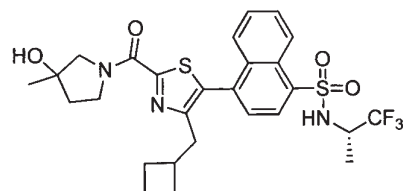
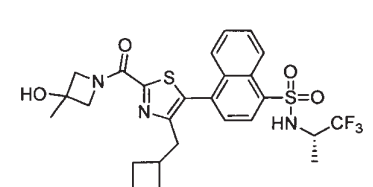
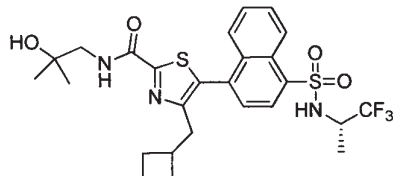
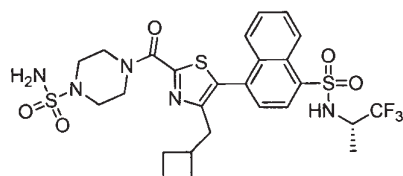
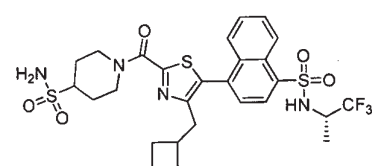
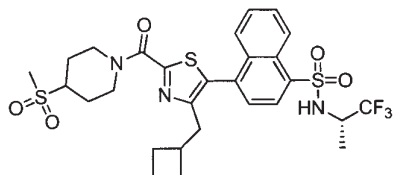
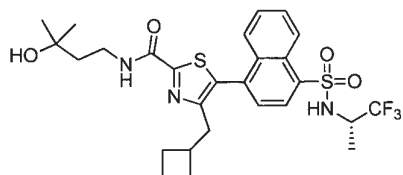
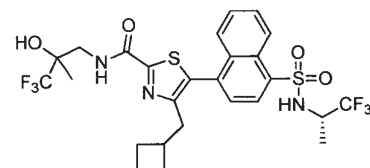
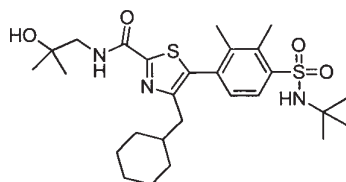
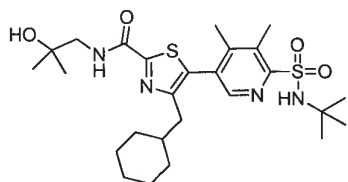
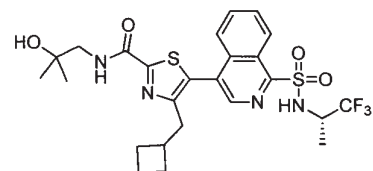
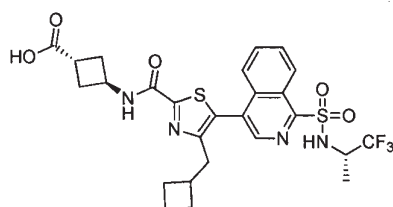
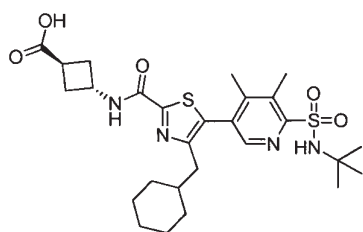
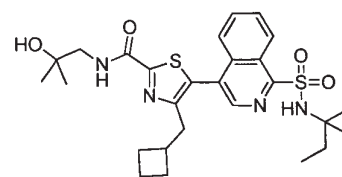
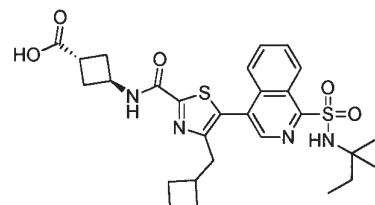
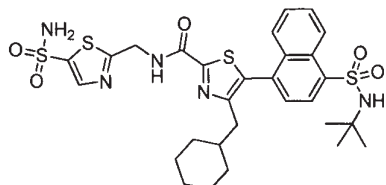
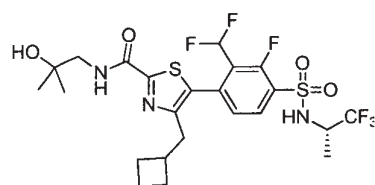
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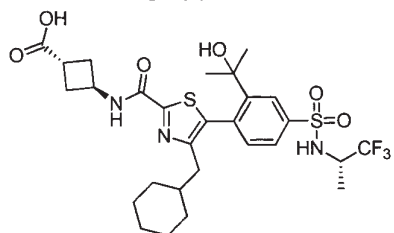
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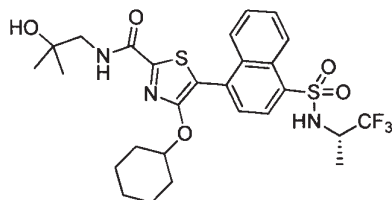
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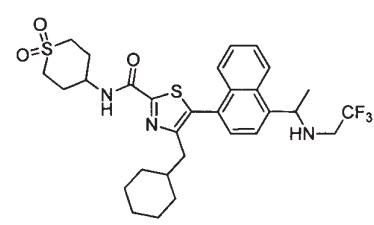
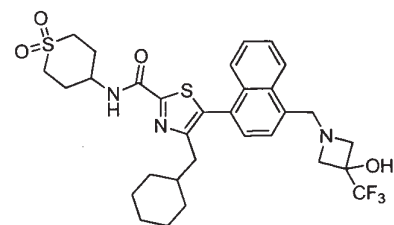
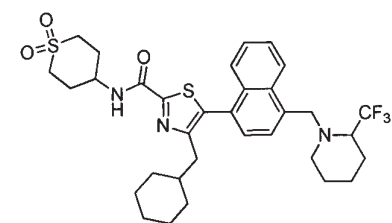
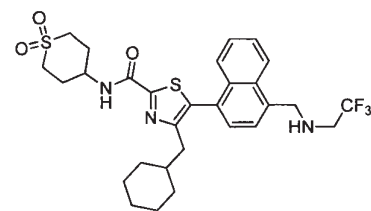
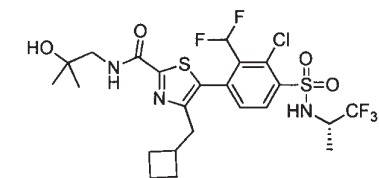
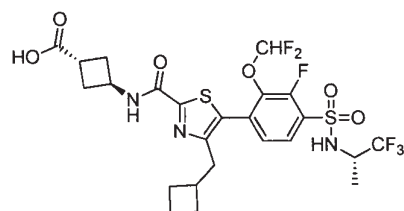
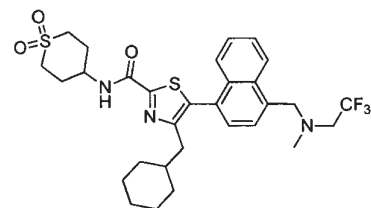
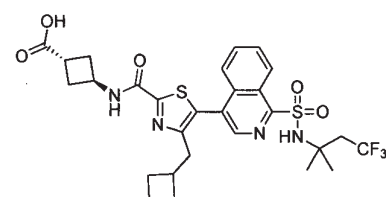
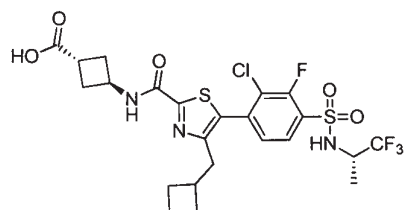
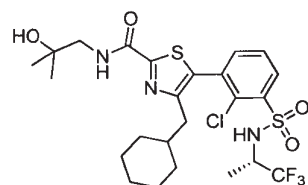
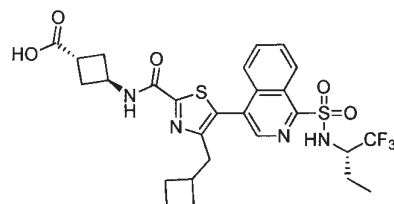
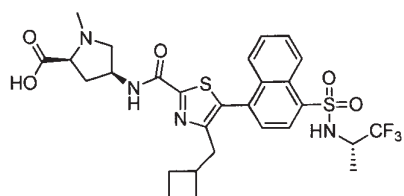
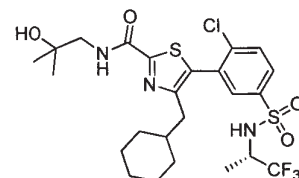
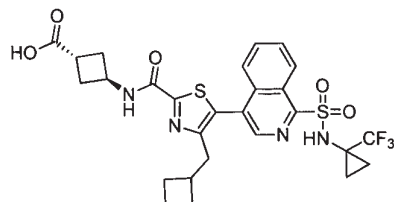
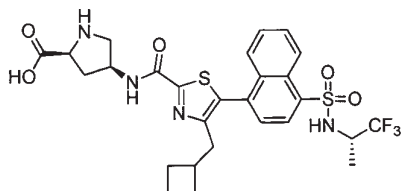
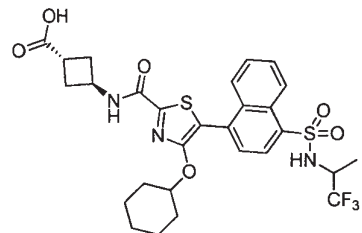
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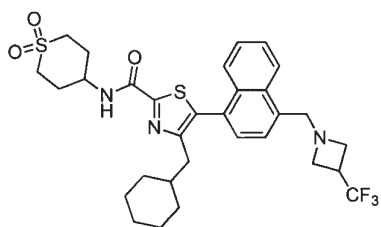
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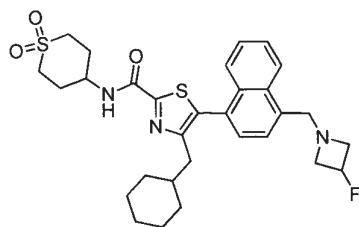
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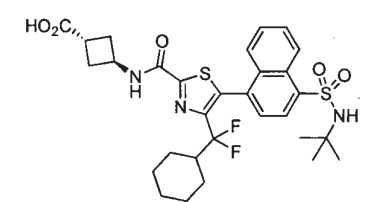
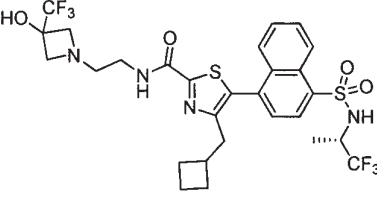
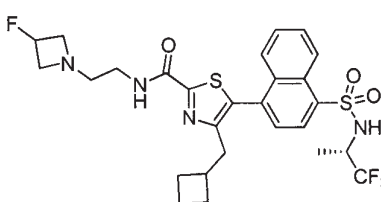
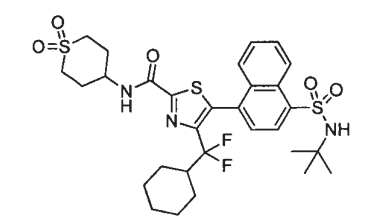
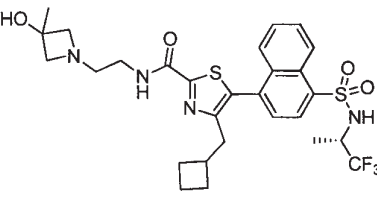
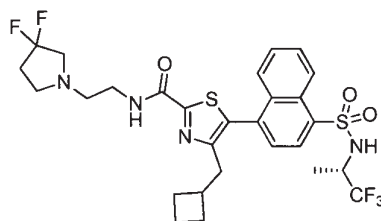
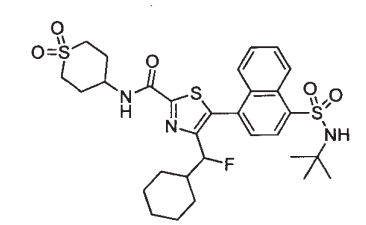
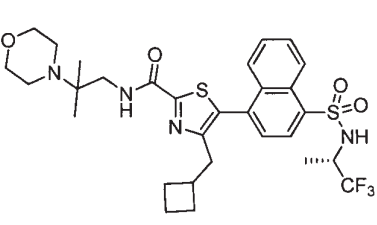
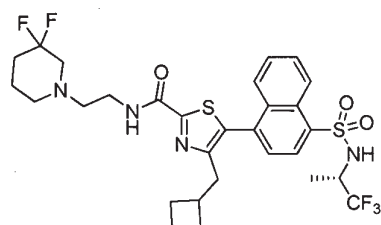
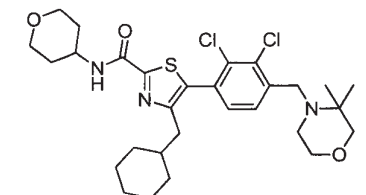
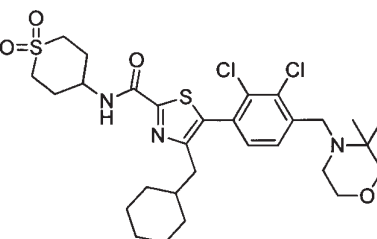
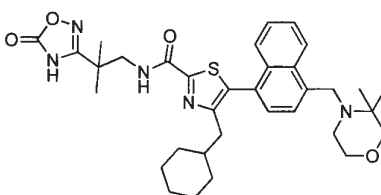
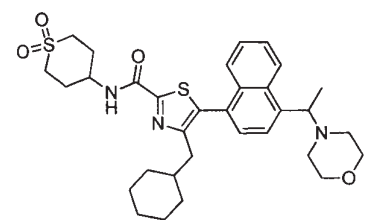
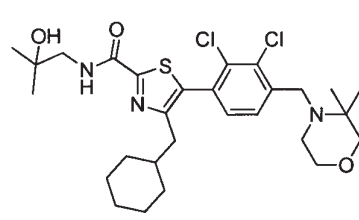
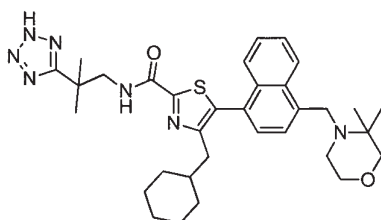
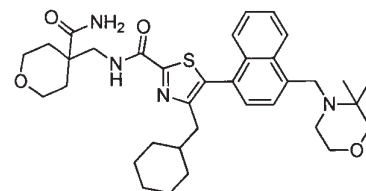
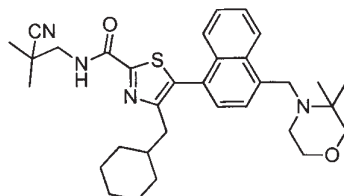
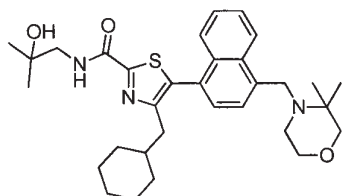
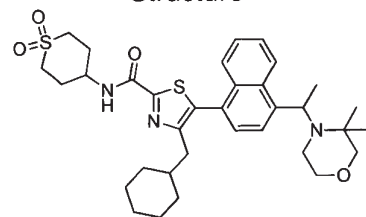
Structure

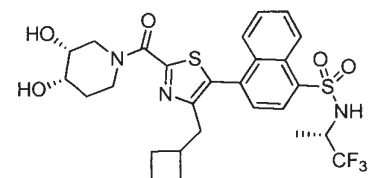
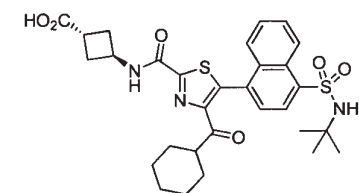
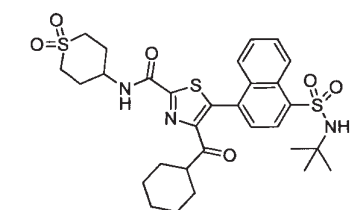
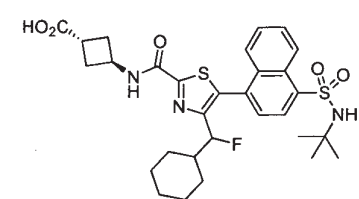
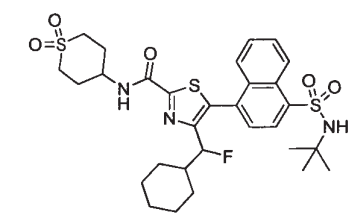
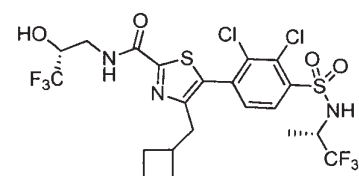
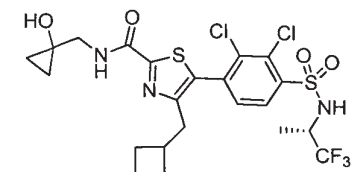
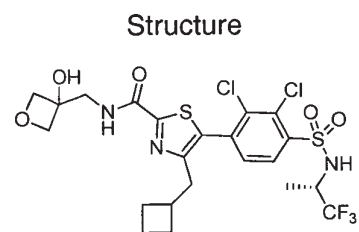
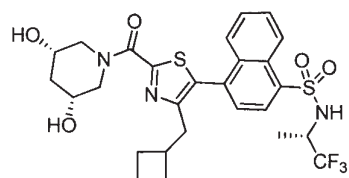
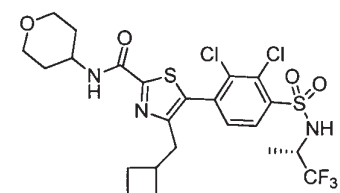
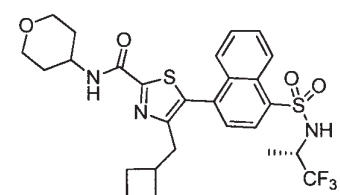
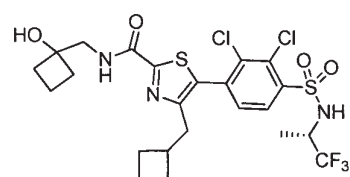
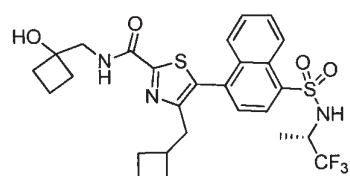
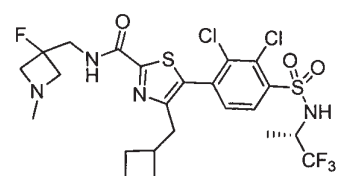
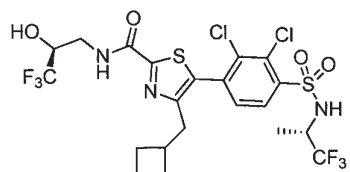
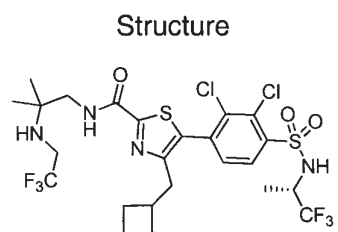
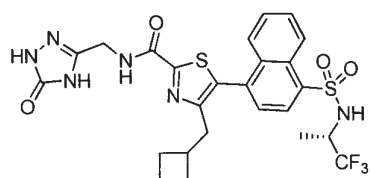
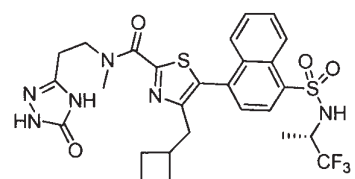
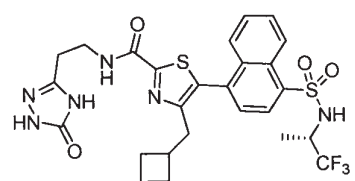
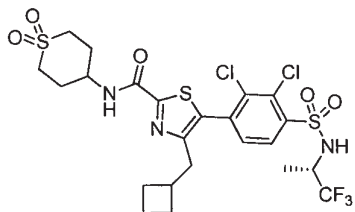
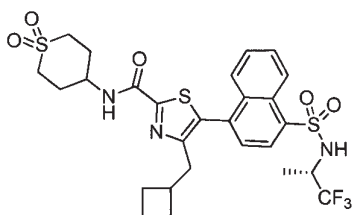
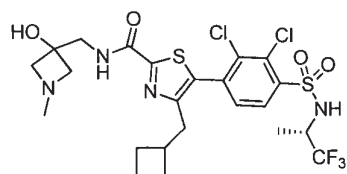
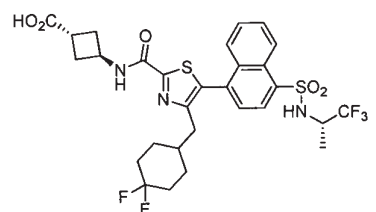
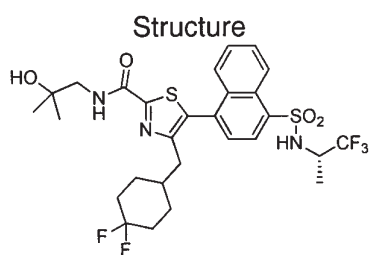


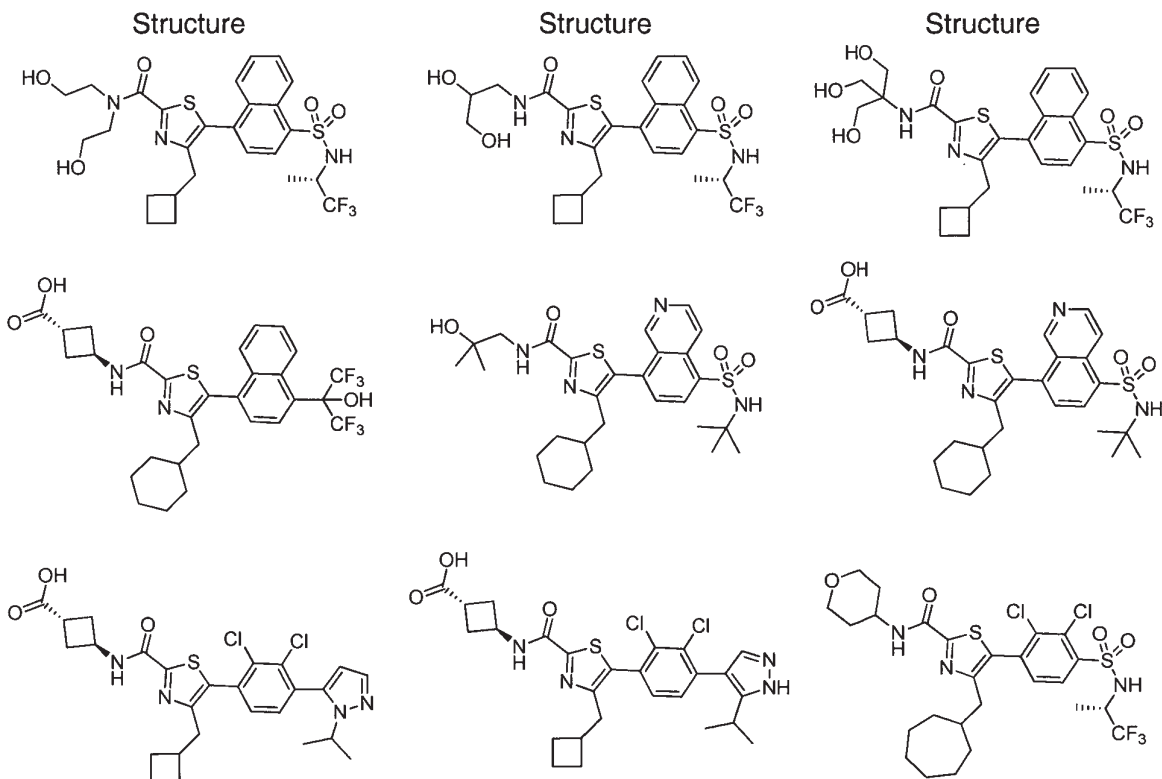
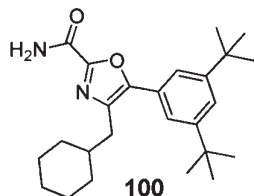
Structure



Structure





**Example 100****Step 1: ((2-Cyclohexyl-1-isocyanoethyl)sulfonyl)benzene (**100a**)**

- 5 To a solution of 1-((isocyanomethyl)sulfonyl)-4-methylbenzene (8.0 g, 80 mmol) in dry DMF (180 mL) was added K₂CO₃ (11.4 g, 160 mmol), bromocyclohexylmethane (11.5 g, 160 mmol) and tetrabutylammonium iodide (1.6 g, 8.0 mmol). The reaction mixture was stirred at rt for 20 h, then heated to 5°C for 4 h, poured into ice water and extracted with DCM (3 x). The combined organic layers were washed with brine, dried over Na₂SO₄, concentrated and
- 10 purified by CC (PE/EA = 10/1) to give compound **100a** (2.2 g, 10%) as a white solid.

Step 2: 4-(Cyclohexylmethyl)-5-(3,5-di-*tert*-butylphenyl)oxazole (100b**)**

- To a solution of compound **100a** (1.0 g, 3.4 mmol) in dry MeOH (20 mL) was added K₂CO₃ (1.0 g, 6.8 mmol) and 3,5-di-*tert*-butylbenzaldehyde (0.8 g, 3.4 mmol). The mixture was heated to reflux for 2 h, cooled to rt and diluted with water. The mixture was extracted with EA
- 15 (3 x). The combined organic layers were washed with brine, dried over Na₂SO₄, concentrated and purified by CC (PE/EA = 15/1) to give compound **100b** (0.65 g, 54%) as a white solid.

Step 3: 2-Bromo-4-(cyclohexylmethyl)-5-(3,5-di-*tert*-butylphenyl)oxazole (100c)

To a solution of compound **100b** (0.65 g, 1.9 mmol) in dry DCM (10 mL) was added NBS (0.5 g, 3.7 mmol). The reaction mixture was stirred at rt until completion, diluted with water and extracted with DCM (3 x). The combined organic layers were washed with brine, dried over Na₂SO₄, concentrated and purified by CC (PE/EA = 20/1) to give compound **100c** (0.5 g, 63%) as a white solid.

Step 4: Methyl 4-(cyclohexylmethyl)-5-(3,5-di-*tert*-butylphenyl)oxazole-2-carboxylate (100d)

To a solution of compound **100c** (0.5 g, 1.2 mmol) in MeOH (30 mL) was added Pd(dppf)Cl₂ (50 mg) and Et₃N (0.6 g, 6 mmol). The reaction was stirred at 60°C overnight under CO atmosphere (1.5 MPa), filtered, concentrated and purified by CC (PE/EA = 20/1) to give compound **100d** (0.3 g, 65%) as a yellow solid.

Step 5: 4-(Cyclohexylmethyl)-5-(3,5-di-*tert*-butylphenyl)oxazole-2-carboxylic acid (100e)

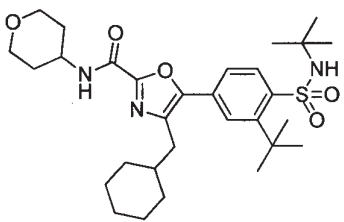
To a solution of compound **100d** (300 mg, 0.7 mmol) in THF (10 mL) and H₂O (2 mL) was added LiOH·H₂O (110 mg, 2.6 mmol) and then the mixture was stirred overnight at rt, concentrated, diluted with H₂O, adjusted to pH 5 with 1N HCl and extracted with DCM. The organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated to give compound **100e** (270 mg, 97%) as a white solid.

Step 6: 4-(Cyclohexylmethyl)-5-(3,5-di-*tert*-butylphenyl)oxazole-2-carboxamide (100)

To a solution of compound **100e** (270 mg, 0.7 mmol) and 1 drop of DMF in DCM (10 mL) at 0°C was added dropwise oxalyl chloride (0.15 mL, 1.5 mmol). The reaction mixture was stirred at rt for 0.5 h and concentrated. A solution of the crude carbonyl chloride in dry THF (5 mL) was added to a NH₃/THF solution (20 mL) and the mixture stirred at rt for 1 h, quenched with aq. NaHCO₃ (30 mL) and extracted with EA (3 x). The combined organic layers were washed with brine, dried over Na₂SO₄, concentrated and purified by CC (PE/EA = 4/1) to give the compound **100** (75 mg, 22%) as a white solid. ¹H-NMR (CDCl₃, 400 MHz) δ: 1.03-1.09 (2H, m), 1.21-1.27 (3H, m), 1.36 (18H, s), 1.65-1.82 (6H, m), 2.65 (2H, d, J = 6.4 Hz), 5.55 (1H, br s), 6.92 (1H, br s), 7.45 (1H, s), 7.51 (2H, s). MS 397.3 (M+H⁺).

Example 100/1 to 100/20

The following Examples were prepared similar as described above:

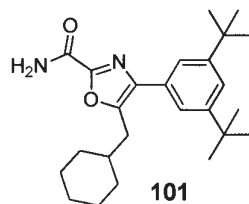
#	Structure	Analytical data
100/1		¹ H-NMR (300 MHz, CDCl ₃) δ: 8.24 (d, J = 8.4 Hz, 1H), 7.93 (d, J = 1.8 Hz, 1H), 7.67 (dd, J = 8.4, 1.8 Hz, 1H), 6.95 (d, J = 7.8 Hz, 1H), 4.54 (s, 1H), 4.25-4.14 (m, 1H), 4.02 (d, J = 10.2 Hz, 2H), 3.54 (td, J = 11.7, 1.8 Hz, 2H), 2.68 (d, J = 6.6 Hz, 2H), 2.04-1.99 (m, 2H), 1.79-1.66 (m, 17H), 1.31-1.10 (m, 12H), 1.09-1.01 (m, 2H). MS 560.3 (M+1) ⁺

#	Structure	Analytical data
100 /2		$^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ : 9.23 (d, J = 7.6 Hz, 1H), 8.25 (d, J = 8.0 Hz, 1H), 7.86 (s, 2H), 7.78 (d, J = 8.0 Hz, 1H), 4.59-4.54 (m, 1H), 2.93-2.89 (m, 1H), 2.71 (d, J = 6.4 Hz, 2H), 2.49-2.43 (m, 4H), 1.80-1.64 (m, 6H), 1.58 (s, 9H), 1.20-1.15 (m, 12H), 1.03-1.00 (m, 2H). MS 574.3 ($M+1$) $^+$
100 /3		$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 8.67 (d, J = 8.8 Hz, 1H), 8.37 (d, J = 7.6 Hz, 1H), 7.87 (d, J = 8.0 Hz, 1H), 7.74-7.68 (m, 1H), 7.65-7.59 (m, 2H), 7.01 (d, J = 8.4 Hz, 1H), 4.63 (s, 1H), 4.26-4.19 (m, 1H), 4.10-4.01 (m, 2H), 3.55 (m, 2H), 2.42 (d, J = 6.8 Hz, 2H), 2.07-2.01 (m, 2H), 1.75-1.01 (m, 7H), 1.30-1.20 (m, 2H), 1.18 (s, 9H), 1.15-0.99 (m, 2H), 0.81-0.71 (m, 2H). MS 552.3 ($M+H$) $^+$
100 /4		$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 8.67 (d, J = 8.0 Hz, 1H), 8.37 (d, J = 7.6 Hz, 1H), 7.96-7.93 (m, 1H), 7.4-7.69 (m, 1H), 7.65-7.60 (m, 2H), 5.12-5.04 (m, $\frac{1}{2}$ H), 4.86-4.79 (m, $\frac{1}{2}$ H), 4.15-4.05 (m, 2H), 3.60-3.43 (m, 2H), 3.38 (s, $\frac{1}{2}$ H), 3.07 (s, $\frac{1}{2}$ H), 2.46 (d, J = 6.8 Hz, 2H), 2.06-1.82 (m, 3H), 1.76-1.55 (m, 6H), 1.27-1.24 (m, 2H), 1.19 (s, 9H), 1.14-1.00 (m, 3H), 0.90-0.75 (m, 2H). MS 568.2 ($M+1$) $^+$
100 /5		$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 0.76-0.79 (m, 2H), 1.14-1.18 (m, 3H), 1.25 (s, 9H), 1.58-1.66 (m, 9H), 1.74-1.80 (m, 2H), 2.37 (s, 1H), 2.42 (d, J = 7.6 Hz, 2H), 3.56 (d, J = 6.0 Hz, 2H), 3.81 (dd, J = 7.6 Hz, 3.2 Hz, 4H), 4.62 (s, 1H), 7.45-7.50 (m, 1H), 7.60-7.65 (m, 2H), 7.71-7.72 (m, 1H), 7.87 (d, J = 8.0 Hz, 1H), 8.37 (d, J = 7.6 Hz, 1H), 8.67 (d, J = 8.8 Hz, 1H). MS 584.3 ($M+1$) $^+$
100 /6		$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 0.76-0.79 (m, 2H), 1.03-1.15 (m, 3H), 1.19 (s, 9H), 1.59-1.61 (m, 7H), 2.32-2.36 (m, 2H), 2.41-2.48 (m, 4H), 3.16-3.18 (m, 4H), 4.28-4.29 (m, 1H), 4.63 (s, 1H), 7.10 (d, J = 8.0 Hz, 1H), 7.60-7.65 (m, 2H), 7.73 (t, J = 7.2 Hz, 1H), 7.85 (d, J = 8.8 Hz, 1H), 8.37 (d, J = 8.0 Hz, 1H), 8.68 (d, J = 8.4 Hz, 1H). MS 602.3 ($M+1$) $^+$
100 /7		$^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ : 0.78-0.82 (m, 2H), 0.96-1.15 (m, 3H), 1.18 (s, 9H), 1.34 (s, 6H), 1.58-1.75 (m, 6H), 1.94 (s, 1H), 2.42 (d, J = 7.2 Hz, 2H), 3.51 (d, J = 6.3 Hz, 2H), 4.61 (s, 1H), 7.45-7.52 (m, 1H), 7.60-7.72 (m, 2H), 7.75-7.80 (m, 1H), 7.85 (d, J = 8.4 Hz, 1H), 8.37 (d, J = 7.5 Hz, 1H), 8.67 (d, J = 8.7 Hz, 1H). MS 542.3 ($M+1$) $^+$
100 /8		$^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ : 0.76-0.80 (m, 2H), 1.09-1.13 (m, 3H), 1.18 (s, 9H), 1.59-1.61 (m, 5H), 2.17-2.19 (m, 4H), 2.43 (d, J = 7.2 Hz, 2H), 2.88-2.95 (m, 4H), 3.39-3.51 (m, 2H), 3.57 (d, J = 6.0 Hz, 2H), 3.77 (s, 1H), 4.67 (s, 1H), 7.57-7.65 (m, 3H), 7.70-7.73 (m, 1H), 7.85 (d, J = 8.7 Hz, 1H), 8.37 (d, J = 7.8 Hz, 1H), 8.68 (d, J = 8.1 Hz, 1H). MS 632.2 ($M+1$) $^+$

#	Structure	Analytical data
100 /9		$^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ : 0.76-0.79 (m, 2H), 1.14-1.17 (m, 3H), 1.18 (s, 9H), 1.58-1.66 (m, 7H), 2.42-2.47 (m, 6H), 3.05-3.09 (m, 4H), 4.04 (s, 2H), 4.51 (s, 2H), 4.66 (s, 1H), 7.58-7.61 (m, 2H), 7.66-7.69 (m, 1H), 7.83 (d, $J = 8.1$ Hz, 1H), 8.36 (d, $J = 7.8$ Hz, 1H), 8.67 (d, $J = 9.0$ Hz, 1H). MS 628.2 ($\text{M}+1$) $^+$
100 /10		$^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ : 0.78-0.82 (m, 2H), 0.96-1.15 (m, 3H), 1.19 (s, 9H), 1.59-1.63 (m, 6H), 1.87 (m, 4H), 2.44 (d, $J = 7.2$ Hz, 2H), 3.67-3.71 (m, 4H), 4.00 (s, 2H), 4.44 (s, 2H), 4.62 (s, 1H), 7.59-7.64 (m, 2H), 7.71-7.72 (m, 1H), 7.88 (d, $J = 8.4$ Hz, 1H), 8.37 (d, $J = 7.8$ Hz, 1H), 8.68 (d, $J = 9.0$ Hz, 1H). MS 580.3 ($\text{M}+1$) $^+$
100 /11		$^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ : 0.76-0.83 (m, 2H), 1.14-1.17 (m, 3H), 1.19 (s, 9H), 1.58-1.66 (m, 6H), 2.09-2.11 (m, 4H), 2.43 (d, $J = 6.9$ Hz, 2H), 2.62-2.64 (m, 4H), 3.90 (s, 2H), 4.34 (s, 2H), 4.62 (s, 1H), 7.60-7.63 (m, 2H), 7.71 (m, 1H), 7.87 (d, $J = 10.8$ Hz, 1H), 8.36 (d, $J = 10.2$ Hz, 1H), 8.66 (d, $J = 10.2$ Hz, 1H). MS 596.3 ($\text{M}+1$) $^+$
100 /12		$^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ : 0.75-0.83 (m, 2H), 0.99-1.17 (m, 3H), 1.18 (s, 9H), 1.61-1.70 (m, 6H), 2.42-2.47 (m, 6H), 3.07 (m, 4H), 4.04 (s, 2H), 4.51 (s, 2H), 4.66 (s, 1H), 7.58-7.61 (m, 2H), 7.72 (m, 1H), 7.85 (d, $J = 8.4$ Hz, 1H), 8.36 (d, $J = 7.8$ Hz, 1H), 8.67 (d, $J = 9.0$ Hz, 1H). MS 612.3 ($\text{M}+1$) $^+$
100 /13		$^1\text{H-NMR}$ (DMSO-d_6 , 300 MHz) δ : 0.66-0.80 (m, 2H), 1.05 (s, 9H), 1.21 (br s, 2H), 1.45-1.65 (m, 4H), 1.77 (s, 4H), 2.29-2.35 (m, 4H), 2.41 (d, $J = 6.9$ Hz, 2H), 4.53-4.59 (m, 2H), 7.68-7.75 (m, 4H), 7.86-7.89 (m, 1H), 8.27 (d, $J = 7.5$ Hz, 1H), 8.78 (d, $J = 8.4$ Hz, 1H), 9.15 (d, $J = 7.5$ Hz, 1H). MS 568.3 ($\text{M}+1$) $^+$
100 /14		$^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ : 0.73-0.78 (m, 2H), 0.96-1.13 (m, 3H), 1.18 (s, 9H), 1.57-1.71 (m, 6H), 1.99-2.14 (m, 12H), 2.40 (d, $J = 6.9$ Hz, 2H), 4.64 (s, 1H), 6.85 (s, 1H), 7.58-7.64 (m, 3H), 7.66-7.71 (m, 1H), 7.88 (d, $J = 8.1$ Hz, 1H), 8.36 (d, $J = 7.5$ Hz, 1H), 8.66 (d, $J = 8.7$ Hz, 1H). MS 622.3 ($\text{M}+1$) $^+$
100 /15		MS 560.2 ($\text{M}+1$) $^+$

#	Structure	Analytical data
100 /16		MS 620.1 (M+1) ⁺
100 /17		MS 586.2 (M+1) ⁺
100 /18		¹ H-NMR (400 MHz, CDCl ₃) δ: 0.75-0.77 (m, 2H), 0.88-0.90 (m, 2H), 1.00-1.08 (m, 2H), 1.16-1.26 (m, 3H), 1.35 (s, 9H), 1.43 (s, 3H), 1.62-1.79 (m, 8H), 2.02 (dd, J = 8.4, 2.0 Hz, 2H), 2.64 (d, J = 6.8 Hz, 2H), 3.54 (td, J = 12.0, 2.0 Hz, 2H), 4.02 (dd, J = 8.4, 2.4 Hz, 2H), 4.14-4.22 (m, 1H), 6.94 (d, J = 8.4 Hz, 1H), 7.30 (t, J = 1.6 Hz, 1H), 7.42 (t, J = 1.6 Hz, 1H), 7.49 (t, J = 1.6 Hz, 1H). MS 479.3 (M+1) ⁺
100 /19		¹ H-NMR (400 MHz, CDCl ₃) δ: 0.70-0.73 (m, 2H), 0.84-0.86 (m, 2H), 0.90-0.98 (m, 2H), 1.05-1.10 (m, 3H), 1.15 (s, 6H), 1.31 (s, 9H), 1.39 (s, 3H), 1.53-1.69 (m, 6H), 2.58 (d, J = 6.8 Hz, 2H), 3.49 (d, J = 6.8 Hz, 2H), 7.26 (s, 1H), 7.35 (s, 1H), 7.43 (s, 1H), 7.87 (t, J = 6.4 Hz, 1H). MS 495.3 (M+1) ⁺
100 /20		¹ H-NMR (400 MHz, CDCl ₃) δ: 0.75-0.77 (m, 2H), 0.88-0.90 (m, 2H), 1.03-1.06 (m, 2H), 1.19-1.25 (m, 3H), 1.35 (s, 9H), 1.43 (s, 3H), 1.63-1.79 (m, 6H), 2.45-2.53 (m, 2H), 2.64 (d, J = 7.2 Hz, 2H), 2.78-2.84 (m, 2H), 3.19-3.21 (m, 1H), 4.75-4.81 (m, 1H), 7.29-7.30 (m, 2H), 7.41 (t, J = 1.6 Hz, 1H), 7.48 (t, J = 1.6 Hz, 1H). MS 493.3 (M+1) ⁺
100 /21		¹ H-NMR (CDCl ₃ , 300 MHz) δ: 0.71-0.77 (m, 2H), 1.03-1.17 (m, 3H), 1.18 (s, 9H), 1.32 (s, 6H), 1.57-.60 (m, 3H), 1.95-2.06 (m, 2H), 2.42 (d, J = 7.2 Hz, 2H), 3.45-3.56 (m, 6H), 4.69 (s, 1H), 7.58-7.72 (m, 4H), 7.84-7.87 (m, 1H), 8.35 (d, J = 7.5 Hz, 1H), 8.65 (d, J = 8.4 Hz, 1H). MS 584.3 (M+1) ⁺
100 /22		¹ H-NMR (CDCl ₃ , 300 MHz) δ: 0.69-0.73 (m, 2H), 1.04-1.16 (m, 3H), 1.18 (s, 9H), 1.25-1.31 (m, 5H), 1.32-1.60 (m, 7H), 2.05-2.08 (m, 2H), 2.30-2.42 (m, 4H), 2.93 (s, 1H), 3.01 (s, 1H), 4.00 (br s, 1H), 4.71 (s, 1H), 7.60-7.75 (m, 3H), 7.83-7.86 (m, 1H), 8.28 (d, J = 7.2 Hz, 1H), 8.37 (d, J = 7.8 Hz, 1H), 8.66 (d, J = 8.4 Hz, 1H). MS 610.3 (M+1) ⁺

#	Structure	Analytical data
100 /23		$^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ : 0.69-0.73 (m, 2H), 1.04-1.16 (m, 3H), 1.18 (s, 9H), 1.57-1.60 (m, 6H), 1.81-1.85 (m, 2H), 1.98-2.01 (m, 2H), 2.18-2.23 (m, 7H), 2.41 (d, $J = 7.2$ Hz, 2H), 4.70 (s, 1H), 7.36 (s, 1H), 7.59-7.72 (m, 3H), 7.87-7.90 (m, 1H), 8.36 (d, $J = 7.5$ Hz, 1H), 8.66 (d, $J = 8.7$ Hz, 1H). MS 608.3 ($\text{M}+1$) $^+$
100 /24		$^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ : 0.69-0.73 (m, 2H), 1.04-1.16 (m, 3H), 1.18 (s, 9H), 1.58-1.72 (m, 6H), 2.42 (d, $J = 6.9$ Hz, 2H), 4.43 (s, 4H), 4.49 (s, 2H), 4.68 (s, 1H), 4.99 (s, 2H), 7.58-7.73 (m, 3H), 7.83-7.86 (m, 1H), 8.37 (d, $J = 7.2$ Hz, 1H), 8.64 (d, $J = 8.4$ Hz, 1H). MS 600.2 ($\text{M}+1$) $^+$
100 /25		$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 0.81-0.89 (m, 2H), 1.12-1.18 (m, 2H), 1.25 (s, 9H), 1.60-1.70 (m, 7H), 2.24-2.46 (m, 7H), 3.14-3.17 (m, 4H), 4.25-4.26 (m, 1H), 5.07 (s, 1H), 7.08 (d, $J = 8.4$ Hz, 1H), 7.45 (d, $J = 8.4$ Hz, 1H), 8.15 (d, $J = 8.4$ Hz, 1H). MS 620.1 ($\text{M}+1$) $^+$
100 /26		$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 0.81-0.88 (m, 2H), 1.11-1.21 (m, 3H), 1.25 (s, 9H), 1.32 (s, 6H), 1.61-1.70 (m, 6H), 2.40 (d, $J = 7.2$ Hz, 2H), 3.48 (d, $J = 6.3$ Hz, 2H), 5.10 (s, 1H), 7.45-7.49 (m, 2H), 8.13 (d, $J = 8.4$ Hz, 1H); MS 560.2 ($\text{M}+1$) $^+$
100 /27		$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 0.81-0.84 (m, 2H), 1.11-1.22 (m, 3H), 1.25 (s, 9H), 1.61-1.71 (m, 6H), 2.38-2.53 (m, 4H), 2.77-2.85 (m, 2H), 3.17-3.19 (m, 1H), 4.81-4.84 (m, 1H), 5.09 (s, 1H), 7.35 (d, $J = 8.1$ Hz, 1H), 7.46 (d, $J = 8.4$ Hz, 1H), 8.14 (d, $J = 8.4$ Hz, 1H). MS 586.2 ($\text{M}+1$) $^+$
100 /28		$^1\text{H-NMR}$ (400 MHz, CD_3OD): δ 0.81-0.84 (m, 2H), 1.16-1.21 (m, 12H), 1.59-1.66 (m, 6H), 2.33-2.36 (m, 4H), 2.55 (d, $J = 7.2$ Hz, 2H), 3.15-3.18 (m, 2H), 3.33-3.36 (m, 2H), 4.29-4.33 (m, 1H), 7.94 (d, $J = 6.0$ Hz, 1H), 8.05 (d, $J = 7.6$ Hz, 1H), 8.47 (d, $J = 7.6$ Hz, 1H), 8.69 (d, $J = 6.4$ Hz, 1H), 10.19 (s, 1H); MS 603.3 ($\text{M}+1$) $^+$

Example 101**Step 1: 4-Methylbenzenesulfonic acid (101a)**

- 5 To a mixture of sodium 4-methylbenzenesulfinate (1.0 g, 5.0 mmol) in TBME (30 mL) was added conc. HCl (2 mL) and the mixture was stirred at rt for 0.5 h. Then water (40 mL) was

added. The layers were separated and the organic layer was dried over Na₂SO₄ and concentrated to give compound **101a** (0.8 g, 93%) as a white solid.

Step 2: *N*-((3,5-Di-*tert*-butylphenyl)(tosyl)methyl)formamide (**101b**)

To a solution of 3,5-di-*tert*-butylbenzaldehyde (873 mg, 4 mmol) in toluene (6 mL) and MeCN (6 mL) was added formamide (540 mg, 12 mmol) and TMSCl (0.52 mL, 4.0 mmol) and the mixture was stirred at 50°C overnight. Then compound **101a** (630 mg, 4.0 mmol) was added. The resulting mixture was stirred at 50°C overnight, then quenched with water (20 mL) and extracted with EA (20 mL). The organic layer was concentrated and the resulting solid was washed with TBME (4 mL) to give compound **101b** (650 mg, 40%) as a white solid.

Step 3: 1,3-Di-*tert*-butyl-5-(isocyano(tosyl)methyl)benzene (**101c**)

To a solution of compound **101b** (0.20 g, 0.49 mmol) in THF (1.5 mL) was added POCl₃ (151 mg, 1.0 mmol) and the mixture was stirred at rt for 10 min. Then the mixture was cooled to 4°C, 2,5-lutidine (321 mg, 3.0 mmol) was added over 3 min, warmed to rt, stirred for 4 h, poured into a mixture of ice and aq. NaHCO₃ (20 mL) and extracted with TBME (20 mL). The organic layer was concentrated to give compound **101c** (50 mg, 26%) as an oil.

Step 4: 5-(Cyclohexylmethyl)-4-(3,5-di-*tert*-butylphenyl)oxazole (**101d**)

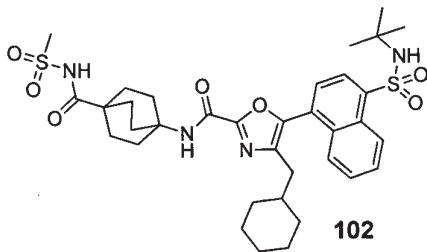
A solution of compound **101c** (0.20 g, 0.50 mmol), 2-cyclohexylacetaldehyde (64 mg, 0.50 mmol) and K₂CO₃ (138 mg, 1.0 mmol) in DMF (3 mL) was stirred overnight at rt, poured into water and extracted with EA (20 mL x 2). The combined organic layers were concentrated and purified by CC (PE/EA = 100/1) to give compound **101d** (80 mg, 45%) as an oil.

Step 5: Ethyl 5-(cyclohexylmethyl)-4-(3,5-di-*tert*-butylphenyl)oxazole-2-carboxylate (**101e**)

To a solution of compound **101d** (0.20 g, 0.56 mmol) in dry THF (20 mL) was added LHMDs solution (1M in THF, 0.6 mL, 0.6 mmol) at -78°C dropwise and the solution was stirred at -78°C for 1h. Then a solution of ethyl chloroformate (108 mg, 1.0 mmol) in dry THF (1 mL) was added. The mixture was warmed to rt, stirred for 2 h, quenched with aq. NH₄Cl and extracted with EA (20 mL x 2). The combined organic layers were concentrated and purified by CC (PE/EA = 100/1) to give compound **101e** (60 mg, 25%) as an oil.

Step 6: 5-(Cyclohexylmethyl)-4-(3,5-di-*tert*-butylphenyl)oxazole-2-carboxamide (**101**)

A mixture of compound **101e** (300 mg, 0.70 mmol) and THF/NH₃ (2M, 5 mL, 10 mmol) in a sealed tube was heated at 90°C for 12 h, concentrated and purified by prep-HPLC to give compound **101** (70 mg, 25%) as a white solid. ¹H-NMR (CDCl₃, 300 MHz) δ: 1.06-1.30 (5H, m), 1.39 (18H, s), 1.59-1.87 (5H, m), 1.88-1.90 (1H, m), 2.80-2.83 (2H, d, J = 9.9 Hz), 5.57 (1H, s), 7.01 (1H, s), 7.42 (1H, t, J = 1.8 Hz), 7.48 (2H, d, J = 1.8 Hz). MS 397.3 (M+1).

Example 102

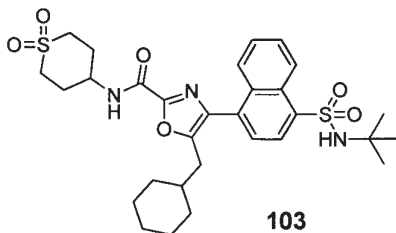
5-(4-(*N*-(*tert*-Butyl)sulfonyl)naphthalen-1-yl)-4-(cyclohexylmethyl)-*N*-(4-((methylsulfonyl)carbamoyl)bicyclo[2.2.2]octan-1-yl)oxazole-2-carboxamide (**102**)

- 5 A solution of compound **100/14** (94 mg, 0.15 mmol), EDCI (105 mg, 0.53 mmol), DMAP (110 mg, 0.85 mmol) and MeSO₂NH₂ (45 mg, 0.44 mmol) in DCM (5 mL) were stirred at 30°C overnight, diluted with EA, washed with H₂O and brine, dried over Na₂SO₄, concentrated and purified by prep-HPLC to give compound **102** (31 mg, 30%) as a white solid. ¹H-NMR (300 MHz, CDCl₃) δ: 0.73-0.81 (m, 2H), 1.05-1.10 (m, 3H), 1.18 (s, 9H), 1.57 (br s, 2H), 1.77 (br s, 4H), 1.94-1.99 (m, 6H), 2.12-2.17 (m, 6H), 2.39 (d, J = 6.9 Hz, 2H), 3.30 (s, 3H), 4.68 (m, 1H), 6.86 (s, 1H), 7.58-7.74 (m, 3H), 7.85-7.93 (m, 2H), 8.36 (d, J = 7.8 Hz, 1H), 8.66 (d, J = 9.9 Hz, 1H). MS 699 [M+1]⁺.

Example 102/1

- 15 The following Example was prepared similar as described in Example **102** above:

#	Structure	Analytical data
102 /1		¹ H-NMR (300 MHz, CDCl ₃) δ: 0.75-0.85 (m, 2H), 1.04-1.06 (m, 3H), 1.18 (s, 9H), 1.58-1.61 (m, 7H), 2.42 (d, J = 6.9 Hz, 2H), 2.53-2.56 (m, 2H), 2.80-2.88 (m, 2H), 3.14-3.18 (m, 1H), 3.34 (s, 3H), 4.68-4.73 (m, 2H), 7.28-7.30 (m, 1H), 7.61 (d, J = 6.9 Hz, 2H), 7.70-7.75 (m, 1H), 7.85 (d, J = 7.5 Hz, 1H), 8.37 (d, J = 9.6 Hz, 1H), 8.66 (d, J = 8.4 Hz, 1H). MS 645 [M+1] ⁺

Example 103Step 1: 2-Cyclohexylacetaldehyde (**103a**)

- 20 To a solution of 2-cyclohexylethanol (25.6 g, 200 mmol) in DCM (500 mL) was added PCC (64.6 g, 300 mmol), and the solution was stirred at rt for 3 h, diluted with Et₂O, stirred at rt for

1 h and filtered through a pad of celite and silica gel (1/1). The filtrate was carefully concentrated to give crude compound **103a** (25.2 g) as a pale yellow oil.

Step 2: 3-Cyclohexyl-2-hydroxypropanenitrile (**103b**)

To a stirred solution of compound **103a** (25.2 g, 200 mmol) in DCM (180 mL) was added titanium isopropoxide (11.8 mL, 40.0 mmol) at 0°C and warmed up to rt. Trimethylsilyl cyanide (39.7 g, 400 mmol) was added and the solution was stirred at rt for 4 h, quenched with 1N HCl and THF at 0°C and extracted with EA. The organic portion was washed with water and brine, dried over Na₂SO₄, filtered, concentrated and purified by CC (PE/EA = 10/1) to give compound **103b** (24.1 g, 72% over two steps) as a colorless oil.

10 Step 3: 1-Amino-3-cyclohexylpropan-2-ol (**103c**)

A solution of compound **103b** (24.1 g, 144 mmol) in dry THF (250 mL) was added LiAlH₄ (8.2 g, 216 mmol) under stirring and the suspension was stirred at rt for 3 h. After cooling to 0 to 5°C, excess LiAlH₄ was neutralized by addition of H₂O (8 mL), 15% aq. NaOH (8 mL) and H₂O (24 mL). The suspension was stirred until all LiAlH₄ was neutralized and a white precipitate was formed, filtered and the precipitate was washed with Et₂O. The combined organic layers were dried over Na₂SO₄, filtered and concentrated to give compound **103c** (21.6 g, 95%) as a colorless oil.

Step 4: Ethyl 2-((3-cyclohexyl-2-hydroxypropyl)amino)-2-oxoacetate (**103d**)

To a solution of compound **103c** (21.6 g, 137 mmol) in dry DCM (200 mL) was added ethyl chloro(oxo)acetate (18.8 g, 137 mmol) followed by TEA (20.8 g, 206.1 mmol) at 0°C and the mixture was slowly warmed to rt. After stirring overnight the mixture was concentrated, diluted with aq. NaHCO₃ and extracted with EA. The organic layer was washed with brine, dried over Na₂SO₄, filtered, concentrated and purified by CC (PE/EA = 1/1) to give compound **103d** (12.4 g, 35%) as a colorless oil.

25 Step 5: Ethyl 2-((3-cyclohexyl-2-oxopropyl)amino)-2-oxoacetate (**103e**)

To a stirred solution of compound **103d** (12.4 g, 48.2 mmol) in dry DCM (150 mL) was added Dess-Martin periodinane (20.4 g, 48.2 mmol) at 0°C and the solution was stirred at rt for 3 h, diluted with water at 0°C and extracted with DCM twice. The combined organic layers were washed with water twice and brine, dried over Na₂SO₄, filtered, concentrated and purified by CC (PE/EA = 1/1) to give compound **103e** (10.1 g, 82%) as colorless solid.

30 Step 6: Ethyl 5-(cyclohexylmethyl)oxazole-2-carboxylate (**103f**)

A solution of compound **103e** (10.1 g, 39.6 mmol) and POCl₃ (6.1 g, 39.6 mmol) in dry toluene (100 mL) was heated at reflux overnight, cooled to rt, concentrated and then partitioned between DCM and 5% aq. Na₂CO₃. The layers were separated and the aq. layer was extracted with DCM. The combined organic layers were dried over Na₂SO₄, filtered, concentrated and purified by CC (PE/EA = 10/1) to give compound **103f** (8.7 g, 92%) as a yellow oil.

Step 7: Ethyl 4-(4-(*N*-(*tert*-butyl)sulfamoyl)naphthalen-1-yl)-5-(cyclohexylmethyl)oxazole-2-carboxylate (**103g**)

The solution of compound **103f** (500 mg, 2.10 mmol), 4-bromo-*N*-(*tert*-butyl)naphthalene-1-sulfonamide (791 mg, 2.30 mmol), PPh₃ (603 mg, 2.3 mmol) and Pd(OAc)₂ (95 mg, 0.40 mmol) in DMF (8 mL) was heated at 125°C overnight, cooled to rt, partitioned between EA and water and the layers were separated. The organic layer was washed with water and brine, dried over Na₂SO₄, filtered, concentrated. This procedure was repeated three times and the combined residues were purified by CC (PE/EA = 5/1) to give compound **103g** (350 mg, 8%) as a yellow solid.

Step 8: Potassium 4-(4-(*N*-(*tert*-butyl)sulfamoyl)naphthalen-1-yl)-5-(cyclohexylmethyl)oxazole-2-carboxylate (**103h**)

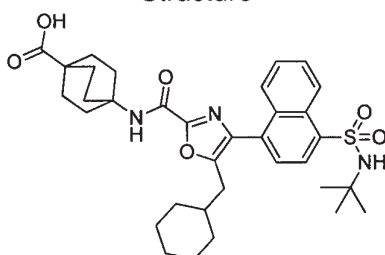
To a solution of compound **103g** (350 mg, 0.70 mmol) in a mixture of MeOH (10 mL) and H₂O (1 mL) was added KOH (56 mg, 1.0 mmol) and the mixture was stirred at rt for 5 h and concentrated to give crude compound **103h** (365 mg) as an off-white solid.

Step 9: 4-(4-(*N*-(*tert*-Butyl)sulfamoyl)naphthalen-1-yl)-5-(cyclohexylmethyl)-*N*-(1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)oxazole-2-carboxamide (**103**)

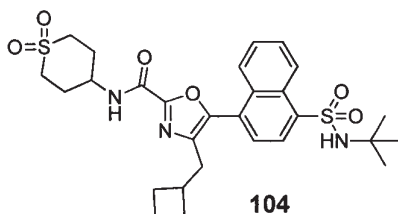
A solution of compound **103h** (150 mg, 0.30 mmol), HATU (136 mg, 0.36 mmol), DIEA (90 mg, 0.70 mmol) and 1,1-dioxo-hexahydrothiopyran-4-ylamine hydrochloride salt (56 mg, 0.36 mmol) in DMF (3 mL) was stirred overnight and diluted with H₂O and EA. The organic layer was washed with brine, dried over Na₂SO₄, filtered, concentrated and purified by prep-HPLC to give compound **103** (31 mg, 18%) as a colorless solid. ¹H-NMR (300 MHz, DMSO-*d*₆) δ: 0.70-0.74 (m, 2H), 0.97-1.02 (m, 12H), 1.46-1.50 (m, 6H), 2.08-2.17 (m, 4H), 2.60 (d, *J* = 7.2 Hz, 2H), 3.04-3.08 (m, 2H), 3.26-3.37 (m, 2H), 4.17-4.21 (m, 1H), 7.64-7.73 (m, 3H), 7.86 (s, 1H), 7.97 (d, *J* = 8.4 Hz, 1H), 8.24 (d, *J* = 8.1 Hz, 1H), 8.76 (d, *J* = 8.4 Hz, 1H), 9.06 (d, *J* = 8.4 Hz, 1H). MS 602.2 [M+1]⁺.

Example 103/1 to 103/3

The following Examples were prepared similar as described in Example **103** above:

#	Structure	Analytical data
103 /1		¹ H-NMR (300 MHz, DMSO- <i>d</i> ₆) δ: 0.69-0.73 (m, 2H), 0.96-1.05 (m, 12H), 1.42-1.47 (m, 6H), 1.74-1.79 (m, 6H), 1.92-1.97 (m, 6H), 2.57 (d, <i>J</i> = 6.9 Hz, 2H), 7.62-7.72 (m, 3H), 7.86 (s, 1H), 7.94-7.97 (m, 2H), 8.23 (d, <i>J</i> = 7.5 Hz, 1H), 8.75 (d, <i>J</i> = 8.4 Hz, 1H), 11.95 (br s, 1H). MS 622.3 [M+1] ⁺

#	Structure	Analytical data
103 /2		¹ H-NMR (300 MHz, CDCl ₃) δ: 0.76-0.78 (m, 2H), 0.88-0.91 (m, 2H), 1.01-1.08 (m, 2H), 1.18-1.33 (m, 3H), 1.36 (s, 9H), 1.45 (s, 3H), 1.63-1.75 (m, 5H), 1.82-1.93 (m, 1H), 2.43-2.53 (m, 2H), 2.78-2.80 (m, 4H), 3.14-3.23 (m, 1H), 4.76-4.84 (m, 1H), 7.29 (t, J = 1.8 Hz, 1H), 7.35 (t, J = 1.8 Hz, 1H), 7.44 (t, J = 1.8 Hz, 1H). MS 493.3 [M+1] ⁺
103 /3		¹ H-NMR (300 MHz, CDCl ₃) δ: 0.76-0.78 (m, 2H), 0.88-0.91 (m, 2H), 1.01-1.08 (m, 2H), 1.18-1.33 (m, 3H), 1.36 (s, 9H), 1.45 (s, 3H), 1.63-1.75 (m, 5H), 1.82-1.93 (m, 1H), 2.29-2.43 (m, 4H), 2.80 (d, J = 7.2 Hz, 2H), 3.13-3.17 (m, 4H), 4.23-4.28 (m, 1H), 7.09-7.12 (m, 1H), 7.29 (t, J = 1.8 Hz, 1H), 7.34 (t, J = 1.8 Hz, 1H), 7.43 (t, J = 1.8 Hz, 1H). MS 527.3 ([M+1] ⁺

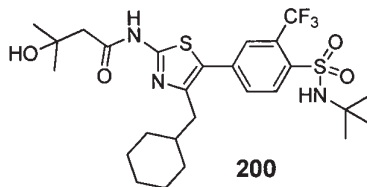
Example 104

Step 1: Ethyl 5-(4-(*N*-(*tert*-butyl)sulfamoyl)naphthalen-1-yl)-4-(cyclobutylmethyl)oxazole-2-carboxylate (104a**)**

To a solution of *N*-(*tert*-butyl)-4-(4-(cyclobutylmethyl)oxazol-5-yl)naphthalene-1-sulfonamide (1.6 g, 4.0 mmol, prepared similar to intermediate **100b**) in THF (20 mL) was added *n*-butyllithium (3.2 mL, 8.0 mmol) at -78°C and then stirred for 30 min at this temperature. Ethyl chloroformate (6.5 g, 6.0 mmol) was added dropwise at -78°C . The solution was stirred at -78°C for 1 h, quenched with sat. aq. NH_4Cl , stirred at rt for 1 h and extracted with DCM. The organic layer was dried with Na_2SO_4 , filtered, concentrated and purified by CC (DCM/MeOH = 60/1) to afford compound **104a** (600 mg, 31%) as a white solid.

Step 2 and Step 3: 5-(4-(*N*-(*tert*-Butyl)sulfamoyl)naphthalen-1-yl)-4-(cyclobutylmethyl)-*N*-(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)oxazole-2-carboxamide (104**)**

Example **104** was prepared from intermediate **104a** similar as described for Example **6** from intermediate **6e**. ¹H-NMR (300 MHz, CDCl₃) δ: 1.10 (s, 9H), 1.40-1.45 (m, 2H), 1.56-1.68 (m, 2H), 1.81-1.85 (m, 2H), 2.20-2.25 (m, 4H), 2.56-2.63 (m, 3H), 2.74 (s, 2H), 3.01-3.06 (m, 2H), 4.20-4.21 (m, 1H), 7.60-7.71 (m, 3H), 7.81 (d, J = 8.4 Hz, 1H), 8.29 (d, J = 7.6 Hz, 1H), 8.76 (d, J = 8.6 Hz, 1H). MS 574.3 (M+1)⁺.

Example 200**Step 1: 4-(Cyclohexylmethyl)thiazol-2-amine (200a)**

A solution of 1-bromo-3-cyclohexylpropan-2-one (2.8 g, 12.8 mmol) and thiourea (1.07 g, 14.1 mmol) in EtOH (20 mL) was refluxed for 4 h, concentrated and portioned between DCM and sat. NaHCO₃. The organic layer was washed with brine, dried over Na₂SO₄, filtered, concentrated and purified by CC (PE/EA = 3/1) to give compound **200a** (1.1 g, 44%) as a yellow solid.

Step 2: 5-Bromo-4-(cyclohexylmethyl)thiazol-2-amine (200b)

A mixture of compound **200a** (7.6 g, 38.8 mmol) and NBS (6.9 g, 38.8 mmol) in MeCN (100 mL) was stirred at 50°C for 10 h, diluted with water (30 mL) and extracted with EA (3x 100 mL). The combined organic layer was washed with brine, dried over Na₂SO₄ and evaporated to obtain compound **200b** (7.5 g, 71%) as yellowish solid.

Step 3: N-(5-Bromo-4-(cyclohexylmethyl)thiazol-2-yl)-3-hydroxy-3-methylbutanamide (200c)

A mixture of compound **200b** (548 mg, 2.0 mmol), DCC (412 mg, 2.0 mmol) and 3-hydroxy-3-methylbutanoic acid (236 mg, 2.0 mmol) in DMF (20 mL) was stirred at rt for 12 h, diluted with water (30 mL) and extracted with EA (3x 50 mL). The combined organic layer was washed with brine, dried over Na₂SO₄ and evaporated to obtain compound **200c** (220 mg, 29%) as yellowish solid.

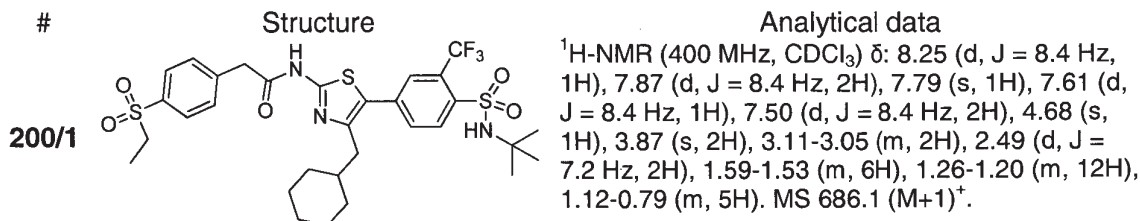
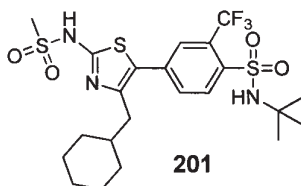
Step 4: N-(5-(4-(N-(tert-Butyl)sulfamoyl)-3-(trifluoromethyl)phenyl)-4-(cyclohexylmethyl)thiazol-2-yl)-3-hydroxy-3-methylbutanamide (200)

A suspension of compound **200c** (75 mg, 0.2 mmol), Cs₂CO₃ (130 mg, 0.4 mmol), N-(tert-butyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trifluoromethyl)benzenesulfonamide (81 mg, 0.2 mmol), Pd(PPh₃)₄ (23 mg, 20 μmol) in toluene/H₂O (10:1, 10mL) was heated overnight under N₂ at 100°C, concentrated and extracted with EA. The organic layer was washed with brine, dried over MgSO₄, filtered, evaporated and purified by prep-HPLC to give compound **200** (30 mg, 25%) as yellowish solid. ¹H-NMR (DMSO-d₆, 300 MHz) δ: 12.10 (br s, 1H), 8.24 (d, 1H, J = 6.3 Hz), 7.86-7.94 (m, 3H), 2.57-2.60 (m, 4H), 1.59-1.75 (m, 6H), 1.07-1.23 (m, 18H), 0.85-0.91 (m, 2H). MS 576.2 (M+1)⁺.

Example 200/1

The following Example was prepared similar as in Example **200**:

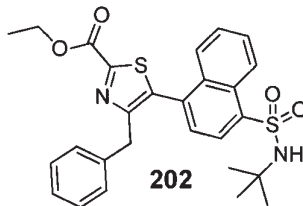
#	Structure	Analytical data
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**Example 201****Step 1: *N*-(5-Bromo-4-(cyclohexylmethyl)thiazol-2-yl)methanesulfonamide (201a)**

- 5 To the mixture of compound **200b** (548 mg, 2.0 mmol) and TEA (404 mg, 4.0 mmol) in DCM (20 mL) at -10°C was added MsCl (262 mg, 2.2 mmol) for 2 h, diluted with water (30 mL) and extracted with DCM (3x 50 mL). The organic layer was washed with brine, dried over Na_2SO_4 , filtered and concentrated to give compound **201a** (640 mg, 91%) as a yellowish solid.

Step 2: *N*-(*tert*-Butyl)-4-(4-(cyclohexylmethyl)-2-(methylsulfonylthiazol-5-yl)-2-(trifluoromethyl)benzenesulfonamide (201)

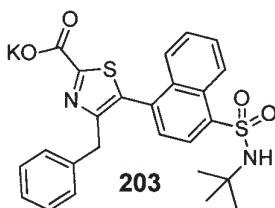
- A suspension of compound **201a** (90 mg, 0.25 mmol), Cs_2CO_3 (162 mg, 0.5 mmol), *N*-(*tert*-butyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trifluoromethyl)benzenesulfonamide (101 mg, 0.25 mmol), $\text{Pd}(\text{PPh}_3)_4$ (35 mg, 0.03 mmol) in toluene/ H_2O (10:1, 10 mL) was heated overnight under N_2 at 100°C , cooled, concentrated and extracted with EA. The organic layer was washed with brine, dried over MgSO_4 , filtered, evaporated and purified by prep-HPLC to give compound **201** (35 mg, 25%) as yellowish solid. $^1\text{H-NMR}$ (DMSO-d_6 , 300 MHz) δ : 12.73 (br s, 1H), 8.25 (d, 1H, J = 6.3 Hz), 7.85-7.93 (m, 3H), 2.97 (s, 3H), 2.50-2.53 (m, 2H), 1.55-1.62 (m, 6H), 1.06-1.17 (m, 11H), 0.80-0.851 (m, 3H). MS 554.1 ($\text{M}+1$) $^+$.

Example 202**Ethyl 4-benzyl-5-(4-(*N*-(*tert*-butyl)sulfamoyl)naphthalen-1-yl)thiazole-2-carboxylate (202)**

- The solution of ethyl 4-benzyl-5-bromothiazole-2-carboxylate (1.50 g, 4.53 mmol), *N*-(*tert*-butyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalene-1-sulfonamide (2.11 g, 5.43 mmol), Na_2CO_3 (1.90 g, 18.0 mmol) and $\text{Pd}(\text{dppf})\text{Cl}_2$ (331 mg, 0.45 mmol) in a mixture of

toluene (30 mL), EtOH (15 mL) and water (15 mL) was heated at 70°C for 15 h, cooled to rt, partitioned between EA and water and separated. The organic phase was washed with water and brine, dried over Na₂SO₄, filtered, concentrated and purified by CC (PE/EA = 10/1 to 5/1) to give compound **202** (1.24 g, 53%) as a white solid. ¹H-NMR (400 MHz, CDCl₃) δ: 0.56-0.66 (m, 2H), 0.93-1.14 (m, 3H), 1.22 (s, 9H), 1.45-1.49 (m, 5H), 1.52-1.58 (m, 3H), 1.74-1.79 (m, 1H), 2.39-2.43 (m, 2H), 4.53 (q, J = 6.8 Hz, 2H), 4.71 (s, 1H), 7.53 (d, J = 7.6 Hz, 1H), 7.57-7.61 (m, 1H), 7.71-7.74 (m, 1H), 8.36 (d, J = 7.6 Hz, 1H), 8.69-8.72 (m, 1H). MS 515.2 [M+1]⁺.

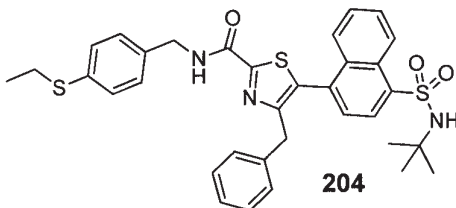
Example 203



Potassium 4-benzyl-5-(4-(*N*-(*tert*-butyl)sulfamoyl)naphthalen-1-yl)thiazole-2-carboxylate (**203**)

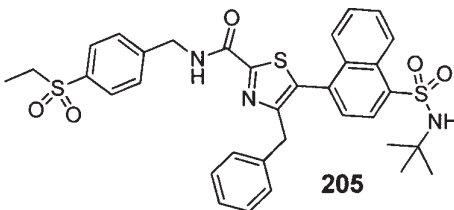
To a solution of compound **202** (1.35 g, 2.63 mmol) in a solution of MeOH (20 mL) and H₂O (5 mL) was added KOH (147 mg, 2.63 mmol) and then the solution was stirred for 30 min at 50°C. The resulting solution was concentrated, washed with Et₂O and dried in vacuum to give compound **203** (1.32 g, 96%) as a yellow solid. ¹H-NMR (400 MHz, CD₃OD) δ: 0.57-0.65 (m, 2H), 0.94-1.07 (m, 3H), 1.13 (s, 9H), 1.48 (d, J = 10.0 Hz, 5H), 1.63-1.67 (m, 1H), 2.38 (br s, 2H), 7.59-7.63 (m, 2H), 7.72 (t, J = 7.2 Hz, 2H), 7.79 (d, J = 8.4 Hz, 1H), 8.31 (d, J = 7.6 Hz, 1H), 8.81 (d, J = 8.4 Hz, 1H). MS 443.2 [M-K+1]⁺.

Example 204



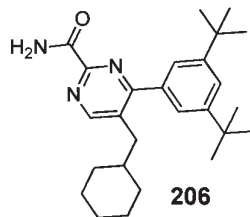
4-Benzyl-5-(4-(*N*-(*tert*-butyl)sulfamoyl)naphthalen-1-yl)-*N*-(4-(ethylthio)benzyl)thiazole-2-carboxamide (**204**)

The solution of compound **203** (200 mg, 0.38 mmol), HATU (72 mg, 0.38 mmol), DIEA (129 mg, 1.00 mmol) and (4-(ethylthio)phenyl)methanamine (72 mg, 0.41 mmol) in DMF (2 mL) was stirred for 1 h at rt, quenched with H₂O and extracted with EA (3x). The combined organic layers were washed with water (3x) and brine consecutively, dried over Na₂SO₄, filtered, concentrated and purified by prep-HPLC to give compound **204** (117 mg, 48%) as a white powder.

Example 205

4-Benzyl-5-(4-(*N*-(*tert*-butyl)sulfamoyl)naphthalen-1-yl)-*N*-(4-(ethylsulfonyl)benzyl)thiazole-2-carboxamide (205**)**

To a solution of compound **204** (117 mg, 0.18 mmol) in DCM (5 mL) was added *m*-CPBA (102 mg, 0.50 mmol) and the solution was stirred at rt for 30 min, quenched with aq. Na₂SO₃ and extracted with EA. The organic layer was washed with water and brine, dried over Na₂SO₄, filtered, concentrated and purified by prep-HPLC to give compound **205** (67 mg, 56%) as a white solid. ¹H-NMR (400 MHz, CDCl₃) δ: 0.60-0.69 (m, 2H), 0.83-1.11 (m, 3H), 1.20 (s, 9H), 1.23-1.32 (m, 5H), 1.48-1.56 (m, 3H), 1.65-1.68 (m, 1H), 2.34 (br s, 2H), 3.13 (q, J = 7.6 Hz, 2H), 4.64 (s, 1H), 4.80 (d, J = 6.4 Hz, 2H), 7.52 (d, J = 7.6 Hz, 1H), 7.56-7.80 (m, 6H), 7.93 (d, J = 8.4 Hz, 2H), 8.36 (d, J = 7.6 Hz, 1H), 8.69 (d, J = 8.0 Hz, 1H). MS 668.2 [M+1]⁺.

Example 206**Step 1: 5-(Bromomethyl)-2,4-dichloropyrimidine (**206a**)**

2,4-Dichloro-5-methylpyrimidine (20.0 g, 123 mmol) was dissolved in ACN (100 mL) and NBS (26.1 g, 147 mmol) and AIBN (1.01 g, 6.13 mmol) were added. The mixture was heated to 90°C and stirred for 16 h at that temperature. The solvent was removed and purification by CC (PE/EA = 99/1) afforded compound **206a** (15 g, 50%) as pale yellow syrup.

Step 2: 2,4-Dichloro-5-(cyclohexylidenemethyl)pyrimidine (206b**)**

Triisopropylphosphite (7.28 g, 35.0 mmol) was added to compound **206a** (5.0 g, 20.6 mmol) in a flask and the mixture was heated to 100°C for 2 h, cooled to 0°C and THF (25 mL) was added followed by cyclohexanone (2.42 g, 24.7 mmol). After 5 min, NaH (822 mg, 20.6 mmol) was added. The mixture was stirred for 15 min at 0°C, then allowed to warm up to rt and stirred for 15 min. After completion of the reaction, the mixture was diluted with sat. NH₄Cl solution (25 mL) and EA (50 mL). The organic layer was separated and the aq. layer was extracted with DCM (2 x 25 mL). The combined organic layers were dried over Na₂SO₄,

evaporated and purified by CC (1.5% EA in PE) to afford compound **206b** (1.8 g, 36%) as an off-white solid.

Step 3: 2-Chloro-5-(cyclohexylidenemethyl)-4-(3,5-di-*tert*-butylphenyl)pyrimidine (**206c**)

A mixture of compound **206b** (2.0 g, 8.26 mmol), 2-(3,5-di-*tert*-butylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.13 g, 9.91 mmol), K₂CO₃ (3.19 g, 23.1 mmol), in 1,4-dioxane (20 mL) were purged with Ar for 15 min in a sealed vial. Pd(PPh₃)₄ (0.477 g, 413 μmol) was added and the mixture was stirred at 140°C for 5 h, filtered through celite and the filtrate was concentrated. Purification by CC (5% EA in PE) afforded compound **206c** (1.1 g, 34%) as an off-white solid.

10 Step 4: 5-(Cyclohexylidenemethyl)-4-(3,5-di-*tert*-butylphenyl)pyrimidine-2-carbonitrile (**206d**)

NaCN (149 mg, 3.06 mmol) was added to a mixture of compound **206c** (1.1 g, 2.78 mmol) and DABCO (31 mg, 0.28 mmol) in DMSO (20 mL). Then the mixture was heated to 40°C and stirred for 16 h, then carefully diluted with water and extracted with DCM (3 x 10 mL). The combined organic layer was washed with ice cold water (3 x 10 mL). The organic layer was dried over Na₂SO₄, evaporated and purified by CC (5% EA in PE) to afford compound **206d** (0.50 g, 45 %) as pale yellow solid.

Step 5: 5-(cyclohexylidenemethyl)-4-(3,5-di-*tert*-butylphenyl)pyrimidine-2-carboxylic acid (**206e**)

Compound **206d** (0.8 g, 2.06 mmol) was dissolved in EtOH (5 mL) and water (5 mL). Then NaOH (0.165 g, 4.13 mmol) was added and the mixture was stirred at 100°C for 16 h, evaporated, diluted with water and extracted with CHCl₃ (3 x 10 mL). The combined organic layer was dried over Na₂SO₄, evaporated and purified by CC (EA/PE = 1/1) to afford compound **206e** (0.3 g, 36%) as pale yellow solid.

Step 6: 5-(Cyclohexylidenemethyl)-4-(3,5-di-*tert*-butylphenyl)pyrimidine-2-carboxamide (**206f**)

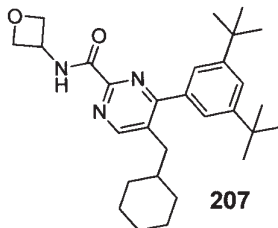
25 A mixture of compound **206e** (150 mg, 369 μmol) and thionylchloride (133 μL, 1.85 mmol) was refluxed for 2 h. The thionylchloride was evaporated and NH₃ (7N in THF, 1 mL) was added at 0°C. The mixture was stirred at rt for 3 h, evaporated and dissolved in CHCl₃ (2 mL) and washed with water (2 x 2 mL). The organic layer was dried over Na₂SO₄, evaporated and purified by CC (30% EtOAc in PE) to afford compound **206f** (0.15 g, quant.) as brown syrup.

30 Step 7: 5-(Cyclohexylmethyl)-4-(3,5-di-*tert*-butylphenyl)pyrimidine-2-carboxamide (**206**)

Compound **206f** (0.15 g, 370 μmol) was dissolved in MeOH (5 mL) and 2N NaOH (0.1 mL) was added. Then Pd/C (20 mg) was added and the mixture was kept under hydrogen atmosphere (ballon pressure), stirred for 30 min, filtered through celite and was washed with MeOH (2 mL). The solvent was evaporated and the obtained crude product was dissolved in CHCl₃ (5 mL) and washed with water (5 mL). The organic layer was dried over Na₂SO₄, evaporated and purified by CC (PE/EA = 1/1) to afford compound **206** (70 mg, 50%) as white

solid. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 0.83-1.51 (m, 11H), 1.37 (s, 18H), 2.61 (d, 2H), 5.69 (br s, 1H), 7.26-7.30 (m, 2H), 7.54-7.55 (m, 1H), 7.84 (br s, 1H), 8.74 (s, 1H). MS 408.6 ($\text{M}+1$) $^+$.

Example 207



5

Step 1: 5-(Cyclohexylidenemethyl)-4-(3,5-di-*tert*-butylphenyl)-*N*-(oxetan-3-yl)pyrimidine-2-carboxamide (**207a**)

Compound **206e** (0.15 g, 369 μmol) was dissolved in DCM (5 mL) and TEA (74 mg, 770 μmol) was added followed by an excess of propylphosphonic acid anhydride and oxetan-3-amine (32 mg, 443 μmol). The mixture was stirred for 16 h at rt and diluted with water. The organic layer was separated, dried over Na_2SO_4 and evaporated to afford crude compound **207a** (0.15 g, 88%).

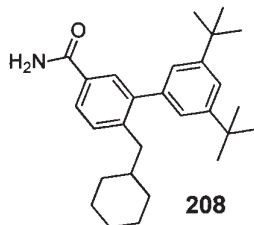
Step 2: 5-(Cyclohexylmethyl)-4-(3,5-di-*tert*-butylphenyl)-*N*-(oxetan-3-yl)pyrimidine-2-carboxamide (**207**)

Compound **207a** (0.15 g, 325 μmol) was dissolved in MeOH (5 mL) and 2N NaOH (0.1 mL) was added. Then Pd/C (20 mg) was added and the mixture was kept under hydrogen atmosphere (balloon pressure). After completion the mixture was filtered through celite and the celite was washed with MeOH (2 mL). The solvent was evaporated and the obtained crude product was dissolved in CHCl_3 (5 mL). The organic layer was washed with water (5 mL), dried over Na_2SO_4 , evaporated and purified by CC (PE/EA = 1/1) to afford compound **207** (65 mg, 50%) as colorless solid. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 0.80-1.60 (m, 11H), 1.35 (s, 18H), 2.58-2.60 (d, 2H), 4.64 (t, 2H), 5.01 (t, 2H), 5.34 (m, 1H), 7.31 (m, 2H), 7.57 (m, 1H), 8.57 (m, 1H), 8.73 (s, 1H). MS 464.6 ($\text{M}+1$) $^+$.

25 Example 207/1

The following Example was prepared similar as described in Example **207**.

#	Structure	Analytical data
207/1		$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ : 0.80-1.60 (m, 11H), 1.12 (s, 6H), 1.35 (s, 18H), 2.60 (d, 2H), 3.29 (m, 2H), 4.66 (s, 1H), 7.37 (m, 2H), 7.54 (m, 1H), 8.50 (m, 1H), 8.83 (s, 1H). MS 480.6 ($\text{M}+1$) $^+$

Example 208**Step 1: Methyl 3-bromo-4-(bromomethyl)benzoate (208a)**

- 5 AIBN (71 mg, 440 μ mol) was added to a solution of methyl 3-bromo-4-methylbenzoate (2.0 g, 8.73 mmol) and NBS (1.87 g, 10.5 mmol) in ACN (10 mL). The mixture was refluxed for 48 h, cooled to rt, evaporated and purified by CC (5% EA in PE) to afford compound **208a** (1.07 g, 40%).

Step 2: 3-Bromo-4-(cyclohexylidenemethyl)benzoic acid (208b)

- 10 A mixture of compound **208a** (0.50 g, 2.18 mmol) and triethyl phosphite (0.62 g, 3.71 mmol) in THF (10 mL) was refluxed for 3 h, cooled to 0°C and then NaH (52 mg, 2.18 mmol) was added followed by THF. The mixture was stirred at rt for 15 min, followed by addition of cyclohexanone (0.26 g, 2.62 mmol) at 0°C. The mixture was stirred at rt for 16 h, diluted with aq. NH_4Cl and EA. The organic layer was separated and aq. layer was acidified with 2N HCl
- 15 at 0°C and extracted with DCM (3 x 10 mL). The combined organic layer was dried over Na_2SO_4 and evaporated to obtain crude product **208b**.

Step 3: 3',5'-Di-*tert*-butyl-6-(cyclohexylidenemethyl)-[1,1'-biphenyl]-3-carboxylic acid (208c)

- A mixture of compound **208b** (0.5 g, 1.69 mmol), 2-(3,5-di-*tert*-butylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.64 g, 2.03 mmol), Na_2CO_3 (0.50 g, 4.74 mmol) in 1,4-dioxane and water was purged with Ar for 15 min. Then $\text{Pd}(\text{PPh}_3)_4$ (97 mg, 85 μ mol) was
- 20 added and the mixture was stirred at 90°C for 14 h, filtered through celite and the filtrate was concentrated and purified by CC (25% EA in PE) to afford compound **208c** (342 mg, 50% over two steps).

Step 4: 3',5'-Di-*tert*-butyl-6-(cyclohexylmethyl)-[1,1'-biphenyl]-3-carboxylic acid (208d)

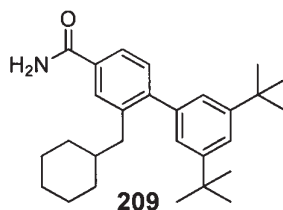
- 25 Pd/C (10 mg) was added to a solution of compound **208c** (100 mg, 247 μ mol) in MeOH and the reaction was performed under 60 psi hydrogen pressure at rt for 16 h. The mixture was filtered through celite and the filtrate was evaporated. The obtained crude product was partitioned between water and 10% MeOH/DCM. The organic layer was separated and dried over Na_2SO_4 and evaporated. The obtained crude product was triturated with Et_2O and the
- 30 solid was filtered off and dried under vacuum to afford compound **208d** (45 mg, 45%) as pale yellow solid.

Step 5: 3',5'-Di-*tert*-butyl-6-(cyclohexylmethyl)-[1,1'-biphenyl]-3-carboxamide (208)

CDI (79 mg, 0.49 mmol) of was added to a solution of compound **208d** (100 mg, 0.25 mmol) in THF (5 mL) and the mixture was stirred at rt for 16 h. Then a 2M solution of NH₃ (5 mL) in THF was added at 0°C and the mixture was stirred at rt for 1 h, evaporated and the obtained crude product was partitioned between EA and water. The organic layer was separated, dried over Na₂SO₄ and evaporated. The obtained crude product was triturated with ACN and dried under vacuum to afford compound **208** (60 mg, 60%). ¹H-NMR (DMSO-d₆, 400 MHz) δ: 0.70-1.55 (m, 11H), 1.30 (s, 18H), 2.45 (d, 2H), 7.08 (m, 2H), 7.24 (m, 1H), 7.33 (br s, 1H), 7.40 (m, 1H), 7.72-7.77 (m, 2H), 7.96 (br s, 1H). MS 406.5 (M+1)⁺.

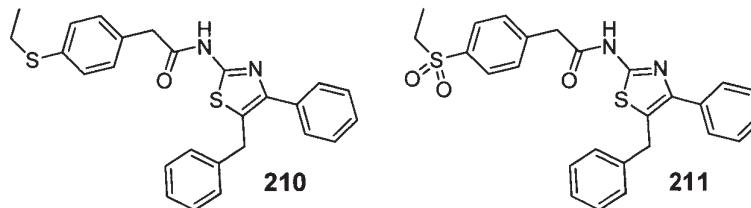
10 **Example 209**

The following Example was prepared using similar procedures as that described in Example 208.



¹H-NMR (DMSO-d₆, 400 MHz) δ: 0.69-1.57 (m, 11H), 1.32 (s, 18H), 2.45 (d, 2H), 7.08 (m, 2H), 7.26-7.32 (m, 2H), 7.40 (m, 1H), 7.68 (m, 1H), 7.78 (m, 1H), 7.94 (br s, 1H). MS 406.5 (M+1)⁺.

Example 210 and Example 211



20 Step 1: 5-Benzyl-4-phenylthiazol-2-amine (**210a**)

(2-Amino-4-phenylthiazol-5-yl)(phenyl)methanone (prepared similar as described in WO2012/028100) was reduced with NaBH₄ and the obtained alcohol was treated with Et₃SiH and TFA to afford compound **210a**.

Step 2: N-(5-Benzyl-4-phenylthiazol-2-yl)-2-(4-(ethylthio)phenyl)acetamide (**210**)

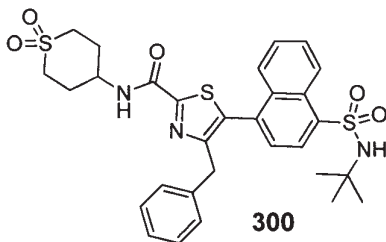
25 Compound **210a** was coupled with 2-(4-(ethylthio)phenyl)acetic acid similar as described in WO2012/028100 to afford compound **210**.

Step 3: N-(5-Benzyl-4-phenylthiazol-2-yl)-2-(4-(ethylsulfonyl)phenyl)acetamide (**211**)

Compound **210** was oxidized with *meta*-chloroperoxybenzoic acid to afford compound **211** as a colorless solid. ¹H-NMR (CDCl₃, 300 MHz) δ: 1.28 (q, J = 7.8 Hz, 3H), 3.08 (q, J = 7.8 Hz, 2H), 4.23 (s, 1H), 7.12 (d, J = 8.1 Hz, 2H), 7.21-7.34 (m, 5H), 7.38-7.48 (m, 3H), 7.64 (dd, J = 6.0, 7.5 Hz, 2H), 7.78 (d, J = 8.1 Hz, 2H), 11.84 (br s, 1H). MS 477.1 (M+1)⁺.

5

Example 300



Step 1: 1-Bromo-3-phenylpropan-2-one (300a)

To a solution of 1-phenylpropan-2-one (6.1 g, 45.5 mmol) in AcOH (15 mL) were added a solution of HBr in AcOH (48%, 10 mL) and a solution of Br₂ (5.0 mL, 97.0 mmol) in AcOH (30 mL) and the resulting mixture was stirred at rt for 6 h, diluted with acetone (100 mL), stirred for a further 16 h, concentrated and extracted with DCM. The organic layer was dried over Na₂SO₄, filtered, concentrated and purified by CC (PE/EA = 20/1) to give compound **300a** (3.6 g, 37%) as a brown oil.

Step 2: Ethyl 4-benzylthiazole-2-carboxylate (300b)

A solution of compound **300a** (3.60 g, 16.9 mmol) and ethylthioxamate (2.37 g, 18.0 mmol) in ethanol (50 mL) was heated at 80°C for 6 h, cooled to 0°C, diluted with water and EA, then neutralized to pH = 7 using NH₄OH. and extracted with EA (3x). The combined organic layers were dried over Na₂SO₄, filtered, concentrated and purified by CC (PE/EA = 20/1) to give compound **300b** (2.5 g, 60%) as a yellow oil.

Step 3: Ethyl 4-benzyl-5-(4-(*N*-(*tert*-butyl)sulfamoyl)naphthalen-1-yl)thiazole-2-carboxylate (300c)

A solution of compound **300b** (250 mg, 1.1 mmol), compound **P1/2** (409 mg, 1.2 mmol), Pd(OAc)₂ (56 mg) and PPh₃ (118 mg, 0.45 mmol) in DMF (10 mL) was bubbled with N₂ for 5 min and then stirred at 110°C for overnight, cooled to rt, concentrated and purified by CC (PE/EA = 15/1) to give compound **300c** (200 mg, 36%) as a pale yellow solid.

Step 4: Potassium 4-benzyl-5-(4-(*N*-(*tert*-butyl)sulfamoyl)naphthalen-1-yl)thiazole-2-carboxylate (300d)

A solution of compound **300c** (200 mg, 0.39 mmol) and KOH (28 mg, 0.5 mmol) in MeOH (5 mL) was stirred at rt for 4 h, concentrated and washed with Et₂O to give crude compound **300d** (210 mg) as an off-white solid.

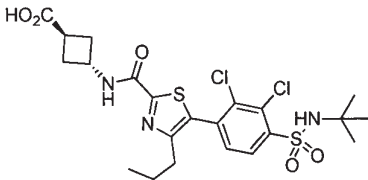
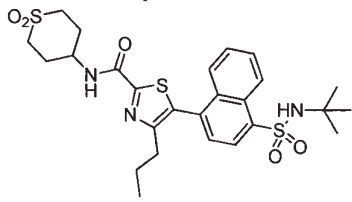
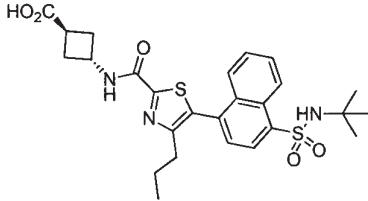
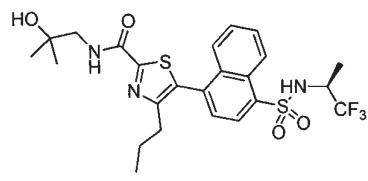
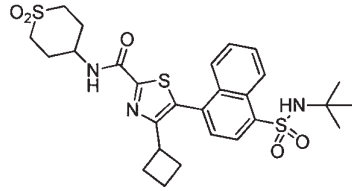
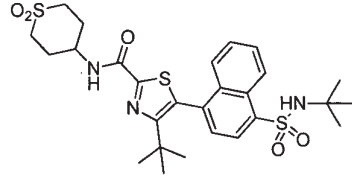
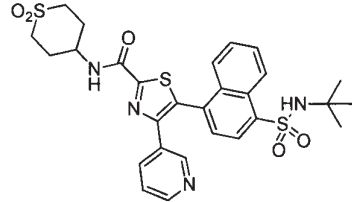
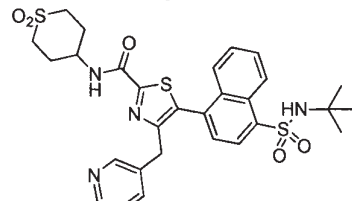
Step 5: 4-Benzyl-5-(4-(*N*-(*tert*-butyl)sulfamoyl)naphthalen-1-yl)-*N*-(1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)thiazole-2-carboxamide (300**)**

A solution of crude compound **300d** (200 mg, 0.39 mmol), 1,1-dioxo-hexahydro-1-thiopyran-4-ylamine (148 mg, 0.80 mmol), DIEA (206 mg, 1.6 mmol) and HATU (304 mg, 0.80 mmol) in DMF (5 mL) was stirred overnight at rt, diluted with water and extracted with EA (3x). The combined organic layers were washed with water (3x) and brine consecutively, dried over Na₂SO₄, filtered, concentrated and purified by prep-HPLC to give compound **300** (57 mg, 24% over two steps) as a white solid. ¹H-NMR (300 MHz, CDCl₃) δ: 1.23 (s, 9H), 2.31-2.48 (m, 4H), 3.15-3.16 (m, 4H), 3.86 (s, 2H), 4.23-4.27 (m, 1H), 4.63 (s, 1H), 6.91-6.94 (m, 2H), 7.14-7.17 (m, 3H), 7.27-7.29 (m, 1H), 7.46 (d, *J* = 7.5 Hz, 1H), 7.50-7.57 (m, 1H), 7.68-7.71 (m, 2H), 8.31 (d, *J* = 7.5 Hz, 1H), 8.69 (d, *J* = 13.2 Hz, 1H). MS 612.2 [M+1]⁺.

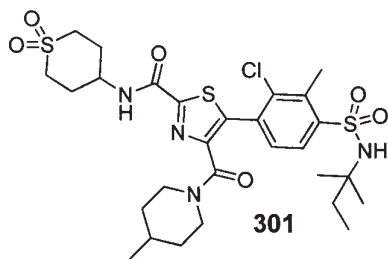
Example 300/1 to 300/18

The following Example was prepared similar as described in Example **300**.

#	Structure	Analytical data
300/1		¹ H-NMR (300 MHz, CDCl ₃) δ: 1.20 (s, 9H), 2.34-2.52 (m, 4H), 3.17-3.20 (m, 4H), 4.29-4.33 (m, 1H), 4.65 (s, 1H), 7.10-7.20 (m, 3H), 7.31-7.34 (m, 2H), 7.41-7.52 (m, 2H), 7.55 (d, <i>J</i> = 7.5 Hz, 1H), 7.65-7.70 (m, 1H), 7.78-7.81 (m, 1H), 8.32 (d, <i>J</i> = 7.5 Hz, 1H), 8.68 (d, <i>J</i> = 8.7 Hz, 1H). MS 598.4 [M+1] ⁺
300/2		¹ H-NMR (300 MHz, CDCl ₃) δ: 0.90-1.16 (m, 2H), 1.23 (s, 9H), 1.66-1.72 (m, 8H), 2.25-2.51 (m, 5H), 3.16-3.21 (m, 4H), 4.28-4.30 (m, 1H), 4.63 (s, 1H), 7.31 (d, <i>J</i> = 8.1 Hz, 1H), 7.49 (d, <i>J</i> = 7.5 Hz, 1H), 7.54-7.59 (m, 1H), 7.69-7.74 (m, 2H), 8.35 (d, <i>J</i> = 7.5 Hz, 1H), 8.69 (d, <i>J</i> = 9.3 Hz, 1H). MS 604.3 [M+1] ⁺
300/3		¹ H-NMR (400 MHz, CDCl ₃) δ: 8.80 (d, 1H, <i>J</i> = 8.4 Hz), 8.35 (m, 1H), 8.25 (m, 1H), 7.95 (s, 1H), 7.75 (m, 4H), 3.32 (d, 2H, <i>J</i> = 6.4 Hz), 2.48 (m, 2H), 1.11 (m, 18H). MS 489.7 (M+1) ⁺
300/4		¹ H-NMR (400 MHz, CDCl ₃) δ: 8.70 (d, 1H, <i>J</i> = 8.8 Hz), 8.35 (d, 1H, <i>J</i> = 7.6 Hz), 7.76 (m, 2H), 7.57 (m, 2H), 4.76 (s, 1H), 4.52 (s, 2H), 4.01 (s, 2H), 3.71 (m, 4H), 2.50 (m, 2H), 1.89 (m, 4H), 1.23 (s, 9H), 1.17 (m, 3H). MS 528.2 (M+1) ⁺
300/5		¹ H-NMR (400 MHz, CDCl ₃) δ: 8.13 (d, 1H, <i>J</i> = 8.0 Hz), 7.39 (d, 1H, <i>J</i> = 8.4 Hz), 7.26 (s, 1H), 5.10 (s, 1H), 4.26 (m, 1H), 3.17 (m, 4H), 2.39 (m, 6H), 1.68 (m, 2H), 1.29 (s, 9H), 0.86 (t, 3H, <i>J</i> = 7.2 Hz). MS 582.2 (M+H) ⁺

#	Structure	Analytical data
300/6		$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 8.13 (d, 1H, $J = 8.0$ Hz), 7.50 (d, 1H, $J = 8.0$ Hz), 7.39 (d, 1H, $J = 8.0$ Hz), 5.10 (s, 1H), 4.82 (m, 1H), 3.20 (m, 1H), 2.82 (m, 2H), 2.51 (m, 4H), 1.67 (m, 2H), 1.29 (s, 9H), 0.86 (t, 3H, $J = 7.6$ Hz). MS 548.2 (M+H) $^+$
300/7		$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 8.71 (d, 1H, $J = 8.0$ Hz), 8.35 (d, 1H, $J = 7.2$ Hz), 7.72 (m, 2H), 7.58 (m, 2H), 7.36 (d, 1H, $J = 8.0$ Hz), 4.86 (s, 1H), 4.29 (m, 1H), 3.19 (m, 4H), 2.40 (m, 6H), 1.62 (m, 2H), 1.24 (s, 9H), 0.76 (t, 3H, $J = 7.6$ Hz). MS 564.2 (M+H) $^+$
300/8		$^1\text{H-NMR}$ (400 MHz, DMSO-d_6) δ : 9.20 (d, 1H, $J = 8.4$ Hz), 8.80 (d, 1H, $J = 8.8$ Hz), 8.26 (d, 1H, $J = 7.6$ Hz), 7.92-7.66 (m, 5H), 4.61 (m, 1H), 2.95 (m, 1H), 2.56 (m, 2H), 2.45 (m, 4H), 1.57 (m, 2H), 1.11 (s, 9H), 0.67 (t, 3H, $J = 7.6$ Hz). MS 530.2 (M+H) $^+$
300/9		MS 544.1 (M+H) $^+$
300/10		MS 576.1 (M+H) $^+$
300/11		MS 578.2 (M+H) $^+$
300/12		MS 599.1 (M+H) $^+$
300/13		MS 613.1 (M+H) $^+$

#	Structure	Analytical data
300 /14		MS 632.1 (M+H) ⁺
300 /15		MS 567.1 (M- ^t Bu+H) ⁺ , 623.2 (M+H) ⁺
300 /16		MS 585.1 (M- ^t Bu+H) ⁺ , 641.2 (M+H) ⁺
300 /17		MS 570.2 (M+H) ⁺
300 /18		MS 578.2 (M+H) ⁺

Example 301**Step 1: 2-(Ethoxycarbonyl)thiazole-4-carboxylic acid (**301a**)**

- 5 The solution of ethyl 2-amino-2-thioxoacetate (6.0 g, 45 mmol) and 3-bromo-2-oxo-propionic acid (7.5 g, 45 mmol) in dioxane (200 mL) was heated at 50°C for 3 h, cooled to rt and concentrated to give compound **301a** (11 g, crude) as a brown solid.

Step 2: Ethyl 4-(4-methylpiperidine-1-carbonyl)thiazole-2-carboxylate (301b**)**

A solution of compound **301a** (11.0 g, 55 mmol), HATU (20.8 g, 55 mmol), DIEA (28.2 g, 219 mmol) and 4-methyl-piperidine (5.4 g, 55 mmol) in DMF (110 mL) was stirred for 4 h, quenched with H₂O and extracted with EA. The organic layer was washed with brine, dried over Na₂SO₄, filtered, concentrated and purified by CC (PE/EA = 4/1) to give compound **301b** (4.2 g, 27% over two steps) as a brown oil.

Step 3: Ethyl 5-(2-chloro-3-methyl-4-(*N*-(*tert*-pentyl)sulfamoyl)phenyl)-4-(4-methylpiperidine-1-carbonyl)thiazole-2-carboxylate (**301c**)

A solution of compound **301b** (200 mg, 0.71 mmol), 4-bromo-3-chloro-2-methyl-*N*-(*tert*-pentyl)benzenesulfonamide (301 mg, 0.85 mmol), KOAc (139 mg, 1.42 mmol), PPh₃ (205 mg, 0.78 mmol) and Pd(OAc)₂ (16 mg, 0.071 mmol) in DMF (8 mL) was heated at 120°C overnight, cooled to rt, diluted with water and extracted with EA. The organic phase was washed with water and brine, dried over Na₂SO₄, filtered, concentrated and purified by CC (PE/EA = 4/1) to give compound **301c** (110 mg, 28%) as a yellow solid.

Step 4: 5-(2-Chloro-3-methyl-4-(*N*-(*tert*-pentyl)sulfamoyl)phenyl)-4-(4-methylpiperidine-1-carbonyl)thiazole-2-carboxylic acid (**301d**)

To a solution of compound **301c** (1.1 g, 1.98 mmol) in a solution of THF (20 mL) and H₂O (4 mL) was added KOH (332 mg, 5.94 mmol) and then the solution was stirred at rt for 4 h, concentrated, diluted with water, adjusted to pH = 5 with 1N HCl and extracted with EA. The organic phase was washed with water and brine, dried over Na₂SO₄, filtered and concentrated to give compound **301d** (0.9 g, 90%) as a pale yellow solid.

Step 5: 5-(2-Chloro-3-methyl-4-(*N*-(*tert*-pentyl)sulfamoyl)phenyl)-*N*-(1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-4-(4-methylpiperidine-1-carbonyl)thiazole-2-carboxamide (**301**)

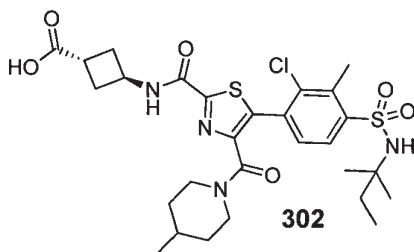
A solution of compound **301d** (120 mg, 0.23 mmol), HATU (86 mg, 0.23 mmol), DIEA (117 mg, 0.91 mmol) and 1,1-dioxo-hexahydrothiopyran-4-ylamine HCl salt (51 mg, 0.27 mmol) in DCM (5 mL) was stirred for overnight, quenched with H₂O and diluted with DCM. The organic layer was washed with brine, dried over Na₂SO₄, filtered, concentrated and purified by prep-HPLC to give compound **301** (40 mg, 27%) as white solid. ¹H-NMR (300 MHz, CDCl₃) δ: 0.56-0.62 (m, 1H), 0.84-0.90 (m, 7H), 0.93-0.98 (m, 1H), 1.20 (s, 6H), 1.49-1.50 (m, 2H), 1.56-1.57 (m, 2H), 2.26-2.33 (m, 2H), 2.40-2.42 (m, 2H), 2.54-2.62 (m, 1H), 2.74-2.79 (m, 4H), 3.14-3.15 (m, 4H), 3.47-3.53 (m, 1H), 4.22-4.26 (m, 1H), 4.50-4.55 (m, 2H), 7.32 (d, J = 8.1 Hz, 1H), 7.44 (d, J = 8.1 Hz, 1H), 8.03 (d, J = 8.7 Hz, 1H). MS 659.2 [M+1]⁺.

Example 301/1 to 301/4

The following Example was prepared similar as described in Example **301**.

#	Structure	Analytical data
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#	Structure	Analytical data
301/1		$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 0.63-0.69 (m, 1H), 0.84-0.93 (m, 7H), 0.93-0.98 (m, 1H), 1.19 (s, 6H), 1.30 (s, 6H), 1.46-1.50 (m, 2H), 1.68-1.71 (m, 2H), 2.28 (s, 1H), 2.53-2.59 (m, 1H), 2.76-2.82 (m, 4H), 3.48 (d, $J = 6.3$ Hz, 2H), 3.52-3.57 (m, 1H), 4.49-4.54 (m, 1H), 4.59 (s, 1H), 7.45 (d, $J = 8.1$ Hz, 1H), 7.67 (t, $J = 6.5$ Hz, 1H), 8.02 (d, $J = 8.4$ Hz, 1H). MS 599.2 $[\text{M}+1]^+$
301/2		$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 0.69-0.72 (m, 1H), 0.86-0.98 (m, 7H), 1.01-1.02 (m, 1H), 1.20 (s, 6H), 1.49-1.54 (m, 2H), 1.63-1.69 (m, 2H), 2.63-2.65 (m, 1H), 2.76 (s, 3H), 2.80-2.84 (m, 1H), 3.56-2.61 (m, 1H), 4.39-4.46 (m, 5H), 4.48-4.53 (m, 3H), 4.99 (s, 2H), 7.44 (d, $J = 8.1$ Hz, 1H), 8.03 (d, $J = 8.4$ Hz, 1H). MS 657.2 $[\text{M}+1]^+$
301/3		n.t.
301/4		n.t.

Example 302

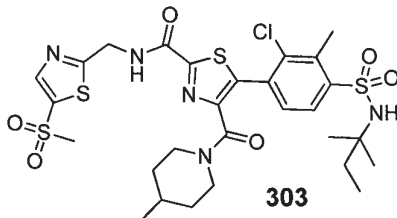
5 **trans-3-(5-(2-Chloro-3-methyl-4-(*N*-(*tert*-pentyl)sulfamoyl)phenyl)-4-(4-methylpiperidine-1-carbonyl)thiazole-2-carboxamido)cyclobutanecarboxylic acid (302)**

To a solution of compound **301/4** (60 mg, 94 μmol) in a mixture of THF (5 mL) and H_2O (1 mL) was added $\text{LiOH}\cdot\text{H}_2\text{O}$ (39 mg, 940 μmol), and then the solution was stirred at rt for 1 h, diluted with water, adjusted to pH = 5 with 1N HCl and extracted with EA. The organic phase was washed with water and brine, dried over Na_2SO_4 , filtered, concentrated and purified by prep-TLC (DCM/MeOH = 15/1) to give compound **302** (40 mg, 68%) as a white solid. $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 0.56-0.61 (m, 1H), 0.84-0.91 (m, 7H), 1.20 (s, 6H), 1.44-1.48 (m, 2H), 1.55-1.63 (m, 3H), 2.43-2.46 (m, 2H), 2.58-2.63 (m, 1H), 2.71-2.82 (m, 6H), 3.15-3.16 (m, 1H),

10

3.49-3.53 (m, 1H), 4.50-4.58 (m, 2H), 4.76-4.84 (m, 1H), 7.45 (d, J = 8.1 Hz, 1H), 7.53 (d, J = 7.8 Hz, 1H), 8.02 (d, J = 8.4 Hz, 1H). MS 625.2 [M+1]⁺.

Example 303



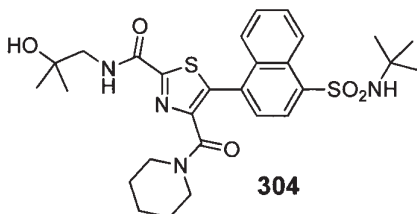
5

5-(2-Chloro-3-methyl-4-(*N*-(*tert*-pentyl)sulfamoyl)phenyl)-4-(4-methylpiperidine-1-carboxyl)-*N*-((5-(methylsulfonyl)thiazol-2-yl)methyl)thiazole-2-carboxamide (303)

A solution of compound **301/3** (125 mg, 0.19 mmol) and *m*-CPBA (80 mg, 0.47 mmol) in DCM (5 mL) was stirred for 2 h, quenched with H₂O and diluted with DCM. The organic layer was washed with brine, dried over Na₂SO₄, filtered, concentrated and purified by prep-HPLC to give compound **303** (70 mg, 53%) as a white solid. ¹H-NMR (300 MHz, CDCl₃) δ: 0.66-0.67 (m, 1H), 0.85-0.99 (m, 8H), 1.20 (s, 6H), 1.47-1.53 (m, 2H), 1.68-1.80 (m, 2H), 2.54-2.64 (m, 1H), 2.76-2.83 (m, 4H), 3.22 (s, 3H), 3.51-3.57 (m, 1H), 4.50-4.53 (m, 2H), 4.99 (d, J = 6.3 Hz, 2H), 7.46 (d, J = 8.4 Hz, 1H), 8.04 (d, J = 8.1 Hz, 1H), 8.24 (s, 1H). MS 702.2 [M+1]⁺.

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Example 304



Step 1: Ethyl 4-(hydroxymethyl)thiazole-2-carboxylate (304a)

A mixture of ethyl 1-bromo-3-hydroxypropan-2-one (129 mg, 0.85 mmol) in 10 mL dry dioxane was treated with 2-amino-2-thioxoacetate (113 mg, 0.85 mmol) for 1.2 h at 50°C and then concentrated at 50°C under vacuum to yield a dry yellow solid. The crude product was dissolved in saturated Na₂CO₃ (15 mL) and water (15 mL), and extracted with EA (6 x 20 mL). The aq. layer was then acidified to pH = 2 with conc. HCl, resulting in the formation of a precipitate. This suspension was extracted with EA. The extracts were pooled, dried with Na₂SO₄, filtered and concentrated to give compound **304a** as a red-brown solid (115 mg, 73%).

25

Step 2: *N*-(2-hydroxy-2-methylpropyl)-4-(hydroxymethyl)thiazole-2-carboxamide (304b)

To a stirred solution of **304a** (115 mg, 0.62 mmol) in 5.5 mL toluene was added 1-amino-2-methylpropan-2-ol (66 mg, 0.74 mmol). The mixture was stirred at 100°C overnight. Water was added and the mixture was extracted with EA. The organic phase was washed with water and brine, dried over Na₂SO₄, filtered, concentrated purified by CC (PE/EA = 10/1 to 5/1) to give compound **304b** (104 mg, 73%) as a white solid.

Step 3: 5-(4-(*N*-(*tert*-butyl)sulfamoyl)naphthalen-1-yl)-*N*-(2-hydroxy-2-methylpropyl)-4-(hydroxymethyl)thiazole-2-carboxamide (**304c**)

A solution of **304b** (103 mg, 0.45 mmol), 4-bromo-*N*-*tert*-butylnaphthalene-1-sulfonamide (153 mg, 0.45 mmol), K₂CO₃ (124 mg, 0.9 mmol), Pd(OAc)₂ (5 mg, 0.01 mmol), PCy₃•HBF₄ (10 mg, 0.02 mmol) and PivOH (14 mg, 0.14 mmol) in a solution of DMA (6 mL) was heated under argon at 100°C overnight, cooled to rt and partitioned between EA and water. The organic phase was washed with water and brine, dried over Na₂SO₄, filtered, concentrated and purified by CC (PE/EA = 10/1 to 5/1) to give compound **304c** (128 mg, 58%) as a white solid.

Step 4: 5-(4-(*N*-(*tert*-butyl)sulfamoyl)naphthalen-1-yl)-2-((2-hydroxy-2-methylpropyl)carbonyl)thiazole-4-carboxylic acid (**304d**)

To a solution of **304c** (128 mg, 0.26 mmol) in MeCN (30 mL) was added iodobenzene diacetate (341 mg, 1.06 mmol) and TEMPO (40 mg, 0.26 mmol). The mixture was stirred for 1 h, concentrated and extracted with EA (20 mL x 2). The organic layer was washed by saturated NaHCO₃ and brine, dried with Na₂SO₄, evaporated and purified by CC (PE/EA = 20/1 to 10/1) to give compound **304d** (95 mg, 73%) as a white solid.

Step 5: 5-(4-(*N*-(*tert*-butyl)sulfamoyl)naphthalen-1-yl)-*N*-(2-hydroxy-2-methylpropyl)-4-(piperidine-1-carbonyl)thiazole-2-carboxamide (**304**)

To a solution of **304d** (47 mg, 0.09 mmol) in 3.0 mL DMF was added HATU (13 mg, 0.13 mmol) and DIPEA (35 mg, 0.27 mmol). The mixture was stirred for 60 min and then piperidine (10 mg, 0.11 mmol) was added, stirred overnight, quenched with water and extracted with EA. The organic layer was separated, washed with brine and dried over Na₂SO₄. After filtration, the filtrate was evaporated and purified by prep-HPLC to give compound **304** (34 mg, 64%) as a white solid. ¹H-NMR (400 MHz, d₆-DMSO) δ: 8.78 (d, 1H, J = 8.0 Hz), 8.52 (t, 1H, J = 6.4 Hz), 8.24 (d, 1H, J = 7.6 Hz), 8.00-7.97 (m, 1H), 7.79-7.65 (m, 3H), 3.32-3.28 (m, 4H), 3.16 (s, 2H), 1.32 (s, 2H), 1.15 (s, 6H), 1.09 (s, 9H), 0.87-0.86 (m, 2H). MS 573.3 (M+1)⁺.

Example 304/1 to 304/27

The following examples were prepared similar to Example 304.

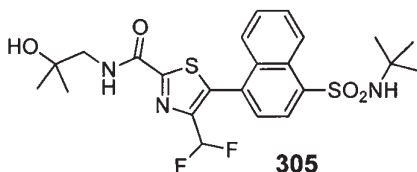
#	Structure	Analytical data
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#	Structure	Analytical data
304/1		$^1\text{H-NMR}$ (400 MHz, d_6 -DMSO) δ : 8.79-8.74 (m, 2H), 8.33 (d, 1H, $J = 8.4$ Hz), 8.19 (d, 1H, $J = 7.2$ Hz), 7.92 (s, 1H), 7.73-7.66 (m, 3H), 7.59 (t, 1H, $J = 8.0$ Hz), 3.46 (s, 1H), 1.66-1.53 (m, 5H), 1.27-1.06 (m, 20H). MS 587.3 (M+1) ⁺
304/2		$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 8.71 (d, 1H, $J = 8.8$ Hz), 8.34 (d, 1H, $J = 7.6$ Hz), 8.00 (d, 1H, $J = 8.4$ Hz), 7.76 (m, 2H), 7.64 (m, 2H), 4.71 (br s, 1H), 3.53 (m, 2H), 3.28 (m, 4H), 1.27 (s, 6H), 1.19 (s, 9H), 0.99 (m, 2H), 0.68 (m, 8H). MS 601.3 (M+1) ⁺
304/3		$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 8.71 (d, 1H, $J = 8.4$ Hz), 8.34 (d, 1H, $J = 7.6$ Hz), 8.02 (d, 1H, $J = 8.8$ Hz), 7.75 (m, 2H), 7.64 (m, 2H), 4.82 (s, 1H), 4.39 (m, 1H), 3.50 (m, 3H), 2.59 (m, 1H), 2.42 (m, 1H), 1.49 (m, 1H), 1.23 (m, 17H), 0.70 (m, 4H), 0.22 (m, 1H). MS 587.3 (M+1) ⁺
304/4		$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 8.70 (d, 1H, $J = 8.4$ Hz), 8.33 (d, 1H, $J = 7.6$ Hz), 8.00 (m, 1H), 7.75 (m, 4H), 4.78 (s, 1H), 3.52 (d, 2H, $J = 6.4$ Hz), 3.30 (m, 4H), 1.27 (m, 16H), 1.12 (m, 3H), 0.80 (m, 6H). MS 601.3 (M+1) ⁺
304/5		$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 8.72 (d, 1H, $J = 8.4$ Hz), 8.33 (d, 1H, $J = 7.6$ Hz), 8.05 (m, 1H), 7.70 (m, 4H), 4.89 (s, 1H), 4.25 (m, 2H), 3.52 (d, 2H, $J = 6.0$ Hz), 3.40 (m, 1H), 2.60 (m, 1H), 2.20 (m, 1H), 1.49 (m, 2H), 1.33 (s, 6H), 1.22 (s, 9H), 0.75 (m, 6H). MS 587.3 (M+1) ⁺
304/6		$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 8.70 (d, 1H, $J = 8.4$ Hz), 8.34 (d, 1H, $J = 7.6$ Hz), 8.01 (d, 1H, $J = 8.4$ Hz), 7.75 (m, 4H), 4.73 (s, 1H), 3.52 (d, 2H, $J = 6.0$ Hz), 3.05 (m, 2H), 1.33 (m, 8H), 1.25 (m, 17H), 0.95 (m, 2H). MS 601.3 (M+1) ⁺
304/7		$^1\text{H-NMR}$ (400 MHz, $\text{DMSO}-d_6$) δ : 8.78 (d, 1H, $J = 8.4$ Hz), 8.50 (m, 1H), 8.24 (d, 1H, $J = 7.6$ Hz), 7.99 (m, 1H), 7.77 (m, 3H), 4.40 (m, 2H), 3.37 (m, 3H), 2.68 (m, 1H), 1.46 (m, 3H), 1.25 (s, 6H), 1.11 (s, 9H), 0.90 (m, 5H). MS 587.3 (M+1) ⁺
304/8		$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 8.70 (d, 1H, $J = 8.4$ Hz), 8.34 (d, 1H, $J = 7.6$ Hz), 8.06 (d, 1H, $J = 8.4$ Hz), 7.77 (m, 2H), 7.64 (m, 2H), 4.78 (s, 1H), 4.45 (m, 1H), 3.52 (d, 2H, $J = 6.8$ Hz), 3.35 (m, 1H), 2.08 (m, 2H), 1.88 (m, 1H), 1.45 (m, 1H), 1.34 (s, 6H), 1.22 (s, 9H), 1.08 (m, 1H), 0.76 (m, 3H), 0.50 (m, 4H). MS 601.3 (M+1) ⁺

#	Structure	Analytical data
304/9		$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 8.72 (m, 1H), 8.34 (m, 1H), 8.05 (m, 1H), 7.73 (m, 4H), 4.86 (s, 1H), 4.40 (m, 1H), 3.55 (m, 3H), 2.58 (m, 1H), 1.54 (m, 1H), 1.34 (s, 6H), 1.22 (m, 10H), 0.76 (m, 9H). MS 601.3 ($\text{M}+1$) ⁺
304/10		$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 8.70 (d, 1H, J = 8.4 Hz), 8.34 (d, 1H, J = 7.6 Hz), 8.03 (d, 1H, J = 8.4 Hz), 7.77 (m, 4H), 4.80 (s, 1H), 4.39 (m, 1H), 3.52 (m, 3H), 2.56 (m, 1H), 1.55 (m, 1H), 1.33 (m, 20H), 0.70 (m, 4H), 0.22 (m, 1H). MS 601.2 ($\text{M}+1$) ⁺
304/11		$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 8.72 (d, 1H, J = 8.8 Hz), 8.34 (d, 1H, J = 7.6 Hz), 7.99 (d, 1H, J = 8.4 Hz), 7.86 (s, 1H), 7.71 (m, 3H), 4.60 (m, 4H), 3.52 (m, 2H), 3.11 (m, 3H), 1.60 (m, 4H), 1.24 (m, 19H). MS 613.3 ($\text{M}+1$) ⁺
304/12		$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 8.66 (d, 1H, J = 8.4 Hz), 8.31 (d, 1H, J = 7.6 Hz), 8.01 (m, 1H), 7.75 (m, 1H), 7.65 (m, 1H), 5.30 (d, 1H, J = 9.2 Hz), 4.37 (m, 1H), 4.01 (m, 1H), 3.50 (m, 3H), 2.60 (m, 1H), 2.40 (m, 1H), 1.50 (m, 1H), 1.30 (m, 11H), 0.70 (m, 4H), 0.33 (m, 1H). MS 627.2 ($\text{M}+1$) ⁺
304/13		$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 8.71 (d, 1H, J = 8.4 Hz), 8.33 (d, 1H, J = 7.6 Hz), 8.02 (d, 1H, J = 8.0 Hz), 7.77-7.58 (m, 4H), 4.71 (s, 1H), 4.39-4.34 (m, 1H), 3.53-3.43 (m, 3H), 2.55 (m, 2H), 1.56-1.49 (m, 3H), 1.36-1.15 (m, 14H), 0.78 (t, J = 8.0 Hz, 3H), 0.66 (m, 4H), 0.25 (m, 1H). MS 601.3 ($\text{M}+1$) ⁺
304/14		$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 8.71 (d, 1H, J = 8.8 Hz), 8.33 (d, 1H, J = 7.6 Hz), 8.02 (d, 1H, J = 8.0 Hz), 7.75 (m, 1H), 7.63 (m, 2H), 7.39 (d, 1H, J = 8.0 Hz), 4.70 (s, 1H), 4.38 (m, 1H), 4.28 (m, 1H), 3.42 (m, 1H), 3.20 (m, 4H), 2.43 (m, 6H), 1.55 (m, 3H), 1.35 (m, 1H), 1.15 (m, 7H), 0.78 (t, J = 8.0 Hz, 3H), 0.66 (m, 4H), 0.16 (m, 1H). MS 661.2 ($\text{M}+1$) ⁺
304/15		$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 8.71 (d, 1H, J = 8.4 Hz), 8.33 (d, 1H, J = 7.6 Hz), 8.02 (d, 1H, J = 8.4 Hz), 7.72 (m, 3H), 7.26 (m, 1H), 4.63 (s, 1H), 4.39 (m, 1H), 4.20 (m, 1H), 4.04 (m, 2H), 3.58 (m, 2H), 3.41 (m, 1H), 2.40 (m, 2H), 1.65 (m, 5H), 1.31 (m, 1H), 1.15 (m, 7H), 0.77 (t, J = 8.0 Hz, 3H), 0.66 (m, 4H), 0.18 (m, 1H). MS 613.3 ($\text{M}+1$) ⁺
304/16		MS 673.2 ($\text{M}+1$) ⁺

#	Structure	Analytical data
304/17		$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 8.69 (d, $J = 8.4$ Hz, 1H), 8.33 (d, $J = 8.8$ Hz, 1H), 7.98 (d, $J = 8.0$ Hz, 1H), 7.75-7.58 (m, 3H), 4.68 (s, 1H), 4.53 (s, 2H), 4.37 (m, 2H), 4.02 (s, 2H), 3.71-3.65 (m, 4H), 3.52 (m, 1H), 2.65 (m, 1H), 2.45 (m, 1H), 1.87 (m, 4H), 1.51 (m, 1H), 1.40-1.20 (m, 11H), 0.80-0.65 (m, 4H), 0.25 (m, 1H). MS 625.2 ($\text{M}+1$) $^+$
304/18		$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 8.69 (d, $J = 8.4$ Hz, 1H), 8.33 (d, $J = 8.8$ Hz, 1H), 7.98 (d, $J = 8.0$ Hz, 1H), 7.75-7.57 (m, 3H), 7.33 (m, 1H), 4.75 (s, 1H), 4.36 (m, 1H), 3.95-3.68 (m, 4H), 3.45 (m, 1H), 2.86 (m, 1H), 2.55 (m, 1H), 2.38 (m, 1H), 1.65-1.40 (m, 4H), 1.39-1.20 (m, 12H), 1.01 (m, 1H), 0.75-0.62 (m, 5H), 0.20 (m, 1H). MS 625.2 ($\text{M}+1$) $^+$
304/19		$^1\text{H-NMR}$ (400 MHz, DMSO-d_6) δ : 8.81 (d, $J = 8.8$ Hz, 1H), 8.51 (m, 1H), 8.14 (d, $J = 8.0$ Hz, 1H), 8.10 (m, 1H), 7.98 (d, $J = 8.4$ Hz, 1H), 7.81-7.66 (m, 3H), 4.13 (m, 1H), 3.59 (m, 1H), 3.32 (m, 2H), 2.80 (m, 1H), 2.64 (m, 2H), 2.43 (m, 1H), 1.46-1.39 (m, 3H), 1.26 (s, 6H), 0.80 (s, 9H), 0.68 (d, $J = 6.4$ Hz, 3H), 0.43 (m, 1H), 0.23 (m, 1H). MS 601.2 ($\text{M}+1$) $^+$
304/20		$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 8.87 (d, $J = 8.4$ Hz, 1H), 8.00 (d, $J = 8.0$ Hz, 1H), 7.96 (d, $J = 7.6$ Hz, 1H), 7.73-7.69 (m, 2H), 7.64-7.59 (m, 2H), 4.40 (m, 1H), 3.64 (m, 2H), 3.50 (m, 2H), 3.40 (m, 1H), 2.62 (m, 1H), 2.44 (m, 1H), 1.51-1.33 (m, 20H), 1.20 (m, 1H), 0.69 (d, $J = 6.4$ Hz, 3H), 0.63 (m, 1H), 0.05 (m, 1H). MS 615.2 ($\text{M}+1$) $^+$
304/21		$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 8.67 (d, $J = 8.4$ Hz, 1H), 8.30 (d, $J = 7.6$ Hz, 1H), 8.03 (d, $J = 8.4$ Hz, 1H), 7.78-7.64 (m, 4H), 5.28 (m, 1H), 4.38 (m, 1H), 3.71 (m, 2H), 3.51 (m, 3H), 2.65 (m, 1H), 2.43 (m, 1H), 1.40-1.26 (m, 9H), 0.76-0.72 (m, 4H), 0.38 (m, 1H). MS 613.1 ($\text{M}+1$) $^+$
304/22		$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 8.77 (d, $J = 7.6$ Hz, 1H), 8.26 (d, $J = 7.6$ Hz, 1H), 7.98 (d, $J = 8.4$ Hz, 1H), 7.84 (m, 1H), 7.74 (m, 1H), 7.65-7.61 (m, 2H), 5.44 (br s, 1H), 4.34 (br s, 1H), 3.52 (m, 3H), 2.92 (m, 2H), 2.67-2.48 (m, 2H), 1.53-1.20 (m, 15H), 0.76-0.74 (m, 4H), 0.32 (m, 1H). MS 603.2 ($\text{M}+1$) $^+$
304/23		$^1\text{H-NMR}$ (400 MHz, DMSO-d_6) δ : 8.81 (d, $J = 8.8$ Hz, 1H), 8.70 (m, 1H), 8.26 (d, $J = 8.0$ Hz, 1H), 8.19 (d, $J = 7.6$ Hz, 1H), 8.02-7.86 (m, 3H), 4.90 (s, 1H), 4.67 (m, 1H), 4.31 (m, 1H), 3.73 (m, 1H), 3.49-3.47 (m, 2H), 2.96 (m, 1H), 2.61 (m, 1H), 1.63-1.47 (m, 11H), 1.36-1.32 (m, 7H), 0.80 (m, 3H), 0.49 (m, 1H), 0.13 (m, 1H). MS 669.2 ($\text{M}+1$) $^+$
304/24		$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 8.72 (d, $J = 8.4$ Hz, 1H), 8.32 (d, $J = 7.2$ Hz, 1H), 8.01 (d, $J = 8.4$ Hz, 1H), 7.82-7.63 (m, 4H), 5.21 (br s, 1H), 4.34 (br s, 1H), 3.99-3.81 (m, 3H), 3.71-3.62 (m, 2H), 3.53 (m, 3H), 2.75-2.40 (m, 2H), 2.06 (m, 1H), 1.73 (m, 1H), 1.39-1.34 (m, 9H), 0.76-0.74 (m, 4H), 0.29 (m, 1H). MS 601.2 ($\text{M}+1$) $^+$

#	Structure	Analytical data
304/25		$^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ : 8.73 (d, J = 8.8 Hz, 1H), 8.52 (m, 1H), 8.17 (d, J = 7.6 Hz, 1H), 8.00 (d, J = 8.0 Hz, 1H), 7.83-7.67 (m, 3H), 4.13 (m, 1H), 3.59 (m, 1H), 3.32 (m, 2H), 3.15 (m, 2H), 2.87-2.77 (m, 3H), 2.45 (m, 1H), 1.59 (m, 2H), 1.46-1.40 (m, 2H), 1.27-1.24 (m, 3H), 1.15 (s, 6H), 0.67 (d, J = 6.4 Hz, 3H), 0.39 (m, 1H), 0.20 (m, 1H). MS 627.2 ($M+1$) $^+$
304/26		$^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ : 8.77 (d, J = 8.8 Hz, 1H), 8.52 (m, 1H), 8.31 (s, 1H), 8.20 (d, J = 7.6 Hz, 1H), 7.98 (d, J = 8.0 Hz, 1H), 7.81-7.66 (m, 3H), 4.10 (m, 1H), 3.57 (m, 1H), 3.32 (m, 2H), 2.77 (m, 1H), 2.41 (m, 1H), 2.14 (m, 1H), 1.69-1.15 (m, 16H), 0.66 (d, J = 6.4 Hz, 3H), 0.43 (m, 1H), 0.23 (m, 1H). MS 599.2 ($M+1$) $^+$
304/27		$^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ : 8.68 (d, J = 8.4 Hz, 1H), 8.52 (m, 1H), 8.23 (d, J = 7.2 Hz, 1H), 7.98 (d, J = 8.0 Hz, 1H), 7.79-7.65 (m, 3H), 4.72 (s, 1H), 4.12 (m, 1H), 3.58 (m, 1H), 3.33 (m, 2H), 2.76 (m, 1H), 2.46 (m, 1H), 1.50-1.15 (m, 9H), 1.06 (s, 3H), 0.52-0.24 (m, 6H). MS 585.2 ($M+1$) $^+$

Example 305

Step 1: Ethyl 5-(4-(*N*-(*tert*-butyl)sulfamoyl)naphthalen-1-yl)-4-formylthiazole-2-carboxylate (305a)

5 A solution of ethyl 5-(4-(*N*-(*tert*-butyl)sulfamoyl)naphthalen-1-yl)-4-(hydroxymethyl)thiazole-2-carboxylate (1.2 g, 2.7 mmol) in DCM (50 mL) was added MnO_2 (0.49 g, 5.4 mmol). The mixture was stirred at rt overnight. Water (20 mL) was added, the aq. phase was extracted with EA (20mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4 ,
 10 concentrated and purified by CC (EA/PE = 1/2) to give compound **305a** (1.1 g, 92%) as a brown solid.

Step 2: Ethyl 5-(4-(*N*-(*tert*-butyl)sulfamoyl)naphthalen-1-yl)-4-(difluoromethyl)thiazole-2-carboxylate (305b)

To a solution of compound **305a** (1.1 g, 2.5 mmol) in dry DCM (50 mL) at 0°C was added
 15 DAST (0.81 g, 5 mmol) dropwise over 30 min. The mixture was stirred at 0°C for 0.5 h and at rt for 3 h, poured into ice-water and extracted with EA (40 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4 , concentrated and purified by CC (PE/EA = 15/1) to afford compound **305b** (655 mg, 56%) as a colorless oil.

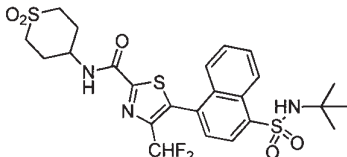
Step 3: 5-(4-(*N*-(*tert*-butyl)sulfamoyl)naphthalen-1-yl)-4-(difluoromethyl)-*N*-(2-hydroxy-2-methylpropyl)thiazole-2-carboxamide (305)

20

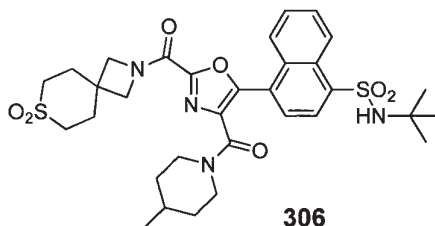
- To a solution of compound **305b** (0.66 g, 1.2 mmol) and 1-amino-2-methylpropan-2-ol (0.21 g, 2.4 mmol) in toluene (20 mL) was heated to 95°C overnight, poured into water (40 mL) and extracted with EA (30 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, concentrated and purified by prep-TLC to afford compound **305** (0.5 g, 82%) as a white solid. ¹H-NMR (400 MHz, CDCl₃) δ: 8.72 (d, 1H, J = 8.8 Hz), 8.38 (d, 1H, J = 7.6 Hz), 7.77 (m, 3H), 7.61 (m, 2H), 6.40 (m, 1H), 4.70 (s, 1H), 3.53 (d, 1H, J = 6.4 Hz), 1.35 (s, 6H), 1.21 (s, 9H). MS 511.7 (M+1)⁺.

Example 305/1

- The following example was prepared similar to Example **305**.

#	Structure	Analytical data
305/1		¹ H-NMR (400 MHz, CDCl ₃) δ: 8.73 (d, 1H, J = 8.8 Hz), 8.38 (d, 1H, J = 7.2 Hz), 7.75 (m, 4H), 7.37 (d, 1H, J = 8.0 Hz), 6.40 (t, J = 53.2 Hz, 1H), 4.67 (s, 1H), 4.28 (m, 1H), 3.18 (m, 4H), 2.40 (m, 4H), 1.21 (s, 9H). MS 572.1 (M+1) ⁺

Example 306



Step 1: Methyl 4-(*N*-(*tert*-butyl)sulfamoyl)-1-naphthoate (**306a**)

- A solution of 4-bromo-*N*-(*tert*-butyl)naphthalene-1-sulfonamide (300 mg, 0.88 mmol), Pd(AcO)₂ (19.7 mg, 88 μmol), DPPP (54.4 mg, 0.132 mmol) and NEt₃ (266.6 mg, 2.64 mmol) in CH₃OH (10 mL) in an autoclave under CO (3.0 MPa pressure) was stirred at 80°C overnight, concentrated and purified by CC (PE/EA = 5/1) to give compound **306a** (160 mg, 57%) as a white solid.

Step 2: 4-(*N*-(*tert*-Butyl)sulfamoyl)-1-naphthoic acid (**306b**)

- A solution of compound **306a** (2.4 g, 7.4 mmol) in CH₃OH/H₂O (10:1, 50 mL) was added LiOH·H₂O (0.94 g, 22.4 mmol) and the solution was stirred at rt overnight, concentrated and dissolved in H₂O. The pH was adjusted to ~5 with 2N HCl under cooling with an ice bath and then the aq. phase was extracted with EA. The combined organic layers were washed with water and brine, dried over Na₂SO₄, filtered and concentrated to give compound **306b** (2.2 g, 95%) as a pale white solid.

Step 3: 4-(*N*-(*tert*-Butyl)sulfamoyl)-1-naphthoyl chloride (**306c**)

To a solution of compound **306b** (307 mg, 1.0 mmol) in dry DCM (5 mL) was added oxalyl chloride (189 mg, 1.5 mmol) slowly and the mixture was stirred at rt for 3 hr and concentrated to give crude compound **306c** as pale yellow oil.

Step 4: Ethyl 5-(4-(*N*-(*tert*-butyl)sulfamoyl)naphthalen-1-yl)oxazole-4-carboxylate (**306d**)

5 To a solution of ethyl 2-isocyanoacetate (124 mg, 1.1 mmol) and compound **306c** (1.0 mmol) in dry THF (5.0 mL) was added NEt₃ (400 mg, 4.0 mmol) slowly and the solution was stirred at rt overnight, diluted with EA, washed with sat. NH₄Cl and brine, dried over Na₂SO₄, filtered, concentrated and purified by CC (PE/EA = 3/1) to give compound **306d** (190 mg, 47%) as a yellow solid.

10 Step 5: 5-(4-(*N*-(*tert*-Butyl)sulfamoyl)naphthalen-1-yl)oxazole-4-carboxylic acid (**306e**)

To a solution of compound **306d** (220 mg, 0.55 mmol) in EtOH (5.0 mL) was added NaOH (65 mg, 1.64 mmol) and the solution was stirred at rt overnight, concentrated and dissolved in H₂O. The pH was adjusted to ~5 with 2N HCl under cooling with an ice bath and then the aq. phase was extracted with EA. The organic layer was washed with water and brine, dried over
15 Na₂SO₄, filtered and concentrated to give compound **306e** (130 mg, 65%) as a pale white solid.

Step 6: *N*-(*tert*-Butyl)-4-(4-(4-methylpiperidine-1-carbonyl)oxazol-5-yl)naphthalene-1-sulfonamide (**306f**)

A mixture of compound **306e** (750 mg, 2.0 mmol), 4-methylpiperidine (300 mg, 3.0 mmol),
20 HATU (1.14 g, 3.0 mmol) and DIPEA (0.77 g, 6.0 mmol) in DMF (10 mL) was stirred overnight at rt, poured into water and extracted with EA. The organic layer was washed with water and brine, dried over Na₂SO₄, filtered, concentrated and purified by CC gel (DCM/MeOH = 100/1 to 50/1) to afford compound **306f** (820 mg, 90%) as a white solid.

25 Step 7: Methyl 5-(4-(*N*-(*tert*-butyl)sulfamoyl)naphthalen-1-yl)-4-(4-methylpiperidine-1-carbonyl)oxazole-2-carboxylate (**306g**)

To a solution of compound **306f** (199 mg, 0.44 mmol) in dry THF (3 mL) was added *n*-butyllithium (2.5M in hexane, 0.53 mL, 1.32 mmol) at -78°C under argon and the solution was stirred for 2 h at -78°C. Then methyl chloroformate (124 mg, 1.32 mmol) was added and the solution was stirred for 1 h, quenched with sat. NH₄Cl, extracted with EA, washed with brine,
30 dried over Na₂SO₄, filtered, concentrated and purified by CC (DCM/MeOH = 100/1) to give compound **306g** (65 mg, 29%) as a white solid.

Step 8: 5-(4-(*N*-(*tert*-Butyl)sulfamoyl)naphthalen-1-yl)-4-(4-methylpiperidine-1-carbonyl)oxazole-2-carboxylic acid (**306h**)

To a solution of compound **306g** (65 mg, 0.13 mmol) in THF/H₂O (3/1, 5 mL) was added
35 LiOH•H₂O (11 mg, 0.26 mmol) and the solution was stirred for 15 min at rt, adjusted to pH 3-4 with 2N HCl under cooling with an ice bath and then extracted with DCM. The organic layer

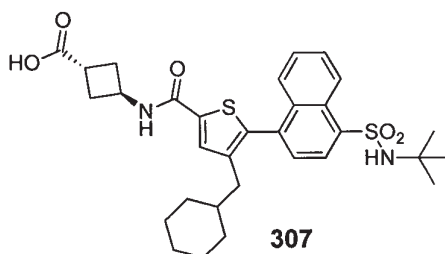
was washed with water and brine, dried over Na₂SO₄, filtered and this DCM solution was used for the next reaction without further purification.

Step 9: *N*-(*tert*-Butyl)-4-(2-(7,7-dioxido-7-thia-2-azaspiro[3.5]nonane-2-carbonyl)-4-(4-methyl-piperidine-1-carbonyl)oxazol-5-yl)naphthalene-1-sulfonamide (**306**)

- 5 A solution of compound **306h** (65 mg, 0.13 mmol, th.), 7-thia-2-azaspiro[3.5]nonane-7,7-dione hemi-oxalate (35 mg, 0.13 mmol), HATU (74 mg, 0.2 mmol) and DIPEA (25 mg, 0.2 mmol) in DCM (2 mL) was stirred overnight at rt, washed with water and brine, dried over Na₂SO₄, filtered, concentrated and purified by prep-HPLC to give compound **306** (24 mg, 28% over two steps) as a white solid. ¹H-NMR (400 MHz, CD₃OD) δ: 0.46-0.53 (m, 1H), 0.76-0.85 (m, 1H), 0.79 (d, J = 6.4 Hz, 3H), 1.16 (s, 9H), 1.36-1.39 (m, 1H), 1.48-1.55 (m, 1H), 1.60-1.64 (m, 1H), 2.40 (t, J = 5.6 Hz, 4H), 2.66 (t, J = 12.0 Hz, 1H), 2.91 (t, J = 8.0 Hz, 4H), 3.11-3.20 (m, 4H), 3.88 (d, J = 12.8 Hz, 1H), 4.06 (s, 2H), 4.42 (d, J = 12.8 Hz, 1H), 4.58 (s, 2H), 7.68-7.72 (m, 1H), 7.76-7.80 (m, 1H), 7.85 (d, J = 8.0 Hz, 1H), 8.06 (d, J = 8.4 Hz, 1H), 8.36 (d, J = 7.6 Hz, 1H), 8.84 (d, J = 8.8 Hz, 1H). MS 657.3 (M+1)⁺.

15

Example 307



Step 1: Cyclohexyl(thiophen-3-yl)methanol (**307a**)

- 20 To a solution of thiophene-3-carbaldehyde (15.0 g, 134 mmol) in Et₂O (200 mL) was added cyclohexylmagnesium chloride (1M in THF, 160 mL, 160 mmol) dropwise at 0°C and the mixture was stirred at rt for 3 h, quenched with sat. NH₄Cl at 0°C and extracted with EA. The organic layer was washed with water and brine, dried over Na₂SO₄, filtered, concentrated and purified by CC (PE/EA = 10/1) to give compound **307a** (22.1 g, 84%) as a pale yellow oil.

Step 2: Cyclohexyl(thiophen-3-yl)methyl methanesulfonate (**307b**)

- 25 To a solution of compound **307a** (18.8 g, 95.9 mmol) and Et₃N (11.6 g, 115 mmol) in DCM (200 mL) was added MsCl (13.1 g, 115 mmol) dropwise at 0°C and the mixture was stirred at 0°C for 30 min, then at rt overnight, concentrated and diluted with a mixture of PE and EA (100 mL/50 mL). The suspension was filtered to remove salt. After concentration at rt, crude compound **307b** (22.0 g) was used for the next step without further purification.

- 30 Step 3: 3-(Cyclohexylmethyl)thiophene (**307c**)

To a solution of compound **307b** (22.0 g, 80.3 mmol) in EA (250 mL) was added 10 % Pd/C (4.5 g) and the suspension was stirred under H₂ (50 psi) at 60°C for 24 h, filtered and the

filtrate was concentrated and purified by CC (PE/EA = 50/1) to give compound **307c** (6.8 g, 37.8 mmol) as a colorless oil.

Step 4: 2-Bromo-3-(cyclohexylmethyl)thiophene (**307d**)

5 To a solution of compound **307c** (6.80 g, 37.8 mmol) in AcOH (40 mL) was added NBS (7.40 g, 41.6 mmol) portionwise and the solution was stirred at 30°C for 7 hr, poured into ice-water and extracted with EA. The organic layer was washed with water and brine and dried over Na₂SO₄, filtered, concentrated and purified by CC (PE/EA = 50/1) to give compound **307d** (5.00 g, 51%) as a red oil.

Step 5: Methyl 5-bromo-4-(cyclohexylmethyl)thiophene-2-carboxylate (**307e**)

10 To a solution of LDA (1M in THF, 21.5 mL, 21.5 mmol) was added a solution of compound **307d** (5.00 g, 19.6 mmol) in dry THF (50 mL) dropwise at -78°C under N₂ and the solution was stirred at -78°C for 45 min. Then a solution of ethyl chloroformate (2.32 g, 21.5 mmol) in dry THF (3 mL) was added dropwise at -78°C, kept stirring for 2 h at -78°C, then quenched with sat. NH₄Cl at -78°C and then warmed to rt. After extraction with EA (3x), the combined
15 organic layers were washed with water and brine consecutively, dried over Na₂SO₄, filtered, concentrated and purified by CC (PE/EA = 10/1) to give compound **307e** (4.50 g, 70%) as a white solid.

Step 6: Methyl 5-(4-(*N*-(*tert*-butyl)sulfamoyl)naphthalen-1-yl)-4-(cyclohexylmethyl)thiophene-2-carboxylate (**307f**)

20 A mixture of compound **307e** (800 mg, 2.42 mmol), compound **P1/2** (1.04 g, 2.67 mmol) Pd(dppf)Cl₂ (297 mg, 0.36 mmol) and Na₂CO₃ (771 mg, 7.27 mmol) in dry DME (40 mL) was bubbled with N₂ for 10 min and then refluxed overnight under N₂. The mixture was cooled to rt, diluted with EA and then filtered. The filtrate was concentrated and purified by prep-HPLC to give compound **307f** (480 mg, 39%) as a white solid.

25 Step 7: 5-(4-(*N*-(*tert*-Butyl)sulfamoyl)naphthalen-1-yl)-4-(cyclohexylmethyl)thiophene-2-carboxylic acid (**307g**)

To a solution of compound **307f** (220 mg, 0.428 mmol) in a mixture of MeOH and H₂O (10 mL/1 mL) was added LiOH·H₂O (36 mg, 0.86 mmol) and the solution was stirred overnight at rt, adjusted pH to 4-5 with 2N HCl, concentrated and dissolved with DCM. The organic layer
30 was dried with Na₂SO₄, filtered and concentrated to give crude compound **307g** (224 mg) as a pale yellow solid.

Step 8: *trans*-3-(5-(4-(*N*-(*tert*-Butyl)sulfamoyl)naphthalen-1-yl)-4-(cyclohexylmethyl)thiophene-2-carboxamido)cyclobutanecarboxylic acid (**307**)

A mixture of compound **307g** (114 mg, 0.24 mmol), *trans* 3-aminocyclobutanecarboxylic acid
35 hydrochloride (58 mg, 0.35 mmol), HATU (134 mg, 0.35 mmol) and DIEA (91 mg, 0.71 mmol) in dry DMF (8 mL) was stirred at 30°C overnight, diluted with water, adjusted pH to 5 with 1N HCl and extracted with EA twice. The combined organic layers were concentrated and purified

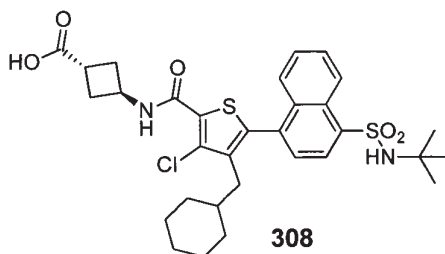
by prep-HPLC to give compound **307** (30 mg, 21%) as a white solid. ¹H-NMR (400 MHz, CDOD₃) δ: 0.48-0.58 (m, 2H), 0.91-0.98 (m, 3H), 1.04 (s, 9H), 1.19-1.23 (m, 2H), 1.30 (m, 1H), 1.37-1.50 (m, 5H), 2.32-2.38 (m, 2H), 2.55-2.58 (m, 2H), 2.98-3.00 (m, 1H), 4.58-4.62 (m, 1H), 7.47-7.53 (m, 2H), 7.62-7.68 (m, 3H), 8.20-8.24 (m, 1H), 8.70-8.75 (m, 1H). MS 583.3 [M+1]⁺.

Example 307/1

The following example was prepared similar to Example **307**.

#	Structure	Analytical data
307/1		¹ H-NMR (400 MHz, DMSO-d ₆) δ: 0.53-0.56 (m, 2H), 0.92-1.03 (m, 3H), 1.06 (s, 9H), 1.32-1.46 (m, 7H), 2.06-2.17 (m, 5H), 3.11-3.15 (m, 2H), 3.30-3.38 (m, 2H), 4.17-4.24 (m, 1H), 7.61-7.67 (m, 2H), 7.70-7.76 (m, 2H), 7.84 (s, 1H), 7.90 (s, 1H), 8.24 (d, J = 7.6 Hz, 1H), 8.50 (d, J = 7.6 Hz, 1H), 8.78 (d, J = 9.2 Hz, 1H). MS 617.3 [M+1] ⁺

Example 308



Step 1: Methyl 4,5-dibromo-3-chlorothiophene-2-carboxylate (**308a**)

To a solution of methyl 3-chlorothiophene-2-carboxylate (5.0 g, 28.3 mmol) and AcONa (17.4 g, 212 mmol) in AcOH (80 mL) was added Br₂ (13.2 mL, 255 mmol) dropwise at rt and the mixture was stirred at 75°C for 3 d, cooled to rt, quenched with sat. Na₂S₂O₃, basified to pH = 8 with sat. NaHCO₃ and extracted with Et₂O. The organic layer was washed with water and brine, dried over Na₂SO₄, filtered, concentrated and washed with a mixture of PE and EA (20 mL, 20/1) to give compound **308a** (4.0 g, 42%) as pale red solid.

Step 2: Methyl 4-bromo-3-chlorothiophene-2-carboxylate (**308b**)

To a solution of compound **308a** (1.0 g, 3.0 mmol) in THF (30 mL) was added *n*-BuLi (2.5 M in THF, 1.2 mL, 3.0 mmol) dropwise at -100°C and the mixture was stirred at -100°C for 5 min, quenched with water and extracted with EA. The organic layer was washed with water and brine, dried over Na₂SO₄, filtered, concentrated and purified by CC (PE/EA = 100/1) to give compound **308b** (500 mg, 65%) as a white solid.

Step 3: Methyl 3-chloro-4-(cyclohexylmethyl)thiophene-2-carboxylate (**308c**)

To a suspension of compound **308b** (500 mg, 2.0 mmol) and Pd(dppf)Cl₂ (156 mg, 0.2 mmol) in THF (10 mL) was added cyclohexylmethyl zinc bromide (0.5M in THF, 19.6 mL, 9.8 mmol) at rt under N₂ and the suspension was stirred at reflux for 6 h, cooled to rt, quenched with water and extracted with EA. The organic layer was washed with water and brine, dried over Na₂SO₄, filtered, concentrated and purified by CC (PE/EA = 100/1) to give compound **308c** (500 mg, 92%) as a colorless oil.

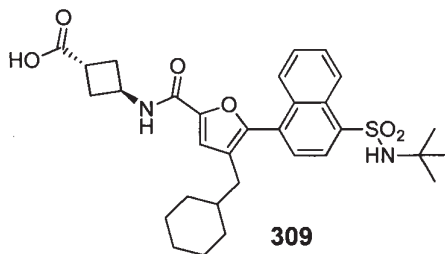
Step 4: Methyl 5-bromo-3-chloro-4-(cyclohexylmethyl)thiophene-2-carboxylate (308d**)**

To a solution of compound **308c** (200 mg, 0.7 mmol) and AcONa (451 mg, 5.5 mmol) in AcOH (10 mL) was added Br₂ (0.2 mL, 3.7 mmol) dropwise at rt and the solution was stirred at 75°C overnight, cooled to rt, quenched with sat. Na₂S₂O₃, adjusted pH = 8 with sat. NaHCO₃ and extracted with EA. The organic layer was washed with water and brine, dried over Na₂SO₄, filtered, concentrated and purified by prep-HPLC to give compound **308d** (40 mg, 16%) as a pale brown solid.

Step 5: *trans*-3-(5-(4-(*N*-(*tert*-Butyl)sulfamoyl)naphthalen-1-yl)-3-chloro-4-(cyclohexylmethyl)thiophene-2-carboxamido)cyclobutanecarboxylic acid (308**)**

If one were to treat compound **308d** similar as described in Example 307, Step 6 to 8 one would obtain compound **308**.

Example 309



Step 1: Methyl 4,5-dibromo-3-methylfuran-2-carboxylate (309a**)**

To a suspension of AlCl₃ (2.28 g, 17.1 mmol) in dry DCM (25 mL) was added solution methyl 3-methylfuran-2-carboxylate (1.2 g, 8.57 mmol) in dry DCM (5.0 mL) slowly at 0°C over 30 min. To this solution, Br₂ (4.11 g, 25.7 mmol) was added under the same condition over 1 h. The suspension was stirred at rt overnight, poured into ice-water and then diluted with EA. The aqueous layer was extracted with EA twice. The combine organic layers were washed with sat. Na₂SO₃ twice and brine consecutively, dried over Na₂SO₄, filtered, concentrated and purified by CC (PE/EA = 20/1) to give compound **309a** (1.0 g, 39%) as a white solid.

Step 2: Methyl 4-bromo-3-methylfuran-2-carboxylate (309b**)**

The solution of compound **309a** (350 mg, 1.17 mmol) in THF (30 mL) was added *n*-BuLi (2.5M in THF, 0.47 mL, 1.18 mmol) dropwise at -78°C under N₂ and the solution was stirred at this temperature for 10 min, quenched with sat. NH₄Cl and extracted with EA (3x). The combined

organic layers were washed with water and brine, dried over Na₂SO₄, filtered, concentrated and purified by prep-HPLC to give compound **309b** (50 mg, 19%) as a white solid.

Step 3: Methyl 4-(cyclohexylmethyl)-3-methylfuran-2-carboxylate (**309c**)

A solution of compound **309b** (150 mg, 0.69 mmol), cyclohexylmethylzinc bromide (0.5M in THF, 7.0 mL, 3.5 mmol) and Pd(dppf)Cl₂ (50 mg, 0.069 mmol) in THF (5.0 mL) was refluxed under N₂ at 85°C for 6 h, evaporated and purified by CC (PE/EA = 20/1) to give compound **309c** (140 mg, 86%) as white solid.

Step 4: Methyl 5-bromo-4-(cyclohexylmethyl)-3-methylfuran-2-carboxylate (**309d**)

To the solution of compound **309c** (100 mg, 0.42 mol) in DCM (10.0 mL) was added Br₂ (200 mg, 1.26 mmol) slowly at 0°C and the solution was stirred at rt overnight, diluted with EA and quenched with sat. Na₂SO₃. The aqueous layer was extracted with EA twice. The combined organic layers were washed with water and brine, dried over Na₂SO₄, filtered, concentrated and purified by CC (PE/EA = 15/1) to give compound **309d** (105 mg, 80%) as a yellow solid.

Step 5: Methyl 5-(4-(*N*-(*tert*-butyl)sulfamoyl)naphthalen-1-yl)-4-(cyclohexylmethyl)-3-methylfuran-2-carboxylate (**309e**)

The suspension of compound **309d** (105 mg, 0.333 mmol), K₂CO₃ (138 mg, 1.0 mmol), compound **P1/2** (130 mg, 0.333 mmol) and Pd(dppf)Cl₂ (20 mg) in DMF (5 mL) was stirred at 100°C overnight, cooled to rt, concentrated and purified by CC (PE/EA = 15/1) to give compound **309e** (81 mg, 49%) as a white solid.

Step 6: 5-(4-(*N*-(*tert*-Butyl)sulfamoyl)naphthalen-1-yl)-4-(cyclohexylmethyl)-3-methylfuran-2-carboxylic acid (**309f**)

To a solution of compound **309e** (81 mg, 0.16 mmol) in MeOH (2 mL) was added NaOH (20 mg, 5.0 mmol) and the solution was stirred at rt overnight, concentrated, diluted with water, adjusted pH to 5 with 1N HCl and extracted with EA. The organic layer was washed with water and brine, dried over Na₂SO₄, filtered and concentrated to give compound **309f** (69 mg, 89%) as a yellow solid.

Step 7: *trans*-3-(5-(4-(*N*-(*tert*-Butyl)sulfamoyl)naphthalen-1-yl)-4-(cyclohexylmethyl)furan-2-carboxamido)cyclobutanecarboxylic acid (**309**)

If one were to treat compound **309f** similar as described in Example 307, Step 8 one would obtain compound **309**.

Additional Examples

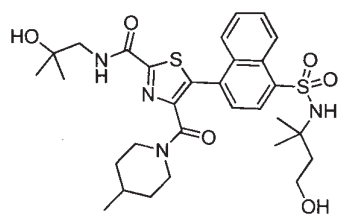
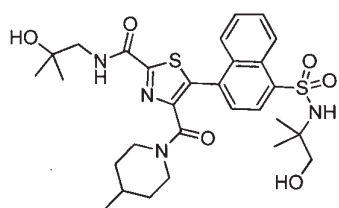
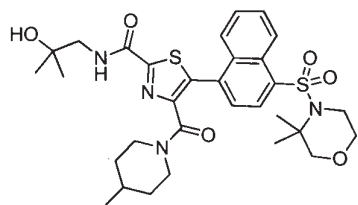
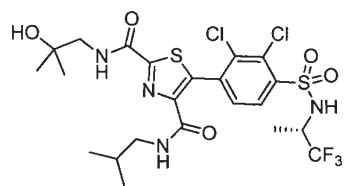
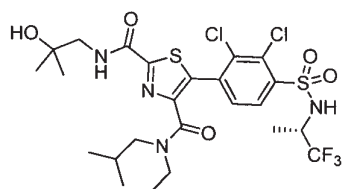
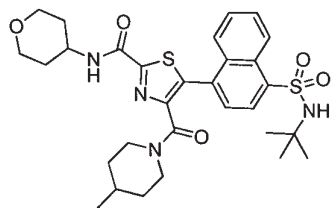
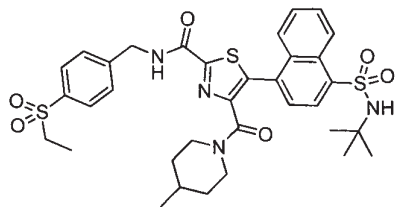
The following compounds can be prepared in the same manner by using the procedures as described above:

Structure

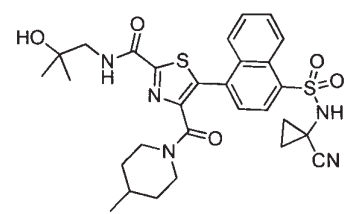
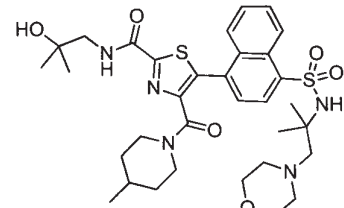
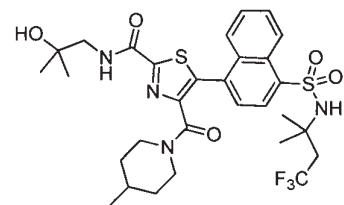
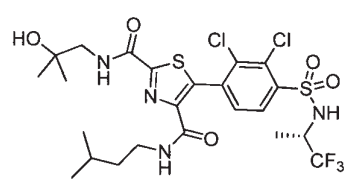
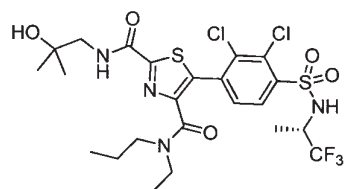
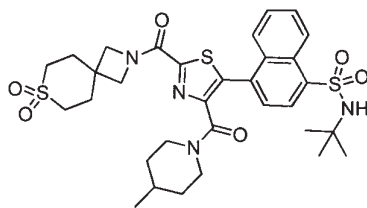
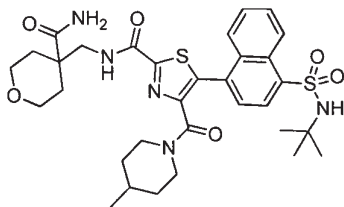
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Structure

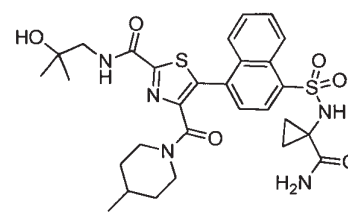
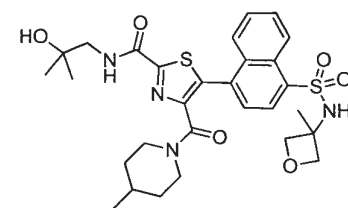
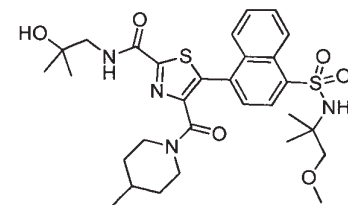
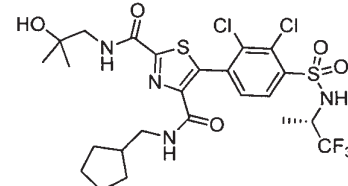
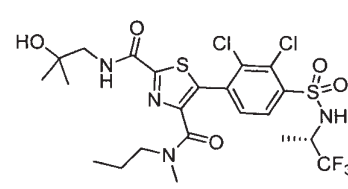
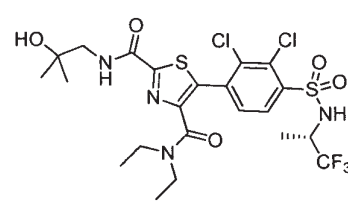
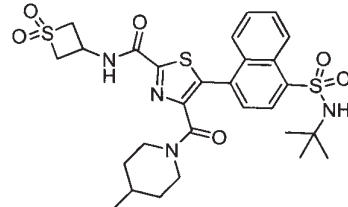
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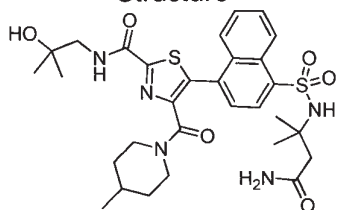
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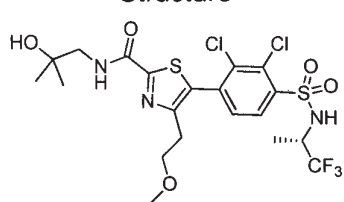
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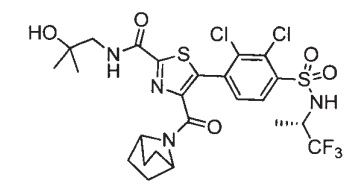
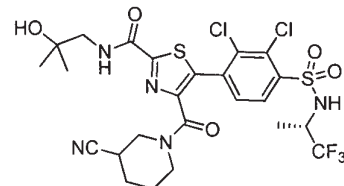
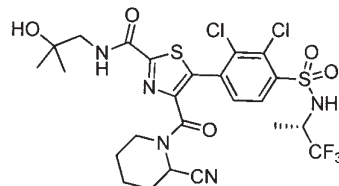
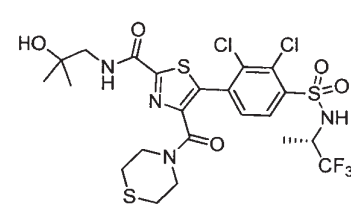
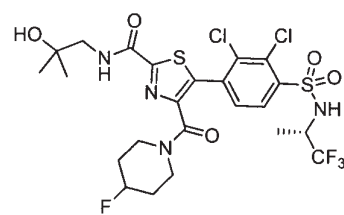
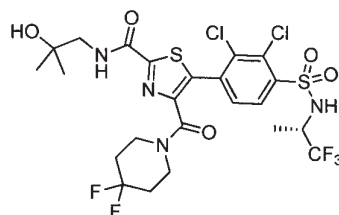
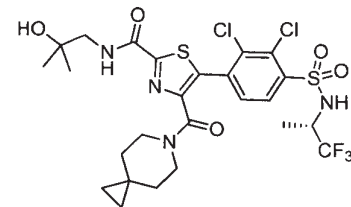
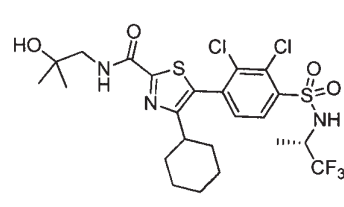
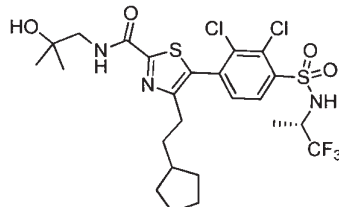
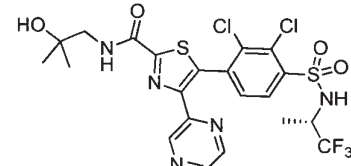
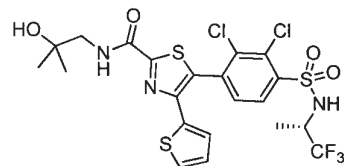
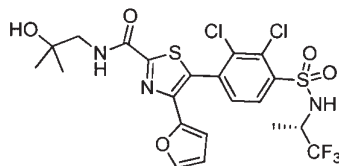
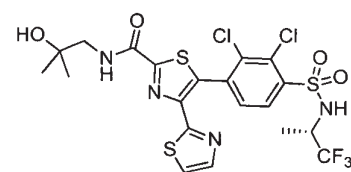
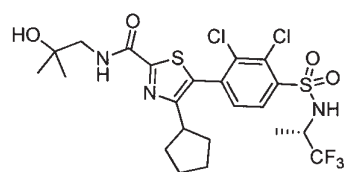
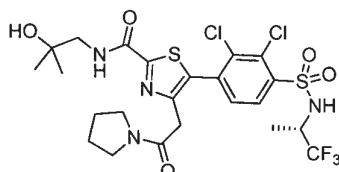
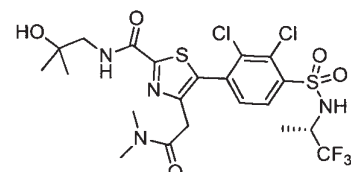
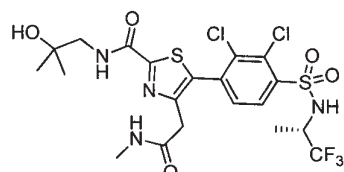
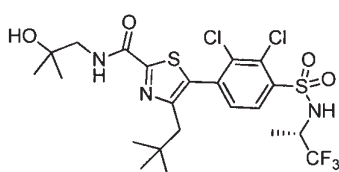
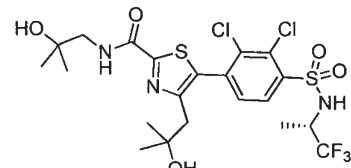
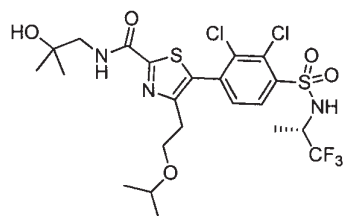
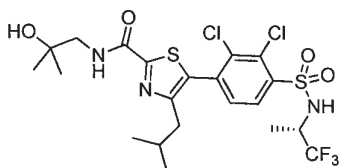
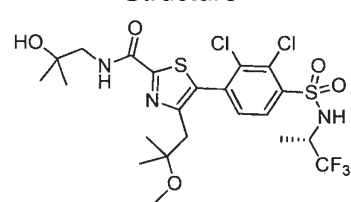
Structure

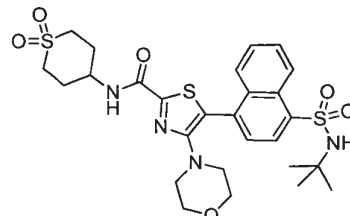
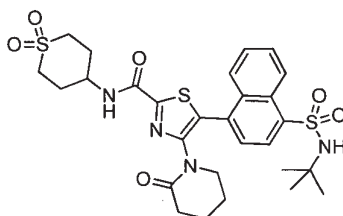
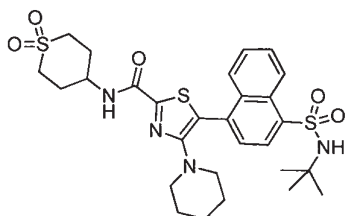
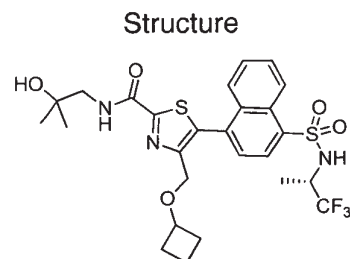
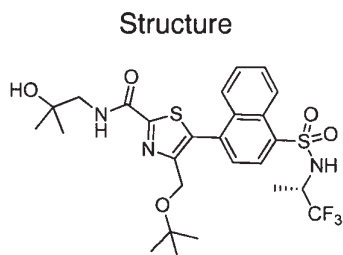
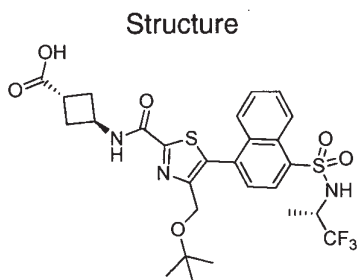


Structure



Structure





Protein Expression and Purification

Protein expression and purification was done as described in WO2010/049144.

TR-FRET Activity Assay

- 5 This method measures the ability of putative ligands to modulate the interaction between the purified bacterial expressed ROR γ ligand binding domain (LBD) and synthetic *N*-terminally biotinylated peptides which are derived from nuclear receptor coactivator proteins such as but not limited to SRC1 (NcoA1), SRC2 (NcoA2,TIF2), SRC3 (NcoA3), PGC1 α , PGC1 β , CBP, GRIP1, TRAP220, RIP140. The peptides used are listed in Table 1 below:

10 Table 1

Peptide Name (aa range)	DB entry Protein	DB entry DNA	Sequence
SRC1(676-700)	NP_003734	NM_003743.4	NH ₂ -CPSSHSSLTERHKILHRLQLQEGSPS-COOH
TRAP220(631-655)	NP_004765	NM_004774.3	NH ₂ -PVSSMAGNTKNHPMLMNLKDNPAQ-COOH
TIF2(628-651)	NP_006531	NM_006540.2	NH ₂ -GQSRLHDSKGQTKLLQLLTTKSDQ-COOH

- The ligand-binding domain (LBD) of ROR γ was expressed as fusion protein with GST in BL-21 (BL3) cells using the vector pDEST15. Cells were lysed by lysozyme-treatment and sonication, and the fusion proteins purified over glutathione sepharose (Pharmacia) according to the manufacturers instructions. For screening of compounds for their influence on the ROR γ -peptide interaction, the LANCE technology (Perkin Elmer) was applied. This method relies on the binding dependent energy transfer from a donor to an acceptor fluorophor attached to the binding partner of interest. For ease of handling and reduction of background from compound fluorescence LANCE technology makes use of generic fluorophore labels and time resolved detection assays were done in a final volume of 25 μ L in a 384 well plate, in a Tris-based buffer system (20 mM Tris-HCl pH 6.8; 60 mM KCl, 1 mM DTT; 5 mM MgCl₂; 35 ng/ μ L BSA), containing 20-60 ng/well recombinantly expressed ROR γ -LBD fused to GST, 200-600 nM *N*-terminally biotinylated peptide, 200 ng/well Streptavidin-xIAPC conjugate

(Prozyme) and 6-10 ng/well Eu W1024 – antiGST (Perkin Elmer). DMSO content of the samples was kept at 1%.

After generation of the Tris-based buffer system, the potentially ROR γ modulating ligands were diluted. After this step, protein, peptide and fluorescent acceptor and donor solutions were mixed in the Tris-based buffer system and have been added to the compound dilutions, after this addition of 'detection mix', the assay was equilibrated for one hour in the dark at rt in FIA-plates black 384 well (Corning). The LANCE signal was detected by a Perkin Elmer EnVision™ Multilabel Counter. The results were visualized by plotting the ratio between the emitted light at 665 nm and 615 nm. A basal level of ROR γ -peptide formation is observed in the absence of added ligand. Ligands that promote the complex formation induce a concentration-dependent increase in time-resolved fluorescent signal. Compounds which bind equally well to both monomeric ROR γ and to the ROR γ -peptide complex would be expected to give no change in signal, whereas ligands, which bind preferentially to the monomeric receptor would be expected to induce a concentration-dependent decrease in the observed signal.

To assess the antagonistic potential of the compounds, IC₅₀ values were determined using a Ligand Sensing Assay based on Time-resolved Fluorescence Energy Transfer (TR-FRET) as described above. The normalised TR-FRET assay values, using the following equation: $1000 * 665 \text{ nm measurement value} / 615 \text{ nm measurement value}$, were transferred to the program GraphPad Prism to generate graphs and dose response curves using the following equation:

Equation: Sigmoidal dose-response (variable slope)

$$Y = \text{Bottom} + (\text{Top} - \text{Bottom}) / (1 + 10^{((\text{LogEC}_{50} - X) * \text{HillSlope}))}$$

X is the logarithm of the concentration. Y is the response.

Y starts at Bottom and goes to Top with a sigmoidal shape.

This is identical to the "four parameter logistic equation". The IC₅₀ values are calculated using this equation. Examples listed below do reduce the signal in the TR-FRET assay in a dose dependent manner. The Examples of the present invention usually have an inhibition activity (IC₅₀ FRET) ranging from below 100 nM to about 20 μ M. The ROR γ modulating compounds of the invention desirably have an inhibition in the TR-FRET Activity Assay ranging from below 100 nM to about 1 μ M. Table 3 lists the pIC₅₀-value of compounds of the invention. It is understood that the data illustrated below may have reasonable variation depending on the specific conditions and procedures used by the person conducting the test.

ROR γ Gal4 Reporter Gene Assay

Determination of a ligand mediated Gal4 promoter driven transactivation to quantify ligand binding to ROR γ was performed as follows: DNA encoding three different ROR γ protein

fragments was cloned into vector pCMV-BD (Stratagene). Expression was under control of a CMV promoter and as fusion to the DNA-binding domain of the yeast protein GAL4. The amino acid boundaries of the three proteins and the respective database entries are listed in Table 2. Other vectors used were pFR-Luc (Stratagene) as regulated reporter plasmid. pFR-Luc contains a synthetic promoter with five tandem repeats of the yeast GAL4 binding sites that control expression of the *Photinus pyralis* (American firefly) luciferase gene. In order to improve experimental accuracy the plasmid pRL-CMV was cotransfected. pRL-CMV contains the constitutive CMV promoter, controlling the expression of the *Renilla reniformis* luciferase.

Table 2

construct name	aa borders (RefSeq)	Ref sequence ID
hRORg-LBD	aa259-518	NP_005051.2
hRORgt	aa1-497	NP_001001523 (RORg, t isoform, 497aa)
mRORg-LBD	aa264-516	NP_035411

All Gal4 reporter gene assays were done in 293T cells (DSMZ (German Collection of Microorganisms and Cell Cultures), Braunschweig, Germany, ACC635) grown in Minimum Essential Medium (MEM) with Phenol Red. The medium is supplemented with 10% fetal bovine serum, 0.1 mM nonessential amino acids, 1 mM sodium pyruvate, 1% Glutamax and 100 units Penicilin/Streptavidin per mL at 37°C in 5% CO₂.

For the assay, 5×10^5 cells were plated per well in 96well plates in 100 μ L per well, incubated over night at 37°C in 5% CO₂. The following day, medium was discarded and the cells were transiently transfected using 20 μ L per well of a OptiMEM - PEI-based transfection-reagent (Sigma-Aldrich, 408727) including the three plasmids described above. About 4 h after addition of the transfection solution, fresh Minimal Essential Medium (MEM, same composition as used for plating cells, but without serum) was added. Then compound stocks, prediluted in MEM (same composition as used for plating cells) were added (final vehicle concentration not exceeding 0.1%).

Cells were incubated for additional 16 h before firefly (FF) and renilla (REN) luciferase activities were measured sequentially in the same cell extract using a Dual-Light-Luciferase-Assay system (Dyer et al., Anal. Biochem. 2000, 282:158). All experiments were done at least in triplicates.

Applying the Gal4 reporter gene assay as described above, the Examples of the present invention usually have an inhibition activity (IC₅₀ FF resp. IC₅₀ RENnorm) ranging from below 10 nM to about 20 μ M, and typically, from about 10 nM to about 1 μ M. The ROR γ modulating

compounds of the invention desirably have an inhibition in the Gal4 reporter gene assay ranging from below 10 nM to about 1 μ M. Table 3 list the pIC₅₀-value of typical examples of compounds of the invention that have an ROR γ activity in the Gal4 reporter gene assay for firefly (FF) and renilla normalised (RENnorm) luciferase measurements (nt = not tested). It is understood that the data illustrated below may have reasonable variation depending on the specific conditions and procedures used by the person conducting the test. The efficacy was determined in comparison to the ROR γ t inhibitor T0901317 (equals 100%) and the pIC₅₀-value is underlined, when the efficacy of the compound is below 50% of the reference.

Table 3**10 Table 3**

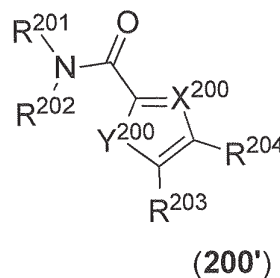
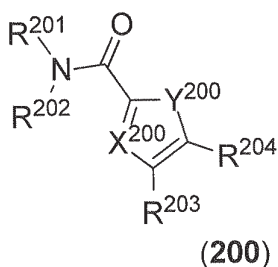
Ex. #	pIC ₅₀ (FRET/FF/REN)	Ex. #	pIC ₅₀ (FRET/FF/REN)	Ex. #	pIC ₅₀ (FRET/FF/REN)
1	6.5/5.8/5.8	2	5.9/ <u>6.1</u> / <u>6.0</u>	3	5.1/<4.7/<4.7
4	6.8/6.4/6.4	5	6.7/6.3/6.1	6	6.7/6.2/6.3
6/1	6.5/7.5/7.7	6/2	7.0/7.5/7.7	6/3	6.5/8.5/8.7
6/4	6.7/8.7/8.7	6/5	6.6/8.5/8.7	6/6	6.7/9.0/9.0
6/7	6.7/7.9/8.0	6/8	6.3/8.2/8.2	6/9	6.4/6.7/6.4
6/10	7.0/8.7/8.7	6/11	7.2/9.0/9.0	6/12	6.9/8.7/8.7
6/13	6.5/8.0/8.0	6/14	6.8/8.7/8.7	6/15	5.9/7.5/7.6
6/16	5.9/7.2/ <u>7.6</u>	6/17	6.2/8.0/8.0	6/18	7.0/8.5/8.7
6/19	6.8/8.5/8.5	6/20	6.9/8.7/8.7	6/21	6.8/8.7/8.7
6/22	6.8/7.7/7.7	6/23	6.6/7.5/7.6	6/24	7.3/7.9/8.0
6/25	5.8/6.7/6.7	6/26	6.6/7.7/7.8	6/27	6.7/7.7/7.7
6/28	6.1/7.7/7.7	6/29	7.2/9.0/9.0	6/30	7.2/8.7/8.7
6/31	7.3/8.0/8.0	6/32	6.9/8.0/8.2	6/33	6.6/7.9/8.0
6/34	7.2/8.5/8.5	6/35	7.0/7.5/7.5	6/36	6.3/7.4/7.4
6/37	6.1/6.9/6.9	6/38	6.8/7.8/7.9	6/39	6.4/8.2/8.2
6/40	7.0/8.2/8.3	6/41	7.3/8.0/8.2	6/42	7.2/8.2/8.4
6/43	7.0/8.7/8.7	6/44	7.4/7.8/8.0	6/45	7.1/7.9/8.0
6/46	nt/8.1/8.1	6/47	nt/8.2/8.2	6/48	nt/8.1/8.1
6/49	5.7/7.3/7.4	6/50	nt/7.6/7.7	6/51	6.3/8.4/8.4
6/52	nt/6.9/6.9	6/53	6.6/7.1/7.4	6/54	6.3/6.8/6.9
6/55	nt/8.0/8.2	6/56	nt/8.1/8.2	6/57	nt/7.9/8.2
6/58	nt/8.7/8.7	6/59	nt/7.6/7.8	6/60	nt/8.5/8.7
6/61	nt/8.3/8.3	6/62	nt/7.5/7.5	6/63	nt/9.2/8.9
6/64	nt/8.9/9.0			7	6.3/7.0/7.0
7/1	6.1/6.8/6.9	7/2	6.2/7.5/7.6	7/3	6.4/7.2/7.3
7/4	6.6/9.0/9.0	7/5	6.3/7.0/7.1	7/6	6.2/7.1/7.2
7/7	6.9/8.7/8.7	7/8	6.6/9.0/9.0	7/9	6.3/8.7/9.0
7/10	6.3/8.5/8.7	7/11	5.9/7.4/7.4	7/12	6.2/8.0/8.2
7/13	6.5/8.4/8.4	7/14	5.8/8.5/8.7	7/15	6.7/8.7/8.5
7/16	6.5/8.5/8.5	7/17	6.5/8.0/8.0	7/18	6.4/7.4/7.4
7/19	nt/7.7/7.9	7/20	<4.7/6.6/6.6	7/21	5.7/6.9/6.9
7/22	<4.7/6.5/6.2	7/23	<4.7/6.8/6.7	7/24	5.7/6.3/6.2
7/25	<u>6.2</u> /6.6/6.5	7/26	6.8/7.7/7.9	7/27	6.5/6.9/6.9

Ex. #	pIC ₅₀ (FRET/FF/REN)	Ex. #	pIC ₅₀ (FRET/FF/REN)	Ex. #	pIC ₅₀ (FRET/FF/REN)
8	7.0/7.3/7.5	8/1	7.0/7.8/7.9	8/2	6.7/7.4/7.7
8/3	6.4/7.5/7.6	8/4	6.5/8.2/8.4	8/5	6.4/8.5/8.7
8/6	7.0/8.2/8.3	8/7	6.3/8.7/9.0	8/8	6.3/7.2/7.1
8/9	6.1/6.9/6.9	8/10	6.2/6.8/6.8	8/11	nt/9.0/9.0
8/12	nt/8.9/8.9			9	7.2/8.0/8.3
9/1	6.5/7.4/7.4	9/2	6.9/8.0/8.0	9/3	6.4/7.2/7.4
9/4	6.5/7.1/7.1	9/5	6.7/7.8/7.9	9/6	6.1/7.5/7.5
9/7	6.2/7.4/7.5	9/8	6.5/7.1/7.1	9/9	<u>5.4</u> /6.9/7.0
9/10	6.3/7.2/7.2	9/11	6.6/8.5/8.5		
		10	5.9/6.9/7.0	10/1	6.2/7.0/7.1
10/2	6.6/7.3/7.4	10/3	nt/7.9/8.0	10/4	nt/7.9/7.9
12	5.5/<4.7/<4.7	13	7.0/6.5/6.7	13/1	6.3/6.6/6.6
13/2	6.5/6.7/6.8	13/3	6.6/7.5/7.7	14	6.7/7.6/7.7
14/1	6.2/7.1/7.1	14/2	6.5/7.4/7.4	14/3	6.6/6.4/6.4
14/4	<u>6.2</u> /6.4/6.3	14/5	6.3/6.6/6.6	14/6	nt/9.0/9.0
14/7	nt/7.6/7.7				
15	6.6/8.3/8.4	15/1	6.7/8.0/8.0	15/2	6.6/7.3/7.3
15/3	6.9/7.9/7.9	15/4	7.3/8.7/9.0	15/5	6.9/8.5/8.4
15/6	7.3/8.1/8.2	15/7	7.2/8.3/8.4	15/8	nt/8.3/8.4
15/9	6.4/7.8/7.9				
16	7.2/8.5/8.5	17	5.0/<4.7/<4.7	17/1	<u>5.6</u> /6.1/6.5
17/2	nt/5.7/5.9	18	6.9/8.1/8.0	19	5.4/6.4/6.6
19/1	6.1/6.7/6.7	19/2	6.1/7.0/7.0	19/3	6.8/7.1/7.1
19/4	6.0/7.3/7.2	19/5	6.4/7.8/8.0	19/6	6.4/7.7/7.7
19/7	5.8/6.8/6.8	19/8	7.0/7.7/7.8	19/9	6.3/7.0/7.1
19/10	6.7/8.4/8.5	19/11	nt/7.6/7.7	19/12	6.1/6.8/6.7
19/13	6.5/6.9/6.9	19/14	6.4/6.8/6.9		
20	nt/8.7/8.9	21	7.0/8.1/8.2	21/1	6.6/7.5/7.4
21/2	6.8/8.4/8.5	21/3	6.4/8.0/8.3	21/4	6.9/8.2/8.4
21/5	6.0/7.8/7.8	21/6	6.3/7.6/7.8	21/7	nt/8.0/8.2
21/8	nt/7.7/7.8	21/9	6.2/7.3/7.4	21/10	5.9/6.7/6.7
21/11	nt/8.0/8.2	21/12	nt/8.0/8.2	21/13	6.3/7.9/7.9
21/14	nt/8.3/8.4	21/15	nt/7.7/7.7	21/16	nt/8.4/8.4
21/17	nt/8.1/8.2	21/18	nt/8.0/8.1	21/19	nt/7.9/7.9
21/20	nt/7.7/7.7	21/21	nt/7.7/7.8	21/22	nt/7.5/7.6
21/23	nt/8.7/8.6	21/24	nt/7.5/7.6	21/25	nt/7.7/7.8
22	6.4/7.1/7.1	22/1	6.4/7.5/7.5	22/2	6.4/7.5/7.6
23	6.2/8.2/8.2	24	6.5/7.5/7.5	25	nt/ <u>6.1</u> / <u>6.1</u>
25/1	nt/8.9/8.8	25/2	nt/9.0/9.0		
100	6.6/ <u>5.8</u> / <u>5.8</u>	100/1	5.9/6.3/6.3	100/2	5.5/6.4/6.3
100/3	6.7/7.8/7.9	100/4	6.6/7.1/7.3	100/5	6.3/8.1/8.2
100/6	6.4/8.5/8.4	100/7	6.6/7.7/7.9	100/8	6.5/8.0/8.2
100/9	6.3/8.5/8.5	100/10	6.4/7.2/7.4	100/11	6.8/7.1/7.3
100/12	4.8/5.9/6.1	100/13	6.1/7.0/7.1	100/14	5.8/7.9/7.9
100/15	6.4/7.4/7.5	100/16	6.6/8.4/8.2	100/17	6.1/7.1/7.0
100/18	6.9/6.9/6.9	100/19	5.9/6.6/6.6	100/20	6.0/6.8/7.0

Ex. #	pIC ₅₀ (FRET/FF/REN)	Ex. #	pIC ₅₀ (FRET/FF/REN)	Ex. #	pIC ₅₀ (FRET/FF/REN)
100/21	nt/7.2/7.1	100/22	5.9/6.8/7.0	100/23	6.1/8.3/8.4
100/24	nt/7.5/7.7	100/25	6.6/8.4/8.2	100/26	6.4/7.4/7.5
100/27	6.1/7.1/7.0	100/28	nt/7.1/7.2		
101	6.0/<4.7/<4.7	102	6.0/7.3/7.4	102/1	6.1/6.7/6.7
103	6.3/7.2/7.3	103/1	6.2/7.4/7.4	103/2	nt/6.4/6.6
103/3	nt/6.6/6.6	104	6.6/7.5/7.9		
200	6.6/7.5/7.8	200/1	<u>7.1/7.4/7.8</u>	201	6.0/ <u>6.5/6.6</u>
202	7.2/7.9/8.0	203	6.1/<4.7/<4.7		
205	7.0/8.7/8.7	206	5.9/6.3/6.2	207	5.4/ <u>6.4/6.5</u>
207/1	6.0/6.2/6.1	208	6.5/6.3/6.3	209	6.4/6.2/6.2
211	<u>5.8/6.3/6.4</u>				
300	7.1/8.2/8.4	300/1	7.2/7.8/7.9	300/2	6.9/8.2/8.2
300/3	6.2/6.7/6.9	300/4	5.9/6.8/6.9	300/5	7.0/7.4/7.5
300/6	6.7/6.9/6.8	300/7	nt/7.7/7.9	300/8	nt/7.1/7.2
300/9	nt/7.9/7.9	300/10	nt/7.2/7.3	300/11	nt/8.0/8.2
300/12	nt/6.1/6.2	300/13	nt/6.4/6.6	300/14	nt/8.2/8.2
300/15	nt/7.3/7.4	300/16	nt/6.0/6.1	300/17	nt/8.0/8.0
300/18	nt/7.577.6				
301	nt/7.8/7.9	301/1	nt/8.5/8.5	301/2	nt/7.7/7.8
302	nt/7.3/ <u>7.5</u>	303	nt/7.7/7.7	304	6.0/7.1/7.2
304/1	5.8/6.6/6.9	304/2	5.9/7.6/7.5	304/3	5.9/7.6/7.5
304/4	5.8/7.4/7.3	304/5	5.9/7.4/7.3	304/6	nt/6.6/6.8
304/7	6.1/7.3/7.3	304/8	6.0/6.9/6.9	304/9	nt/7.3/7.4
304/10	nt/7.5/7.5	304/11	5.9/7.2/7.3	304/12	nt/7.7/7.7
304/13	nt/7.6/7.7	304/14	nt/7.5/7.6	304/15	nt/7.6/7.7
304/16	nt/6.6/6.6	304/17	nt/7.2/7.2	304/18	nt/7.5/7.7
304/19	nt/7.4/7.5	304/20	nt/7.4/ <u>7.7</u>	304/21	nt/7.4/7.4
304/22	nt/5.8/5.8	304/23	nt/7.5/7.7	304/24	nt/6.6/6.7
304/25	nt/8.0/ <u>7.6</u>	304/26	nt/8.0/7.9	304/27	nt/7.6/7.5
305	nt/6.6/7.2	304/1	nt/6.5/6.6	306	nt/5.6/5.6
307	nt/8.2/8.3	307/1	nt/8.4/8.5		

Claims:

1. A compound represented by Formula (200) and Formula (200')



an enantiomer, diastereomer, tautomer, *N*-oxide, solvate, formulation and pharmaceutically acceptable salt thereof,

wherein

X^{200} is N;

Y^{200} is S;

R^{201} and R^{202} are independently selected from H, C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl, C_{3-10} -cycloalkyl, C_{3-10} -heterocycloalkyl, C_{1-10} -alkylene- C_{3-10} -cycloalkyl, C_{1-10} -alkylene- C_{3-10} -heterocycloalkyl, C_{1-10} -alkylene-(5-membered heteroaryl), C_{1-10} -alkylene-(6-membered aryl), C_{1-10} -alkylene-(6-membered heteroaryl), SO_2 - C_{1-10} -alkyl, wherein alkyl, alkenyl, alkynyl, alkylene, cycloalkyl, heterocycloalkyl, aryl and heteroaryl is unsubstituted or substituted with 1 to 7 substituents independently selected from the group consisting of oxo, CN, OR^{211} , O - C_{2-6} -alkylene- OR^{211} , C_{1-6} -alkyl, halo- C_{1-6} -alkyl, halogen, CO_2R^{211} , $CONR^{211}R^{212}$, $CONR^{211}SO_2R^{211}$, COR^{211} , SO_xR^{211} , SO_3H , $SO_2NR^{211}R^{212}$, $NR^{211}COR^{211}$, $NR^{211}SO_2R^{211}$, $NR^{211}-CO-NR^{211}R^{212}$, $NR^{211}-SO_2-NR^{211}R^{212}$, C_{3-10} -cycloalkyl, O - C_{3-10} -cycloalkyl, C_{3-10} -heterocycloalkyl, O - C_{3-10} -heterocycloalkyl and $NR^{211}R^{212}$;

or R^{201} and R^{202} when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing 1 or 2 heteroatoms selected from O, S or N, wherein the ring is unsubstituted or substituted with 1 to 4 substituents independently selected from the group consisting of halogen, oxo, CN, OR^{211} , SO_xR^{211} , SO_3H , $NR^{211}SO_2R^{211}$, $SO_2NR^{211}R^{212}$, C_{0-6} -alkylene- CO_2R^{211} , $CONR^{211}R^{212}$, $CONR^{211}SO_2R^{211}$, COR^{211} , $NR^{211}-CO-R^{211}$, $NR^{211}-CO-NR^{211}R^{212}$, $NR^{211}-SO_2-NR^{211}R^{212}$, $NR^{211}R^{212}$, C_{1-6} -alkyl, halo- C_{1-6} -alkyl, hydroxy- C_{1-6} -alkyl, C_{3-8} -cycloalkyl, O - C_{3-8} -cycloalkyl, C_{3-8} -heterocycloalkyl and O - C_{3-8} -heterocycloalkyl,

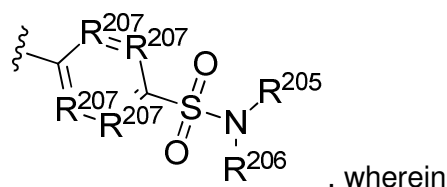
wherein cycloalkyl and heterocycloalkyl are unsubstituted or substituted with 1 to 4 substituents independently selected from the group consisting of halogen, C₁₋₃-alkyl, halo-C₁₋₃-alkyl, OH, O-C₁₋₃-alkyl, O-halo-C₁₋₃-alkyl, SO₂-C₁₋₃-alkyl, COOH and oxo;

R²⁰³ is selected from C₁₋₁₀-alkyl, fluoro-C₁₋₁₀-alkyl, C₁₋₆-alkylene-C₃₋₁₀-cycloalkyl, C₁₋₆-alkylene-C₃₋₁₀-heterocycloalkyl, C₁₋₆-alkylene-(6- to 10-membered aryl), and C₁₋₆-alkylene-(5- to 10-membered heteroaryl),

wherein alkyl, alkylene, cycloalkyl, heterocycloalkyl, aryl and heteroaryl is unsubstituted or substituted with 1 to 6 substituents independently selected from the group consisting of oxo, halogen, CN, C₁₋₆-alkyl, halo-C₁₋₆-alkyl, C₃₋₆-cycloalkyl, C₃₋₆-heterocycloalkyl, OR²¹², CO₂R²¹², CONR²¹²R²¹² and COR²¹²; and

wherein optionally one CH₂ unit in alkyl or alkylene can be replaced by O, SO_x, NH or N(C₁₋₃-alkyl);

R²⁰⁴ is



R²⁰⁵ and R²⁰⁶ is independently selected from H, C₁₋₆-alkyl, halo-C₁₋₆-alkyl, C₀₋₆-alkylene-C₃₋₈-cycloalkyl, C₀₋₆-alkylene-C₃₋₈-heterocycloalkyl, 5- or 6-membered heteroaryl and 6-membered aryl, wherein alkyl, alkylene, cycloalkyl, heterocycloalkyl, aryl and heteroaryl are unsubstituted or substituted with 1 to 6 substituents independently selected from the group consisting of halogen, CN, OH, oxo, C₁₋₃-alkyl, halo-C₁₋₃-alkyl, O-C₁₋₃-alkyl, O-halo-C₁₋₃-alkyl and SO₂-C₁₋₃-alkyl, NR²¹¹R²¹², CO₂R²¹² and CONR²¹¹R²¹²;

and optionally wherein R²⁰⁵ and R²⁰⁶ when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing 1 or 2 heteroatoms selected from O, S or N, wherein the ring is unsubstituted or substituted with 1 to 4 substituents independently selected from the group consisting of fluoro, OH, oxo, C₁₋₄-alkyl and halo-C₁₋₄-alkyl;

R²⁰⁷ is independently selected from N and CR²⁰⁸; or

two adjacent R²⁰⁷ form a 5- or 6-membered unsaturated or partially saturated ring containing carbon atoms and optionally containing 1 or 2 heteroatoms selected from O, S or N, wherein the ring is unsubstituted or substituted with 1 to 4 substituents independently selected from the group consisting of halogen, OH, oxo, C₁₋₄-alkyl and fluoro-C₁₋₄-alkyl;

R²⁰⁸ is independently selected from H, halogen, CN, C₁₋₆-alkyl, fluoro-C₁₋₆-alkyl, C₁₋₄-alkylene-OH, C₁₋₄-alkylene-O-C₁₋₃-alkyl, C₁₋₄-alkylene-O-fluoro-C₁₋₃-alkyl, OH, O-C₁₋₆-alkyl, O-fluoro-C₁₋₆-alkyl and C₃₋₁₀-cycloalkyl,

wherein alkylene is unsubstituted or substituted with 1 to 3 substituents selected from F and cycloalkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of F, C₁₋₃-alkyl and fluoro-C₁₋₃-alkyl;

R^{211} is independently selected from H, C_{1-6} -alkyl, C_{0-6} -alkylene- C_{3-10} -cycloalkyl and C_{0-6} -alkylene- C_{3-10} -heterocycloalkyl,

wherein alkyl, alkylene, cycloalkyl and heterocycloalkyl is unsubstituted or substituted with 1 to 6 substituents independently selected from the group consisting of halogen, CN, OH, oxo, C_{1-3} -alkyl, halo- C_{1-3} -alkyl, O- C_{1-3} -alkyl, O-halo- C_{1-3} -alkyl, NH_2 , $NH(C_{1-3}$ -alkyl), $N(C_{1-3}$ -alkyl)₂, C_{3-6} -heterocycloalkyl, C_{3-6} -cycloalkyl and SO_2 - C_{1-3} -alkyl,

wherein cycloalkyl and heterocycloalkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of F, OH, oxo, CH_3 and CF_3 ;

R^{212} is independently selected from H, C_{1-6} -alkyl, halo- C_{1-6} -alkyl and C_{3-6} -cycloalkyl;

x is independently selected from 0, 1 and 2.

2. The compound according to claim 1 wherein

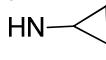
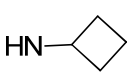
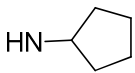
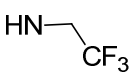
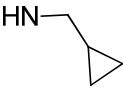
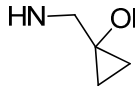
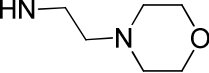
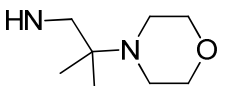
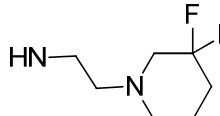
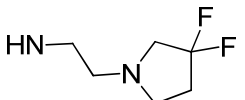
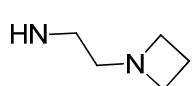
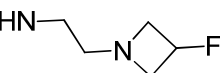
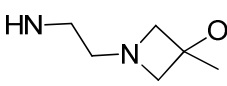
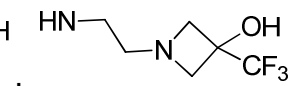
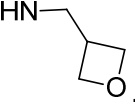
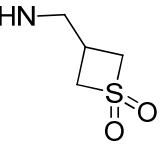
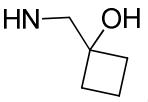
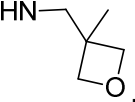
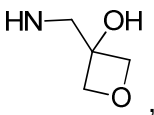
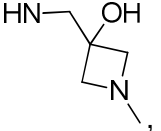
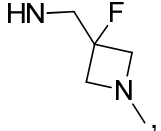
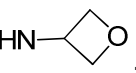
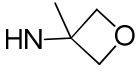
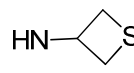
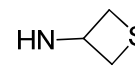
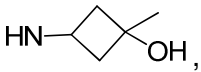
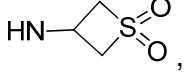
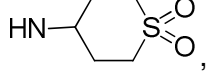
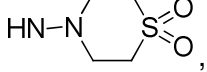
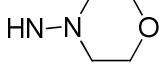
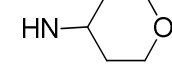
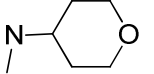
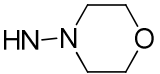
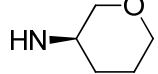
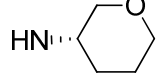
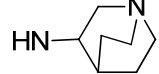
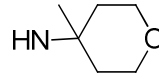
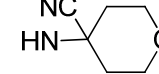
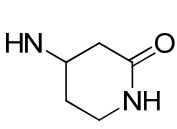
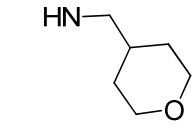
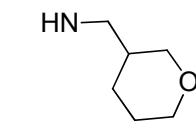
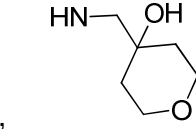
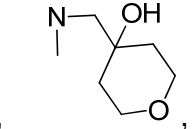
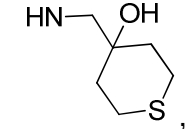
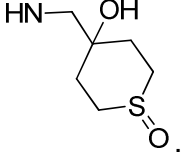
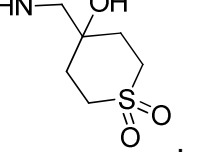
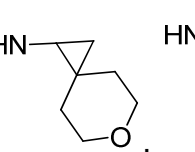
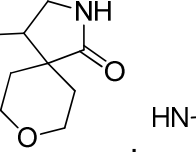
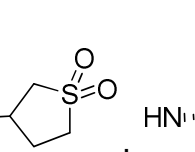
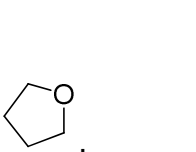
R^{201} is selected from H, C_{1-10} -alkyl, C_{3-10} -cycloalkyl, C_{3-10} -heterocycloalkyl, C_{1-10} -alkylene- C_{3-10} -cycloalkyl, C_{1-10} -alkylene- C_{3-10} -heterocycloalkyl, C_{1-10} -alkylene-(5-membered heteroaryl), C_{1-10} -alkylene-(6-membered aryl), C_{1-10} -alkylene-(6-membered heteroaryl) and SO_2 - C_{1-10} -alkyl, wherein alkyl, alkenyl, alkynyl, alkylene, cycloalkyl, heterocycloalkyl, aryl and heteroaryl is unsubstituted or substituted with 1 to 7 substituents independently selected from the group consisting of oxo, CN, OR^{211} , O- C_{2-6} -alkylene- OR^{211} , C_{1-6} -alkyl, halo- C_{1-6} -alkyl, halogen, CO_2R^{211} , $CONR^{211}R^{212}$, $CONR^{211}SO_2R^{211}$, COR^{211} , SO_xR^{211} , SO_3H , $SO_2NR^{211}R^{212}$, $NR^{211}COR^{211}$, $NR^{211}SO_2R^{211}$, $NR^{211}-CO-NR^{211}R^{212}$, $NR^{211}-SO_2-NR^{211}R^{212}$, C_{3-10} -cycloalkyl, O- C_{3-10} -cycloalkyl, C_{3-10} -heterocycloalkyl, O- C_{3-10} -heterocycloalkyl and $NR^{211}R^{212}$;

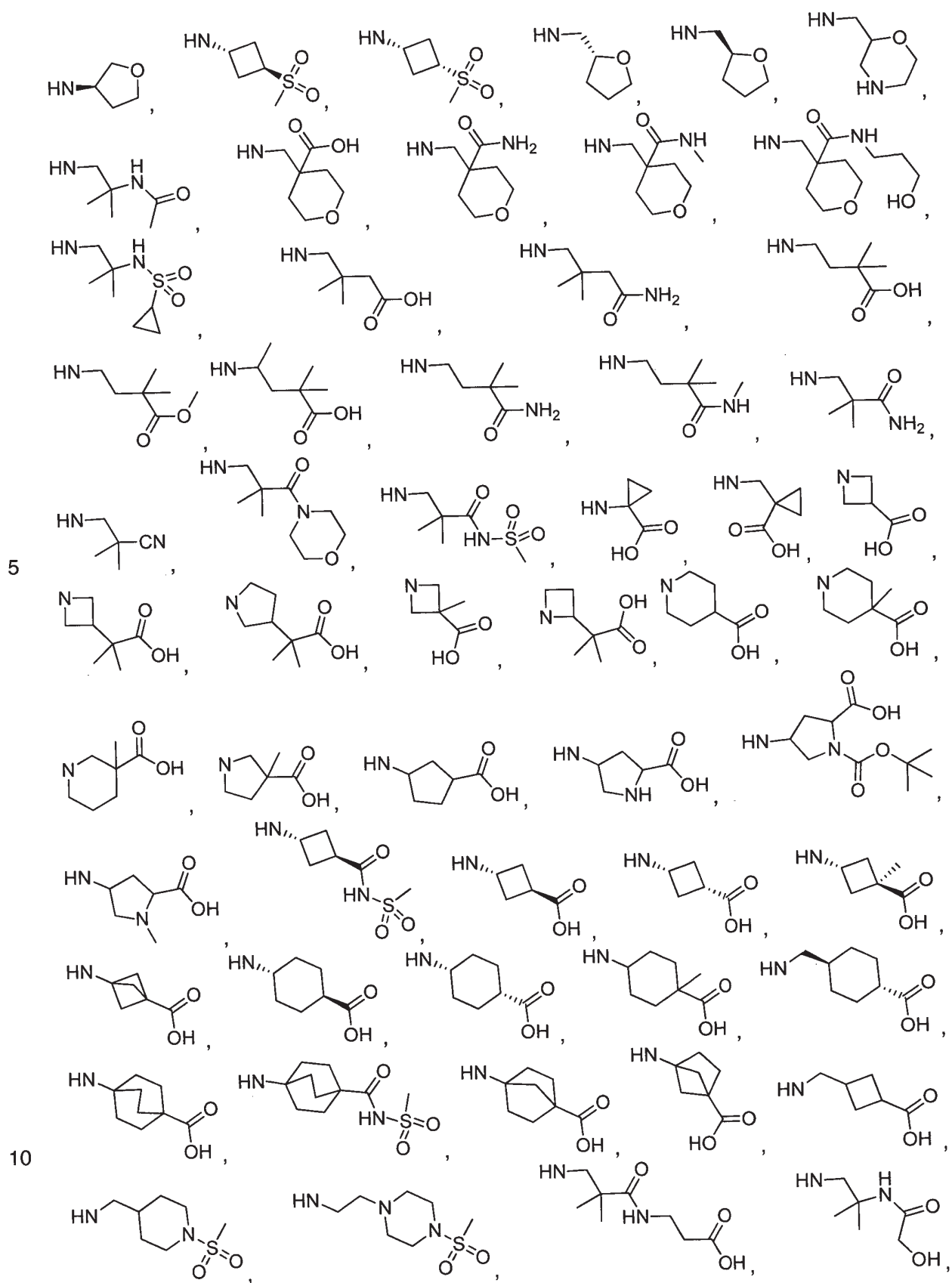
R^{202} is selected from H, C_{1-6} -alkyl, halo- C_{1-6} -alkyl and hydroxy- C_{1-6} -alkyl;

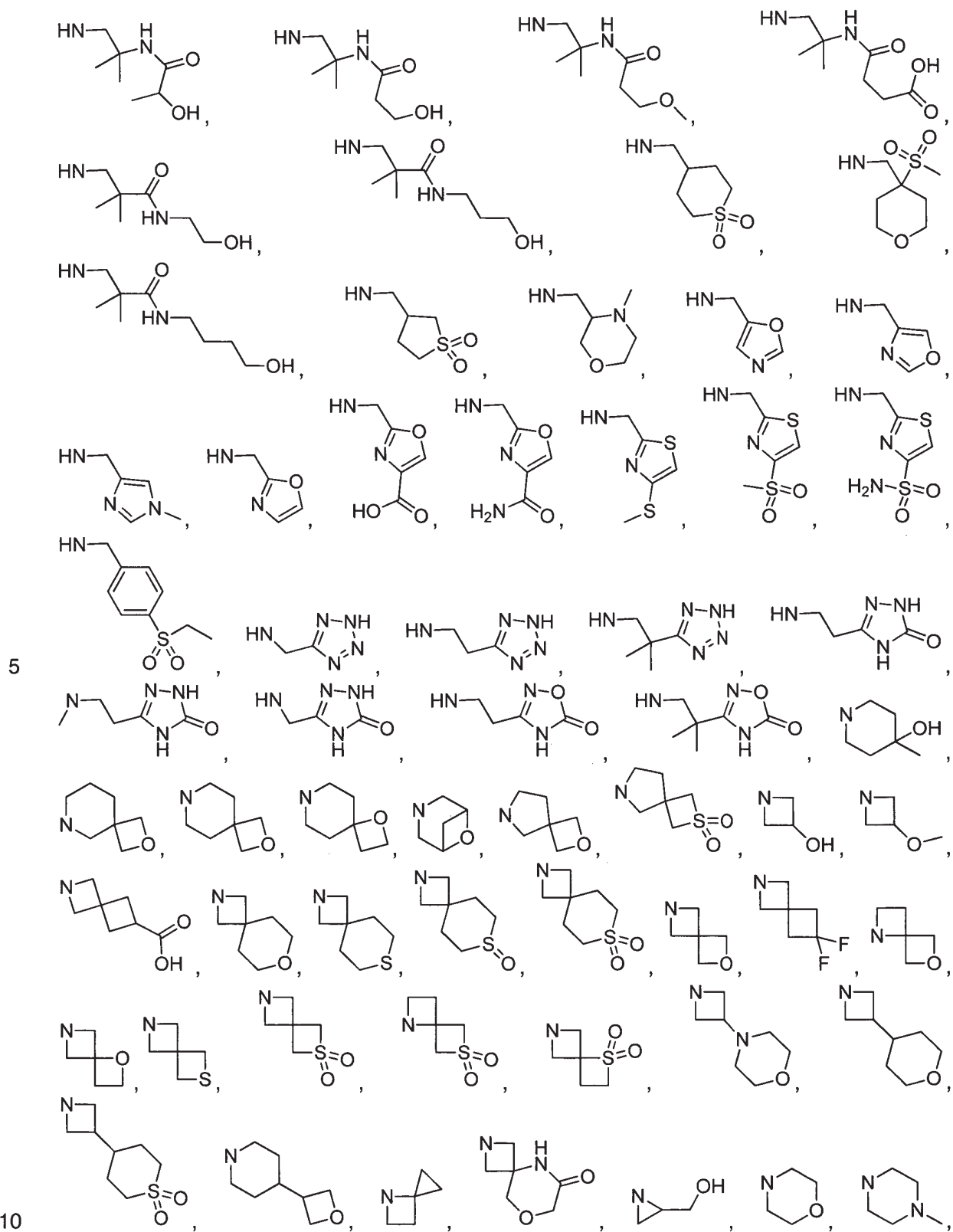
or R^{201} and R^{202} when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing 1 or 2 heteroatoms selected from O, S or N, wherein the ring is unsubstituted or substituted with 1 to 4 substituents independently selected from the group consisting of halogen, oxo, CN, OR^{211} , SO_xR^{211} , SO_3H , $NR^{211}SO_2R^{211}$, $SO_2NR^{211}R^{212}$, C_{0-6} -alkylene- CO_2R^{211} , $CONR^{211}R^{212}$, $CONR^{211}SO_2R^{211}$, COR^{211} , $NR^{211}-CO-R^{211}$, $NR^{211}-CO-NR^{211}R^{212}$, $NR^{211}-SO_2-NR^{211}R^{212}$, $NR^{211}R^{212}$, C_{1-6} -alkyl, halo- C_{1-6} -alkyl, hydroxy- C_{1-6} -alkyl, C_{3-8} -cycloalkyl, O- C_{3-8} -cycloalkyl, C_{3-8} -heterocycloalkyl and O- C_{3-8} -heterocycloalkyl,

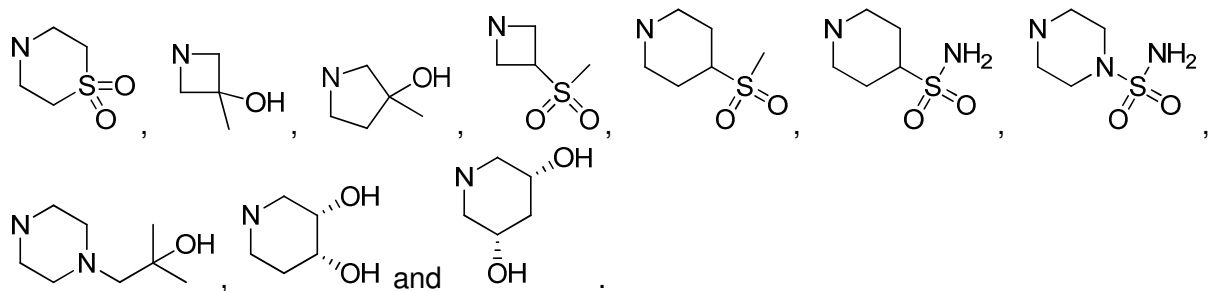
wherein cycloalkyl and heterocycloalkyl are unsubstituted or substituted with 1 to 4 substituents independently selected from the group consisting of halogen, C₁₋₃-alkyl, halo-C₁₋₃-alkyl, OH, O-C₁₋₃-alkyl, O-halo-C₁₋₃-alkyl, SO₂-C₁₋₃-alkyl, COOH and oxo.

3. The compound according to any of claims 1 to 2 wherein NR²⁰¹R²⁰² is selected from

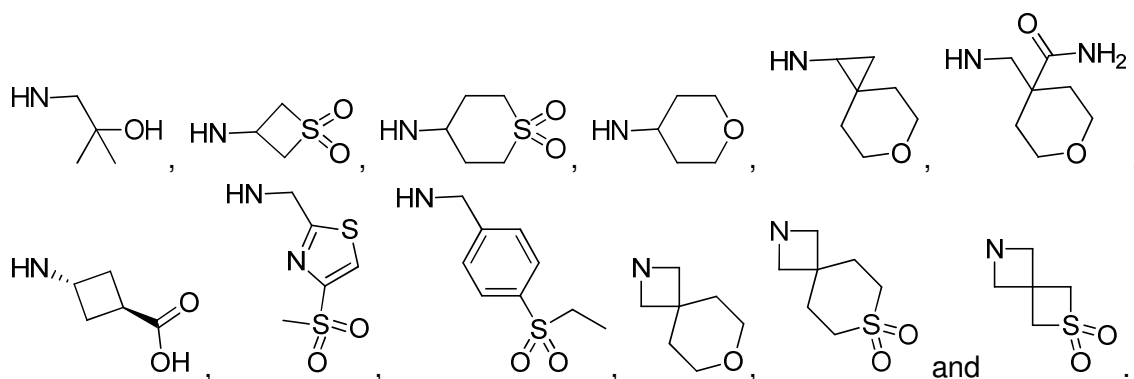
NHMe, NH*Et*, NH*Pr*, NH*t*Bu, NHCH₂CONH₂, NHCH₂CONMe₂, NHCH₂CH₂OH, NHCH₂CH₂OMe, NHCH₂CH₂SO₂Me, NHCH₂CH₂SO₂NH₂, NH(CH₂)₃OH, NH(CH₂)₃OMe, NH(CH₂)₄OH, NH(CH₂)₄OMe, NH(CH₂)₅OH, NH(CH₂)₂CO₂H, NH(CH₂)₃CO₂H, NH(CH₂)₄CO₂H, NH(CH₂)₅CO₂H, NHCH₂CH(CF₃)OH, NHCH₂C(Me)(CF₃)OH, NHCH₂CMe₂OH, NHCH₂CH₂CMe₂OH, NHCH₂CMe₂NHCH₂CF₃, NHCH(Me)CMe₂OH, NHCH₂CMe₂OMe, NHCH₂CMe₂CO₂H, NHCH₂CMe₂CONHMe, NHCH₂CMe₂CONMe₂, NHCH₂CMe₂NHSO₂Me, NH(CH₂)₃SOMe, NH(CH₂)₅SO₂Me, NH(CH₂)₅SO₂NH₂, NH(CH₂)₃NHSO₂Me, NH(CH₂)₂O(CH₂)₂OH, NHCH₂CHMeOH, NH(CH₂)₅SOMe, NH(CH₂)₃SO₂Me, NHC(CH₂OH)₃, NHCH₂CH(OH)CH₂OH, N(CH₂CH₂OH)₂, , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , 



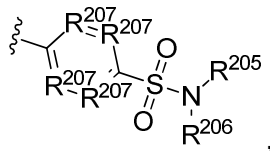




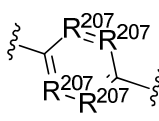
4. The compound according to any of claims 1 to 3 wherein $\text{NR}^{201}\text{R}^{202}$ is selected from

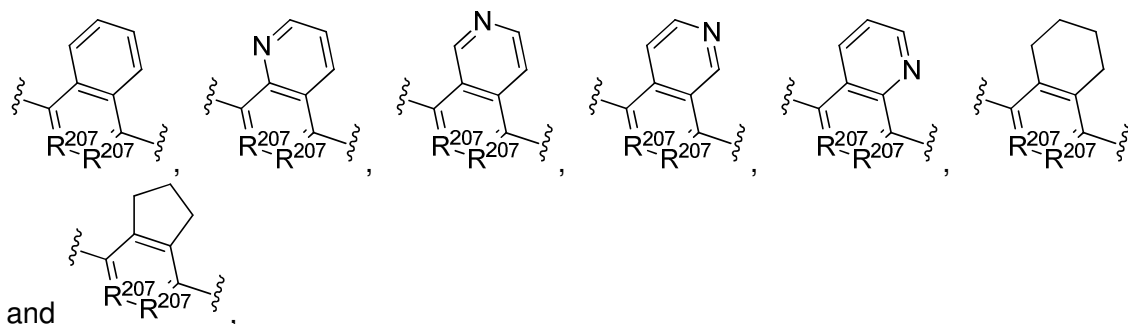


5. The compound according to any of claims 1 to 4 wherein R^{204} is selected from



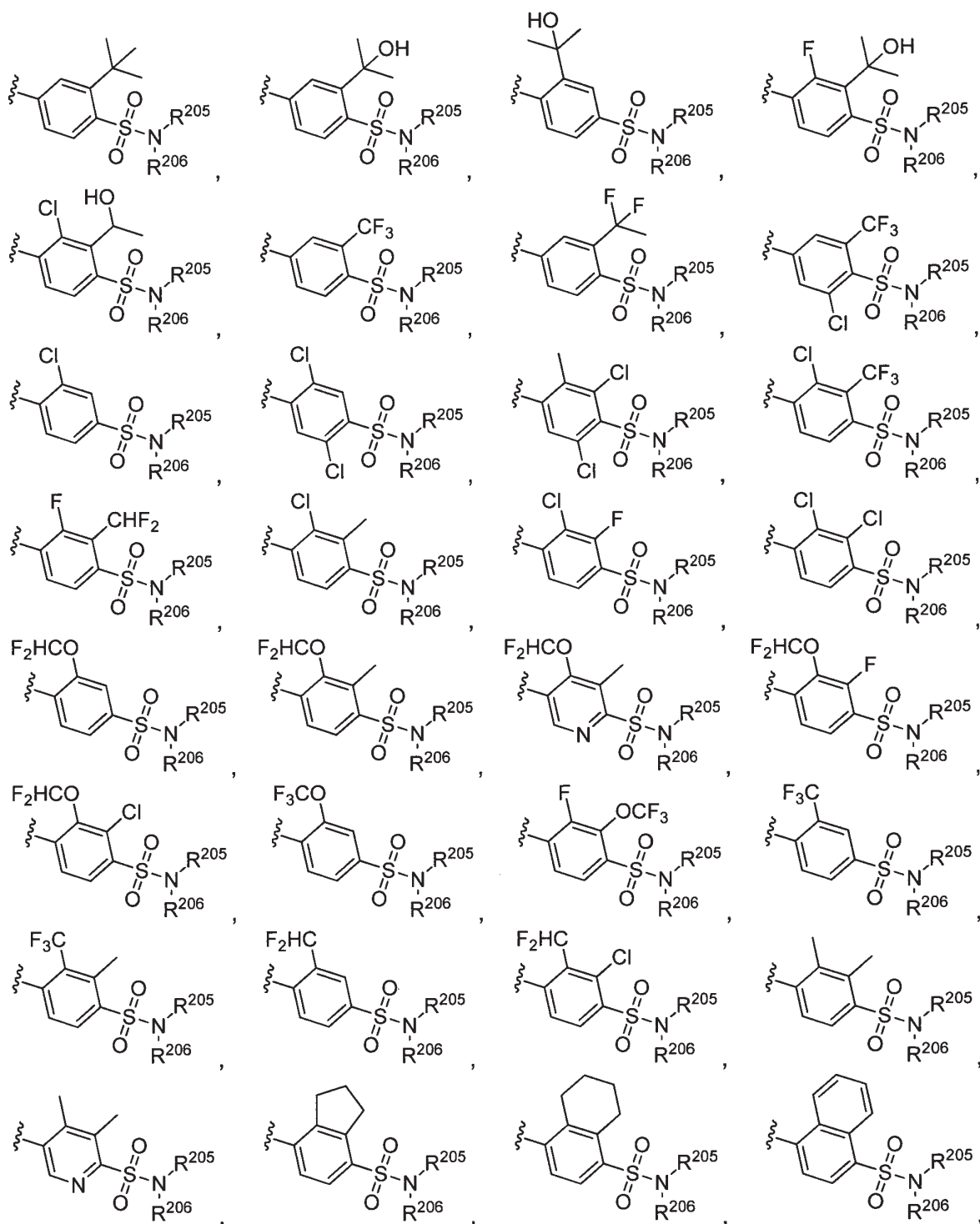
wherein all R^{207} are CR^{208} or one R^{207} is N and the three other R^{207} are CR^{208} ; or

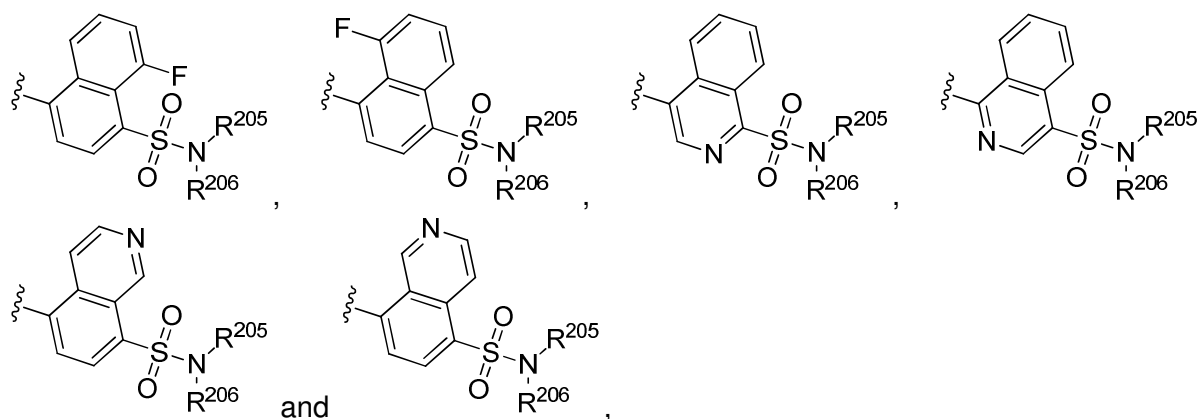
wherein  is selected from



wherein the additional ring is unsubstituted or substituted with 1 to 4 substituents independently selected from the group consisting of halogen, OH, oxo, C_{1-4} -alkyl and fluoro- C_{1-4} -alkyl.

5



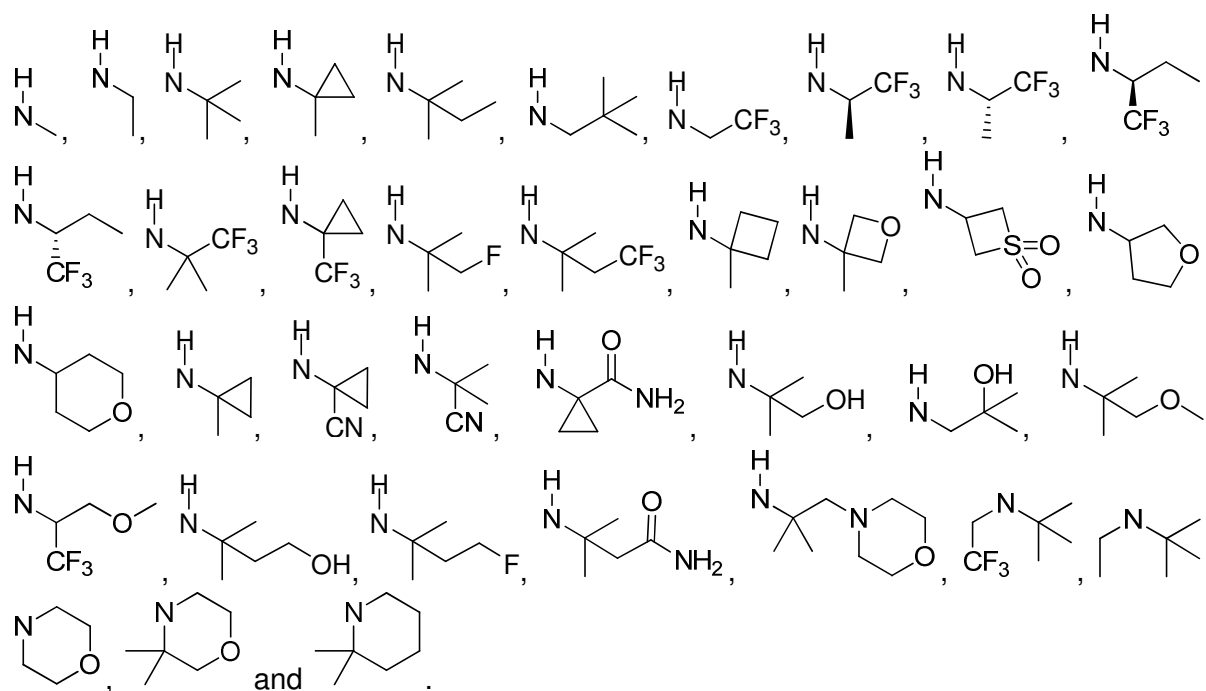


wherein

R^{205} and R^{206} is independently selected from H, C_{1-6} -alkyl, halo- C_{1-6} -alkyl, C_{0-6} -alkylene- C_{3-8} -cycloalkyl, C_{0-6} -alkylene- C_{3-8} -heterocycloalkyl, 5- or 6-membered heteroaryl and 6-membered aryl, wherein alkyl, alkylene, cycloalkyl, heterocycloalkyl, aryl and heteroaryl are unsubstituted or substituted with 1 to 6 substituents independently selected from the group consisting of halogen, CN, OH, oxo, C_{1-3} -alkyl, halo- C_{1-3} -alkyl, O- C_{1-3} -alkyl, O-halo- C_{1-3} -alkyl, SO_2 - C_{1-3} -alkyl, $NR^{211}R^{212}$, CO_2R^{212} and $CONR^{211}R^{212}$;

and optionally wherein R^{205} and R^{206} when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing 1 or 2 heteroatoms selected from O, S or N, wherein the ring is unsubstituted or substituted with 1 to 4 substituents independently selected from the group consisting of fluoro, OH, oxo, C_{1-4} -alkyl and halo- C_{1-4} -alkyl.

7. The compound according to any of claims 1 to 6 wherein $NR^{205}R^{206}$ is selected from



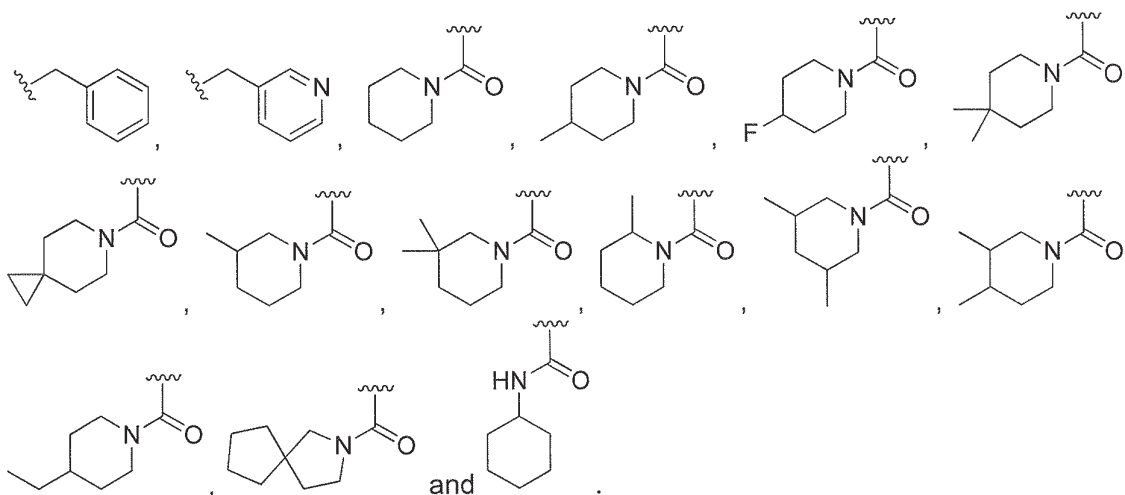
8. The compound according to any of claims 1 to 7 wherein

R^{203} is selected from C_{1-8} -alkyl, fluoro- C_{1-8} -alkyl, C_{1-2} -alkylene- C_{3-8} -cycloalkyl, C_{1-2} -alkylene- C_{3-6} -heterocycloalkyl, C_{1-2} -alkylene-(6- to 10-membered aryl) and C_{1-2} -alkylene-(5- to 10-membered heteroaryl),

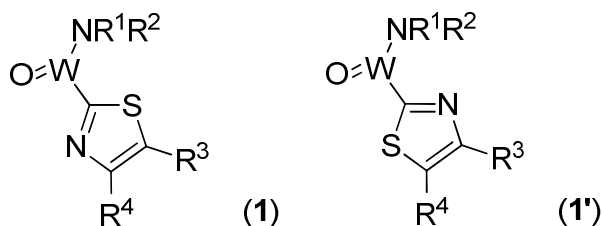
wherein alkyl, alkylene, cycloalkyl, heterocycloalkyl, aryl and heteroaryl is unsubstituted or substituted with 1 to 6 substituents independently selected from the group consisting of oxo, fluoro, chloro, CN, $CONH_2$, C_{1-3} -alkyl, fluoro- C_{1-3} -alkyl, C_{3-6} -cycloalkyl, C_{3-6} -heterocycloalkyl and OC_{1-4} -alkyl.

9. The compound according to any of claims 1 to 7 wherein

R^{203} is selected from CHF_2 , CH_2CH_3 , $CH_2CH_2CH_3$, $C(CH_3)_3$, $CH_2OC(CH_3)_3$,



10. A compound represented by Formula (1) or Formula (1')



an enantiomer, diastereomer, tautomer, *N*-oxide, solvate, formulation and pharmaceutically acceptable salt thereof, wherein

R¹ and R² are independently selected from H, C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl, C₃₋₁₀-cycloalkyl, C₃₋₁₀-heterocycloalkyl, C₁₋₁₀-alkylene-C₃₋₁₀-cycloalkyl, C₁₋₁₀-alkylene-C₃₋₁₀-heterocycloalkyl, C₁₋₁₀-alkylene-(5-membered heteroaryl) and SO₂-C₁₋₁₀-alkyl, wherein alkyl, alkenyl, alkynyl, alkylene, cycloalkyl, heterocycloalkyl and heteroaryl is unsubstituted or substituted with 1 to 7 substituents independently selected from the group consisting of oxo, CN, OR¹¹, O-C₂₋₆-alkylene-OR¹¹, C₁₋₆-alkyl, halo-C₁₋₆-alkyl, halogen, CO₂R¹¹, CONR¹¹R¹², CONR¹¹SO₂R¹¹, COR¹¹, SO_xR¹¹, SO₃H, SO₂NR¹¹R¹², NR¹¹COR¹¹, NR¹¹SO₂R¹¹, NR¹¹-CO-NR¹¹R¹², NR¹¹-SO₂-NR¹¹R¹², C₃₋₁₀-cycloalkyl, O-C₃₋₁₀-cycloalkyl, C₃₋₁₀-heterocycloalkyl, O-C₃₋₁₀-heterocycloalkyl and NR¹¹R¹²;

or R¹ and R² when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing 1 or 2 heteroatoms selected from O, S or N, wherein the ring is unsubstituted or substituted with 1 to 4 substituents independently selected from the group consisting of halogen, oxo, CN, OR¹¹, SO_xR¹¹, SO₃H, NR¹¹SO₂R¹¹, SO₂NR¹¹R¹², C₀₋₆-alkylene-CO₂R¹¹, CONR¹¹R¹², CONR¹¹SO₂R¹¹, COR¹¹, NR¹¹-CO-R¹¹, NR¹¹-CO-NR¹¹R¹², NR¹¹-SO₂-NR¹¹R¹², NR¹¹R¹², C₁₋₆-alkyl, halo-C₁₋₆-

alkyl, hydroxy- C_{1-6} -alkyl, C_{3-8} -cycloalkyl, O- C_{3-8} -cycloalkyl, C_{3-8} -heterocycloalkyl and O- C_{3-8} -heterocycloalkyl,

wherein cycloalkyl and heterocycloalkyl are unsubstituted or substituted with 1 to 4 substituents independently selected from the group consisting of halogen, C_{1-3} -alkyl, halo- C_{1-3} -alkyl, OH, O- C_{1-3} -alkyl, O-halo- C_{1-3} -alkyl, SO_2 - C_{1-3} -alkyl, COOH and oxo;

R^3 is a 6-10 membered mono- or bicyclic aryl or a 5-14 membered mono-, bi- or tricyclic heteroaryl containing 1 to 5 heteroatoms independently selected from the group consisting of N, O and S,

wherein aryl and heteroaryl is unsubstituted or substituted with 1 to 5 substituents independently selected from the group consisting of halogen, C_{1-6} -alkyl, C_{1-6} -alkenyl, C_{1-6} -alkynyl, halo- C_{1-6} -alkyl, OH, O- C_{1-6} -alkyl, O-halo- C_{1-6} -alkyl, C_{0-6} -alkylene- C_{3-10} -cycloalkyl, C_{0-6} -alkylene- C_{3-10} -heterocycloalkyl, C_{0-6} -alkylene-(5- or 6-membered heteroaryl), C_{1-6} -alkylene-O- R^{31} , C_{0-6} -alkylene-CN, C_{0-6} -alkylene-N(R^{31})₂, C_{0-6} -alkylene-O- C_{3-10} -cycloalkyl, O- C_{1-6} -alkylene-O- R^{31} , C_{0-6} -alkylene-O- C_{3-10} -heterocycloalkyl, C_{0-6} -alkylene-COOR³¹, C_{0-6} -alkylene-C(O)R³¹, C_{0-6} -alkylene-C(O)N(R^{31})₂, C_{0-6} -alkylene-N(R^{31})C(O)R³¹, C_{0-6} -alkylene-SO- R^{31} , C_{0-6} -alkylene-SO₂- R^{31} , C_{0-6} -alkylene-SO₂-N(R^{31})₂, C_{0-6} -alkylene-N(R^{31})SO₂- R^{31} , C_{0-6} -alkylene-SO₂- C_{3-10} -heterocycloalkyl and C_{0-6} -alkylene-SO₂- C_{3-10} -heterocycloalkyl,

wherein alkyl, alkenyl, alkynyl, alkylene, cycloalkyl, heterocycloalkyl and the 5- or 6-membered heteroaryl is optionally substituted by 1 to 4 substituents independently selected from the group consisting of halogen, CN, C_{1-3} -alkyl, halo- C_{1-3} -alkyl, OH, oxo, =N-OR³², O- C_{1-6} -alkyl, O-halo- C_{1-3} -alkyl, N(R^{31})₂, COOH, CON(R^{31})₂, NR³¹-COR³¹, C_{3-10} -cycloalkyl, C_{3-10} -heterocycloalkyl, 6-10-membered mono- or bicyclic aryl and 6-10-membered mono- or bicyclic heteroaryl,

or wherein two adjacent substituents complete a 3- to 8-membered saturated or partially unsaturated ring containing carbon atoms and optionally containing 1 to 3 heteroatoms selected from O, S, N, SO, SO₂ or NR³¹, wherein the ring is unsubstituted or substituted with 1 to 7 substituents independently selected from the group consisting of halogen, C_{1-6} -alkyl, halo- C_{1-6} -alkyl, C_{3-6} -cycloalkyl, C_{3-6} -heterocycloalkyl, oxo, =N-OR³², OH, O- C_{1-6} -alkyl and O-halo- C_{1-6} -alkyl;

R^4 is selected from (CR⁸R⁹)R⁴⁰, (C=O)R⁴⁰, OR⁴⁰, NR⁴¹R⁴⁰, SO_y-R⁷ and C_{3-6} -cycloalkyl, which is spirocyclic fused with R⁴⁰,

wherein cycloalkyl is unsubstituted or substituted with 1 to 4 substituents independently selected from the group consisting of F, CH₃ and CF₃;

R^7 is selected from C_{3-10} -cycloalkyl and C_{3-10} -heterocycloalkyl,

wherein cycloalkyl and heterocycloalkyl are unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of halogen, OH, oxo, O-C₁₋₆-alkyl, O-halo-C₁₋₆-alkyl, C₁₋₆-alkyl, halo-C₁₋₆-alkyl, cycloalkyl and heterocycloalkyl;

R⁸ and R⁹ are independently selected from H, F, C₁₋₃-alkyl, halo-C₁₋₃-alkyl, OH, O-C₁₋₃-alkyl and O-halo-C₁₋₃-alkyl;

R¹¹ is independently selected from H, C₁₋₆-alkyl, C₀₋₆-alkylene-C₃₋₁₀-cycloalkyl and C₀₋₆-alkylene-C₃₋₁₀-heterocycloalkyl,

wherein alkyl, alkylene, cycloalkyl and heterocycloalkyl is unsubstituted or substituted with 1 to 6 substituents selected from the group consisting of halogen, CN, OH, oxo, C₁₋₃-alkyl, halo-C₁₋₃-alkyl, O-C₁₋₃-alkyl, O-halo-C₁₋₃-alkyl, NH₂, NH(C₁₋₃-alkyl), N(C₁₋₃-alkyl)₂, C₃₋₆-heterocycloalkyl, C₃₋₆-cycloalkyl and SO₂-C₁₋₃-alkyl,

wherein cycloalkyl and heterocycloalkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of F, OH, oxo, CH₃ and CF₃;

R¹² is independently selected from H, C₁₋₆-alkyl, halo-C₁₋₆-alkyl and C₃₋₆-cycloalkyl;

R³¹ is independently selected from H, C₁₋₆-alkyl, halo-C₁₋₆-alkyl, C₀₋₆-alkylene-C₃₋₈-cycloalkyl, C₀₋₆-alkylene-C₃₋₈-heterocycloalkyl, 5- or 6-membered heteroaryl and 6-membered aryl, wherein alkyl, alkylene, cycloalkyl, heterocycloalkyl, aryl and heteroaryl are unsubstituted or substituted with 1 to 6 substituents independently selected from the group consisting of halogen, CN, OH, oxo, =N-OR³², C₁₋₃-alkyl, halo-C₁₋₃-alkyl, O-C₁₋₃-alkyl, O-halo-C₁₋₃-alkyl and SO₂-C₁₋₃-alkyl;

and optionally wherein two R³¹ when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing 1 or 2 heteroatoms selected from O, S or N, wherein the ring is unsubstituted or substituted with 1 to 4 substituents independently selected from the group consisting of fluoro, OH, oxo, C₁₋₄-alkyl and halo-C₁₋₄-alkyl;

R³² is independently selected from H, C₁₋₆-alkyl, halo-C₁₋₆-alkyl and C₃₋₆-cycloalkyl;

R⁴⁰ is C₃₋₁₀-cycloalkyl, which is unsubstituted or substituted with 1 to 5 substituents independently selected from the group consisting of halogen, OH, oxo, O-C₁₋₆-alkyl, O-halo-C₁₋₆-alkyl, C₁₋₆-alkyl, halo-C₁₋₆-alkyl, C₃₋₈-cycloalkyl and C₃₋₈-heterocycloalkyl;

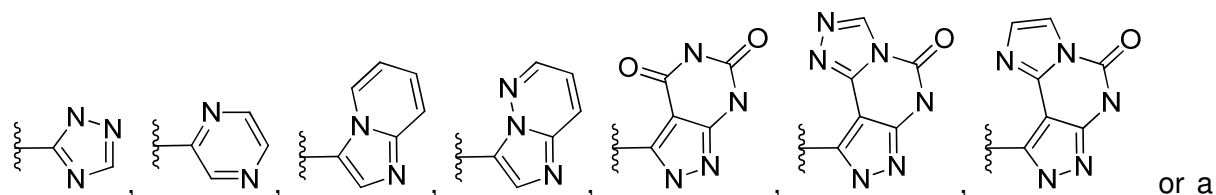
R⁴¹ is selected from H, C₁₋₆-alkyl, C₃₋₆-cycloalkyl and C₃₋₆-heterocycloalkyl,

wherein alkyl, cycloalkyl and heterocycloalkyl is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of OH, oxo, CN, halogen, O-C₁₋₆-alkyl, O-halo-C₁₋₆-alkyl, C₃₋₆-heterocycloalkyl and C₃₋₆-cycloalkyl;

x and y are independently selected from 0, 1 and 2;

W is selected from C or S=O;

with the proviso that for R³ the 5-14 membered mono-, bi- or tricyclic heteroaryl containing ring is not



or a 5-membered aromatic heterocyclic group containing at least one oxygen atom.

11. The compound according to claim 10 wherein W is C.

12. The compound according to any of claims 10 to 11 wherein

R⁴ is selected from (CR⁸R⁹)R⁴⁰, (C=O)R⁴⁰ and OR⁴⁰;

R⁸ is selected from H, F, CH₃, CF₃ and O-CH₃;

R⁹ is selected from H, F and CH₃;

R⁴⁰ is C₃₋₈-cycloalkyl, which is unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of fluoro, CH₃ and CF₃.

13. The compound according to any of claims 10 to 12 wherein

R¹ is selected from H, C₁₋₁₀-alkyl, C₃₋₁₀-cycloalkyl, C₃₋₁₀-heterocycloalkyl, C₁₋₁₀-alkylene-C₃₋₁₀-cycloalkyl, C₁₋₁₀-alkylene-C₃₋₁₀-heterocycloalkyl and C₁₋₁₀-alkylene-(5-membered heteroaryl), wherein alkyl, alkenyl, alkynyl, alkylene, cycloalkyl and heterocycloalkyl is unsubstituted or substituted with 1 to 7 substituents independently selected from the group consisting of oxo, CN, OR¹¹, O-C₂₋₆-alkylene-OR¹¹, C₁₋₆-alkyl, halo-C₁₋₆-alkyl, halogen, CO₂R¹¹, CONR¹¹R¹², CONR¹¹SO₂R¹¹, COR¹¹, SO_xR¹¹, SO₃H, SO₂NR¹¹R¹², NR¹¹COR¹¹, NR¹¹SO₂R¹¹, NR¹¹-CO-NR¹¹R¹², NR¹¹-SO₂-NR¹¹R¹², C₃₋₁₀-cycloalkyl, O-C₃₋₁₀-cycloalkyl, C₃₋₁₀-heterocycloalkyl, O-C₃₋₁₀-heterocycloalkyl and NR¹¹R¹²;

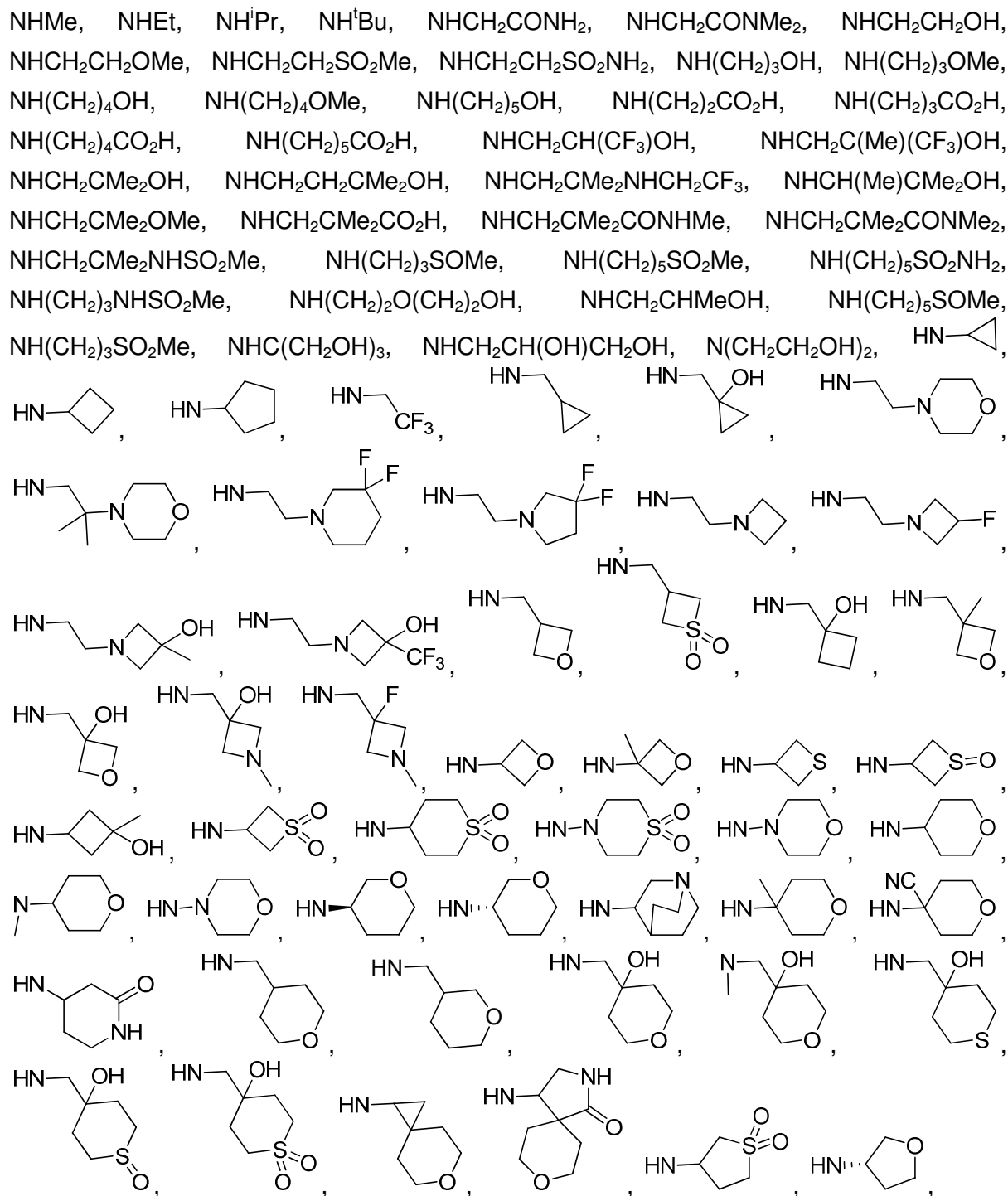
R² is selected from H, C₁₋₆-alkyl, halo-C₁₋₆-alkyl and hydroxy-C₁₋₆-alkyl;

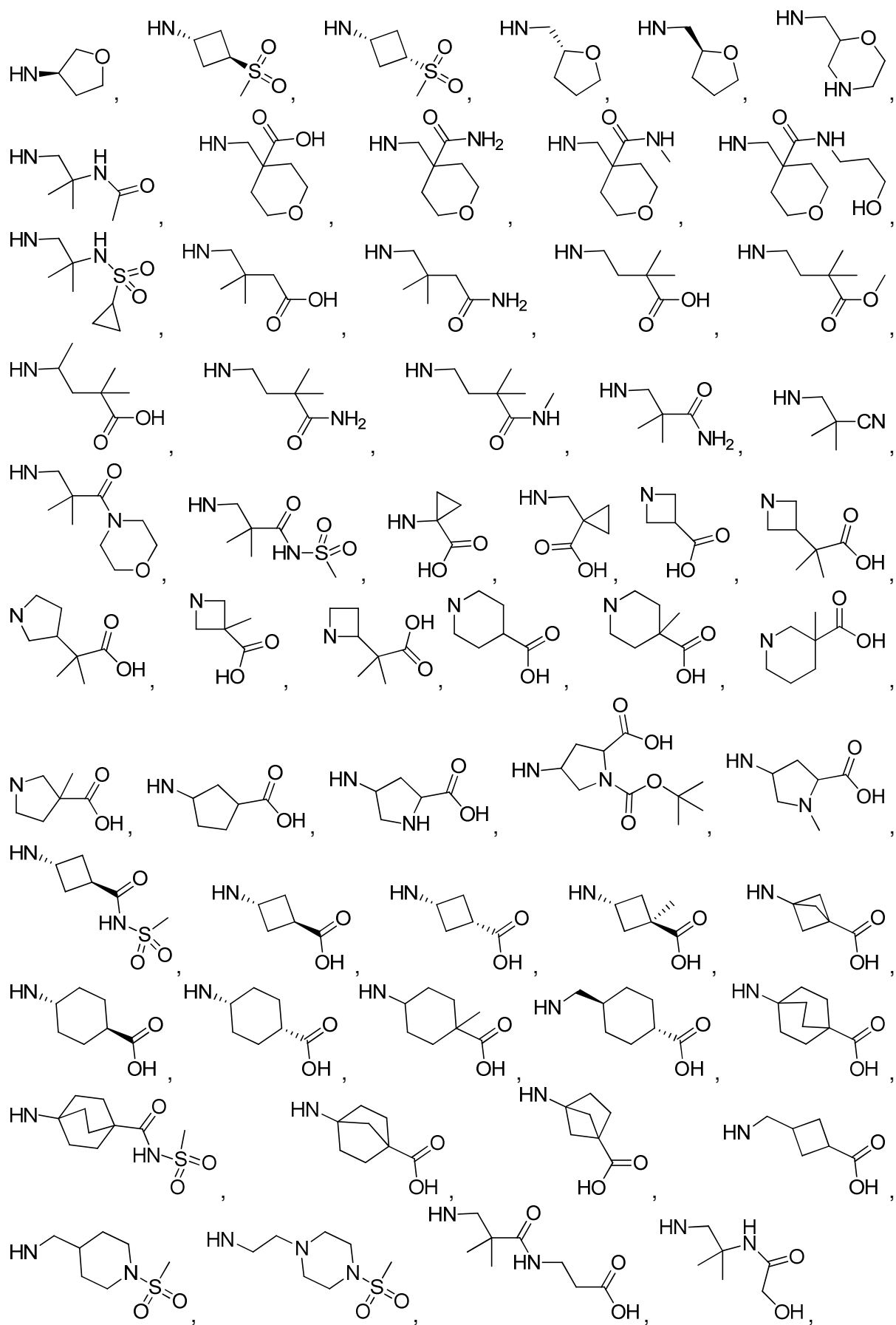
or R¹ and R² when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing 1 or 2 heteroatoms selected from O, S or N, wherein the ring is unsubstituted or substituted with 1 to 4 substituents independently selected from the group consisting of halogen, oxo, CN, OR¹¹, SO_xR¹¹, SO₃H, NR¹¹SO₂R¹¹, SO₂NR¹¹R¹², C₀₋₆-alkylene-CO₂R¹¹, CONR¹¹R¹², CONR¹¹SO₂R¹¹, COR¹¹, NR¹¹-CO-R¹¹, NR¹¹-CO-NR¹¹R¹², NR¹¹-SO₂-NR¹¹R¹², NR¹¹R¹², C₁₋₆-alkyl, halo-C₁₋₆-

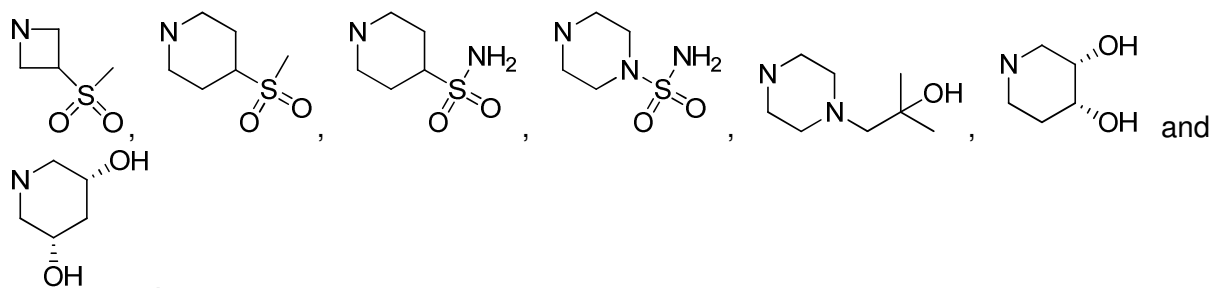
alkyl, hydroxy-C₁₋₆-alkyl, C₃₋₈-cycloalkyl, O-C₃₋₈-cycloalkyl, C₃₋₈-heterocycloalkyl and O-C₃₋₈-heterocycloalkyl,

wherein cycloalkyl and heterocycloalkyl are unsubstituted or substituted with 1 to 4 substituents independently selected from the group consisting of halogen, C₁₋₃-alkyl, halo-C₁₋₃-alkyl, OH, O-C₁₋₃-alkyl, O-halo-C₁₋₃-alkyl, SO₂-C₁₋₃-alkyl, COOH and oxo.

14. The compound according to any of claims 10 to 13 wherein NR¹R² is selected from







15. The compound according to any of claims 10 to 14 wherein

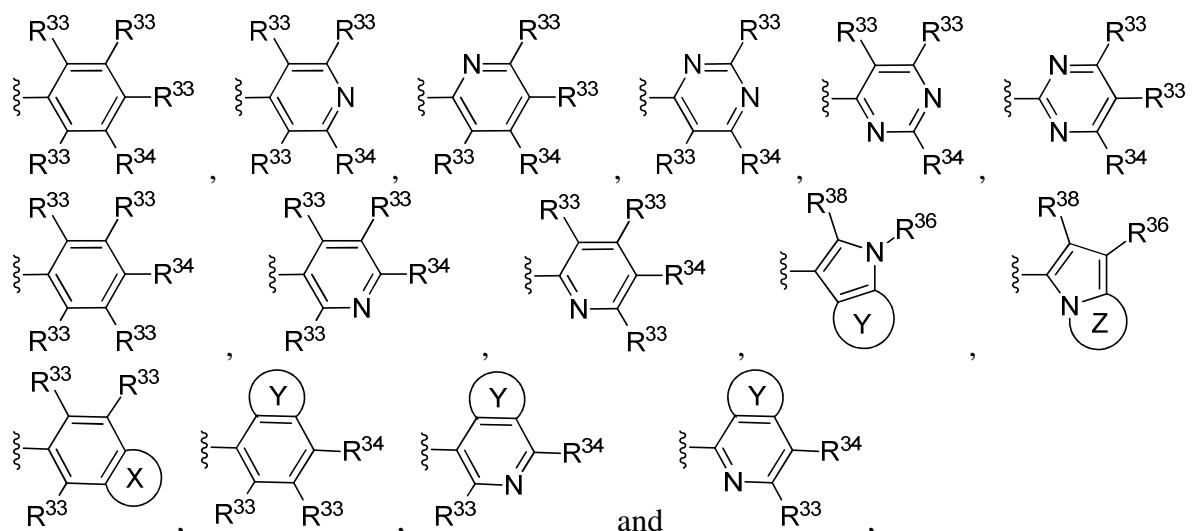
R^3 is a 6-10 membered mono- or bicyclic aryl or a 5-10 membered mono- or bicyclic heteroaryl containing 1 to 4 heteroatoms independently selected from the group consisting of N, O and S

wherein aryl and heteroaryl are unsubstituted or substituted with 1 to 5 substituents independently selected from the group consisting of halogen, CN, C_{1-6} -alkyl, halo- C_{1-6} -alkyl, OH, O- C_{1-6} -alkyl, O-halo- C_{1-6} -alkyl, C_{0-6} -alkylene- C_{3-10} -cycloalkyl, C_{0-6} -alkylene-O- C_{3-10} -cycloalkyl, C_{0-6} -alkylene- C_{3-10} -heterocycloalkyl, C_{0-6} -alkylene-COOR³¹, C_{0-6} -alkylene-C(O)R³¹, C_{0-6} -alkylene-C(O)N(R³¹)₂, C_{0-6} -alkylene-SO₂-N(R³¹)₂, C_{0-6} -alkylene-SO₂-R³¹, C_{0-6} -alkylene-(5-membered heteroaryl), C_{0-6} -alkylene-(6-membered heteroaryl),

wherein alkyl, alkylene, cycloalkyl, heterocycloalkyl and heteroaryl are unsubstituted or substituted by 1 to 3 substituents independently selected from the group consisting of halogen, OH, oxo, =N-OR³², N(R³¹)₂, O- C_{1-6} -alkyl, COOH, CON(R³¹)₂, CN, NR³¹-COR³¹, C_{3-10} -cycloalkyl, C_{3-10} -heterocycloalkyl, 6-10-membered mono- or bicyclic aryl and 6-10-membered mono- or bicyclic heteroaryl,

or wherein two adjacent substituents may complete a 3- to 8-membered saturated or partially unsaturated ring containing carbon atoms and optionally containing 1 to 3 members selected from O, S, SO, SO₂ or NR³¹, wherein the ring is unsubstituted or substituted with 1 to 4 substituents independently selected from halogen, oxo, =N-OR³², OH, O- C_{1-6} -alkyl, O-halo- C_{1-6} -alkyl, C_{1-6} -alkyl, C_{3-6} -cycloalkyl and halo- C_{1-6} -alkyl.

16. The compound according to any of claim 10 to 15 wherein R^3 is selected from



wherein

R³³ is independently selected from H, halogen, CN, C₁₋₆-alkyl, fluoro-C₁₋₆-alkyl, C₁₋₄-alkylene-OH, C₁₋₄-alkylene-O-C₁₋₃-alkyl, C₁₋₄-alkylene-O-fluoro-C₁₋₃-alkyl, OH, O-C₁₋₆-alkyl, O-fluoro-C₁₋₆-alkyl, NH-C₁₋₆-alkyl, NH-fluoro-C₁₋₆-alkyl, C₃₋₁₀-cycloalkyl,

wherein alkylene is unsubstituted or substituted with 1 to 3 substituents selected from F and cycloalkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from F, C₁₋₃-alkyl and fluoro-C₁₋₃-alkyl;

R³⁴ are independently selected from H, halogen, CN, C₁₋₆-alkyl, fluoro-C₁₋₆-alkyl, C₁₋₄-alkylene-OH, C₁₋₄-alkylene-O-C₁₋₃-alkyl, C₁₋₄-alkylene-O-fluoro-C₁₋₃-alkyl, OH, O-C₁₋₆-alkyl, O-fluoro-C₁₋₆-alkyl, NH-C₁₋₆-alkyl, NH-fluoro-C₁₋₆-alkyl, C₃₋₁₀-cycloalkyl, C₀₋₆-alkylene-C₃₋₁₀-heterocycloalkyl, 5-membered heteroaryl, 6-membered heteroaryl, C(O)N(R³⁷)₂ and SO₂N(R³⁷)₂,

wherein alkylene is unsubstituted or substituted with 1 to 3 substituents selected from F and cycloalkyl, heterocycloalkyl and heteroaryl is unsubstituted or substituted with 1 to 3 substituents independently selected from F, C₁₋₃-alkyl, fluoro-C₁₋₃-alkyl, OH, O-C₁₋₃-alkyl, fluoro-O-C₁₋₃-alkyl;

R³⁵ is selected from halogen, C₁₋₆-alkyl, halo-C₁₋₆-alkyl, C₃₋₆-cycloalkyl, C₃₋₆-heterocycloalkyl, oxo, OH, O-C₁₋₆-alkyl and O-halo-C₁₋₆-alkyl;

R³⁶ is selected from C₁₋₆-alkyl, fluoro-C₁₋₆-alkyl, C(O)N(R³⁷)₂, SO₂N(R³⁷)₂;

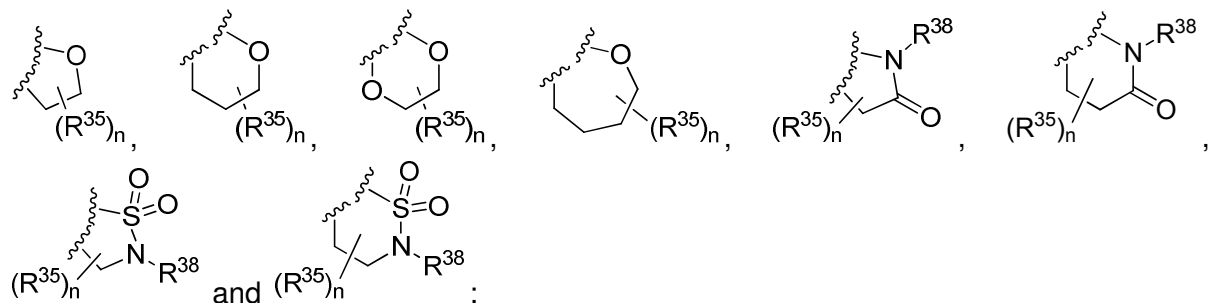
R³⁷ is independently selected from H, C₁₋₆-alkyl, halo-C₁₋₆-alkyl, C₀₋₄-alkylene-C₃₋₆-cycloalkyl, C₀₋₄-alkylene-C₃₋₆-heterocycloalkyl, wherein alkyl and alkylene is unsubstituted or substituted with 1 to 4 substituents selected from halogen, OH, O-C₁₋₃-alkyl, CN, CONH₂; and cycloalkyl or heterocycloalkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from F, CN, OH, oxo, C₁₋₃-alkyl and fluoro-C₁₋₃-alkyl;

or wherein two R³⁷ when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing 1 or 2

heteroatoms selected from O, S or N, wherein the ring is unsubstituted or substituted with 1 to 4 substituents independently selected from fluoro, OH, oxo, C₁₋₄-alkyl and halo-C₁₋₄-alkyl;

R³⁸ is selected from H, C₁₋₃-alkyl and fluoro-C₁₋₃-alkyl;

X is an annulated saturated heterocycle selected from the group consisting of

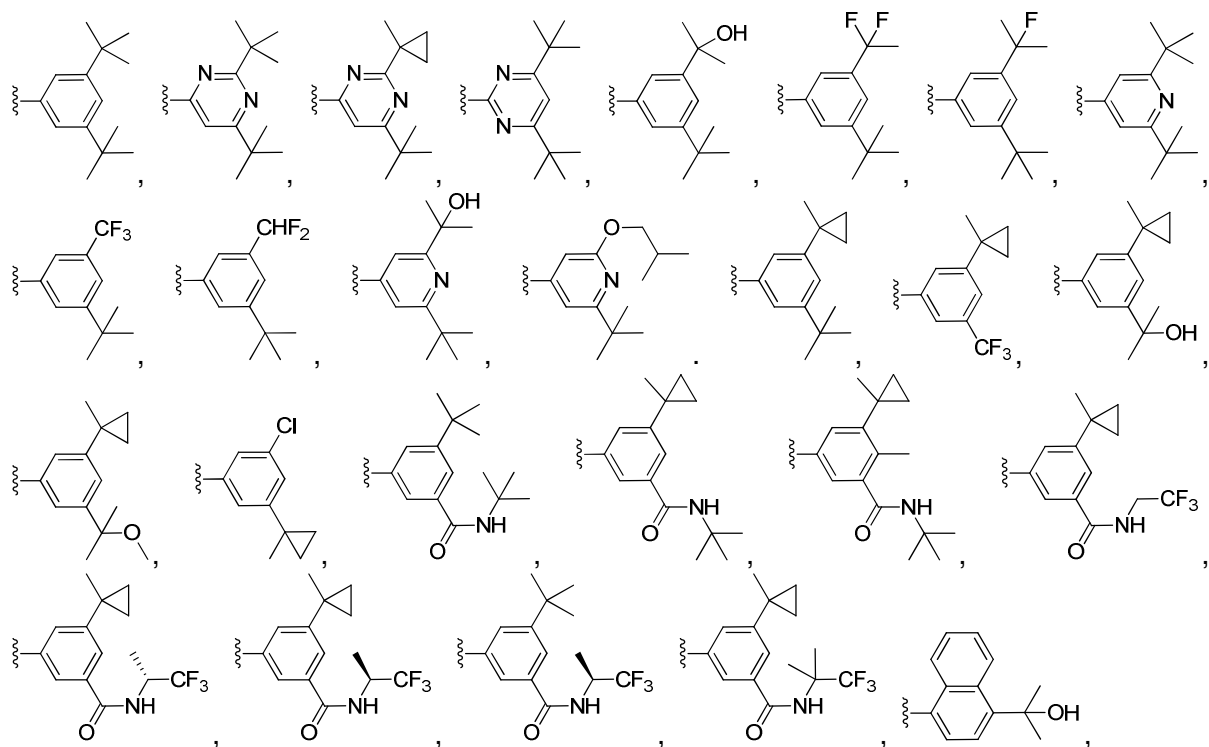


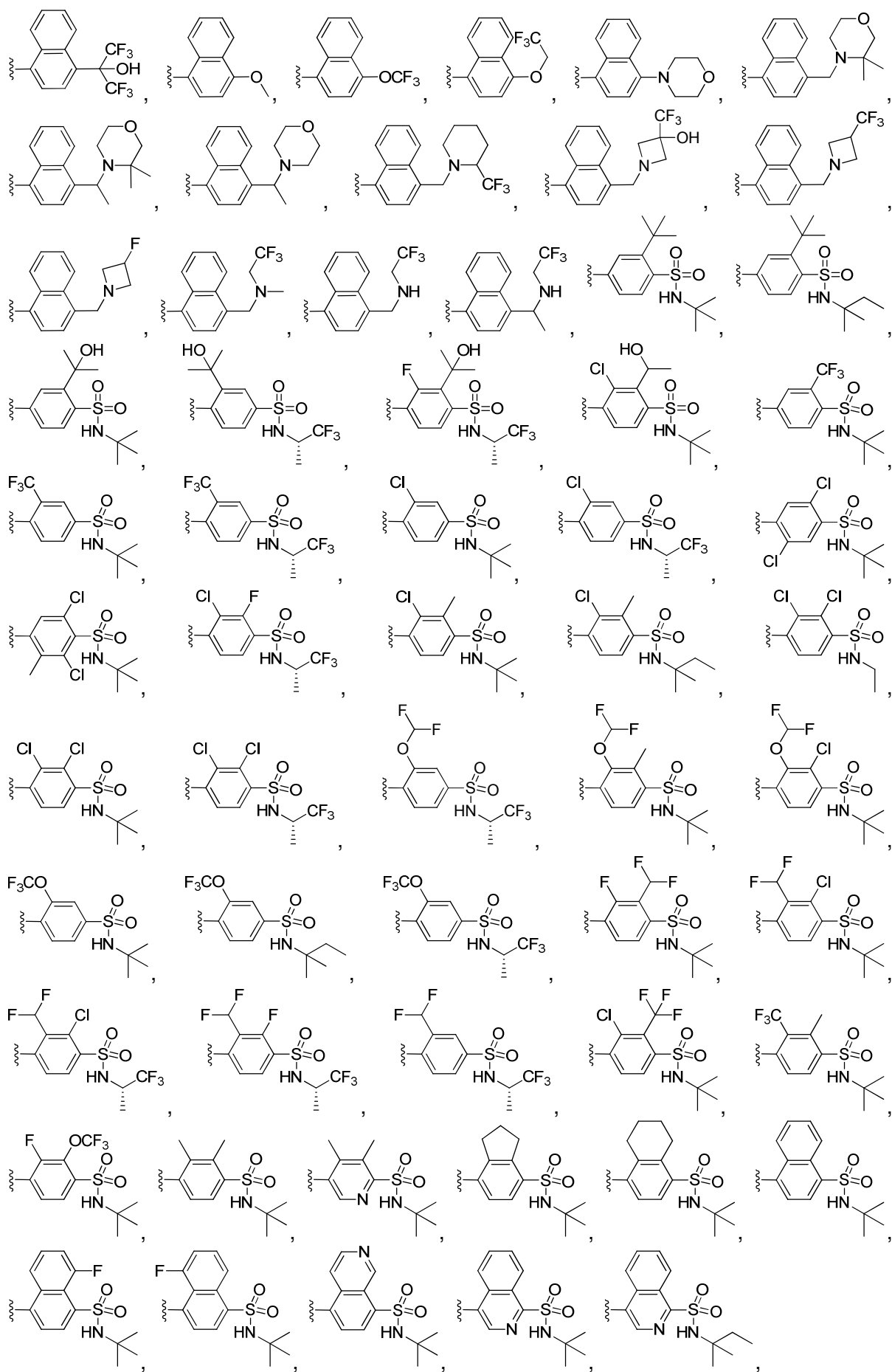
Y is an annulated 5- or 6-membered carbocycle, an annulated 6-membered aryl or an annulated 6-membered heteroaryl containing 1 to 2 nitrogen atoms, wherein the carbocycle, aryl or heteroaryl is unsubstituted or substituted with 1 to 3 substituents selected from halogen, C₁₋₃-alkyl and fluoro-C₁₋₃-alkyl;

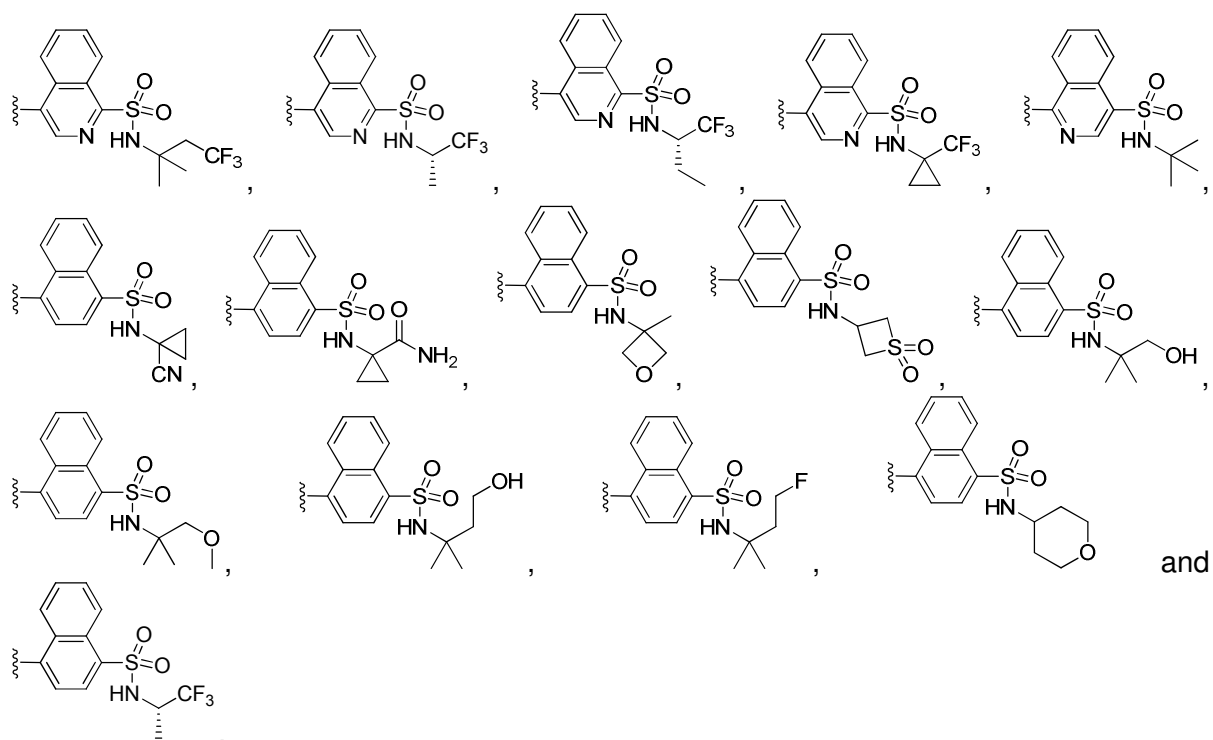
Z is an annulated 6-membered cycle forming a heteroaryl containing 1 to 2 nitrogen atoms, wherein the heteroaryl is unsubstituted or substituted with 1 to 3 substituents selected from fluoro, C₁₋₃-alkyl and fluoro-C₁₋₃-alkyl;

n is selected from 1 to 4.

17. The compound according to any of claims 10 to 16 wherein R³ is selected from

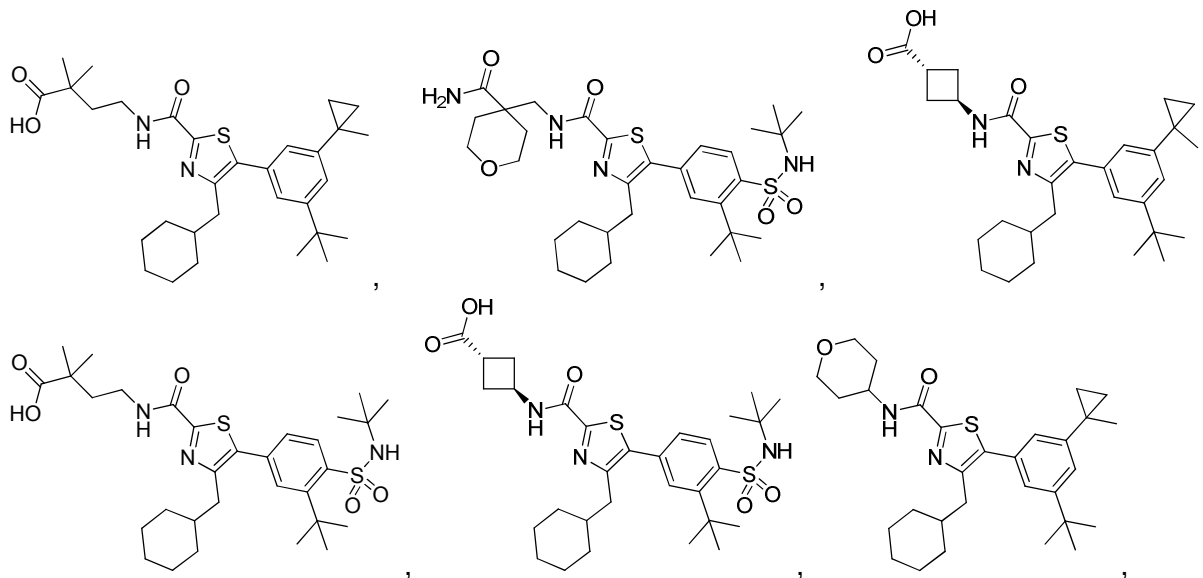


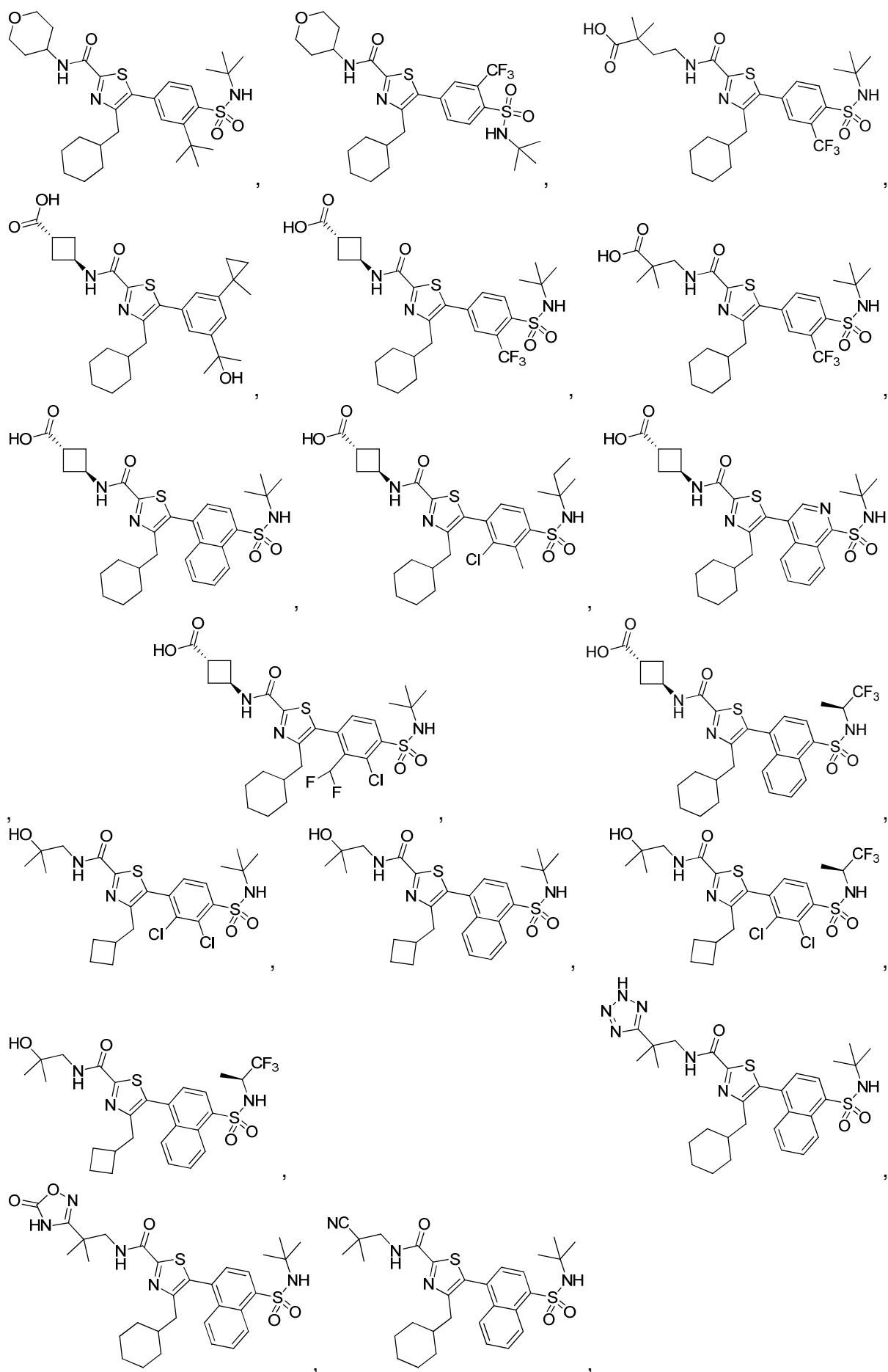


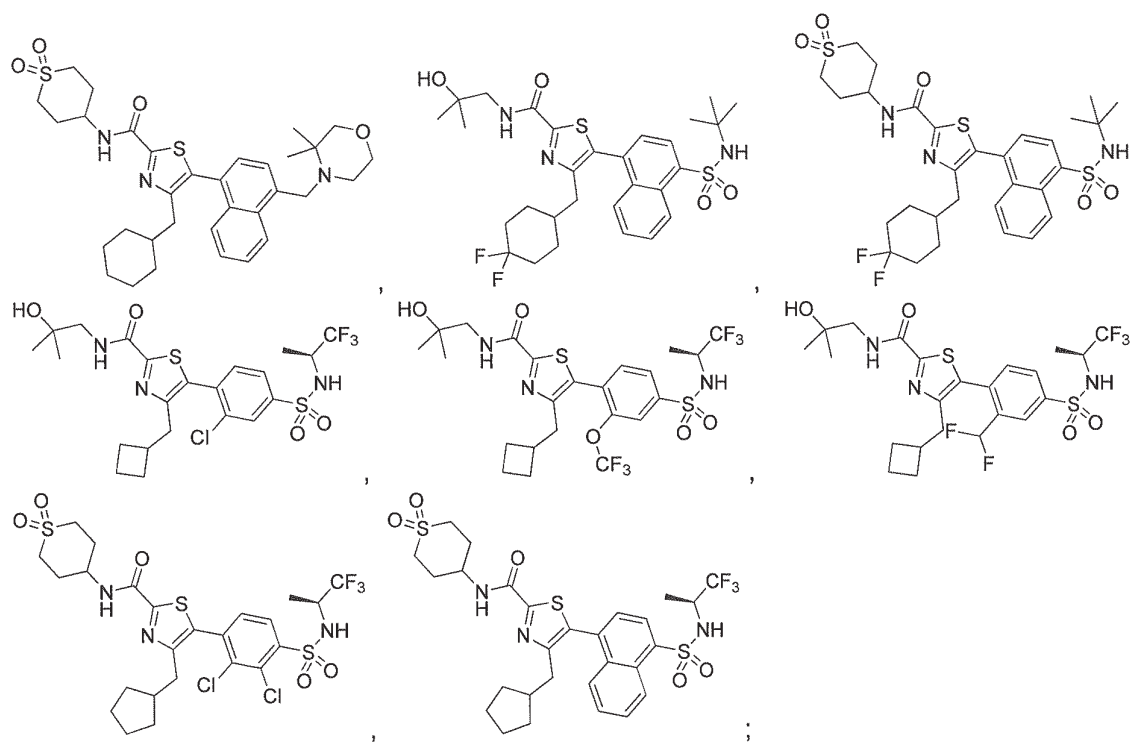


18. The compound according to any of claims 10 to 17 represented by Formula (1).

19. The compound according to any of claims 10 to 18, wherein the compound is selected from







and an enantiomer, diastereomer, tautomer, *N*-oxide, solvate and pharmaceutically acceptable salt thereof.

20. The compound according to any of claims 1 to 19 for use as medicament.

21. Use of the compound according to any of claims 1 to 19 in the manufacture of a medicament for the treatment or prophylaxis of a disease or disorder associated with the inhibition or activation of the ROR γ receptor, wherein the disease is selected from the group consisting of rheumatoid arthritis, ankylosing spondylitis, lupus erythematosus, psoriasis, psoriatic arthritis, atopic eczema, inflammatory bowel diseases such as Crohn's disease, mucosal leishmaniasis, systemic sclerosis, Kawasaki disease, Hashimoto's thyroiditis, chronic graft-versus-host disease, acute graft-versus-host disease, Celiac Sprue, idiopathic thrombocytopenic thromobotic purpura, myasthenia gravis, Sjorgren's syndrome, scleroderma, ulcerative colitis, epidermal hyperplasia, glomerulonephritis, and chronic obstructive pulmonary disease .

22. A pharmaceutical composition comprising a compound according to any of claims 1 to 19 and a pharmaceutically acceptable carrier or excipient.