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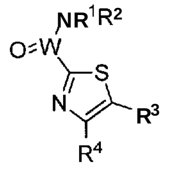
(54) Title: CARBOXAMIDE OR SULFONAMIDE SUBSTITUTED THIAZOLES AND RELATED DERIVATIVES AS MODULATORS FOR THE ORPHAN NUCLEAR RECEPTOR ROR[GAMMA]



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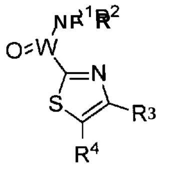

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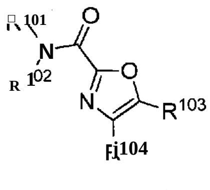

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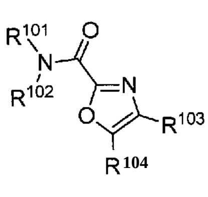

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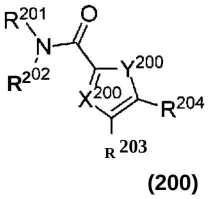

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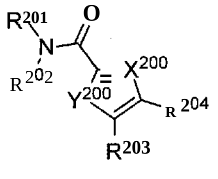

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(57) Abstract: The invention provides modulators for the orphan nuclear receptor RORy and methods for treating RORy mediated diseases by administering these novel RORy modulators to a human or a mammal in need thereof. Specifically, the present invention provides carboxamide or sulfonamide containing cyclic compounds of Formula (1), (1'), (100), (100'), (200) and (200') and the enantiomers, diastereomers, tautomers, N-oxides, solvates and pharmaceutically acceptable salts thereof.

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

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

The retinoid-receptor related orphan receptors consist of three family members, namely RORa (Beckerandre et al., *Biochem. Biophys. Res. Commun.* 1993, 194:1371), RORp (Andre et al., *Gene* 1998, 516:277) and RORy (He et al., *Immunity* 1998, 9:797) and constitute the NR1 F (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 /V-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 /V-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 RORy) 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 RORa and RORy (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 RORy should reduce the transcriptional activity of RORy and influence the biological pathways controlled by RORy.

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 RORα isoforms have been identified (RORa 1-4) while only two isoforms are known for both RORβ (1 and 2) and RORy (1 and 2) (Andre et al., *Gene* 1998, 216:277; Villey et al., *Eur. J. Immunol.* 1999, 29:4072). RORy is used herein as a term describing both, RORyl and/or RORy2 (also called RORyt).

The ROR isoforms show different tissue expression patterns and regulate different target genes and physiological pathways. For example, the RORyt is highly restricted to $CD4^+CD8^+$ thymocytes and to interleukin-17 (IL-17) producing T cells while other tissues express RORyl (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-ErbAa and Rev-Erbβ (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 ERRcc (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).

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

Analysis of RORa$^{sg/sg}$ 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. SREBPIc and the cholesterol transporters ABCA1 and ABCG1 are reduced in livers of staggerer mice and CHIP analysis suggest that RORa is directly recruited to and regulates the SREBPIc promoter. In addition, PGC1a, PGC1β, lipinl and p2-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).

RORp expression is mainly restricted to the brain and most abundantly found in the retina. RORβ 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.

RORy (particularly RORyt) 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 RORy null mice (Sun et al., *Science* 2000, 288:2369) due to a reduction in double-positive CD4$^+$CD8$^+$ and single positive CD4$^-$CD8$^+$ or CD4$^+$CD8$^-$ cells suggesting a very important role of RORyt 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 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. RORyt 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 and downregulated during differentiation in single-positive thymocytes. RORy 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 allergic phenotype in the RORy 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-y 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 response. This suggests that down-modulation of RORy 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 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).

RORγt is exclusively expressed in cells of the immune system and has been identified as a master regulator of Th17 cell differentiation. Expression of RORγt is induced by TGF-beta or IL-6 and overexpression of RORγt results in increased Th17 cell lineage and IL-17 expression. RORγt 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, 126:1 121).

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 RORγt 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. Naive T-cells are differentiated into Tregs upon stimulation by *TGFβ*. This results in upregulation of the transcriptional modulator FoxP3 resulting in $CD4^+FoxP3^+$ Tregs. In case the naive T-cells are co-stimulated by IL-6, FoxP3 expression is suppressed and RORγt expression is induced. These $CD4^+FoxP3^-ROR\gamma t^+$ 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 $IL\text{-}17^+$ Th17 cells and it is believed that interception of ROR-γt by a small molecule inverse agonist or antagonist should result in a reduction of these $IL\text{-}17^+$ Th17 cells ultimately leading to alleviation of disease symptoms and outcome (Crome et al., *Clin. Exp. Immunol.* 2010, 159:109).

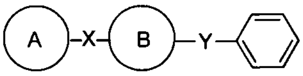
Th1 and Th17 subtype effector $CD4^+$ T cells are thought to play a critical role in the pathogenesis of human and experimental crescentic glomerulonephritis (Paust et al., *Kidney Int.* 2012, doi: 10.1038/ki.2012.101). IL-17 modulators may thus be beneficial for treating acute glomerulonephritis (Velden et al., *Am. J. Physiol. Renal Physiol.* 2012, in press; Hopfer et al., *Kidney Int.* 2012, doi: 10.1038/ki.201 2.73).

Liqands for the RORs:

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

Recently, 7-oxygenated sterols such as 7-hydroxy-cholesterol and 7-keto-cholesterol were identified as highly potent modulators of RORy 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, T0901 3 17 ([/V-(2,2,2-trifluoroethyl)-A/-[4-[2,2,2-trifluoro-1 -hydroxy-1 -(trifluoromethyl)ethyl]phenyl]-benzenesulfonamide]) acts as a RORy 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 RORy 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 proteins prevent a meaningful animal study that allows drawing conclusions on the role of RORy. In case of the T0901317 its polypharmacodynamic properties, acting on at least six different nuclear receptors (LXRa/β, FXR, PXR, RORa/y) 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).

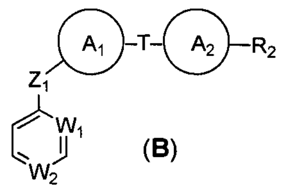
WO201 1/109059 (US201 1/0257196) describes compounds with anti-cancer activity of general structure **(A)**



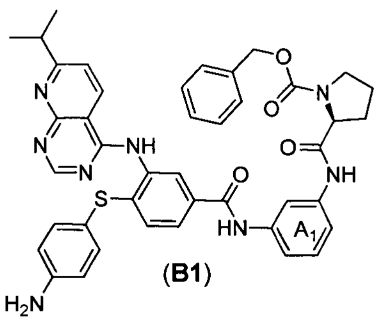
(A)

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 described in the examples.

In WO201 0/075376 compounds of general structure **(B)** for inhibiting replication of Hepatitis C virus are described. A_1 is defined to be a 3-14 membered carbo- or heterocycle, T can be e.g. $CONR^6$ and $S0_2NR^6$ while A_2 can be a carbo- or heterocycle. However, no thiazole, oxazole, thiophene or furan (representing A_1) is described in the examples - a typical example is e.g. **B1.**

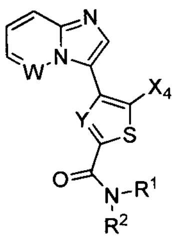


(B)



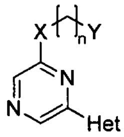
(B1)

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 X_4 can be $(CH_2)_{q=0\text{ to }3}$-C_{3-6}-cycloalkyl. No thiazole or thiophene examples with X_4 equals -Z-C_{3-10}-cycloalkyl (Z = optionally sustituted carbon, oxygen, nitrogen or sulfur) are presented (in the closest stucture X_4 equals benzyl).



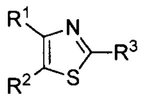
(C)

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.

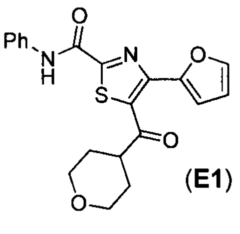


(D)

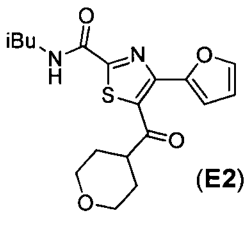
WO2007/015528 (EP1921077) and WO2006/137527 (EP1894930) describe compounds of general structure **(E)** for treating and/or preventing sleep disorders. R^1 is defined to be a 5-membered aromatic heterocyclic group having at least one oxygen atom, while R^2 can be a optionally substituted lower alkyl, NR^4R^5 (with R^4 and R^5 e.g. cycloalkyi) or COR^6 (R^6 e.g. cycloalkyi). Five thiazole examples with a carboxamide moiety are mentioned, e.g. compound **(E1)** and **(E2)**. However, in all of those examples the group R^1 is a 5-membered oxygen-containing ring.



(E)

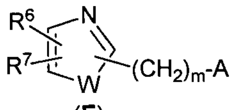


(E1)

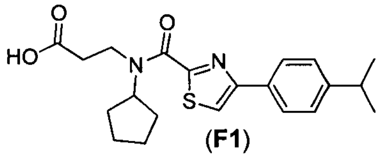


(E2)

In WO2005/1 03022 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. R^6 can be L-D^2-cycloalkyl (with L e.g. bond and D^2 e.g. nitrogen or alkylene) and R^7 can be L-D^1-aryl (with L and D^1 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.

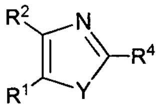


(F)

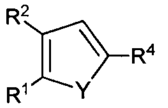


(F1)

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 Ft^1, R^2 and R^4 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.

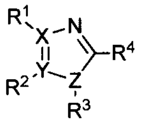


(G)

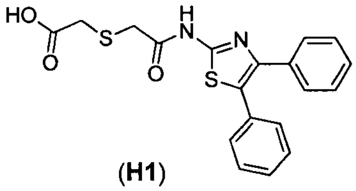


(G')

US2005/1 13283 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:



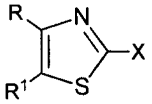
(H)



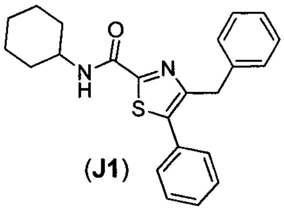
(H1)

R^1 to R^4 is selected from CONHR, $CONR_2$, phenyl, $(CH_2)_{m=0\ to\ 8}$-R^5 (R^5 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 R^1 can be a phenyl or pyridyl moiety optionally substituted with Me, Et, Pr, OMe, OEt, OH, hydroxymethyl, hydroxyethyl, halogen, CF_3, OCF_3, S0$_2$Me, SOMe, S0$_2$CF$_3$, phenyl or CN while R can be R^1 or alkyl-cycloalkyl. 2 1 thiazole examples are shown, the closest example is structure **(J1)** with an CH_2-phenyl moiety in position 4 of the thiazole ring.

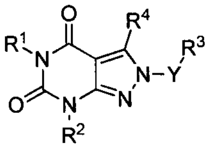


(J)

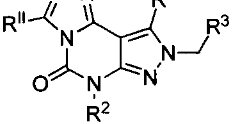


(J1)

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.

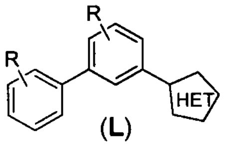


(K)



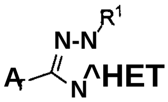
(K')

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.



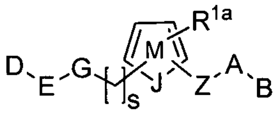
(L)

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.



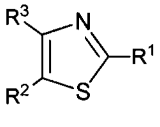
(M)

In W01 998/028282 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.

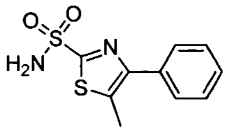


(N)

W01 995/029904 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 C_{1-3} alkyl). The closest example to the compounds of the present invention is compound **(P1).**

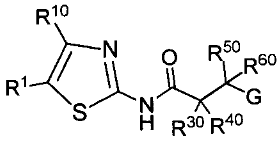


(P)



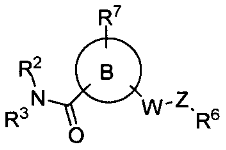
(P1)

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 R^1 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 R^1 is always hydrogen.



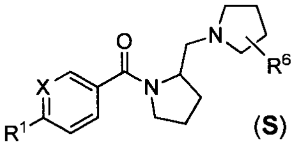
(Q)

WO2010/111059 decribes P2x3 receptor antagonists for the treatment of pain of structure (R), wherein R^2 represents H, (halo)alkyl or OH; R^3 represents a broad range of optionally substituted alkyl substituents; B can be a oxazole cylce, R^7 represents for example an optionally substituted aryl moiety and with the rest W-Z-R^6 a X-cycloalkyl residue (X = CR^2, CO or $S0_2$) can be constructed. However no oxazole containing a carboxamide in 2-position is described in the examples nor an oxazole, having such a hypthetical X-cycloalkyl residue.



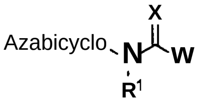
(R)

WO2006/023462 decribes 1-(hetero)aroyl-2-(pyrrolidin-1-ylmethyl)pyrrolidine as histamine H3 receptor agents of structure (S), wherein R^1 selected from a broad variety of heterocycles, including oxazole. This heterocycle can be optionally substituted with, e.g. CO-cycloalkyl, $CONR^7R^8$. However no example is described, where R^1 is an oxazole.

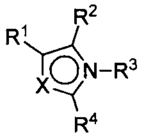


(S)

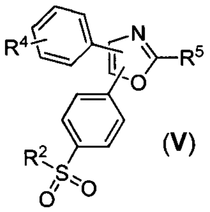
WO2003/040147 describes the preparation of /V-(azabicyclyl)arylamides for therapeutic use as nicotinic acetylcholine receptor agonists of formula **(T),** wherein R^1 is hydrogen or optionally substituted alkyl, X is oxygen or sulfur and W is a cyclic heteroeromatic moiety, which can be susbtituted with e.g. CO-cycloalkyl or $S0_2$-cycloalkyl. From the presented oxazoles no compounds with two additional substituents are shown, only some of them contain a substituted aryl as substituent.


(T)

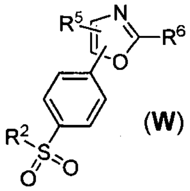
In WO2000/033836 selectin antagonists of formula (U) are disclosed, however no oxazole is presented.


(U)

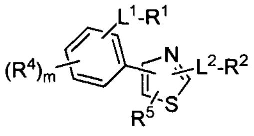
In W01 996/03661 7 substituted oxazoles of formula (V) as antiinflammatories are described. R^5 can be selected from a broad range of substitutents, including aminocarbonyl. R^2 is selected from amino and lower alkyl.


(V)

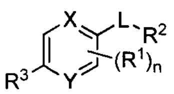
In W01 996/003392 substituted oxazoles of formula (W) for the treatment of inflammation are described. R^6 can be selected from a broad range of substitutents, including aminocarbonyl and alkylaminoarbonyl. R^2 is selected from amino and lower alkyl. No 2-carboxamide substituted oxazoles are shown.


(W)

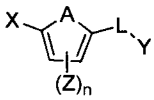
WO2008/1 54601 describes thiazole derivatives as ant-viral inhibitors of structure (X), wherein L^2-R^2 can be a substituted carboxamide, R^5 is selected from e.g. optionally substituted alkyl or cycloalkyl and L^1-R^1 can be a substituted sulfonamide. However, no compound is shown, wherein L^1-R^1 is a substituted sulfonamide.


(X)

In WO2007/087429, phenyl and pyridyl compounds as Ca^{2+} ion channel inhibitors with structure (Y) are described, wherein L is selected from various linker elements including $S0_2$NR (R = H or alkyl) and R^2 can be an optionally substituted phenyl or heteroaryl. R^3 can be an optionally substituted 5-membered heteroaryl, however no 2-carboxamide substituted thiazole, oxazole, thiophene or furan is shown in the examples.

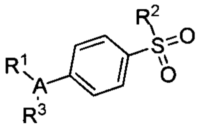

(Y)

WO2005/009954 and WO2005/009539 describe compounds of structure **(Z),** wherein A is selected from abroad 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 shown.



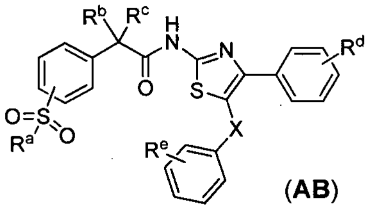
(Z)

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

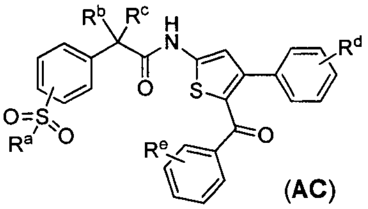


(AA)

WO201 2/027965 and WO201 2/0281 00 describe thiazole compounds of structure **(AB)** as RORy receptor modulators, wherein R^a represents a optionally substituted $C_{1\text{-e}}$-alkyl, NH$_2$ or **NHCi** $_{-3}$-alkyl; R^b and R° represents H or $C_{1\text{-}6}$-alkyl; X is **C=0** and R^d and R^e are optional substituents. In WO201 2/1 00734 compounds are described, wherein X represents O, NH, N-**Ci.6**-alkyl or C^-alkyl, optionally substituted with OH. Similarly in WO201 2/1 00732, the same derivatives with a thiophene core are described (structure **AC).**

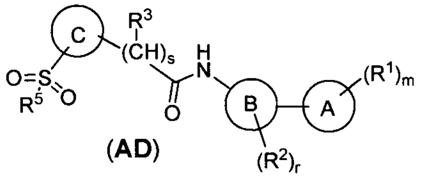


(AB)



(AC)

In WO201 3/029338 similar RORy receptor modulators are described of structure **(AD),** wherein ring A, B and **C** is broadly defined as phenyl or heteroaryl and R^2 can be selected from e.g. **$C_{1\text{-e}}$**-alkylene-cycloalkyl, heterocycloalkyl, O-heteroaryl. In the examples ring B is limited to 6-membered (hetero)aryl.



(AD)

Modulators of the RORy receptor were recently disclosed in WO201 1/107248, WO201 1/1 12263, WO201 1/1 12264, WO201 1/1 15892, WO20 12/027965, WO201 2/0281 00, WO201 2/064744, WO20 12/074547, WO201 2/1 00732, WO20 12/1 00734, WO2012/101261 , WO2012/101263, WO201 2/1 06995, WO201 2/1 39775, WO20 12/1 45254, WO2012/147916, WO201 2/1 58784, WO20 13/000869, WO20 13/000871, WO201 3/01 8695, WO201 3/01 9621 , WO2013/019626, WO2013/019635, WO2013/019653, WO2013/019682, WO2013/036912, WO2013/041519, WO2013/042782, WO2013/045431 which are based upon other structural classes.

Summary of the invention

It is therefore the object of the present invention to provide compounds, which bind to the orphan nuclear receptors **RORγ1** and/or **RORγt** and, thus, to open new methods for treating diseases associated with the modulation of **RORγ,** such as autoimmune diseases, inflammatory skin diseases or multiple sclerosis.

This object is solved by claims 1 to 38.

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

The present invention relates to a **RORγ** 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 **RORγ.**

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

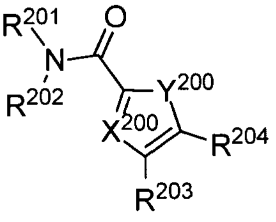
Preferably, the disease or disorder is selected from the group consisting of autoimmune diseases. Autoimmune diseases comprise a group of diseases with a similar etiology of an overshooting immune response against endogenous targets resulting in chronic inflammation and physical disabilities or other severe symptoms. Autoimmune diseases comprise e.g. rheumatoid arthritis, ankylosing spondylitis, lupus erythematosus, psoriasis, psoriatic arthritis, 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 thromobotic purpura, myasthenia gravis, Sjorgren's syndrome, scleroderma, ulcerative colitis, epidermal hyperplasia, glomerulonephritis, chronic obstructive pulmonary disease and amyotrophic lateral sclerosis.

The present invention provides novel compounds to be used in the treatment of diseases or disorders associated with the inactivation or activation of the **RORγ** receptor.

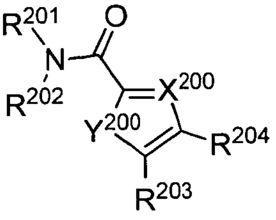
Further, the present invention relates to a method for treating autoimmune diseases comprising rheumatoid arthritis, ankylosing spondylitis, lupus erythematosus, psoriasis, psoriatic arthritis, atopic eczema, inflammatory bowel diseases such as Crohn's disease, asthma, mucosal leishmaniasis, multiple 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 thromobotic 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')**



(200)



(200')

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

wherein

R^{201} and R^{202} are independently selected from H, $C_{1\text{-}10}$-alkyl, $C_{2\text{-}10}$-alkenyl, C_2-io-alkynyl, $C_{3\text{-}10}$-cycloalkyl, $C_{3\text{-}10}$-heterocycloalkyl, Ci.io-alkylene-$C_{3\cdot10}$-cycloalkyl, Ci-i$_0$-alkylene-$C_{3\text{-}10}$-heterocycloalkyl, Ci.$_{10}$-alkylene-(5-membered heteroaryl), $C_{1\text{-}1}$o-alkylene-iB-membered aryl), $C_{1\text{-}10}$-alkylene-(6-membered heteroaryl), SO_2-Ci.$_{10}$-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}, 0-$C_{2\text{-}6}$-alkylene-OR^{211}, $C_{1\text{-}6}$-alkyl, halo-$C_{1\text{-}6}$-alkyl, halogen, $C0_2R^{211}$, $CONR^{211}R^{212}$, $CONR^{211}S0_2R^{211}$, COR^{211}, SO_xR^{211}, $S0_3H$, $S0_2NR^{211}R^{212}$, $NR^{211}COR^{211}$, $NR^{211}S0_2R^{211}$, NR^{211}-CO-$NR^{211}R^{212}$, NR^{211}-$S0_2$-$NR^{211}R^{212}$, $C_{3\text{-}10}$-cycloalkyl, O-$C_{3\text{-}10}$-cycloalkyl, $C_{3\text{-}10}$-heterocycloalkyl, O-$C_{3\text{-}10}$-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 substitutents independently selected from halogen, oxo, CN, OR^{211}, SO_xR^{211}, $S0_3H$, $NR^{211}S0_2R^{211}$, $S0_2NR^{211}R^{212}$, $C_{0\text{-}6}$-alkylene-CO_2R^{211}, $CONR^{211}R^{212}$, $CONR^{211}S0_2R^{211}$, COR^{211}, NR^{211}-CO-R^{211}, NR^{211}-CO-$NR^{211}R^{212}$, NR^{211}-$S0_2$-$NR^{211}R^{212}$, $NR^{211}R^{212}$, C^-alkyl, halo-$C_{1\text{-}6}$-

alkyl, hydroxy-^. $_6$-alkyl, **C**$_{3\cdot 8}$-cycloalkyl, 0 **-C**$_{3\cdot 8}$-cycloalkyl, **C**$_{3\text{-}8}$-heterocycloalkyl and **0-C**$_{\mathbf{3\text{-}8}}$-heterocycloalkyl,

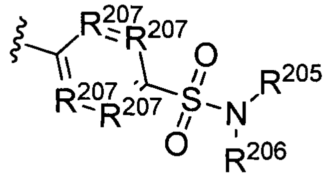
wherein cycloalkyi and heterocycloalkyi are unsubstituted or substituted with 1 to 4 substitutents independently selected from halogen, $C_{1\text{-}3}$-alkyl, halo-d $_{-3}$-alkyl, **OH,** *O-C^.* $_3$-alkyl, 0-halo-d. $_3$-alkyl, S0 $_2$-d. $_3$-alkyl, **COOH** and oxo;

R$^{\mathbf{203}}$ is selected from $C_{1\text{-}1_0}$-alkyl, fluoro **-C**$_{1\text{-}1_0}$-alkyl, **C**$_{\mathbf{0\text{-}6}}$-alkylene **-C**$_{3\cdot 1_0}$-cycloalkyl, **C**$_{0\text{-}6}$-alkylene-**C**$_{\mathbf{3}\text{\_io}}$-heterocycloalkyl, $C_{0\text{-}6}$-alkylene-(6- to 10-membered aryl), **C**$_{\mathbf{0\text{-}6}}$-alkylene-(5- to 10-membered heteroaryl),

wherein alkyl, alkylene, cycloalkyi, heterocycloalkyi, aryl and heteroaryl is unsubstituted or substituted with 1 to 6 substituents independently selected from oxo, halogen, **CN,** d -$_{\mathbf{6}}$-alkyl, halo-d-e-alkyl, **C**$_{3\cdot 6}$-cycloalkyl, **C**$_{3\cdot 6}$-heterocycloalkyl, **OR**$^{\mathbf{212}}$, **C0** $_{\mathbf{2}}$**R**$^{\mathbf{212}}$, **CONR**$^{\mathbf{212}}$**R**$^{\mathbf{212}}$, **COR**$^{\mathbf{212}}$; and

wherein optionally one **CH**$_{\mathbf{2}}$ unit in alkyl or alkylene can be replaced by **O, SO**$_{\mathbf{x}}$**, NH** or N(d. $_3$-alkyl);

R^{204} is



, wherein

R^{205} and R^{206} is independently selected from H, d-e-alkyl, halo-d. $_{\mathbf{6}}$-alkyl, $C_{0\text{-}6}$-alkylene-$C_{3\cdot 8}$-cycloalkyl, C$_{\mathbf{0\text{-}6}}$-alkylene-$C_{3\cdot 8}$-heterocycloalkyl, 5- or 6-membered heteroaryl and 6-membered aryl, wherein alkyl, alkylene, cyclolalkyl, heterocycloalkyi, aryl and heteroaryl are unsubstituted or substituted with 1 to 6 substituents independently selected from halogen, CN, OH, oxo, $C_{1\text{-}3}$-alkyl, halo-d. $_3$-alkyl, O-d $_{-3}$-alkyl, 0-halo-d. $_3$-alkyl and S0 $_2$-d -$_3$-alkyl, NR^{211}R^{212}, C0 $_2$R^{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 substitutents independently selected from fluoro, OH, oxo, **C**$_{\mathbf{1\text{.}4}}$-alkyl and halo-d. $_4$-alkyl;

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

two adjacent R^{207} 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 substitutents independently selected from halogen, OH, oxo, d $_{\cdot 4}$-alkyl and fluoro-d. $_4$-alkyl;

R^{208} is independently selected from H, halogen, CN, d $_{-e}$-alkyl, fluoro-$C_{1\cdot 6}$-alkyl, C_{1_4}-alkylene-OH, d^-alkylene-O-C^-alkyl, d^-alkylene-O-fluoro-d $_{-3}$-alkyl, OH, **O-d-e-**alkyl, 0-fluoro-d- $_{6}$-alkyl, $C_{3\cdot 10}$-cycloalkyl,

wherein alkylene is unsubstituted or substituted with 1 to 3 substituents selected from F and cycloalkyi is unsubstituted or substituted with 1 to 3 substituents independently selected from F, $C_{1\text{-}3}$-alkyl and fluoro-d. $_{3}$-alkyl;

R^{209} is selected from H, halogen, CN, $C_{1\text{-}3}$-alkyl and fluoro-d. $_{3}$-alkyl;

R^{211} is independently selected from H, **Ci-6**-alkyl, $C_{0\text{-}6}$-alkylene-$C_{3\text{-}io}$-cycloalkyl and $C_{0\text{-}e}$-alkylene-$C_{3\cdot 10}$-heterocycloalkyl,

wherein alkyl, alkylene, cycloalkyi and heterocycloalkyi is unsubstituted or substituted with 1 to 6 substituents selected from the group consisting of halogen, CN, OH, oxo, d -$_{3}$-alkyl, halo-**Ci** $_{\cdot 3}$-alkyl, 0-d. $_{3}$-alkyl, 0-halo-d. $_{3}$-alkyl, NH_2, NH(d $_{-3}$-alkyl), N(d $_{-3}$-alkyl)$_2$, $C_{3\cdot 6}$-heterocycloalkyl, $C_{3\text{-}6}$-cycloalkyl and S0 $_2$-d. $_3$-alkyl,

wherein cycloalkyi and heterocycloalkyi 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, d $_{-e}$-alkyl, halo-d. $_{6}$-alkyl and $C_{3\cdot 6}$-cycloalkyl;

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

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

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;

R^{203} is selected from $(CR^8R^9)R^{40}$, (C=0)R $^{4\circ}$, C_3-cycloalkylene-R^{40}, OR^{40}, $NR^{41}R^{40}$ and SO_y-R^7, wherein

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

wherein cycloalkyi and heterocycloalkyi are unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of halogen, OH, oxo, O-d $_{-6}$-alkyl, O-halo-d $_{-s}$-alkyl, d $_{-e}$-alkyl, halo-d $_{-e}$-alkyl, cycloalkyi and heterocycloalkyi;

R^8 and R^9 are independently selected from H, F, $C_{1\text{-}3}$-alkyl, halo-$C_{1\text{-}3}$-alkyl, OH, O-$C_{1\text{-}3}$-alkyl and 0-halo-d. $_{3}$-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, 0-C $_{1-6}$-alkyl, 0-halo-Ci. $_6$-alkyl, C_{1_6}-alkyl and halo-Ci.$_6$-alkyl; and

y is selected from 0, 1 and 2;

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, d-io-alkyl, C_{3-10}-cycloalkyl, $C_{3\cdot10}$-heterocycloalkyl, C_{1-10}-alkylene-$C_{3\cdot10}$-cycloalkyl, C_{1_10}-alkylene-C_{3-10}-heterocycloalkyl, $C_{1\cdot10}$-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}, 0-C $_{2-6}$-alkylene-OR^{211}, C_{1-6}-alkyl, halo-d-e-alkyl, halogen, $C0_2R^{211}$, $CONR^{211}R^{212}$, $CONR^{211}S0_2R^{211}$, COR^{211}, SO_xR^{211}, $S0_3H$, $S0_2NR^{211}R^{212}$, $NR^{211}COR^{211}$, $NR^{211}S0_2R^{211}$, NR^{211}-CO-$NR^{211}R^{212}$, NR^{211}-$S0_2$-$NR^{211}R^{212}$, $C_{3\cdot10}$-cycloalkyl, O-C_3.io-cycloalkyl, $C_{3\cdot10}$-heterocycloalkyl, O-$C_{3\cdot10}$-heterocycloalkyl and $NR^{211}R^{212}$;

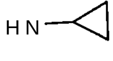
R^{202} is selected from H, C_{1-6}-alkyl, halo-Ci.$_6$-alkyl and hydroxy-C^-alkyl, more preferably R^{202} is hydrogen;

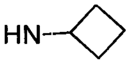
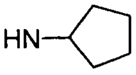
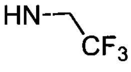
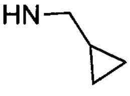
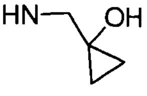
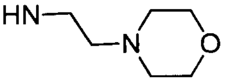
or R^{201} and R^{202} when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing 1 or 2 heteroatoms selected from O, S or N, wherein the ring is unsubstituted or substituted with 1 to 4 substitutents independently selected from halogen, oxo, CN, OR^{211}, SO_xR^{211}, $S0_3H$, $NR^{211}S0_2R^{211}$, $S0_2NR^{211}R^{212}$, $C_{0\text{-}6}$-alkylene-CO_2R^{211}, $CONR^{211}R^{212}$, $C0NR^{211}SO_2R^{211}$, COR^{211}, NR^{211}-CO-R^{211}, NR^{211}-CO-$NR^{211}R^{212}$, NR^{211}-$S0_2$-$NR^{211}R^{212}$, $NR^{211}R^{212}$, C^-alkyl, halo-C^-alkyl, hydroxy-d-e-alkyl, $C_{3\cdot8}$-cycloalkyl, 0-C $_{3\cdot8}$-cycloalkyl, $C_{3\cdot8}$-heterocycloalkyl and 0-C $_{3\cdot8}$-heterocycloalkyl,

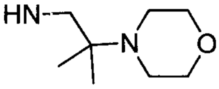
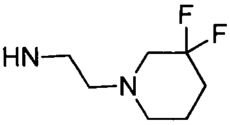
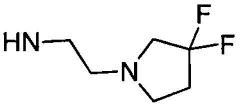
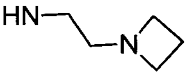
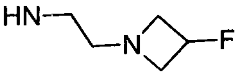
> wherein cycloalkyl and heterocycloalkyl are unsubstituted or substituted with 1 to 4 substitutents independently selected from halogen, C_{1-3}-alkyl, halo-C^-alkyl, OH, O-d. $_3$-alkyl, 0-halo-Ci. $_3$-alkyl, $S0_2$-Ci.$_3$-alkyl, COOH and oxo.

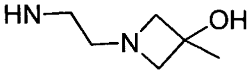
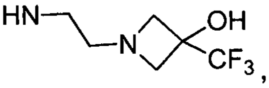
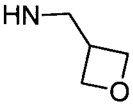
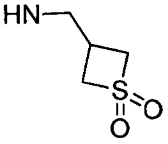
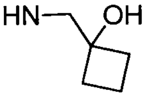
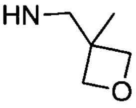
More preferably, R^{201} and R^{202} when taken together with the nitrogen to which they are attached complete a 4- to 6-membered ring containig carbon atoms and optionally containing one additional nitrogen atom, wherein the ring is unsubstituted or substituted with 1 to 4 substitutents independently selected from fluoro, oxo, OR^{211}, $S0_2R^{211}$, $NR^{211}S0_2R^{211}$, $S0_2NR^{211}R^{212}$, $C_{0\text{-}6}$-alkylene-CO_2H, $CONR^{211}R^{212}$, COR^{211}, $NR^{211}R^{212}$, d-e-alkyl, halo-$C_{1\text{-}6}$¬alky!, hydroxy-Ci-$_6$-alkyl, $C_{3\text{-}8}$-cycloalkyl and $C_{3\text{-}8}$-heterocycloalkyl,

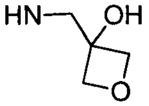
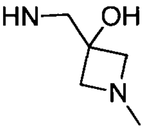
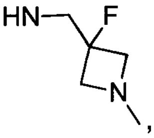
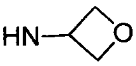
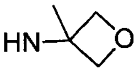
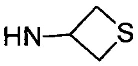
> wherein cycloalkyl and heterocycloalkyl are unsubstituted or substituted with 1 to 4 substitutents independently selected from halogen, C_{1-3}-alkyl, halo-C^-alky!, $S0_2$-Ci_$_3$-alkyl, COOH and oxo.

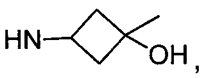
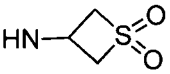
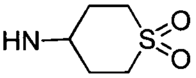
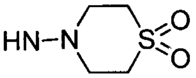
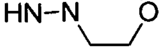
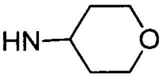
In a preferred embodiment in combination with any of the above or below embodiments of the first alternative $NR^{201}R^{202}$ is selected from NHMe, NHEt, NH^{i}Pr, NH^{t}Bu, $NHCH_2CONH_2$, $NHCH_2CONMe_2$, $NHCH_2CH_2OH$, $NHCH_2CH_2OMe$, $NHCH_2CH_2S0_2Me$, $NHCH_2CH_2S0_2NH_2$, $NH(CH_2)_3OH$, $NH(CH_2)_3OMe$, $NH(CH_2)_4OH$, $NH(CH_2)_4OMe$, $NH(CH_2)_5OH$, $NH(CH_2)_2C0_2H$, $NH(CH_2)_3C0_2H$, $NH(CH_2)_4C0_2H$, $NH(CH_2)_5C0_2H$, $NHCH_2CH(CF_3)OH$, $NHCH_2C(Me)(CF_3)OH$, $NHCH_2CMe_2OH$, $NHCH_2CH_2CMe_2OH$, $NHCH_2CMe_2NHCH_2CF_3$, $NHCH(Me)CMe_2OH$, $NHCH_2CMe_2OMe$, $NHCH_2CMe_2C0_2H$, $NHCH_2CMe_2CONHMe$, $NHCH_2CMe_2CONMe_2$, $NHCH_2CMe_2NHS0_2Me$, $NH(CH_2)_3SOMe$, $NH(CH_2)_5S0_2Me$, $NH(CH_2)_5S0_2NH_2$, $NH(CH_2)_3NHS0_2Me$, $NH(CH_2)_20(CH_2)_2OH$, $NHCH_2CHMeOH$, $NH(CH_2)_5SOMe$, $NH(CH_2)_3S0_2Me$, $NHC(CH_2OH)_3$, $NHCH_2CH(OH)CH_2OH$, $N(CH_2CH_2OH)_2$, ,

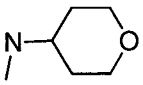
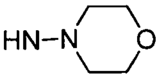
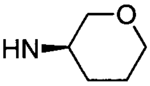
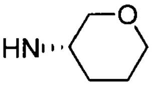
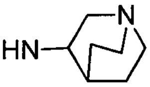
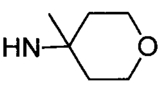
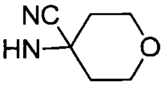
, , , , , ,

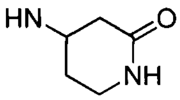
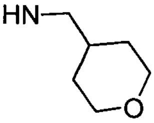
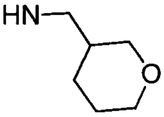
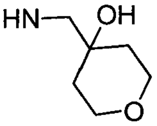
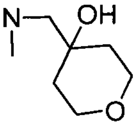
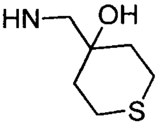
, , , , ,

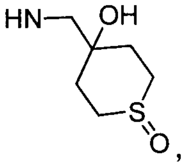
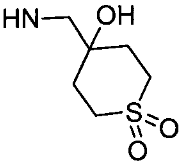
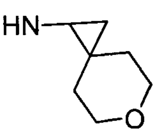
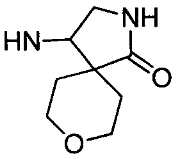
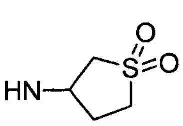
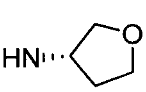
, , , , , ,

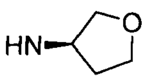
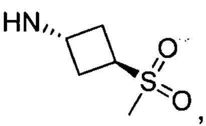
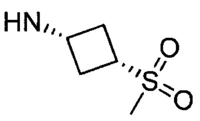
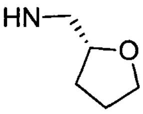
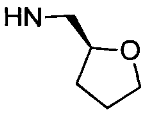
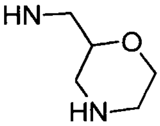
, , , , , , ,

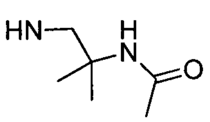
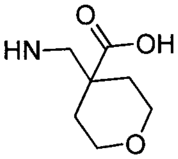
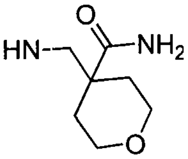
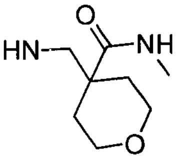
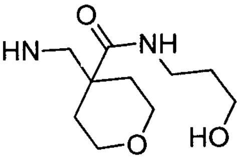
, , , , , ,

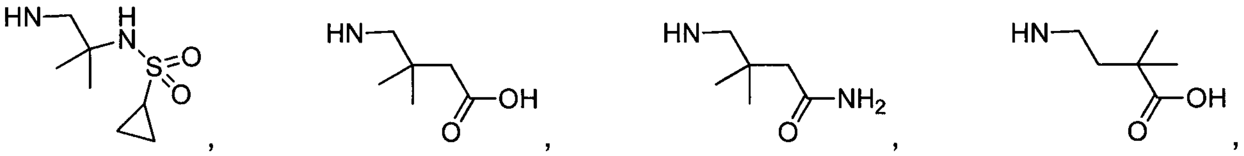
, , , , , , ,

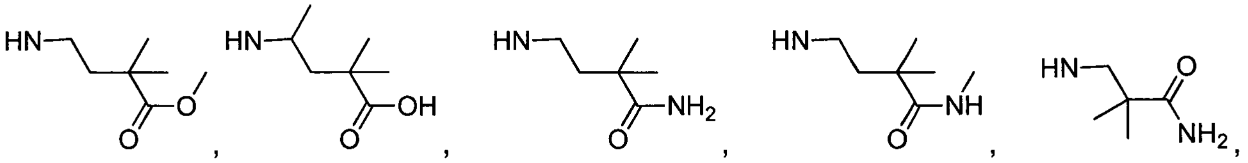
, , , , , ,

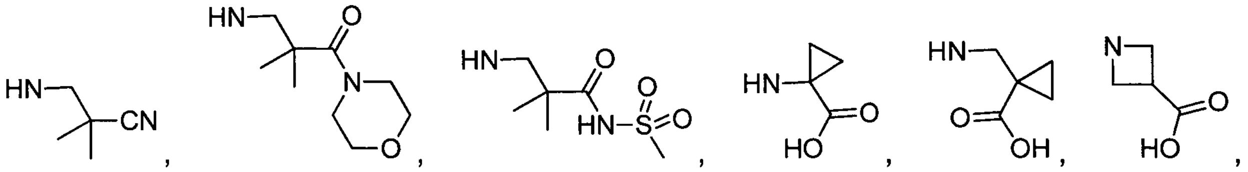
, , , , , ,

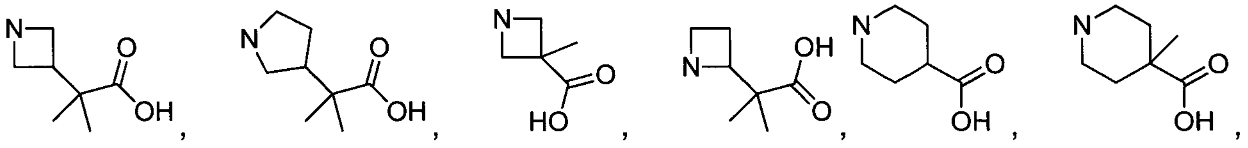
, , , , , ,

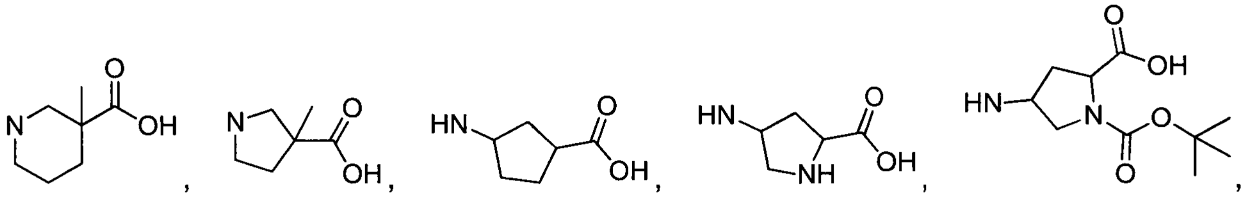
, , , , ,

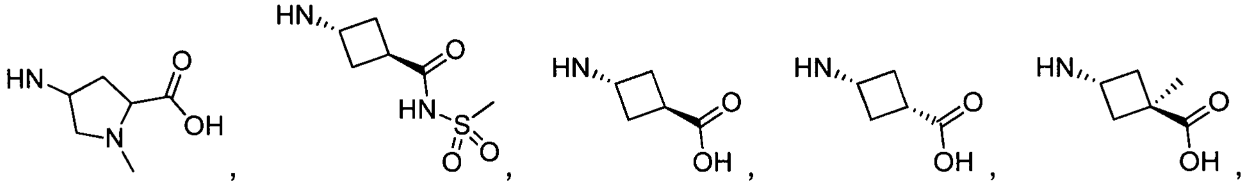


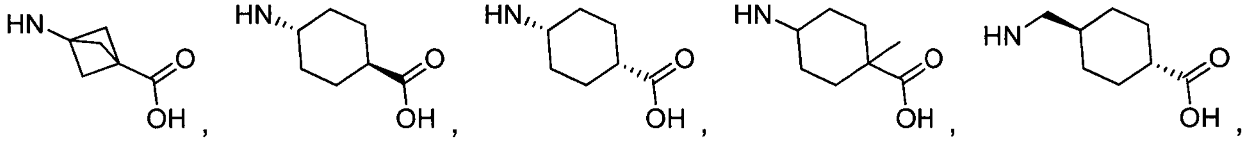


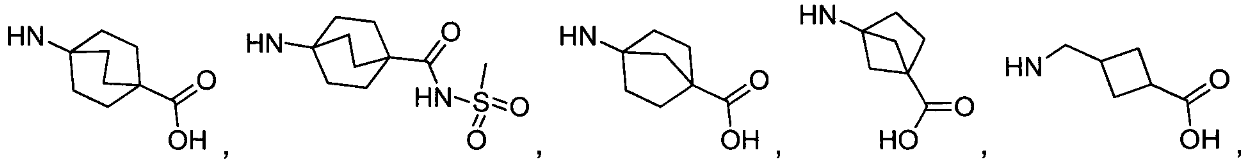


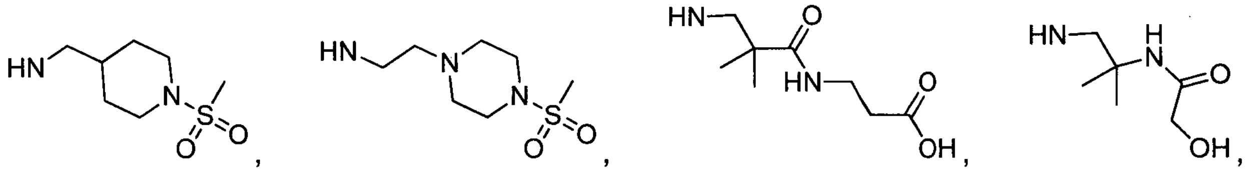


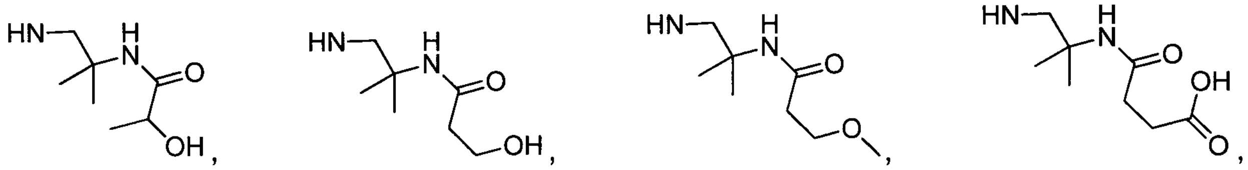


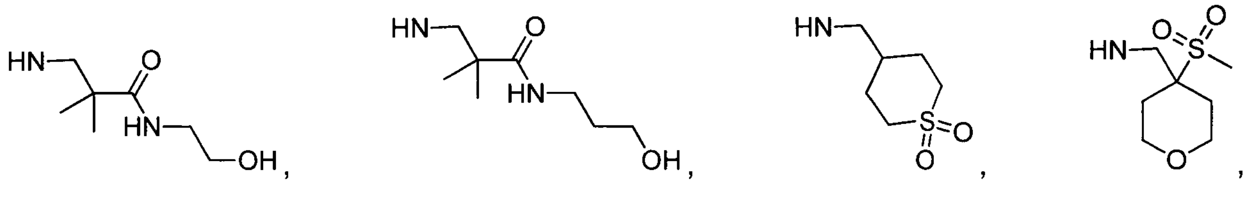


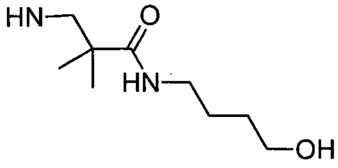
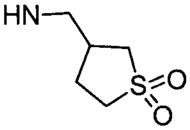
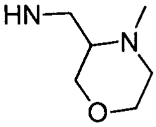
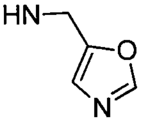
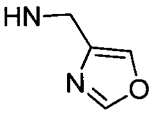
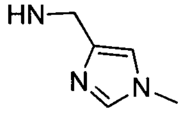
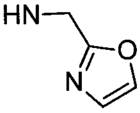
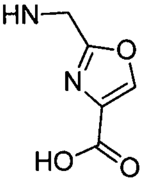
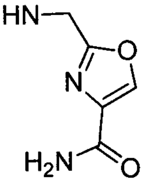
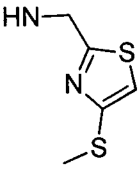
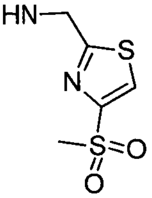
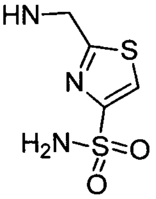
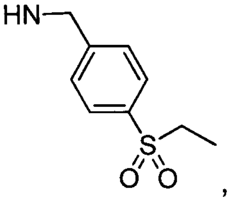
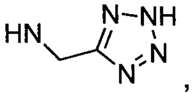
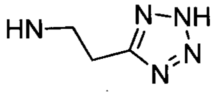
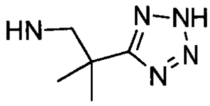
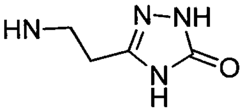
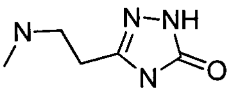
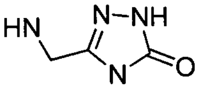
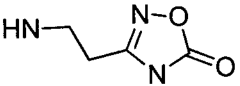
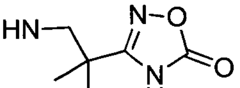
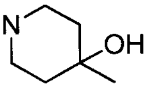
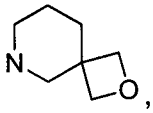
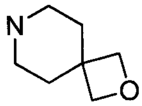
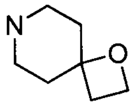
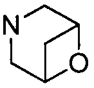
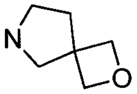
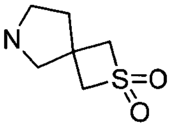
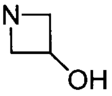
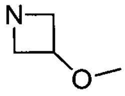
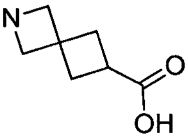
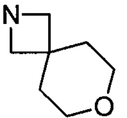
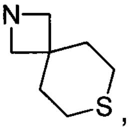
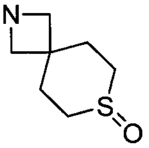
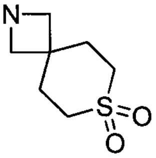
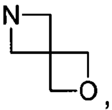
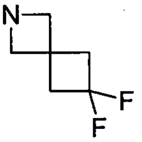
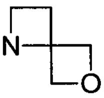
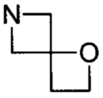
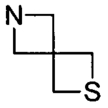
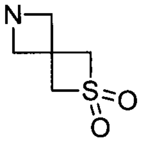
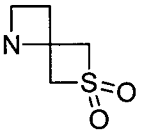
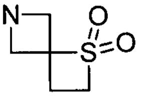
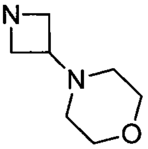
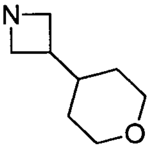
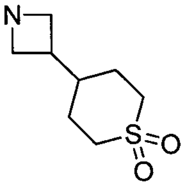
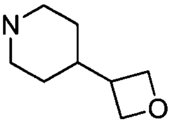
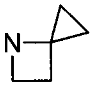
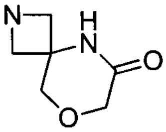
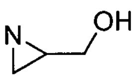
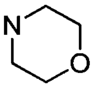
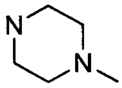
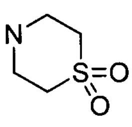
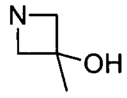
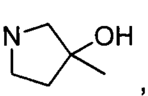
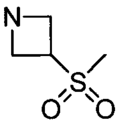
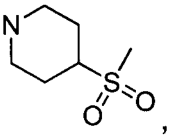
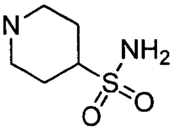
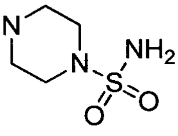
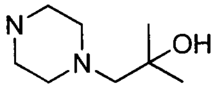
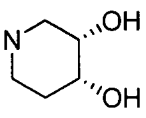
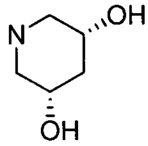




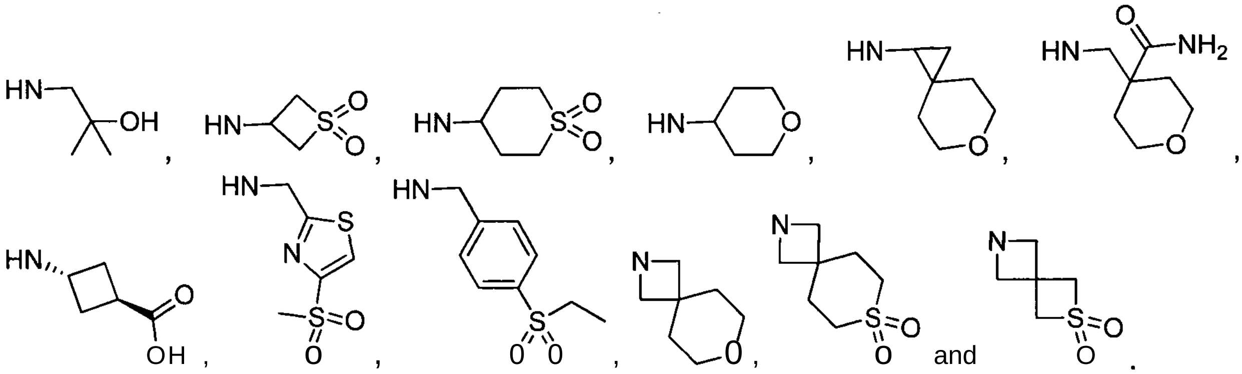




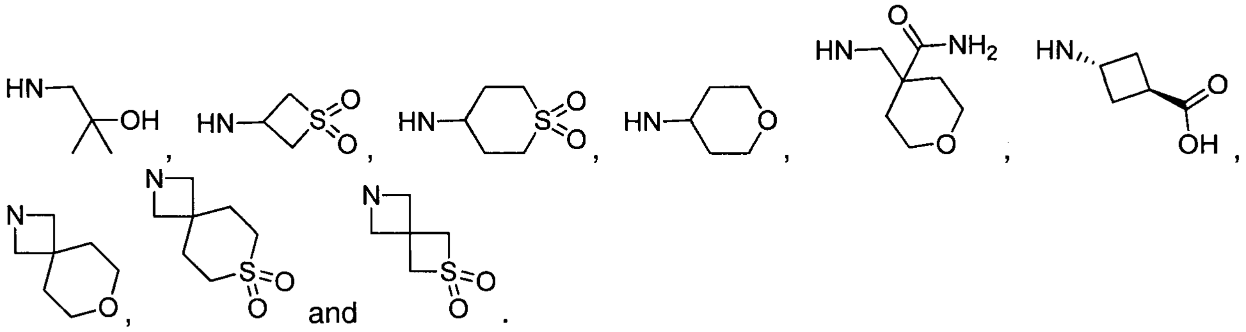


,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
 and
.

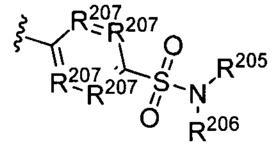
In a more preferred embodiment in combination with any of the above or below embodiments of the first alternative $NR^{201}R^{202}$ is selected from



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



In another preferred embodiment in combination with any of the above or below embodiments of the first alternative R^{204} is



, wherein

R^{205} and R^{206} is independently selected from H, C^-alkyl, halo-C^e-alkyl, $C_{0\text{-}6}$-alkylene-$C_{3\text{-}8}$-cycloalkyl, Co-6-alkylene-$C_{3\text{-}8}$-heterocycloalkyl, 5- or 6-membered heteroaryl and 6-membered aryl, wherein alkyl, alkylene, cyclolalkyi, heterocycloalkyi, aryl and heteroaryl are unsubstituted or substituted with 1 to 6 substituents independently selected from halogen, CN, OH, oxo, $C_{1\text{-}3}$-alkyl, halo-d.a-alkyl, 0-Ci. $_3$-alkyl, O-halo-d-a-alkyl and $S0_2$-$C_{1\text{-}3}$-alkyl, $NR^{211}R^{212}$, $C0_2R^{212}$ 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 substitutents independently selected from fluoro, OH, oxo, d-4-alkyl and halo-Ci-$_4$-alkyl;

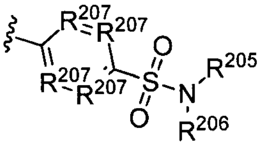
R^{207} is independently selected from N and CR^{208}; or

two adjacent R^{207} 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 substitutents independently selected from halogen, **OH,** oxo, **C**$_{1\text{-}4}$-alkyl and fluoro**-Ci**$_{\cdot 4}$-alkyl;

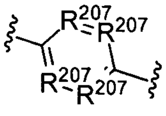
R^{208} is independently selected from **H,** halogen, **CN,** $C_{1\text{-}6}$-alkyl, fluoro**-C**$_{1\cdot 6}$-alkyl, **C**^-alkylene-**OH,** **C**$_{1\cdot 4}$-alkylene-0 **-C**$_{1\text{-}3}$-alkyl, **C**^-alkylene **-O**-fluoro-d $_{\text{-}3}$-alkyl, **OH,** O-C^-alkyl, **O**-fluoro**-C,.** $_6$-alkyl, **C**$_{3\text{-}10}$-cycloalkyl,

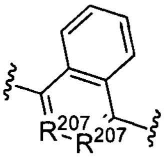
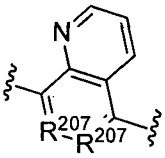
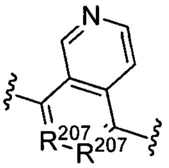
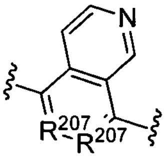
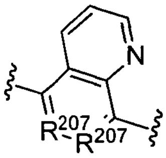
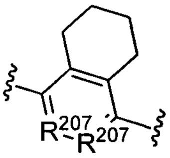
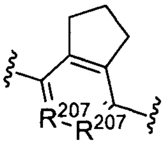
wherein alkylene is unsubstituted or substituted with 1 to 3 substituents selected from F and cycloalkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from F, $C_{1\text{-}3}$-alkyl and fluoro-d $_{\text{-}3}$-alkyl.

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

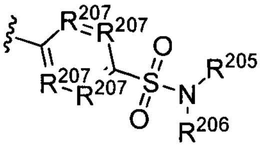

,

wherein all R^{207} are CR^{208} or one R^{207} is N and the three other R^{207} are CR^{208}; or

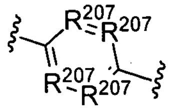
wherein  is selected from

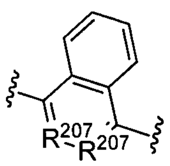
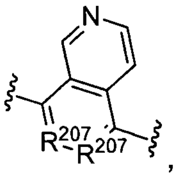
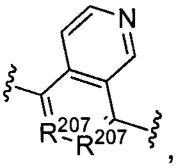
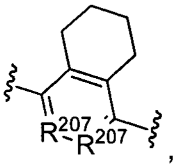
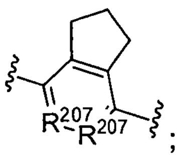
,
,
,
,
,
,
, wherein the additional ring is unsubstituted or substituted with 1 to 4 substitutents independently selected from halogen, **OH,** oxo, **Ci**$_{\text{-}4}$-alkyl and fluoro-C $_{1\text{-}4}$-alkyl.

In an even more preferred embodiment in combination with any of the above or below embodiments of the first alternative R^{204} is


,

wherein all R^{207} are CR^{208} or one R^{207} is N and the three other R^{207} are CR^{208}; and

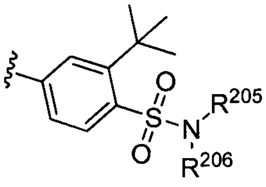
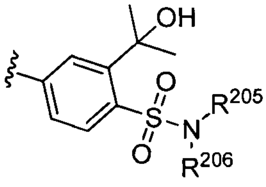
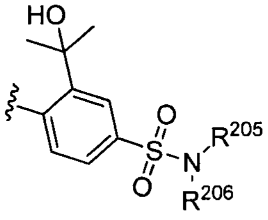
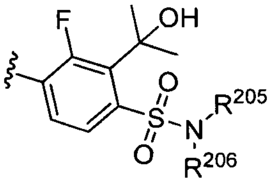
wherein one R^{208} is independently selected from or two adjacent R^{208} are independently selected from fluoro, chloro, methyl, CHF_2, CF_3, CMe_2OH, $OCHF_2$ and OCF_3 while the remaining R^{208} residues are hydrogen; or wherein  is selected from

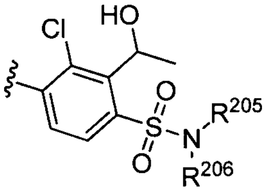
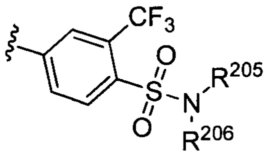
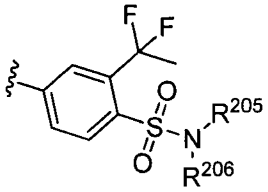
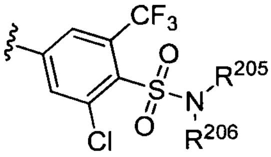
, , , , ; and

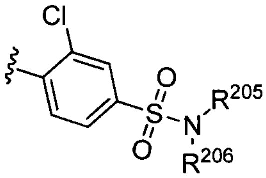
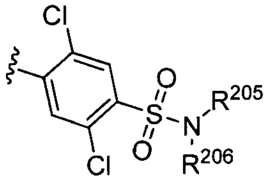
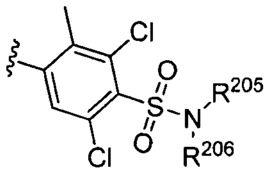
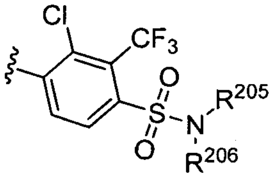
wherein both R^{207} are CR^{208} or one R^{207} is N and the other is CR^{208}; and

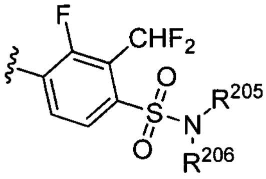
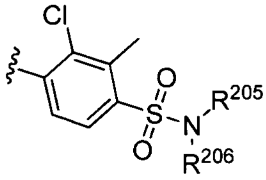
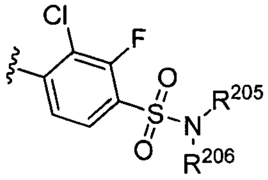
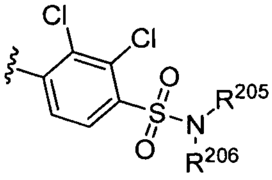
R^{208} is independently selected from H, fluoro, chloro, CH_3 and CF_3.

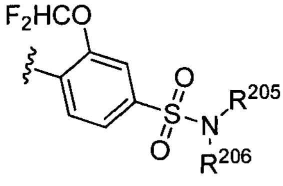
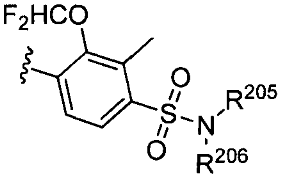
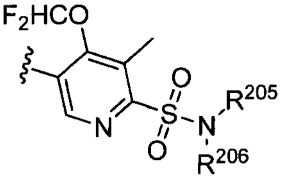
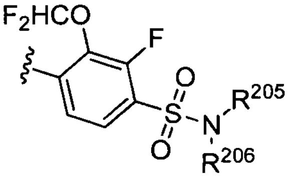
In an alternative preferred embodiment in combination with any of the above or below embodiments of the first alternative R^{204} is selected from

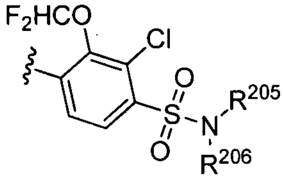
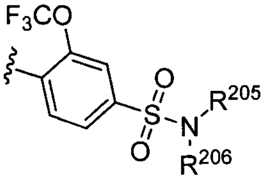
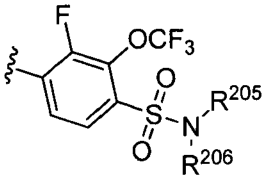
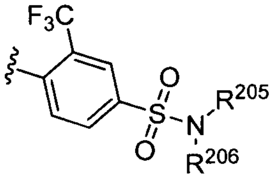
, , , ,

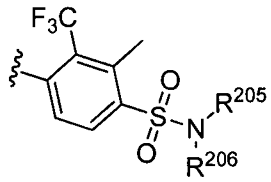
, , , ,

, , , ,

, , , ,

, , , ,

, , , ,



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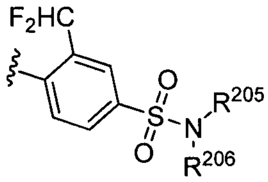

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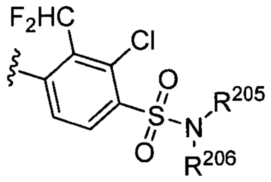

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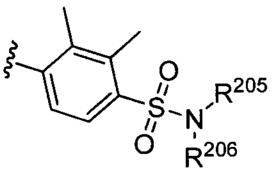

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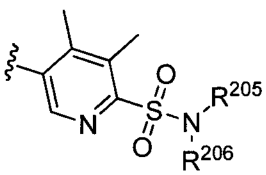

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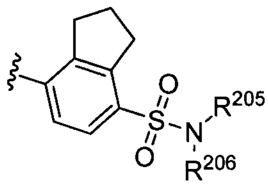

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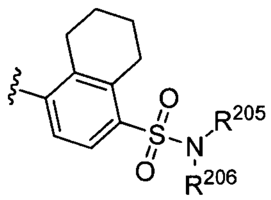

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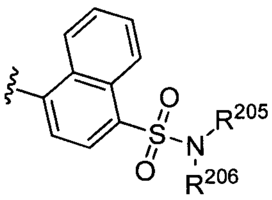

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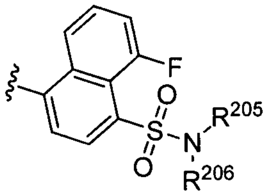

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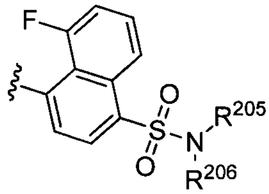

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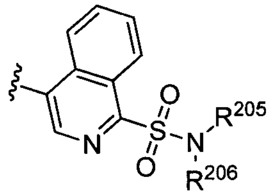

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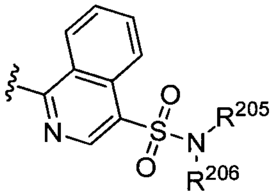

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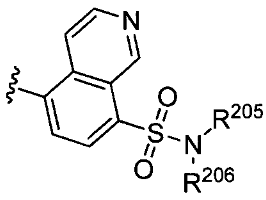

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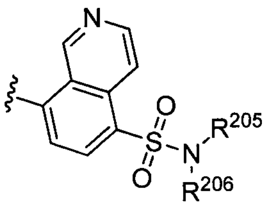


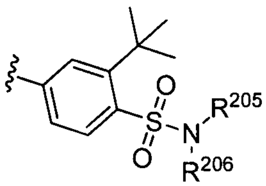
,

wherein

R^{205} and R^{206} is independently selected from H, Ci.$_6$-alkyl, halo-Ci-e-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, cyclolalkyi, heterocycloalkyi, aryl and heteroaryl are unsubstituted or substituted with 1 to 6 substituents independently selected from halogen, CN, OH, oxo, C_{1-3}-alkyl, halo-C^-alkyl, O-C^-alkyl, O-halo-C^-alkyl and SO_2-Ci.$_3$-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 substitutents independently selected from fluoro, OH, oxo, C_{1-4}-alkyl and halo-Ci-$_4$-alkyl.

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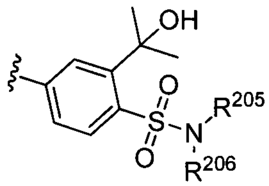
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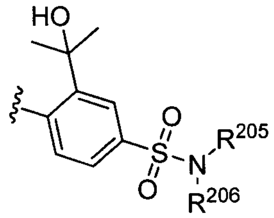
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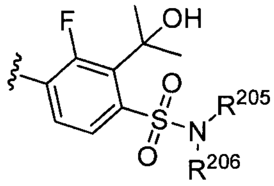
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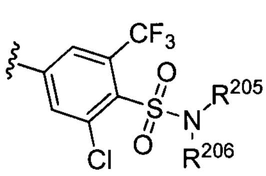
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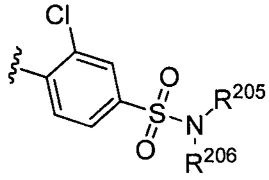
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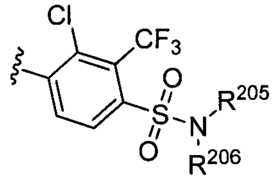
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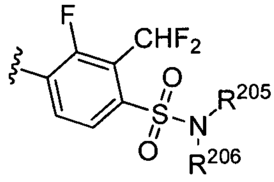
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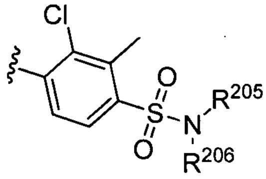
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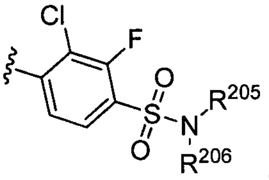
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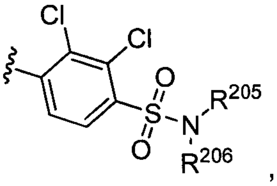
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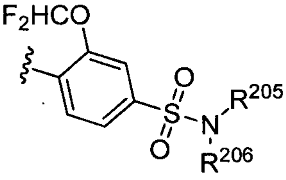
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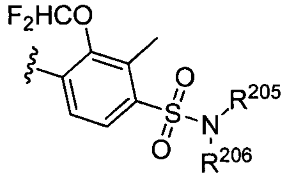
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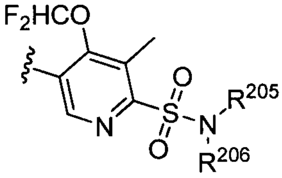
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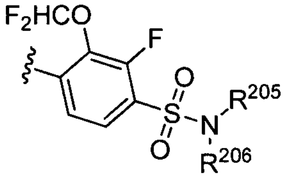
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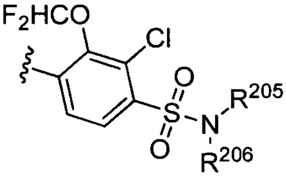
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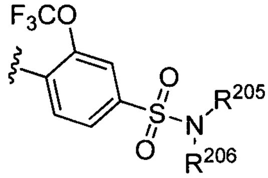
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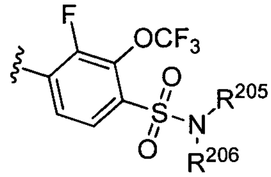
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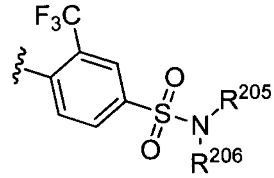
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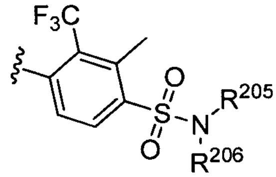
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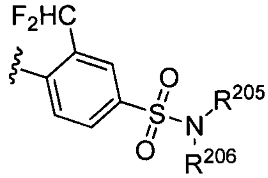
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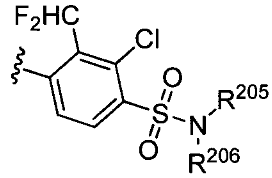
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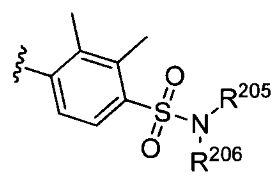
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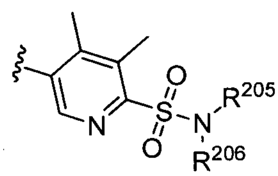
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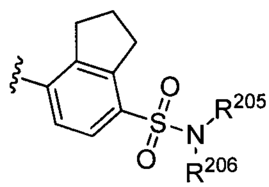
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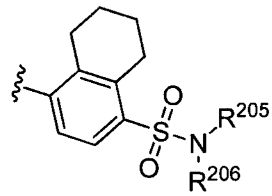
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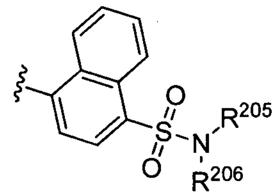
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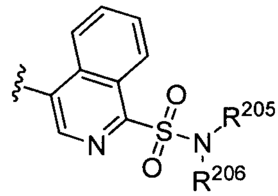
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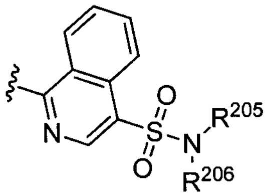
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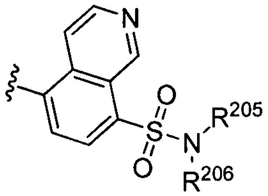
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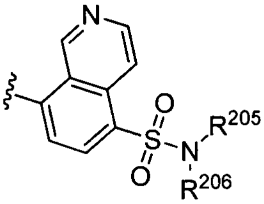
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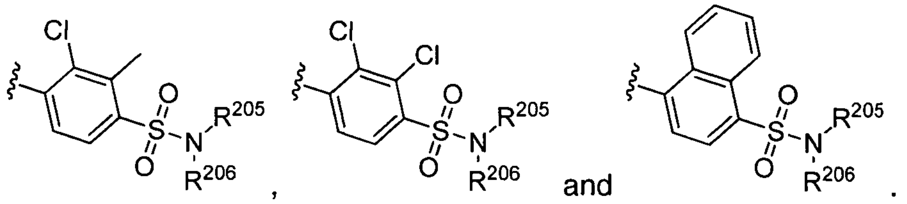
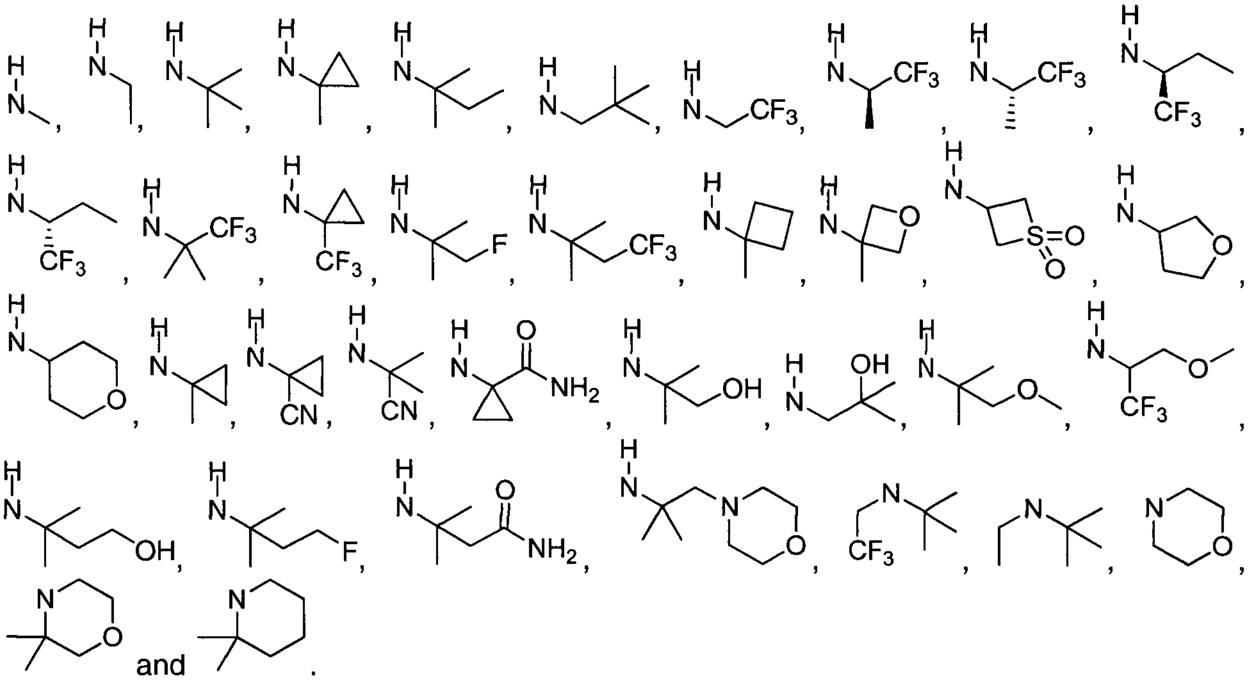
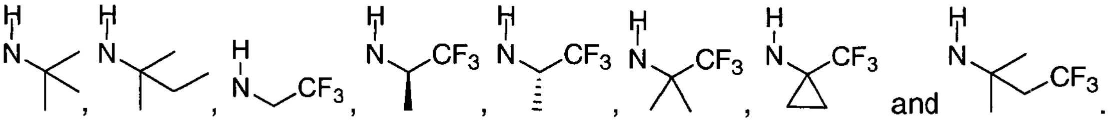
Even more preferably in combination with any of the above or below embodiments of the first alternative, R^{204} is selected from



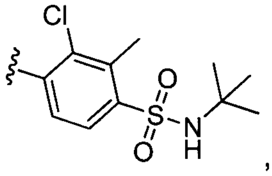
In another preferred embodiment in combination with any of the above or below embodiments of the first alternative $NR^{205}R^{206}$ is selected from



In a more preferred embodiment in combination with any of the above or below embodiments of the first alternative $NR^{205}R^{206}$ is preferably



In another preferred embodiment in combination with any of the above or below embodiments of the first alternative R^{204} is selected from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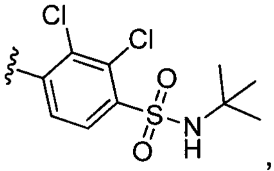
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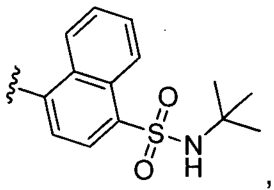
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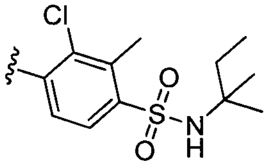
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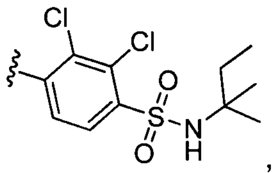
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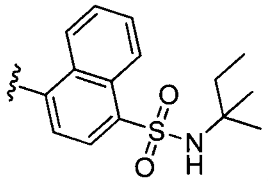
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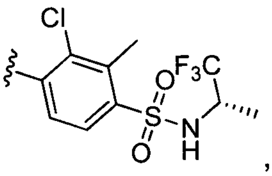
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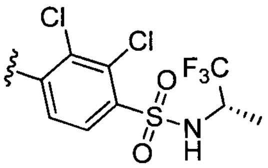
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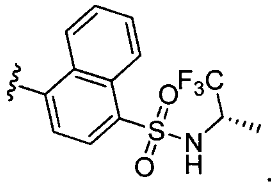
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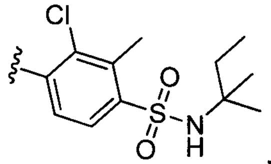
In a more preferred embodiment in combination with any of the above or below embodiments of the first alternative R^{204} is selected from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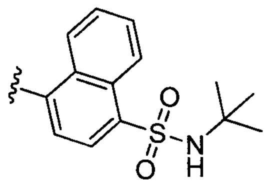
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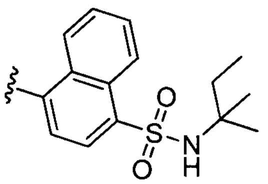
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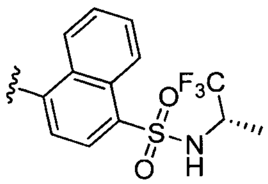
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In another preferred embodiment in combination with any of the above or below embodiments of the first alternative R^{203} is selected from C$_{1\text{-}10}$-alkyl, fluoro-Ci-i $_0$-alkyl, Co-$_6$-alkylene-C $_{3\text{-}10}$-cycloalkyl, C$_{0\text{-}6}$-alkylene-C $_3$.io-heterocycloalkyl, C$_{0\text{-}6}$-alkylene-(6- to 10-membered aryl), C$_{0\text{-}6}$-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, C$_1$.$_6$-alkyl, halo-d. $_6$-alkyl, C$_{3\text{-}6}$-cycloalkyl, C$_{3\text{-}6}$-heterocycloalkyl, OR^{212}, C0 $_2$R^{212}, CONR^{212}R^{212}, COR^{212}; and

wherein optionally one CH$_2$ unit in alkyl or alkylene can be replaced by O, SO$_x$, NH or N(Ci. $_3$-alkyl).

In an equally preferred embodiment in combination with any of the above or below embodiments of the first altenative, R^{203} is selected from d $_{\text{-}10}$-alkyl, fluoro-Ci-i $_0$-alkyl, **C$_{0\text{-}6}$**-alkylene-C $_3$_io-cycloalkyl, C$_0$.$_6$-alkylene-C $_{3\text{-}10}$-heterocycloalkyl, C$_{0\text{-}6}$-alkylene-(5- to 10-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$_{1\text{-}6}$-alkyl, halo-d-e-alkyl, C$_{3\text{-}6}$-cycloalkyl, C$_{3\text{-}6}$-heterocycloalkyl, OR^{212}, C0 $_2$R^{212}, CONR ^{212}R^{212}, COR^{212}; and wherein optionally one CH_2 unit in alkyl or alkylene can be replaced by O, SO_x, NH or N($C_{1\text{-}3}$-alkyl).

In a more preferred embodiment in combination with any of the above or below embodiments of the first altenative, R^{203} is selected from $C_{1\text{-}10}$-alkyl, fluoro-Ci $_{-10}$-alkyl, $C_{0\text{-}6}$-alkylene-$C_{3\text{-}10}$-cycloalkyl and Co-6-alkylene-$C_{3\text{-}10}$-heterocycloalkyl,

wherein alkyl, alkylene, cycloalkyl and heterocycloalkyl is unsubstituted or substituted with 1 to 6 substituents independently selected from oxo, halogen, CN, d $_{-e}$-alkyl, halo-$C_{1\text{-}e}$-alkyl, $C_{3\text{-}6}$-cycloalkyl, $C_{3\text{-}6}$-heterocycloalkyl, OR^{212}, $C0_2R^{212}$, $CONR^{212}R^{212}$, COR^{212}; and

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

In a more preferred embodiment in combination with any of the above or below embodiments of the first alternative R^{203} is selected from $C_{1\text{-}8}$-alkyl, fluoro-$C_{1\text{-}8}$-alkyl, $C_{0\text{-}2}$-alkylene-$C_{3\text{-}8}$-cycloalkyl, $C_{0\text{-}2}$-alkylene-$C_{3\text{-}8}$-heterocycloalkyl, $C_{0\text{-}2}$-alkylene-(6- to 10-membered aryl), $C_{0\text{-}2}$-alkylene-(5- to 10-membered heteroaryl),

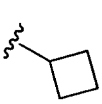
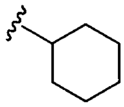
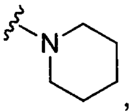
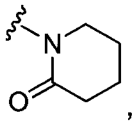
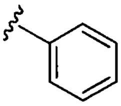
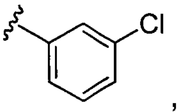
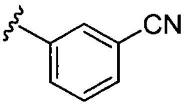
wherein alkyl, alkylene, cycloalkyl, heterocycloalkyl, aryl and heteroaryl is unsubstituted or substituted with 1 to 6 substituents independently selected from oxo, fluoro, chloro, CN, $CONH_2$, Ci-3-alkyl, fluoro-Ci $_{-3}$-alkyl, $C_{3\text{-}6}$-cycloalkyl, $C_{3\text{-}6}$-heterocycloalkyl and $OC_{1\text{-}4}$-alkyl.

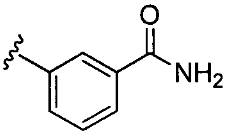
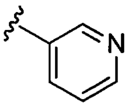
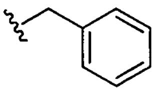
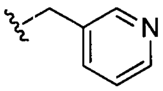
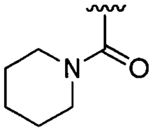
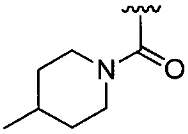
In a more preferred embodiment in combination with any of the above or below embodiments of the first alternative R^{203} is selected from C^-alkyl, fluoro-Ci $_{-6}$-alkyl, $C_{3\text{-}8}$-cycloalkyl, $C_{3\text{-}8}$-heterocycloalkyl, 6-membered aryl, 6-membered heteroaryl, CH_2-(6-membered aryl), CH_2-(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),

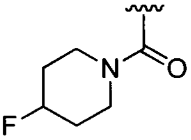
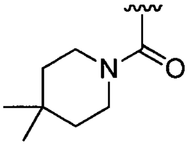
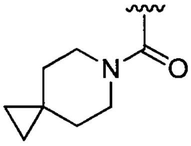
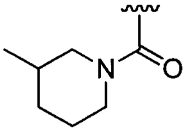
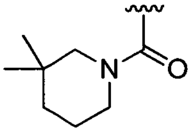
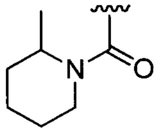
wherein cycloalkyl and heterocycloalkyl is unsubstituted or optionally substituted with 1 to 4 substituents independently selected from oxo, $C_{1\text{-}3}$-alkyl, fluoro-$C_{1\text{-}3}$-alkyl and $C_{3\text{-}8}$-cycloalkyl; and

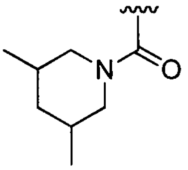
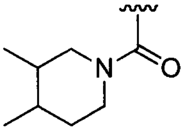
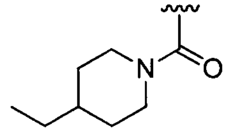
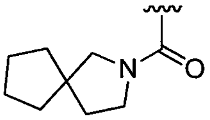
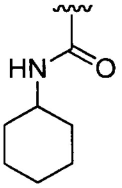
wherein aryl and heteroaryl is optionally substituted with 1 to 3 substituents independently selected from fluoro, chloro, CN, C^-alkyl and fluoro-Ci $_{-3}$-alkyl.

In a more preferred embodiment in combination with any of the above or below embodiments of the first alternative R^{203} is selected from CHF_2, CH_2CH_3, $CH_2CH_2CH_3$, CMe_3, CH_2OCMe_3,

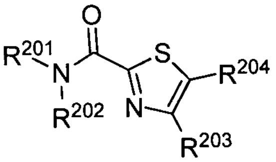
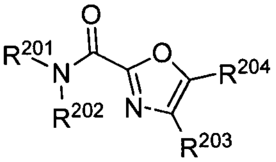
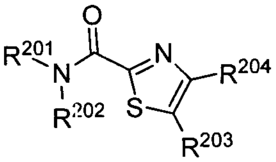
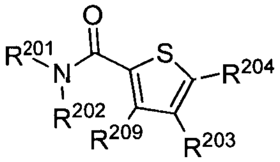
, , , , , , ,

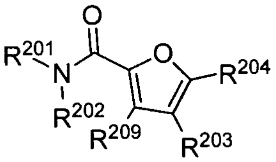
, , , , , ,

, , , , , ,

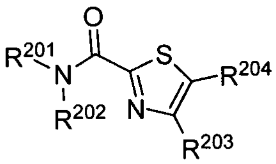
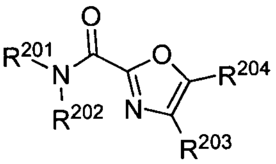
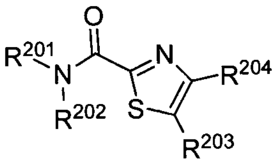
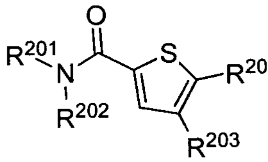
, , , , and .

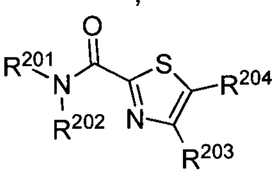
In another preferred embodiment in combination with any of the above or below embodiments of the first alternative the compound is represented by a Formula selected from

, , ,  and

, wherein R^{209} is selected from H, fluoro, chloro and methyl.

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

, ,  and ;

even more preferably by Formula .

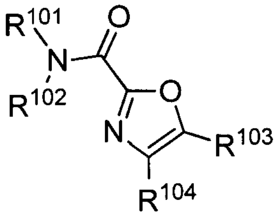
The invention also provides the compound of the first alternative of the invention for use as a medicament.

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 RORγ receptor.

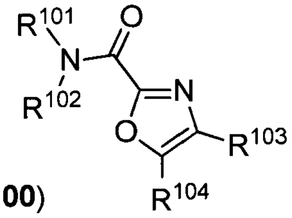
Also provided is the compound of the first alternative of the invention in treating **ROFty** mediated inflammatory and autoimmune diseases. Preferably, the disease is selected from the group consisting of rheumatoid arthritis, ankylosing spondylitis, lupus erythematosus, psoriasis, psoriatic arthritis, 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 thromobotic 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 first alternative of the invention and a pharmaceutically acceptable carrier.

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



(100)



(100')

an enantiomer, diastereomer, tautomer, /V-oxide, solvate, formulation and pharmaceutically acceptable salt thereof,

wherein

R^{101} and **R^{102}** 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}-alky!, 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^{111}**, 0-C_{2-6}-alkylene **-OR^{111}**, **C_{1-6}**-alky!, halo-d -e-alkyl, halogen, **$C0_2R^{111}$**, **$CONR^{111}R^{112}$**, **$CONR^{111}S0_2R^{111}$**, **COR^{111}**, **SO_xR^{111}**, $S0_3H$, **$S0_2NR^{111}R^{112}$**, **$NR^{111}COR^{111}$**, **$NR^{111}S0_2R^{111}$**, **NR^{111}-CO-$NR^{111}R^{112}$**, **NR^{111}**-$S0_2$-**$NR^{111}R^{112}$**, **C_{3-10}**-cycloalkyl, **O-C_{3-10}**-cycloalkyl, **C_{3-10}**-heterocycloalkyl, **O-C_{3-10}**-heterocycloalkyl and **$NR^{111}R^{112}$**;

or **R^{101}** and **R^{102}** 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 substitutents independently selected from halogen, oxo, **CN, OR^{111}, SO_xR^{111}**, $S0_3H$, NR^{111}S0$_2$R^{111}, S0$_2$NR^{111}R^{112}, C$_{0\text{-}6}$-alkylene-CO$_2$R^{111}, CONR^{111}R^{112}, CONR^{111}S0$_2$R^{111}, COR^{111}, NR^{111}-CO-R^{111}, NR^{111}-CO-NR^{111}R^{112}, NR^{111}-S0$_2$-NR^{111}R^{112}, NR^{111}R^{112}, d-e-alkyl, halo-Ch¬ alky!, hydroxy-Ci-6-alkyl, C$_{3\text{-}8}$-cycloalkyl, 0-C$_{3\text{-}8}$-cycloalkyl, C$_{3\text{-}8}$-heterocycloalkyl and 0-C$_{3\text{-}8}$-heterocycloalkyl,

wherein cycloalkyi and heterocycloalkyl are unsubstituted or substituted with 1 to 4 substitutents independently selected from halogen, C$_{1\text{-}3}$-alkyl, halo-Ci$_{\text{-}3}$-alkyl, OH, O-C1-3-alkyl, 0-halo-d.$_3$-alkyl, S0$_2$-d.$_3$-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 N, O and S,

wherein aryl and heteroaryl is optionally substituted with 1 to 5 substituents independently selected from halogen, C$_{1\text{-}6}$-alkyl, C$_{1\text{-}6}$-alkenyl, C$_{1\text{-}6}$-alkynyl, halo-Ci$_{\text{-}6}$-alkyl, OH, O-Ci-6 -alkyl, 0-halo-d.$_6$-alkyl, Co-6 -alkylene-C$_{3\text{-}10}$-cycloalkyl, C$_{0\text{-}6}$-alkylene-C$_{3\text{-}10}$-heterocycloalkyl, C$_{0\text{-}6}$-alkylene-(5- or 6-membered heteroaryl), C$_{1\text{-}6}$-alkylene-0-R^{131}, C$_{0\text{-}6}$-alkylene-CN, C$_{0\text{-}6}$-alkylene-N(R^{131})$_2$, 0-C$_{3\text{-io}}$ -cycloalkyl, 0-d.$_6$-alkylene-0-R^{131}, O-C$_{3\text{-}10}$-heterocycloalkyl, C$_{0\text{-}6}$-alkylene-COOR^{131}, C$_{0\text{-}6}$-alkylene-C(O)R^{131}, C$_{0\text{-}6}$-alkylene-C(0)N(R^{131})$_2$, C$_{0\text{-}6}$-alkylene-N(R^{131})C(O)R^{131}, C$_{0\text{-}6}$-alkylene-SO-R^{131}, C$_{0\text{-}6}$-alkylene-SO$_2$-R^{131}, Co-6 -alkylene-S0$_2$-N(R^{131})$_2$, C$_{0\text{-}6}$-alkylene-N(R^{131})SO$_2$-R^{131}, C$_{0\text{-}6}$-alkylene-SO$_2$-C$_{3\text{-}10}$-heterocycloalkyl and C$_{0\text{-}6}$-alkylene-S0$_2$-C$_{3\text{-io}}$ -heterocycloalkyl,

wherein alkylene, cycloalkyi, 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$_{1\text{-}3}$-alkyl, halo-d.$_3$-alkyl, OH, oxo, =N-OR^{132}, O-C$_{1\text{-}3}$-alkyl and O-halo-Ci$_{\text{-}3}$-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, d-e-alkyl, halo-d.$_6$-alkyl, C$_{3\text{-}6}$-cycloalkyl, C$_{3\text{-}6}$-heterocycloalkyl, oxo, =N-OR^{132}, OH, 0-d.$_6$-alkyl and 0-halo-d-$_6$-alkyl;

R^{104} is selected from (CR^{108}R^{109})R^{140}, (C=0)R^{140}, OR^{140}, SO$_y$-R^{107} and C$_{3\text{-}6}$-cycloalkyl, which is spirocyclic fused with R^{140},

wherein cycloalkyi is unsubstituted or substituted with 1 to 4 substituents independently selected from the group consisting of F, methyl and CF$_3$;

R^{107} is selected from C$_{3\text{-}10}$-cycloalkyl and C$_{3\text{-}10}$-heterocycloalkyl, wherein cycloalkyl and heterocycloalkyi are unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of halogen, OH, oxo, O-Ci-e-alkyl, O-halo-C $_1$-e-alkyl, C_{1-6}-alkyl, halo-C^e-alkyl, cycloalkyl and heterocycloalkyi;

R^{108} is independently selected from H, F, d $_{-3}$-alkyl, halo-Ci. $_3$-alkyl, OH, 0-Ci- $_3$-alkyl and O-halo-C $_{1-3}$-alkyl;

R^{109} is selected from H, F, d $_{-3}$-alkyl and halo-C^-alkyl;

R^{111} is independently selected from H, C_{1-6}-alkyl, C_{0-6}-alkylene-C $_3$.io-cycloalkyl and C_{0-6}-alkylene-C $_{3\cdot10}$-heterocycloalkyl,

wherein alkyl, alkylene, cycloalkyl and heterocycloalkyi is unsubstituted or substituted with 1 to 6 substituents selected from the group consisting of halogen, ON, OH, oxo, d -$_3$-alkyl, halo-d. $_3$-alkyl, O-d $_{.3}$-alkyl, 0-halo-d. $_3$-alkyl, NH_2, NH(Ci. $_3$-alkyl), N(d $_{.3}$-alkyl)$_2$, C_{3-6}-heterocycloalkyl, $C_{3\cdot6}$-cycloalkyl and S0 $_2$-C_{1-3}-alkyl,

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

R^{112} is independently selected from H, Ci-e-alkyl, halo-Ci_6-alkyl and $C_{3\cdot6}$-cycloalkyl;

R^{131} is independently selected from H, $C_{1\cdot6}$-alkyl, halo-Ci. $_6$-alkyl, C_{0-6}-alkylene-C $_{3\cdot8}$-cycloalkyl, C_{0-6}-alkylene-C $_{3-8}$-heterocycloalkyl, 5- or 6-membered heteroaryl and 6-membered aryl, wherein alkyl, alkylene, cyclolalkyi, heterocycloalkyi, aryl and heteroaryl are unsubstituted or substituted with 1 to 6 substituents independently selected from halogen, ON, OH, oxo, =N-OR^{132}, C_{1-3}-alkyl, halo-d. $_3$-alkyl, 0-d. $_3$-alkyl, 0-halo-d. $_3$-alkyl and S0 $_2$-$C_{1\cdot3}$-alkyl;

and optionally wherein two R^{131} 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 substitutents independently selected from fluoro, OH, oxo, C_{1-4}-alkyl and halo-Ci $_{-4}$-alkyl;

R^{132} is independently selected from H, d $_{-6}$-alkyl and halo-C^-alkyl and C_{3-6}-cycloalkyl;

R^{140} 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, 0 -C_{1-6}-alkyl, O-halo-Ci. $_6$-alkyl, $C_{1\cdot6}$-alkyl, halo-Ci. $_6$-alkyl, $C_{3\cdot8}$-cycloalkyl and $C_{3\cdot8}$-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 R^{101} is selected from H, d $_{\cdot10}$-alkyl, $C_{3\cdot10}$-cycloalkyl, C_{3-10}-heterocycloalkyl, $C_{1\cdot10}$-alkylene-C $_{3\cdot10}$-cycloalkyl, C_{1-1}o-alkylene-d-io-heterocycloalkyl, O_{1-10}-alkylene-(5-membered heteroaryl), C_{1-10}-alkylene-(6-membered aryl), d $_{\cdot10}$-alkylene-(6-

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, OR^{111}, 0-C$_{2\text{-}6}$-alkylene-OR^{111}, d-e-alkyl, halo-Ci-$_6$-alkyl, halogen, C0$_2$R^{111}, CONR^{111}R^{112}, CONR^{111}S0$_2$R^{111}, COR^{111}, SO$_x$R^{111}, S0$_3$H, S0$_2$NR^{111}R^{112}, NR^{111}COR^{111}, NR^{111}S0$_2$R^{111}, NR^{111}-CO-NR^{111}R^{112}, NR^{111}-S0$_2$-NR^{111}R^{112}, C$_{3\text{-}8}$-cycloalkyl, 0-C$_{3\text{-}8}$-cycloalkyl, C$_{3\text{-}8}$-heterocycloalkyl, 0-C$_{3\text{-}8}$-heterocycloalkyl and NR^{111}R^{112};

R^{102} are selected from the group consisting of H, C$_{1\text{-}3}$-alkyl, fluoro-C$_{1\text{-}}$s-alkyl and hydroxy-Ci_$_3$-alkyl, more preferably R^{102} is hydrogen;

or R^{1o1} and R^{102} 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 substitutents independently selected from halogen, oxo, CN, OR^{111}, SO$_x$R^{111}, S0$_3$H, NR^{111}S0$_2$R^{111}, S0$_2$NR^{111}R^{112}, C$_{0\text{-}6}$-alkylene-CO$_2$R^{111}, CONR^{111}R^{112}, CONR^{111}S0$_2$R^{111}, COR^{111}, NR^{111}-CO-R^{111}, NR^{111}-CO-NR^{111}R^{112}, NR^{111}-S0$_2$-NR^{111}R^{112}, NR^{111}R^{112}, d-e-alkyl, halo-d-e-alkyl, hydroxy-Ci.$_6$-alkyl, C$_{3\text{-}8}$-cycloalkyl, 0-C$_{3\text{-}8}$-cycloalkyl, C$_{3\text{-}8}$-heterocycloalkyl and 0-C$_{3\text{-}8}$-heterocycloalkyl,

> wherein cycloalkyl and heterocycloalkyl are unsubstituted or substituted with 1 to 4 substitutents independently selected from halogen, **Ci**.$_3$-alkyl, halo-Ci.$_3$-alkyl, OH, **O-C1-**$_3$-alkyl, 0-halo-Ci-$_3$-alkyl, S0$_2$-Ci.$_3$-alkyl, COOH and oxo.

More preferably, R^{101} and R^{102} 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 substitutents independently selected from fluoro, oxo, OR^{111}, S0$_2$R^{111}, NR^{111}S0$_2$R^{111}, S0$_2$NR^{111}R^{112}, C$_{0\text{-}6}$-alkylene-CO$_2$H, CONR^{111}R^{112}, COR^{111}, NR^{111}R^{112}, d-e-alkyl, halo-C^-alkyl, hydroxy-**C**$_{1\text{-}6}$-alkyl, C$_{3\text{-}8}$-cycloalkyl and C$_{3\text{-}8}$-heterocycloalkyl,

> wherein cycloalkyl and heterocycloalkyl are unsubstituted or substituted with 1 to 4 substitutents independently selected from halogen, C$_{1\text{-}3}$-alkyl, halo-d$_{\text{-}3}$-alkyl, S0$_2$-Ci.$_3$-alkyl, COOH and oxo.

In a preferred embodiment in combination with any of the above or below embodiments of the second alternative NR^{101}R^{102} is selected from NHMe, NHEt, NH'Pr, NH'Bu, NHCH$_2$CONH$_2$, NHCH$_2$CONMe$_2$, NHCH$_2$CH$_2$OH, NHCH$_2$CH$_2$OMe, NHCH$_2$CH$_2$S0$_2$Me, NHCH$_2$CH$_2$S0$_2$NH$_2$, NH(CH$_2$)$_3$OH, NH(CH$_2$)$_3$OMe, NH(CH$_2$)$_4$OH, NH(CH$_2$)$_4$OMe, NH(CH$_2$)$_5$OH, NH(CH$_2$)$_2$C0$_2$H, NH(CH$_2$)$_3$C0$_2$H, NH(CH$_2$)$_4$C0$_2$H, NH(CH$_2$)$_5$C0$_2$H, NHCH$_2$CH(CF$_3$)OH, NHCH$_2$C(Me)(CF$_3$)0H, NHCH$_2$CMe$_2$OH, NHCH$_2$CH$_2$CMe$_2$OH, NHCH$_2$CMe$_2$NHCH$_2$CF$_3$, NHCH(Me)CMe$_2$OH, NHCH$_2$CMe$_2$OMe, NHCH$_2$CMe$_2$C0$_2$H, NHCH$_2$CMe$_2$CONHMe, NHCH$_2$CMe$_2$CONMe$_2$, NHCH$_2$CMe$_2$NHS0$_2$Me, NH(CH$_2$)$_3$SOMe, NH(CH$_2$)$_5$S0$_2$Me, NH(CH$_2$)$_5$S0$_2$NH$_2$, NH(CH$_2$)$_3$NHS0$_2$Me, NH(CH$_2$)$_2$0(CH$_2$)$_2$OH, NHCH$_2$CHMeOH, NH(CH$_2$)$_5$SOMe,

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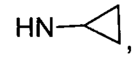
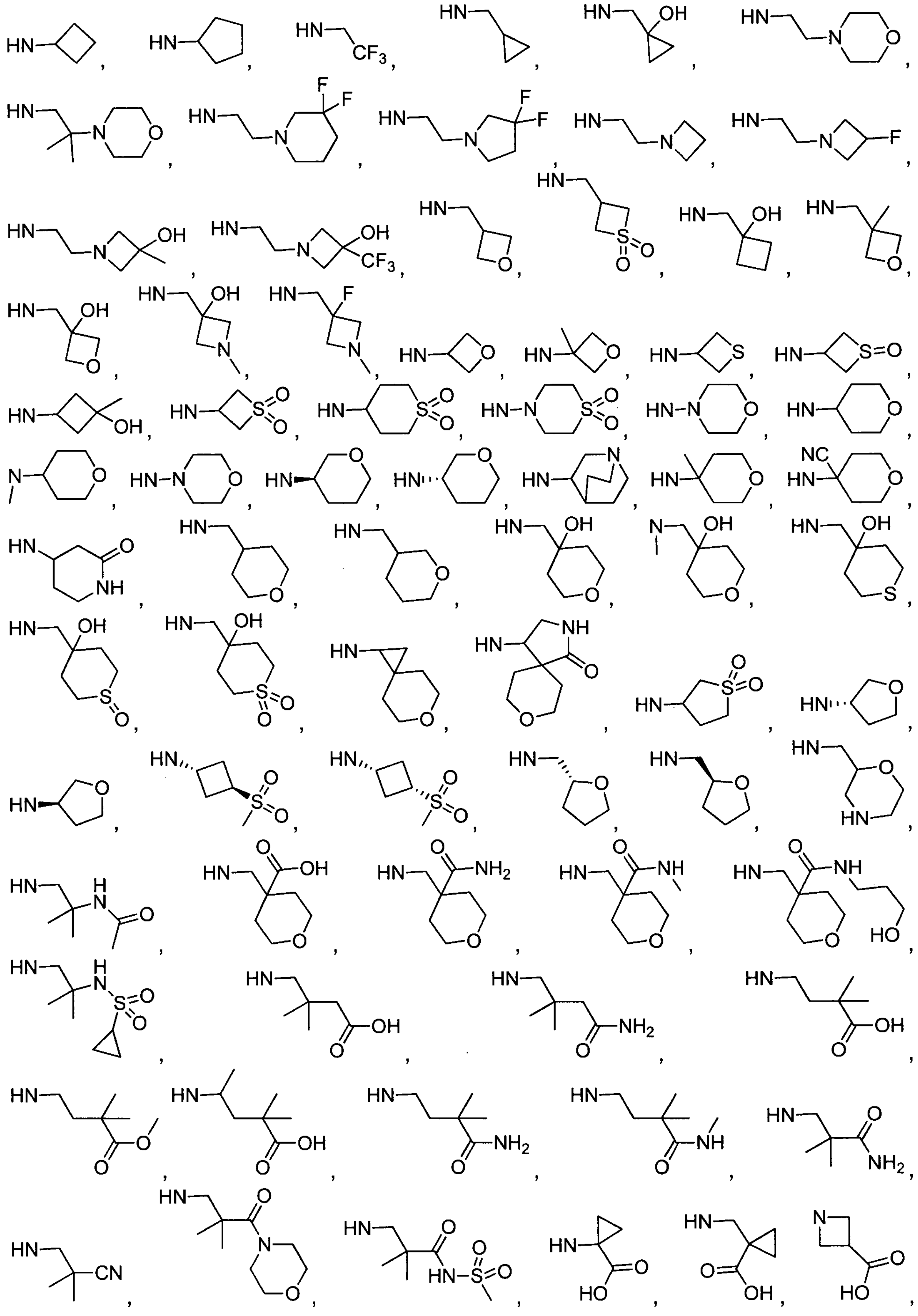
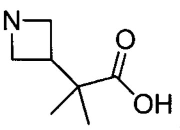
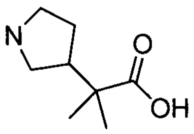
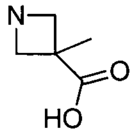
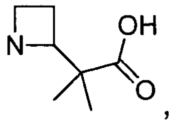
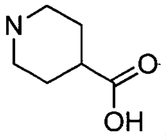
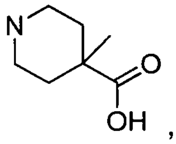
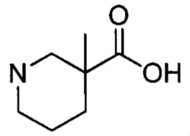
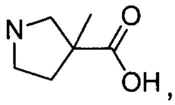
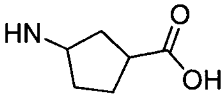
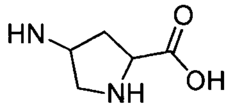
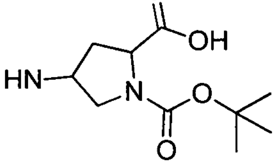
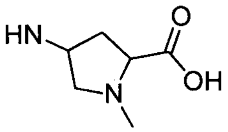
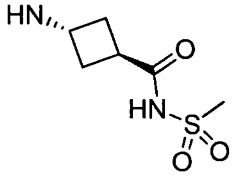
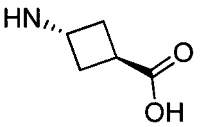
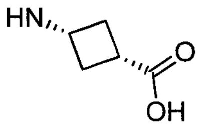
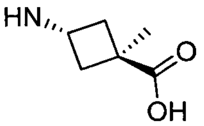
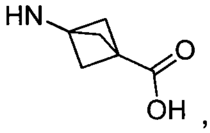
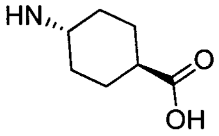
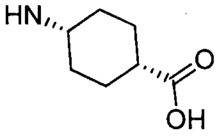
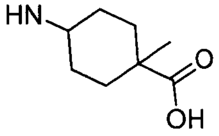
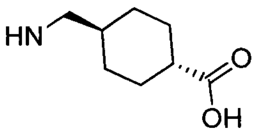


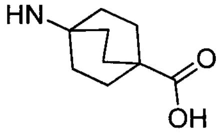
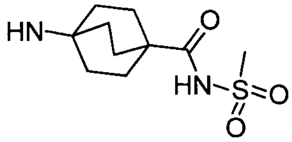
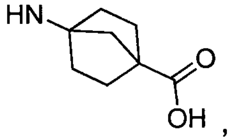
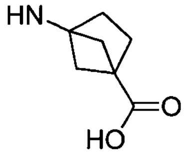
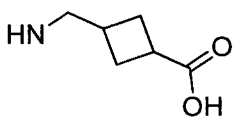


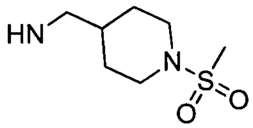
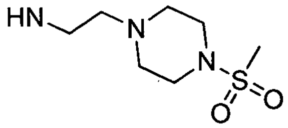
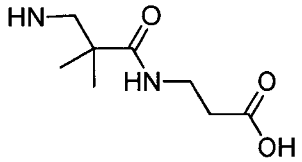
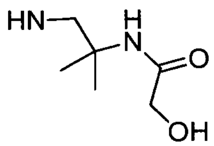
,
,
,
,
,
,

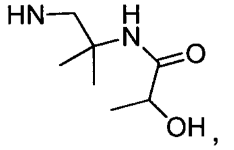
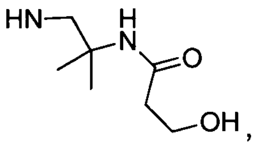
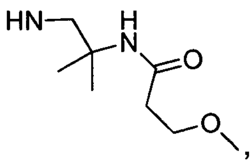
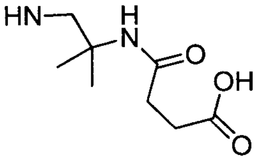
,
,
,
,
,

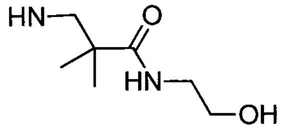
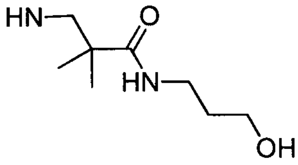
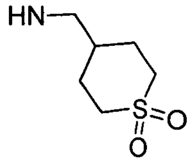
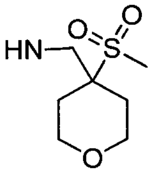
,
,
,
,
,

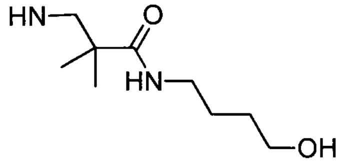
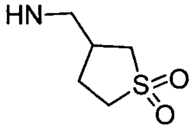
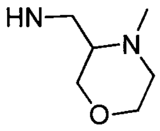
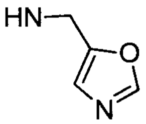
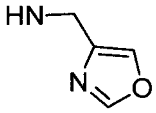
,
,
,
,
,

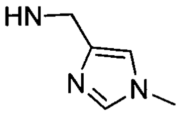
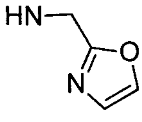
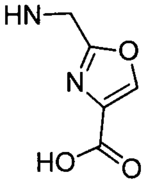
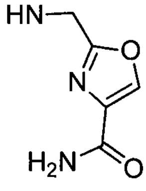
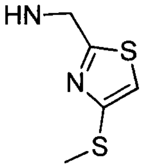
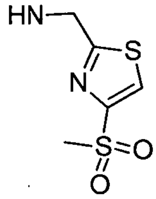
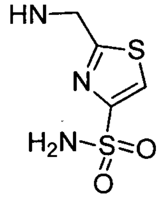
,
,
,
,
,

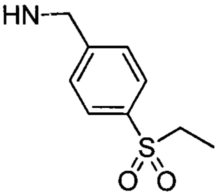
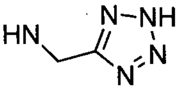
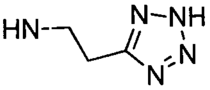
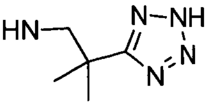
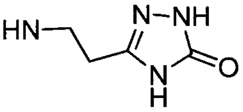
,
,
,
,

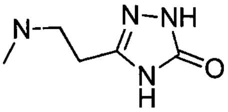
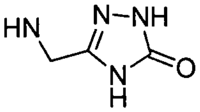
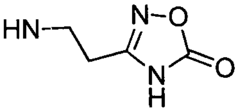
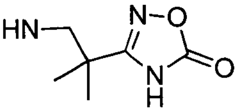
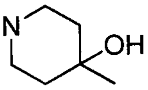
,
,
,
,

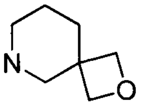
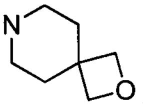
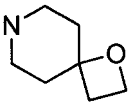
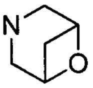
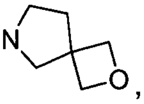
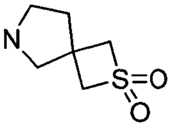
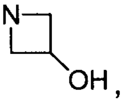
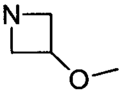
,
,
,
,

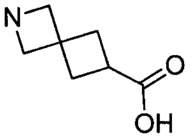
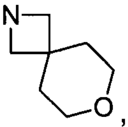
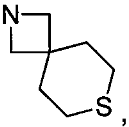
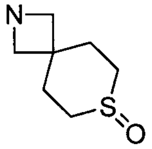
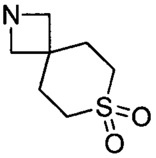
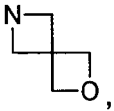
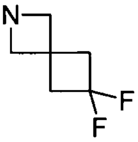
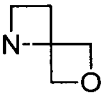
,
,
,
,
,

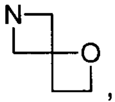
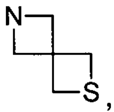
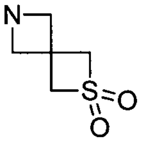
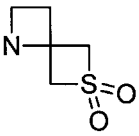
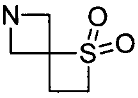
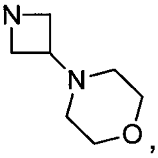
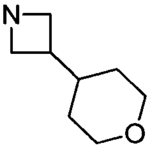
,
,
,
,
,
,
,

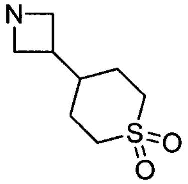
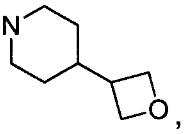
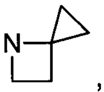
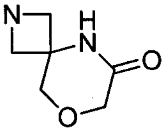
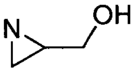
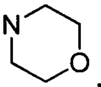
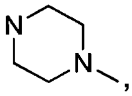
 ,  ,  ,  ,  ,

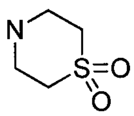
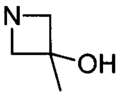
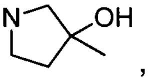
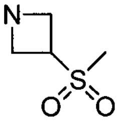
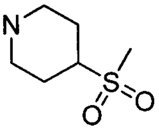
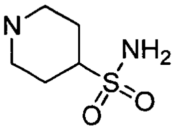
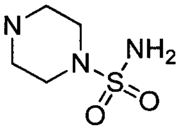
 ,  ,  ,  ,  ,

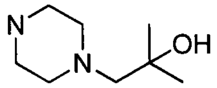
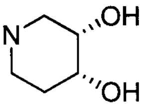
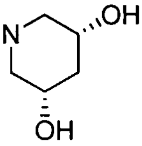
 ,  ,  ,  ,  ,  ,  ,  ,

 ,  ,  ,  ,  ,  ,  ,  ,

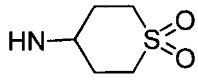
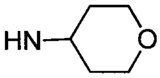
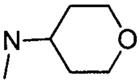
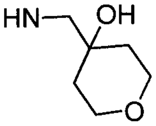
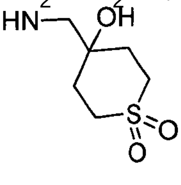
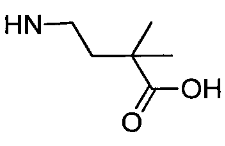
 ,  ,  ,  ,  ,  ,  ,

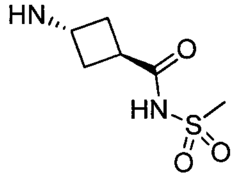
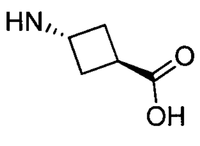
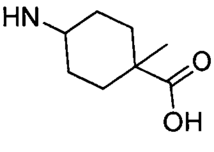
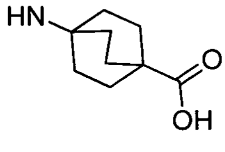
 ,  ,  ,  ,  ,  ,  ,

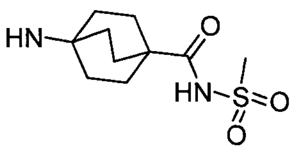
 ,  ,  ,  ,  ,  ,  ,

 ,  and  .

In a more preferred embodiment in combination with any of the above or below embodiments of the second alternative NR^{101}R^{102} is selected from NHCH$_2$CMe$_2$OH, NHCH$_2$CMe$_2$C0$_2$H,

 ,  ,  ,  ,  ,  ,

 ,  ,  ,  ;



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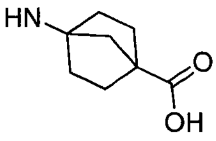

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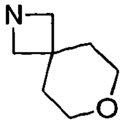

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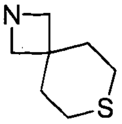

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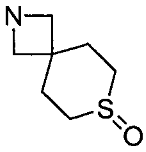

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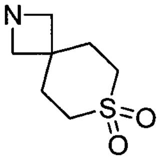

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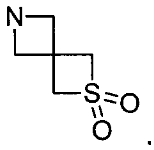

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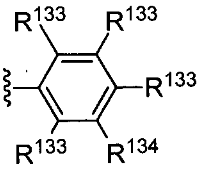
In another preferred embodiment in combination with any of the above or below embodiments of the second alternative R^{103} is selected from



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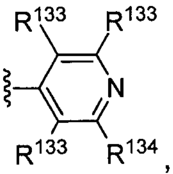

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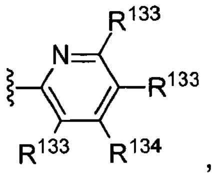

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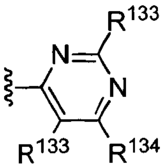

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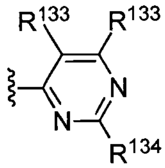

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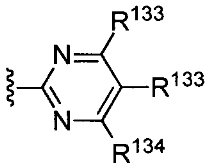

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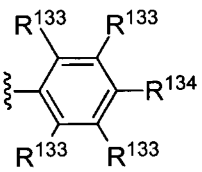

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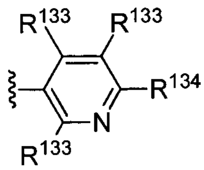

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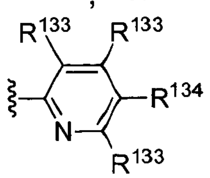

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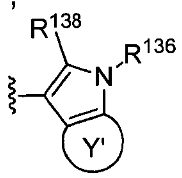

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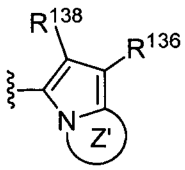

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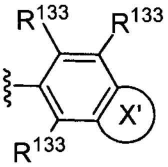

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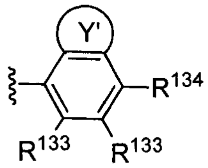

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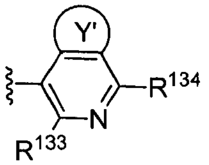

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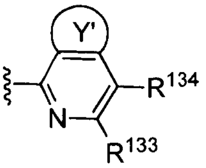

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wherein

R^{133} is independently selected from H, halogen, CN, d-e-alkyl, fluoro-Ci-$_6$-alkyl, d -$_4$-alkylene-OH, C_{1-4}-alkylene-O-C_{1-3}-alkyl, d -$_4$-alkylene-0-fluoro-d -$_3$-alkyl, OH, O-d-e-alkyl, 0-fluoro-Ci. $_6$-alkyl, NH-d. $_6$-alkyl, NH-fluoro-d-e-alkyl, $C_{3\cdot10}$-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-Ci. $_3$-alkyl;

R^{134} are independently selected from H, halogen, CN, C_{1-6}-alkyl, fluoro-Ci-e-alkyl, C_{1-4}-alkylene-OH, d -$_4$-alkylene-0-d -$_3$-alkyl, d .$_4$-alkylene-0-fluoro-Ci. $_3$-alkyl, OH, O-d-e-alkyl, O-fluoro-d-e-alkyl, NH-C_{1-e}-alkyl, NH-fluoro-d-e-alkyl, C_{3-10}-cycloalkyl, Co-$_6$-alkylene-C $_{3\text{-}1}{}_0$-heterocycloalkyl, 5-membered heteroaryl, 6-membered heteroaryl, C(0)N(R ^{137})$_2$ and S0 $_2$N(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, d -$_3$-alkyl, fluoro-d -$_3$-alkyl, OH, 0-d. $_3$-alkyl, fluoro-0-Ci -$_3$-alkyl;

R^{135} is selected from halogen, Ci-$_6$-alkyl, halo-C^-alkyl, $C_{3'6}$-cycloalkyl, $C_{3'6}$-heterocycloalkyl, oxo, =N-OR ^{132}, OH, O-Ci $_{-6}$-alkyl and O-halo-d-e-alkyl;

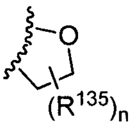
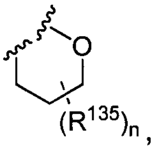
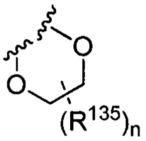
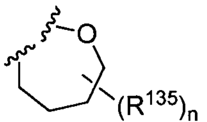
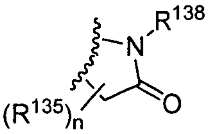
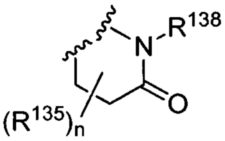
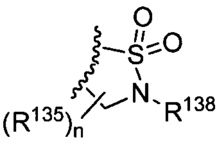
R^{136} is selected from C_{1-6}-alkyl, fluoro-C^-alkyl, C(0)N(R ^{137})$_2$, S0 $_2$N(R^{137})$_2$;

R^{137} is independently selected from H, d-e-alkyl, halo-Ci.$_6$-alkyl, C_0-$_4$-alkylene-C $_{3-6}$-cycloalkyl, C_0-$_4$-alkylene-C $_{3'6}$-heterocycloalkyl, wherein alkyl and alkylene is unsubtituted or substituted with 1 to 4 substituents selected from halogen, OH, 0-Ci $_{-3}$-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-Ci. $_3$-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 heteroatoms selected from O, S or N, wherein the ring is unsubstituted or substituted with 1 to 4 substitutents independently selected from fluoro, OH, oxo, C_{1-4}-alkyl and halo-Ci. $_4$-alkyl;

R^{138} is selected from H, C_{1-3}-alkyl and fluoro-Ci_$_3$-alkyl;

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

,
,
,
,
,
,

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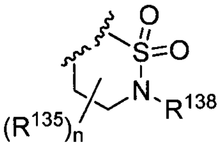
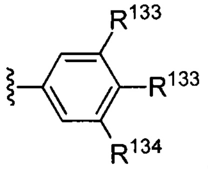
;

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-Ci-$_3$-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, Ci.$_3$-alkyl and fluoro-C $_{1-3}$-alkyl;

n is selected from 1 to 4.

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



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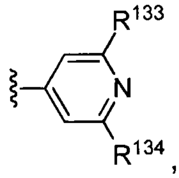

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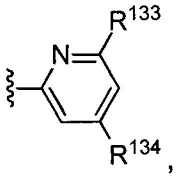

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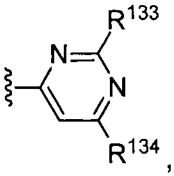

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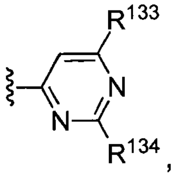

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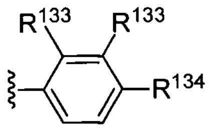

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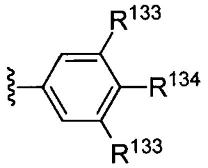

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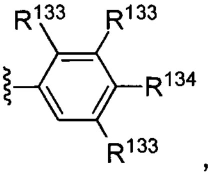

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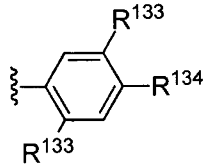

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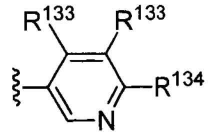

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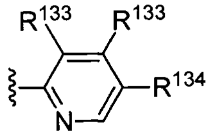

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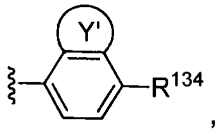

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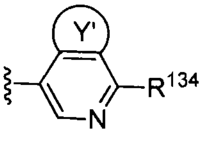

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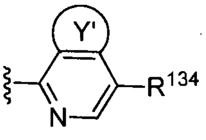

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wherein

R133 is independently selected from **H,** halogen, **CN,** $C_{1\text{-}6}$-alkyl, fluoro**-**$C_{1\text{-}6}$-alkyl, $C_{1\text{-}4}$-alkylene-**OH,** Ci-$_4$-alkylene-0 **-Ci-3**-alkyl, C^-alkylene **-O**-fluoro-d .$_3$-alkyl, **OH,** 0-C^-alkyl, 0-fluoro **-Ci.** e-alkyl, **NH-Ci** .$_6$-alkyl, **NH**-fluoro-$C_{1\text{-}6}$-alkyl, C_3-i$_0$-cycloalkyl, **C(0)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 selected from F, $C_{1\text{-}3}$-alkyl and fluoro-d .$_3$-alkyl;

R134 is selected from $C_{1\text{-}4}$-alkylene**-OH,** $C_{1\text{-}4}$-alkylene-O-$C_{1\text{-}3}$-alkyl, $C_{1\text{-}4}$-alkylene-O-fluoro-$C_{1\text{-}3}$-alkyl, $C_{3\text{-}10}$-cycloalkyl, **C(0)N(R** ^{137})$_2$, **S0** $_2$**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 selected from F, $C_{1\text{-}3}$-alkyl and fluoro**-**$C_{1\text{-}3}$-alkyl;

R137 is independently selected from **H,** Ci$_{\text{-}e}$-alkyl, halo-d. $_6$-alkyl, $C_{0\text{-}4}$-alkylene**-**$C_{3\text{-}6}$-cycloalkyl, $C_{0\text{-}4}$-alkylene**-**$C_{3\text{-}6}$-heterocycloalkyl,

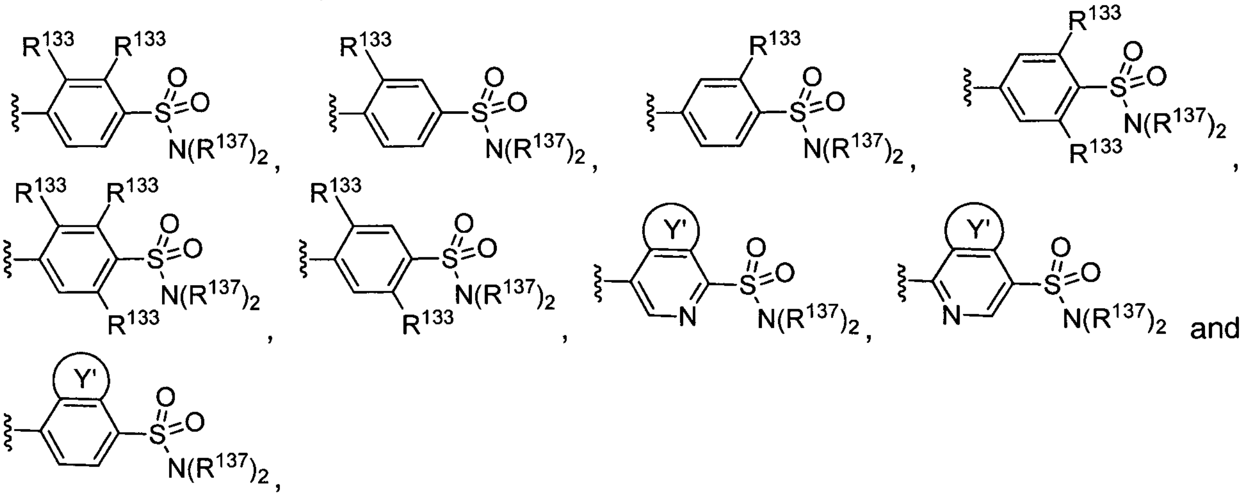
wherein alkyl and alkylene is unsubtituted or substituted with 1 to 4 substituents selected from halogen, **OH,** O-C^-alkyl, **CN, CONH$_2$;** and

wherin cycloalkyl or heterocycloalkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from F, **CN, OH,** oxo, 0 **-**$C_{1\text{-}3}$-alkyl, $C_{1\text{-}3}$-alkyl and fluoro-d .$_3$-alkyl;

or wherein two **R137** 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 substitutents independently selected from fluoro, **OH,** oxo, $C_{1\text{-}4}$-alkyl and halo**-Ci** .$_4$-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 CF_3.

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



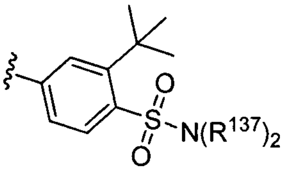
wherein R^{133} is independently selected from H, halogen, C_{1-6}-alkyl, fluoro-ct-e-alkyl, C_{1-4}-alkylene-OH, C_{1-4}-alkylene-O-C_{1-3}-alkyl, 0-ci $_{-6}$-alkyl, and 0-fluoro-ci $_{-6}$-alkyl, more preferably R^{33} is independently selected from fluoro, chloro, CF_3, CHF_2, OCF_3, $OCHF_2$, methyl, 'butyl and CMe_2OH;

one R^{137} is selected from H, C_{1-e}-alkyl, fluoro-c $_{1-e}$-alkyl and the other R^{137} is selected from C_{1-6}-alkyl, fluoro-Ci. $_6$-alkyl, c $_{0-4}$-alkylene-C_{3-6}-cycloalkyl, c $_{0-4}$-alkylene-C_{3-6}-heterocycloalkyl, wherein alkyl and alkylene is unsubtituted or substituted with a substituent selected from halogen, OH, 0-c $_{1-3}$-alkyl, CN, $CONH_2$; and cycloalkyl or heterocycloalkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from F, CN, $CONH_2$, OH, oxo, ch-alky! and fluoro-ci $_{-3}$-alkyl,

or wherein two R^{137} 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 substitutents independently selected from fluoro, OH, oxo, c $_{1-4}$-alkyl and halo-ci $_{-4}$-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 CF_3.

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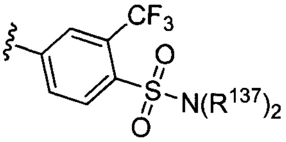
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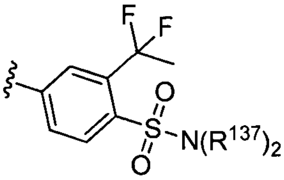
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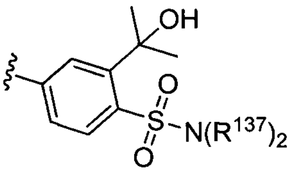
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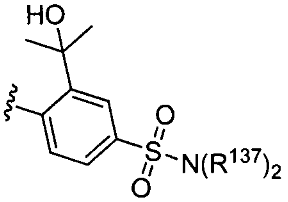
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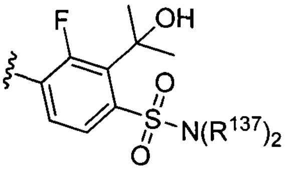
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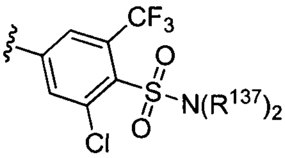
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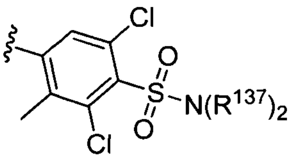
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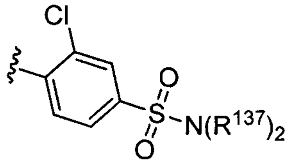
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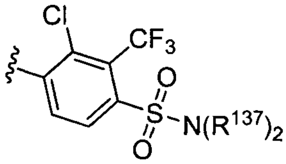
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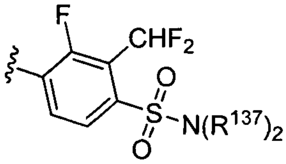
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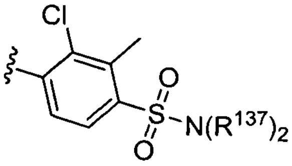
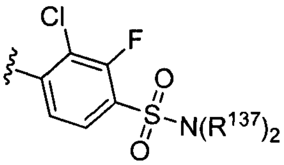
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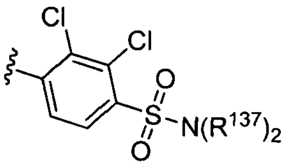
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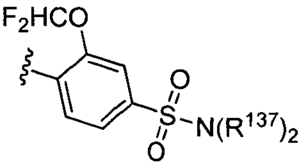
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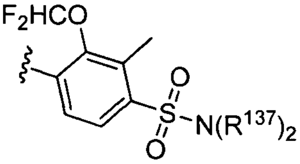
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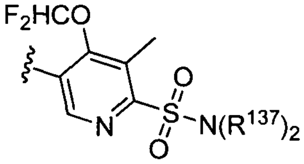
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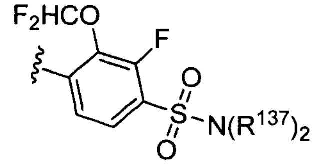
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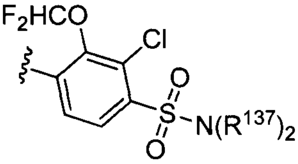
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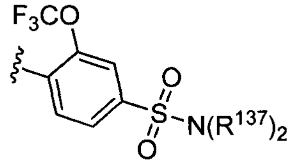
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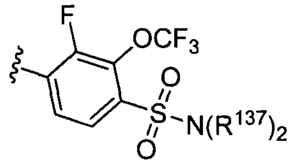
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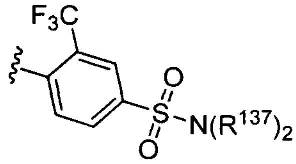
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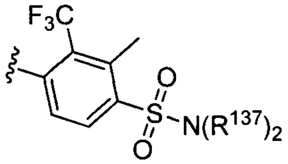
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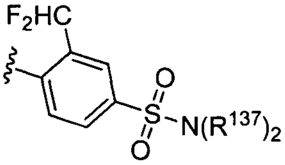
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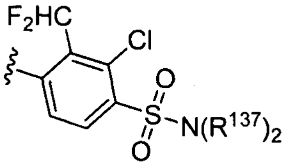
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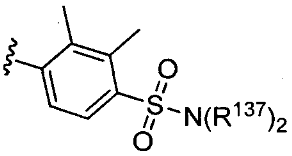
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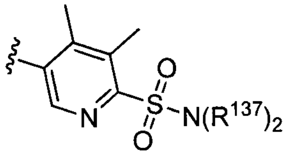
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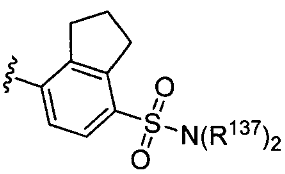
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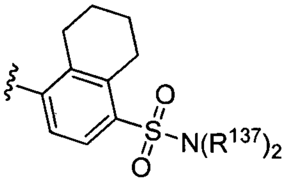
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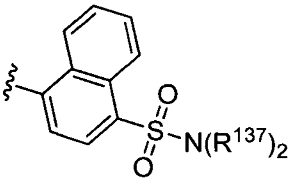
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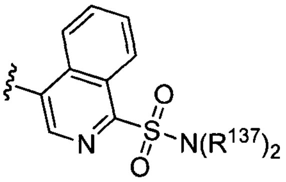
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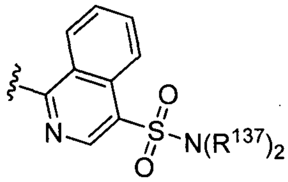
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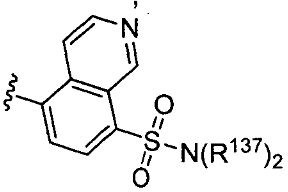
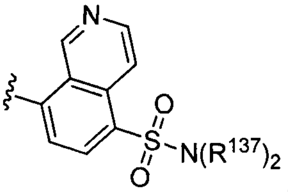
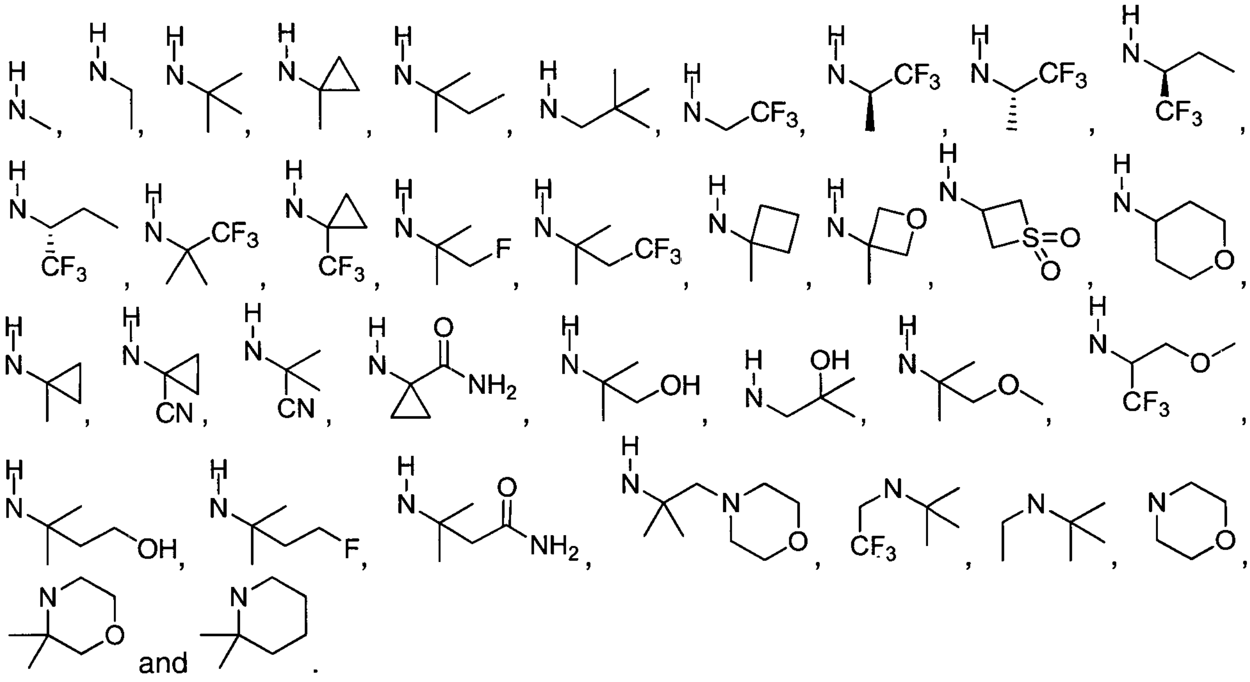


and  .

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



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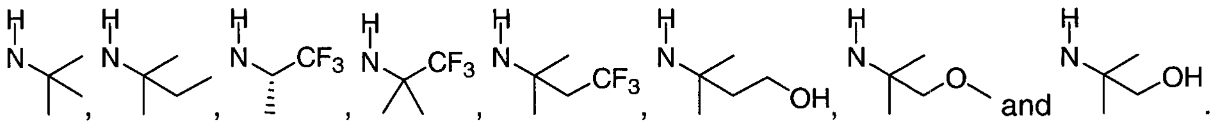
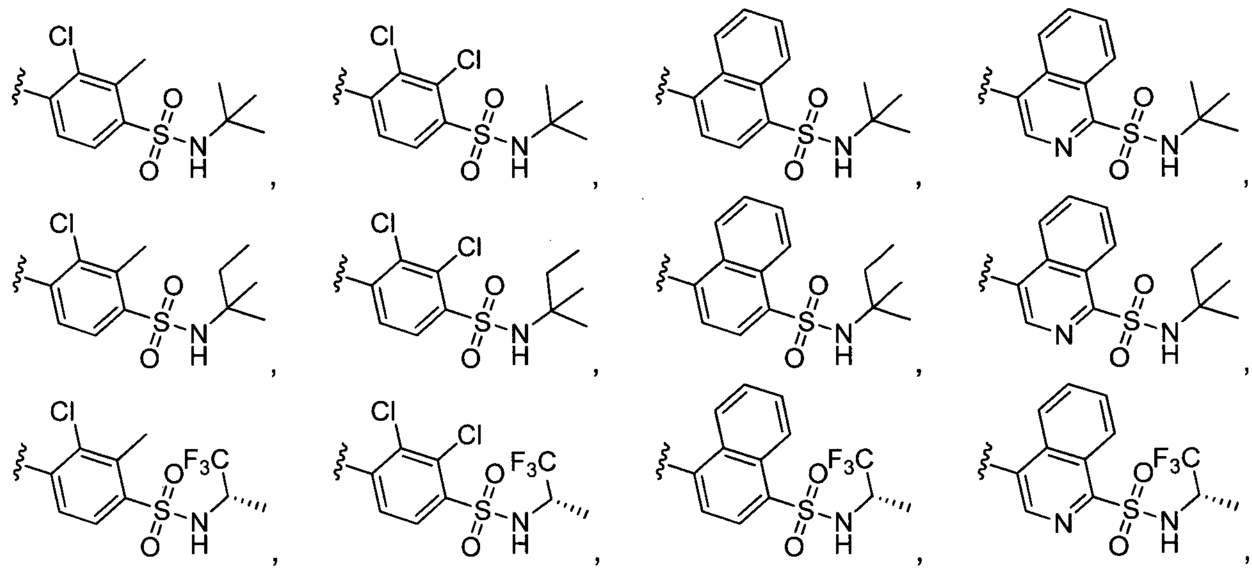
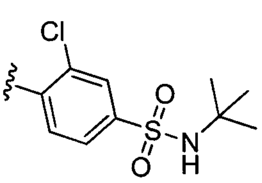
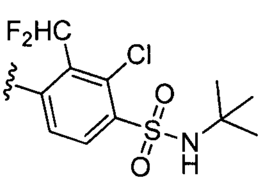
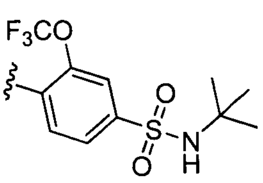
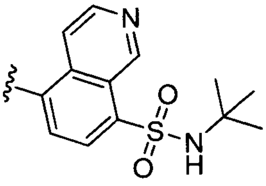
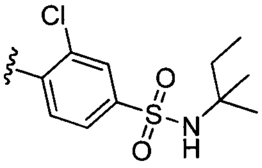
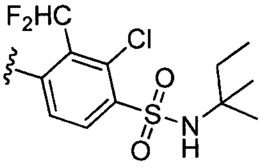
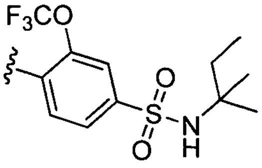
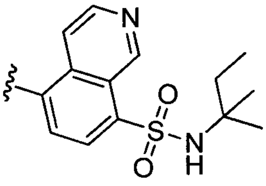
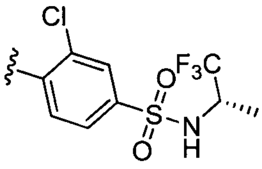
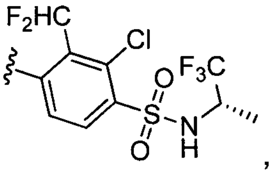
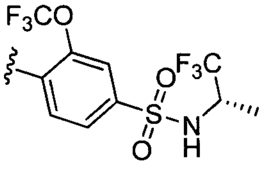
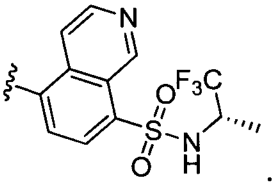


In another preferred embodiment in combination with any of the above or below embodiments of the second alternative R^{103} is selected from



,
,
,
,
,
,
,
,
,
,
 and
.

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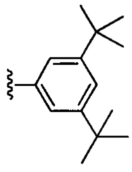
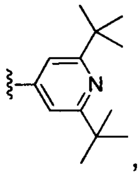
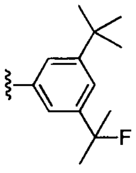
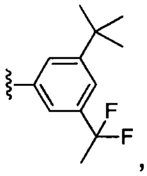
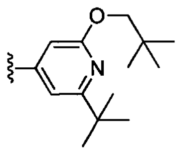
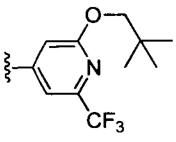
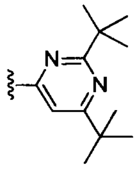
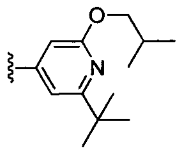
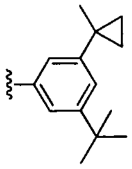
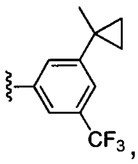
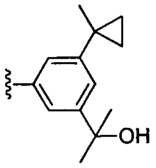
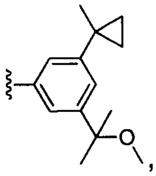
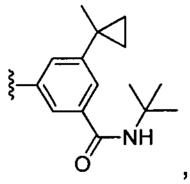
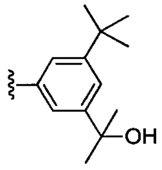
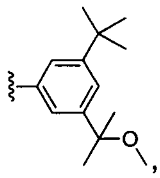
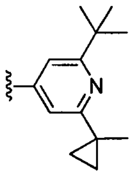
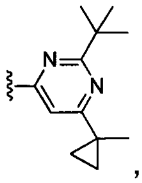
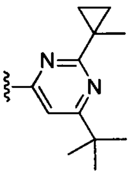
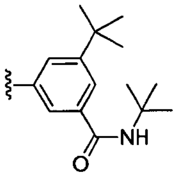
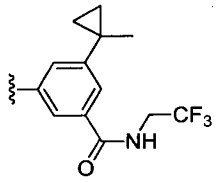
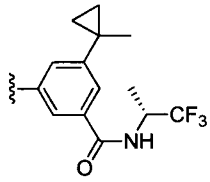
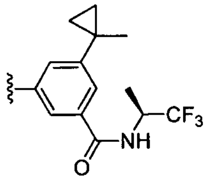
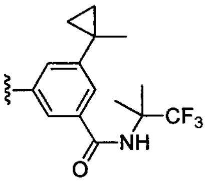
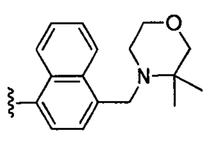
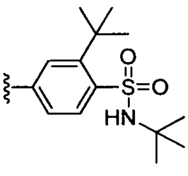
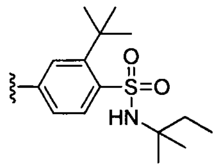
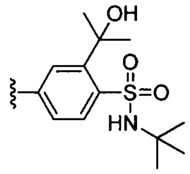
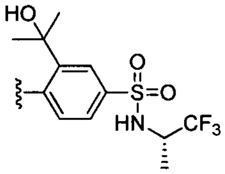
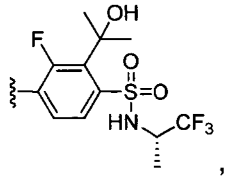
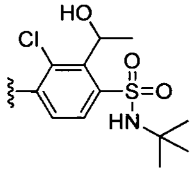
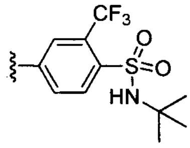
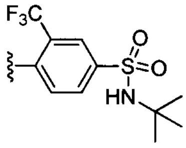
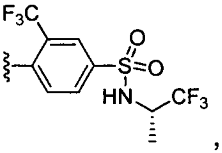
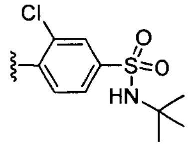
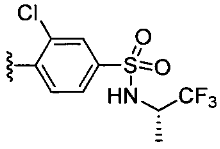
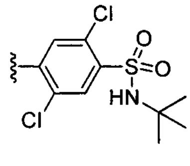
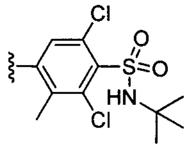
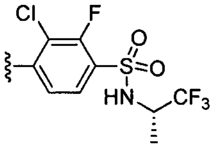
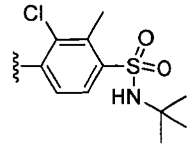
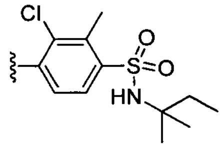
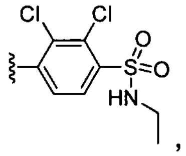
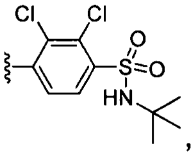
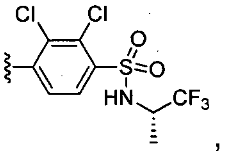
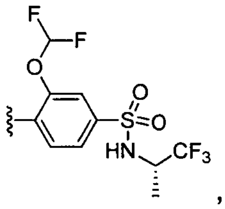
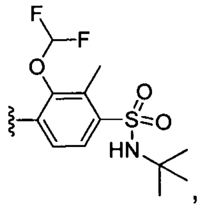
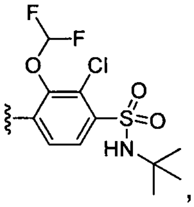
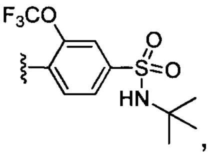
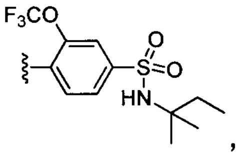
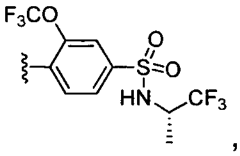
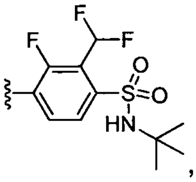
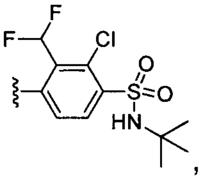
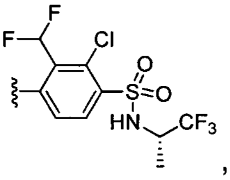
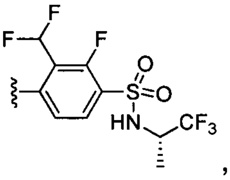
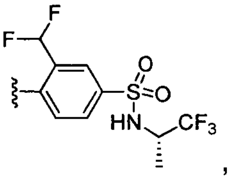
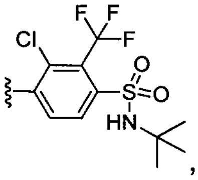
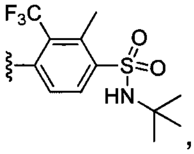
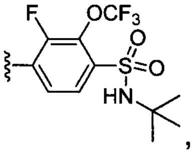
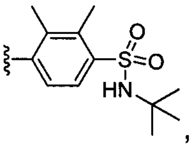
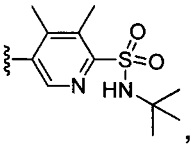
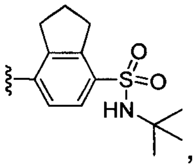
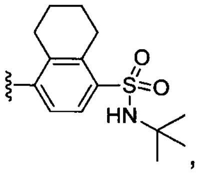
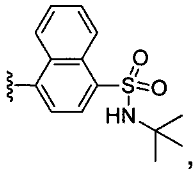
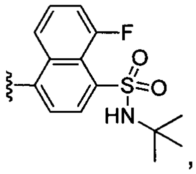
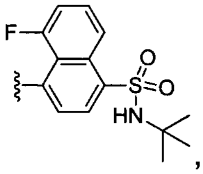
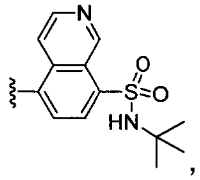
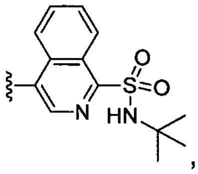
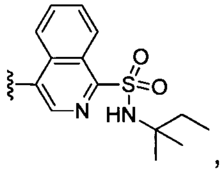
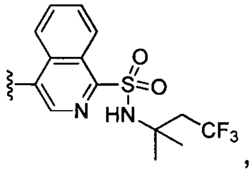
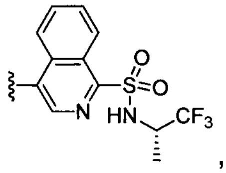
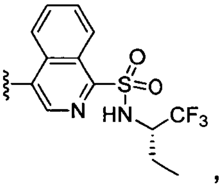
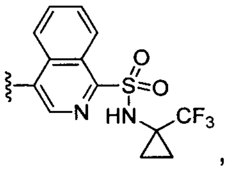
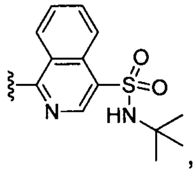
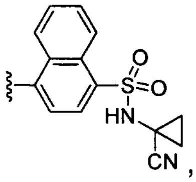
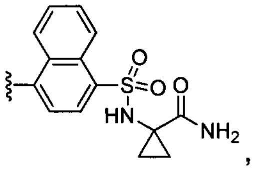
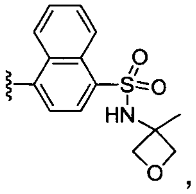
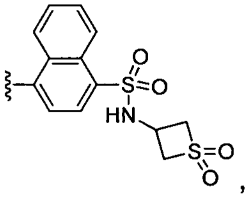
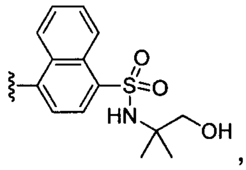
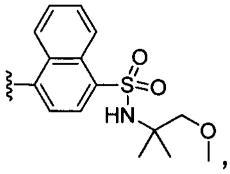
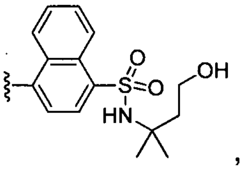
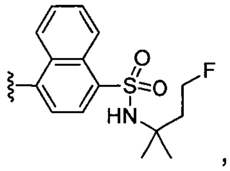
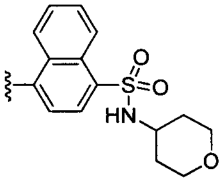
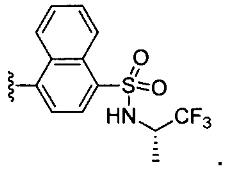
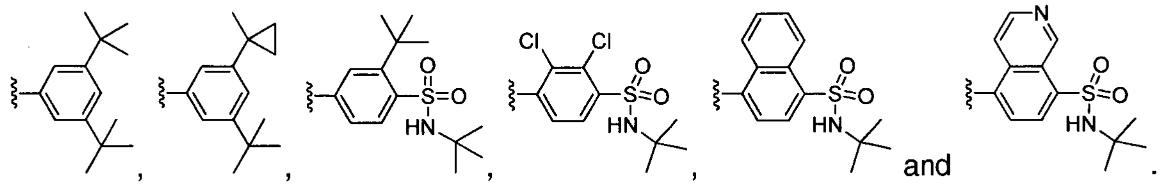
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,

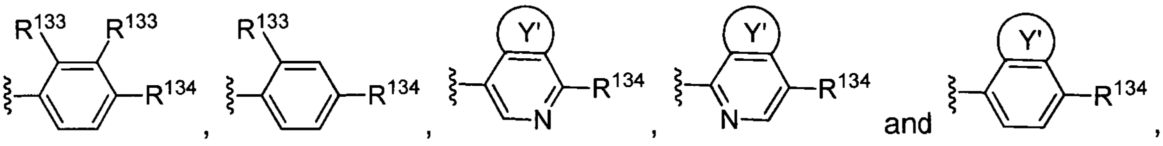
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,

and .

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



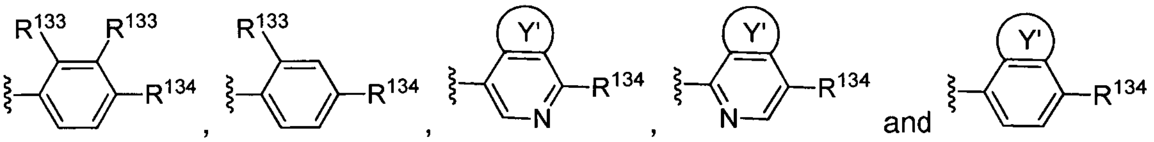
wherein R^{133} is independently selected from H, halogen, $C_{1.6}$-alkyl, fluoro-C^-alkyl, $C_{1\text{-}4}$-alkylene-OH, $C_{1\text{-}4}$-alkylene-O-$C_{1\text{-}3}$-alkyl, 0-d. $_6$-alkyl, and O-fluoro-$C_{1.e}$-alkyl, more preferably R^{133} is independently selected from fluoro, chloro, CF_3, CHF_2, OCF_3, $OCHF_2$, methyl, 'butyl and CMe_2OH;

R^{134} is selected from $C_{1\text{-}6}$-alkyl, halo-Ci $_{.6}$-alkyl and $C_{0\text{-}6}$-alkylene-C3 $_{.10}$-heterocycloalkyl,

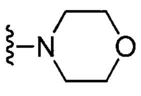
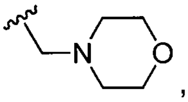
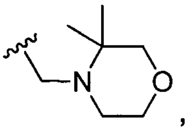
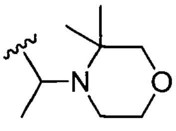
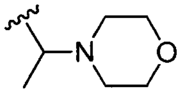
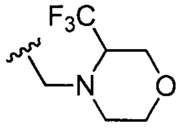
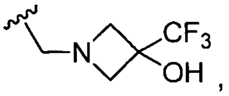
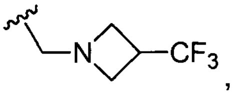
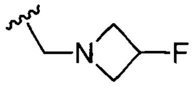
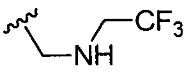
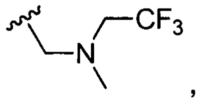
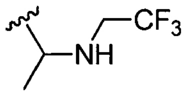
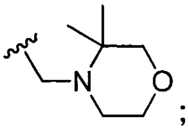
wherein alkyl, alkylene and heterocycloalkyl are unsubstituted or substituted by 1 to 3 substituents independently selected from the group consisting of halogen, $C_{1\text{-}6}$-alkyl, halo-Ci-6-alkyl, OH, oxo, $N(R^{131})_2$, **0-Ci** $_{\text{-}6}$-alkyl, $C_{3\text{-}10}$-cycloalkyl, $C_{3\text{-}i0}$-heterocycloalkyl; 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 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



wherein R^{133} is independently selected from H, halogen, $C_{1\text{-}6}$-alkyl, fluoro-$C_{1.6}$-alkyl, $Ci_{\text{-}4}$-alkylene-OH, d^-alkylene-O-d $_{\text{-}3}$-alkyl, O-d -e-alkyl, and 0-fluoro-d. $_6$-alkyl, more preferably R^{133} is independently selected from fluoro, chloro, CF_3, CHF_2, OCF_3, $OCHF_2$, methyl, 'butyl and CMe_2OH;

R^{134} is selected from , , , , , , , , , , ,  ; more preferably R^{134} is  ;

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 another preferred embodiment in combination with any of the above or below embodiments of the second alternative R^{104} is selected from $(CR^{108}R^{109})R^{140}$ and $(C=0)R^{140}$;

R^{108} is independently selected from H, F, C_{1-3}-alkyl, halo-Ci.$_3$-alkyl, OH, 0-Ci. $_3$-alkyl and O-halo-Ci-$_3$-alkyl;

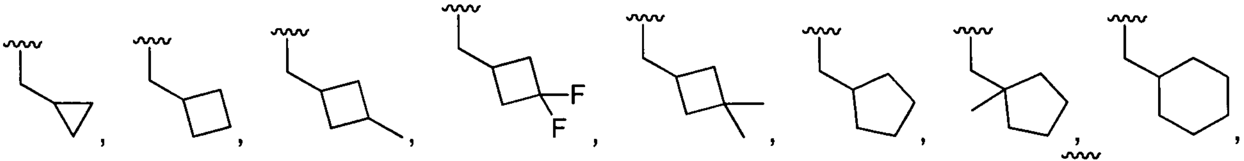
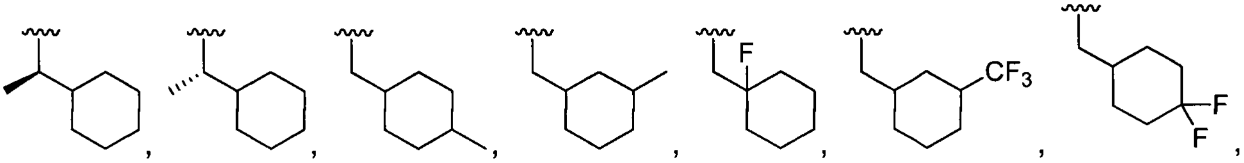
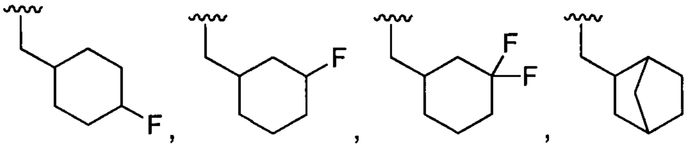
R^{109} is selected from H, F and methyl;

R^{140} is C_3.io-cycloalkyl, which is unsubstituted or substituted with 1 to 5 substituents independently selected from the group consisting of halogen, OH, oxo, 0-Ci $_6$-alkyl, O-halo-C_{1-6}-alkyl, C_{1-e}-alkyl, halo-Ci.$_6$-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, R^{104} is $(CH_2)R^{140}$, wherein R^{140} 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 another preferred embodiment in combination with any of the above or below embodiments of the second alternative R^{104} is selected from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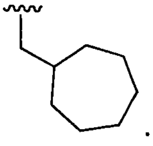
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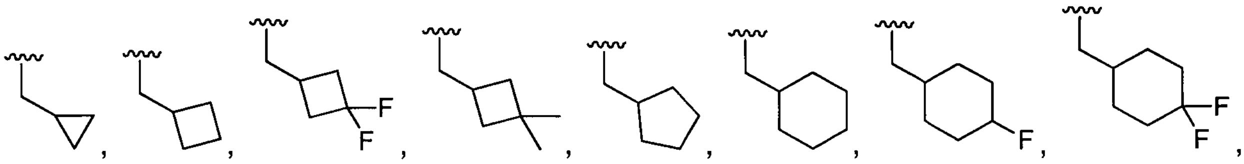
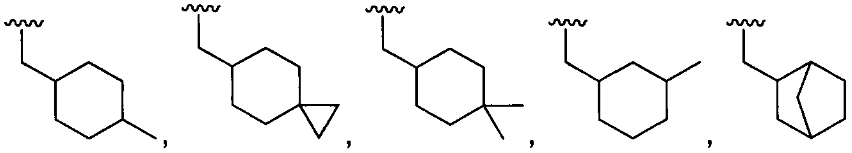
In a more preferred embodiment in combination with any of the above or below embodiments of the second alternative, R^{104} is selected from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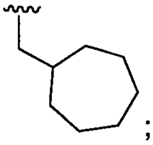
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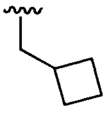
even more preferably, R^{104} is selected from

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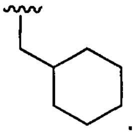
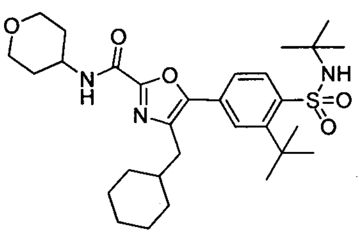

.

In another preferred embodiment in combination with any of the above or below embodiments 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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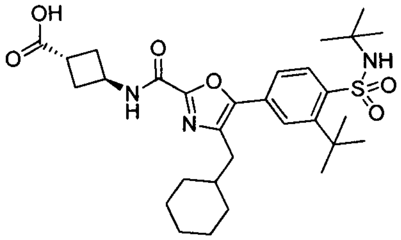
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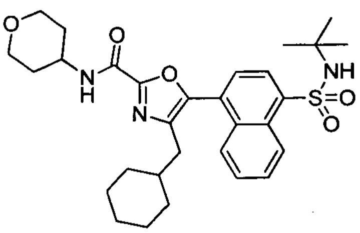
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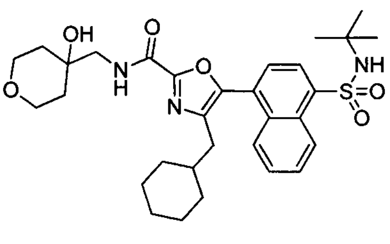
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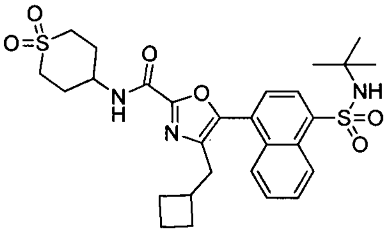
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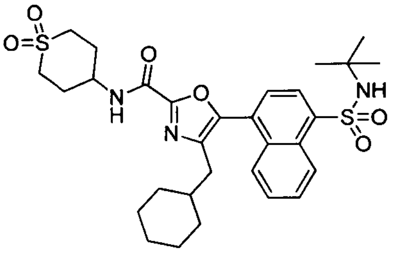
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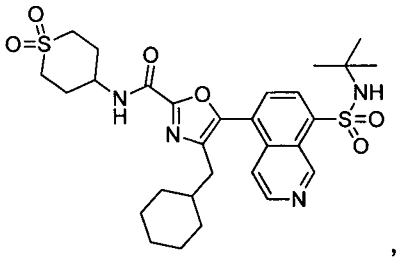
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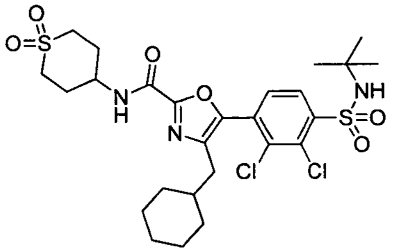
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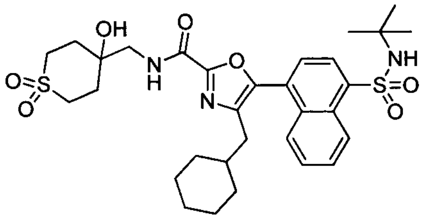
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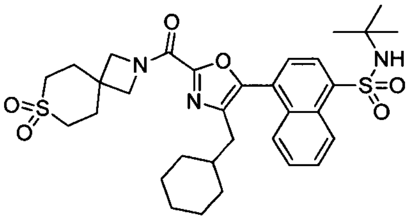
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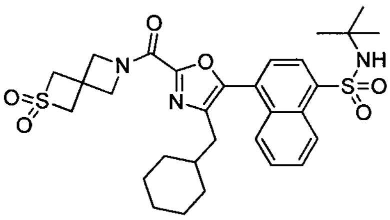
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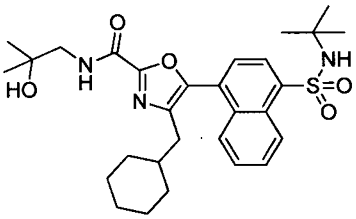
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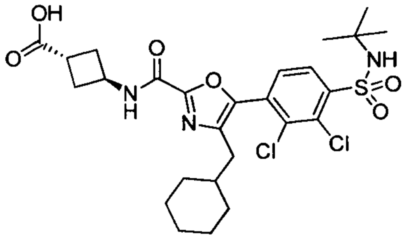
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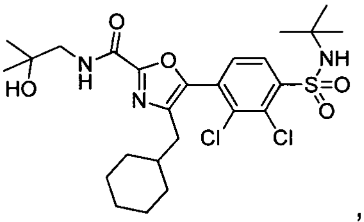
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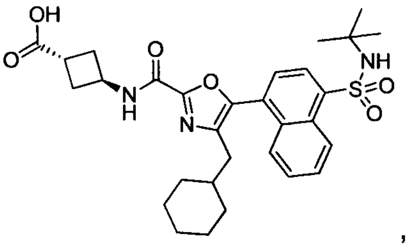
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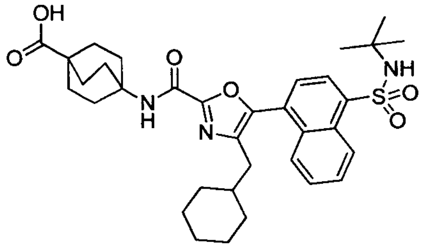
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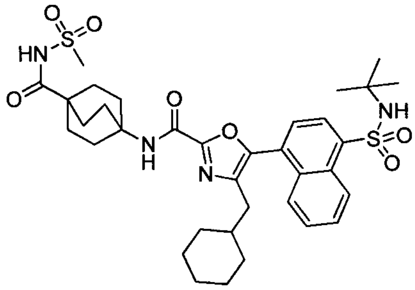
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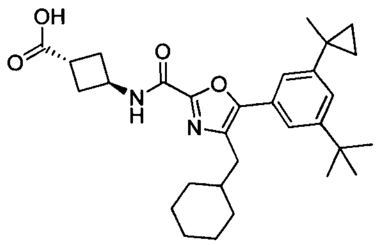
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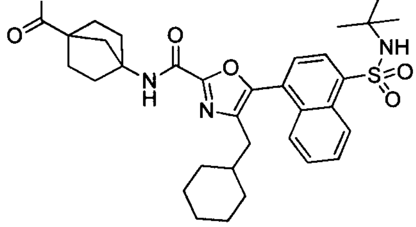
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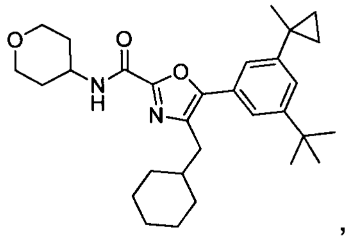
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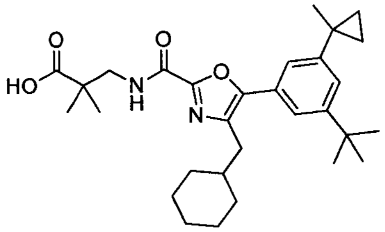

;

and an enantiomer, diastereomer, tautomer, AAoxide, solvate and pharmaceutically acceptable salt thereof.

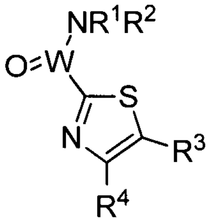
The invention also provides the compound of the second alternative of the invention for use as a medicament.

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 RORy receptor.

Also provided is the compound of the second alternative of the invention in treating RORy 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 thromobotic 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')**



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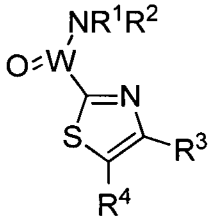


(1')

an enantiomer, diastereomer, tautomer, /V-oxide, solvate, formulation and pharmaceutically acceptable salt thereof,

R^1 and R^2 are independently selected from H, **$C_{1\text{-io}}$**-alkyl, $C_{2\text{-}10}$-alkenyl, $C_{2\cdot 10}$-alkynyl, **$C_{3\text{-}10}$**-cycloalkyl, $C_{3\cdot 10}$-heterocycloalkyl, $C_{1\cdot 10}$-alkylene-$C_{3\cdot 10}$-cycloalkyl, $C_{1\text{-}1o}$-alkylene-C-Mo-heterocycloalkyl, **$C_{1\text{-}10}$-alkylene-(5-membered heteroaryl), SO_2-$C_{1\text{-}10}$-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}, 0-$C_{2\text{-}6}$-alkylene-$OR^{1}{}_{1}$, C^-alky!, halo-d. $_{6}$-alkyl, halogen, $C0_{2}R^{11}$, $CONR^{11}R^{12}$, $CONR^{11}S0_{2}R^{11}$, COR^{11}, $SO_{x}R^{11}$, $S0_{3}H$, $S0_{2}NR^{11}R^{12}$, $NR^{11}COR^{11}$, $NR^{1}{}_{1}S0_{2}R^{11}$, $NR^{1}{}_{1}$-CO-$NR^{11}R^{12}$, $NR^{1}{}_{1}$-$S0_{2}$-$NR^{11}R^{12}$, $C_{3\text{-}1o}$-cycloalkyl, O-$C_{3\cdot 10}$-cycloalkyl, $C_{3\cdot 10}$-heterocycloalkyl, O-$C_{3\cdot 10}$-heterocycloalkyl and $NR^{1}{}_{1}R^{12}$;

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 substitutents independently selected from halogen, oxo, CN, OR11, SO_xR^{11}, $S0_3H$, $NR^{11}S0_2R11$, $S0_2NR^{11}R12$, $C_{0\text{-}6}$-alkylene-CO_2R1^1, CONR ^{11}R12, CONR $^{11}S0_2R1^1$, COR 11, NR^{11}-CO-R ^{11}, $NR^1$1-CO-NR $^{11}R^12$, NR^{11}-$S0_2$-NR 1^1R12, NR11R^12, C_1-e-alkyl, halo-d. $_6$-alkyl, hydroxy-d. $_6$-alkyl, $C_{3\text{-}8}$-cycloalkyl, 0-$C_{3\text{-}8}$-cycloalkyl, $C_{3\text{-}8}$-heterocycloalkyl and 0-$C_{3\text{-}8}$-heterocycloalkyl,

wherein cycloalkyi and heterocycloalkyi are unsubstituted or substituted with 1 to 4 substitutents independently selected from halogen, $C_{1\text{-}3}$-alkyl, halo-$C_{1\text{-}3}$-alkyl, OH, O-C1. 3-alkyl, 0-halo-d. $_3$-alkyl, S0 $_2$-d. $_3$-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 optionally substituted with 1 to 5 substituents independently selected from halogen, $C_{1\text{-}6}$-alkyl, $C_{1\text{-}6}$-alkenyl, $C_{1\text{-}6}$-alkynyl, halo-Ci $_{-6}$-alkyl, OH, 0-$C_{1\text{-}6}$-alkyl, 0-halo-$C_{1\text{-}6}$-alkyl, $C_{0\text{-}6}$-alkylene-$C_{3\text{-}10}$-cycloalkyl, $C_{0\text{-}6}$-alkylene-$C_{3\text{-}10}$-heterocycloalkyl, $C_{0\text{-}6}$-alkylene-(5- or 6-membered heteroaryl), $C_{1\text{-}6}$-alkylene-0-R31, $C_{0\text{-}6}$-alkylene-CN, $C_{0\text{-}6}$-alkylene-N(R $3^1)_2$, $C_{0\text{-}6}$-alkylene-O-C $_{3\text{-}10}$-cycloalkyl, 0-Ci $_{-6}$-alkylene-0-R31, $C_{0\text{-}6}$-alkylene-0-$C_{3\text{-}10}$-heterocycloalkyl, $C_{0\text{-}6}$-alkylene-COOR 31, $C_{0\text{-}6}$-alkylene-C(O)R 31, Co-6-alkylene-C(0)N(R31$)_2$, $C_{0\text{-}6}$-alkylene-N(R 3^1)C(O)R 31, $C_{0\text{-}6}$-alkylene-SO-R31, $C_{0\text{-}6}$-alkylene-S0 $_2$-R31, $C_{0\text{-}6}$-alkylene-S0 $_2$-N(R $3^1)_2$, $C_{0\text{-}6}$-alkylene-N(R31)SO $_2$-R31, $C_{0\text{-}6}$-alkylene-S0 $_2$-$C_{3\text{-}10}$-heterocycloalkyl and $C_{0\text{-}6}$-alkylene-SO $_2$-$C_{3\text{-}10}$-heterocycloalkyl,

wherein alkyl, alkenyl, alkynyl, alkylene, cycloalkyi, heterocycloalkyi and the 5- or 6-membered heteroaryl is optionally substituted by 1 to 4 substituents independently selected from the group consisting of halogen, CN, $C_{1\text{-}3}$-alkyl, halo-Ci.3-alkyl, OH, oxo, =N-OR 32, 0-d. $_6$-alkyl, 0-halo-d. $_3$-alkyl, N(R $3^1)_2$, COOH, CON(R $^{31})_2$, NR31-COR 3^1, $C_{3\text{-}10}$-cycloalkyl, $C_{3\text{-}10}$-heterocycloalkyl, 6-10-membered 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, S0 $_2$, or NR3^1, wherein the ring is unsubstituted or substituted with 1 to 7 substituents independently selected from halogen, $C_{1\text{-}6}$-alkyl, halo-d -e-alkyl, $C_{3\text{-}6}$-cycloalkyl, $C_{3\text{-}6}$-heterocycloalkyl, oxo, =N-OR 32, OH, 0-$C_{1\text{-}6}$-alkyl and 0-halo-d .e-alkyl;

R4 is selected from (CR ^{8}R9)R40, (C=0)R40, OR40, NR4^{1}R40, SO_y-R7 and $C_{3\text{-}6}$-cycloalkyl, which is spirocyclic fused with R40,

wherein cycloalkyi is unsubstituted or substituted with 1 to 4 substituents independently selected from the group consisting of F, methyl and CF_3;

R7 is selected from $C_{3\text{-}10}$-cycloalkyl and $C_{3\text{-}10}$-heterocycloalkyl, wherein cycloalkyl and heterocycloalkyi are unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of halogen, OH, oxo, O-**$C_{1\text{-}6}$**-alkyl, 0-halo-d. $_6$-alkyl, $C_{1\text{-}6}$-alkyl, halo-d. $_6$-alkyl, cycloalkyl and heterocycloalkyi;

R^8 and R^9 are independently selected from H, **F,** $C_{1\text{-}3}$-alkyl, halo-d. $_3$-alkyl, OH, 0 **-$C_{1\cdot3}$**-alkyl and 0-halo **-$C_{1\cdot3}$**-alkyl;

R^{11} is independently selected from H, **$C_{1\text{-}6}$**-alkyl, **Co**6-alkylene-$C_{3\cdot10}$-cycloalkyl and $C_{0\text{-}6}$-alkylene-$C_{3\cdot10}$-heterocycloalkyl,

wherein alkyl, alkylene, cycloalkyl and heterocycloalkyi is unsubstituted or substituted with 1 to 6 substituents selected from the group consisting of halogen, **CN,** OH, oxo, C_1. $_3$-alkyl, halo-**Ci** .$_3$-alkyl, 0-d. $_3$-alkyl, O-halo-d -a-alkyl, NH_2, NH(d -3-alkyl), N(d.3-alkyl) $_2$, $C_{3\cdot6}$-heterocycloalkyl, $C_{3\text{-}6}$-cycloalkyl and S0 $_2$-d. $_3$-alkyl,

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

R^{12} is independently selected from H, d $_{-6}$-alkyl, halo-d_ $_6$-alkyl and $C_{3\cdot6}$-cycloalkyl;

R^{31} is independently selected from H, d .$_6$-alkyl, halo-d. $_6$-alkyl, $C_{0\text{-}6}$-alkylene-$C_{3\cdot8}$-cycloalkyl, $C_{0\text{-}6}$-alkylene-$C_{3\cdot8}$-heterocycloalkyl, 5- or 6-membered heteroaryl and 6-membered aryl, wherein alkyl, alkylene, cyclolalkyi, heterocycloalkyi, aryl and heteroaryl are unsubstituted or substituted with 1 to 6 substituents independently selected from halogen, CN, OH, oxo, =N-OR^{32}, d-3-alkyl, halo-d. $_3$-alkyl, 0-d. $_3$-alkyl, 0-halo-d. $_3$-alkyl and S0 $_2$-d. $_3$-alkyl;

and optionally wherein two R^{31} 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 substitutents independently selected from fluoro, OH, oxo, d $_{-4}$-alkyl and **halo-Ci.** $_4$-alkyl;

R^{32} is independently selected from H, d .$_6$-alkyl and halo-**Ci-e**-alkyl and $C_{3\text{-}6}$-cycloalkyl;

R^{40} is d-10-cycloalkyl, which is unsubstituted or substituted with 1 to 5 substituents independently selected from the group consisting of halogen, OH, oxo, 0-d. $_6$-alkyl, O-halo-d. $_6$-alkyl, d .$_6$-alkyl, halo-**Ci-e**-alkyl, $C_{3\cdot8}$-cycloalkyl and $C_{3\cdot8}$-heterocycloalkyl;

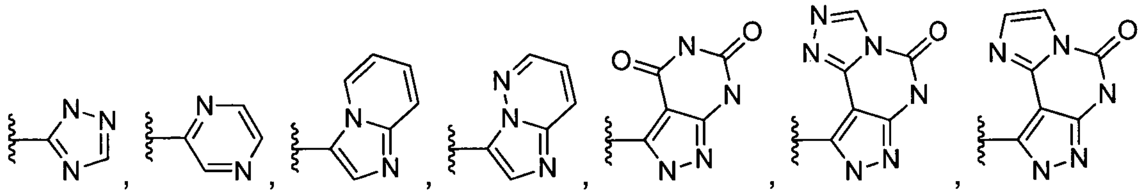
R^{41} is selected from H, d .$_6$-alkyl, $C_{3\cdot6}$-cycloalkyl and $C_{3\cdot6}$-heterocycloalkyl,

wherein alkyl, cycloalkyl and heterocycloalkyi is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of OH, oxo, CN, halogen, 0 **-$C_{1\cdot6}$**-alkyl, O-halo-d -e-alkyl, $C_{3\cdot6}$-heterocycloalkyl and $C_{3\cdot6}$-cycloalkyl;

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

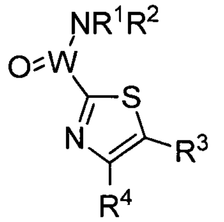
W is selected from C or S=0;

with the proviso that for R^3 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.

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



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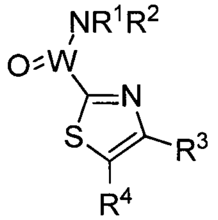

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an enantiomer, diastereomer, tautomer, solvate, formulation and pharmaceutically acceptable salt thereof,

wherein

R^1 and R^2 are independently selected from H, $C_{1\text{-}10}$-alkyl, C_2-io-alkenyl, C_2-i$_0$-alkynyl, $C_{0\text{-}}$io-alkylene-$C_{3\text{-}10}$-cycloalkyl, C_0.io-alkylene-c3 .$_{10}$-heterocycloalkyl, C_0-i$_0$-alkylene-(5-membered monocyclic heteroaryl), SO_2-$C_{1\text{-}10}$-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}, 0-$C_{2\text{-}6}$-alkylene-OR^{11}, Ci.$_6$-alkyl, halo-Ci-$_6$-alkyl, halogen, $C0_2R^{11}$, $CONR^{11}R^{12}$, $CONR^{11}S0_2R^{12}$, COR^{11}, SO_yR^{11}, $S0_3H$, $S0_2NR^{11}R^{12}$, $NR^{11}COR^{11}$, $NR^{11}S0_2R^{11}$, NR^{11}-CO-$NR^{11}R^{12}$, NR^{11}-$S0_2$-$NR^{11}R^{12}$, $C_{3\text{-}6}$-cycloalkyl, 0-$C_{3\text{-}6}$-cycloalkyl, $C_{3\text{-}6}$-heterocycloalkyl, 0-$C_{3\text{-}6}$-heterocycloalkyl and $NR^{11}R^{12}$;

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, OR^{11}, SO_yR^{11}, $S0_3H$, $NR^{11}S0_2R^{11}$, $S0_2NR^{11}R^{12}$, $C0_2R^{11}$, $CONR^{11}R^{12}$, $CONR^{11}S0_2R^{12}$, COR^{11}, NR^{11}-CO-R^{11}, NR^{11}-CO-$NR^{11}R^{12}$, NR^{11}-$S0_2$-$NR^{11}R^{12}$, $NR^{11}R^{12}$, $C_{1\text{-}6}$-alkyl, halo-C^-alkyl, hydroxy-d-e-alkyl, $C_{3\text{-}6}$-cycloalkyl, 0-$C_{3\text{-}6}$-cycloalkyl, $C_{3\text{-}6}$-heterocycloalkyl and 0-$C_{3\text{-}6}$-heterocycloalkyl,

> wherein cycloalkyl and heterocycloalkyl are unsubstituted or substituted with with 1 to 3 substituents selected from oxo, OH, methyl, CF_3 and fluoro;

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 are unsubstituted or substituted with 1 to 5 substituents independently selected from halogen, CN, C_{1-6}-alkyl, C_{1-6}-alkenyl, $C_{1.6}$-alkynyl, halo-Ci-$_{6}$-alkyl, OH, O-C^-alkyl, O-ftalo-Ci¾-alkyl, $C_{0.6}$-alkylene-C_{3-10}-cycloalkyl, C_{0-6}-alkylene-O-C_{3-10}-cycloalkyl, Co6-alkylene-C_{3-10}-heterocycloalkyl, C_{0-6}-alkylene-COOR^{31}, C_{0-6}-alkylene-C(0)R^{31}, $C_{0.6}$-alkylene-C(O)N(R^{31})$_2$, C_{0-6}-alkylene-SO$_2$-N(R^{31})$_2$, C_{0-6}-alkylene-S0$_2$-R^{31}, C_{0-6}-alkylene-(5-membered heteroaryl), C_{0-6}-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 Ci.6-alkyl, halo-Ci.$_{6}$-alkyl, halogen, OH, oxo, =N-OR^{32}, N(R^{31})$_2$, O-d-e-alkyl, 0-halo-C_{1-6}-alkyl, COOH, CON(R^{31})$_2$, CN, NR^{31}-COR^{31}, $C_{3.10}$-cycloalkyl, $C_{3.10}$-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, S0$_2$ or NR^{31}, wherein the ring is unsubstituted or substituted with one to four substituents independently selected from halogen, oxo, =N-OR^{32}, OH, O-d-e-alkyl, 0-halo-Ci.$_{6}$-alkyl, C_{1-6}-alkyl, $C_{3.6}$-cycloalkyl and halo-d-e-alkyl;

R^4 is selected from (CR^{8}R^9)R^{40}, (C=0)R^{40}, C_3-cycloalkylene-R^{40}, OR^{40}, NR^{41}R^{40} and SO$_y$-R^7;

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-C_{1-6}-alkyl, O-halo-Ci-e-alkyl, C_{1-6}-alkyl, halo-Ci-$_{6}$-alkyl, cycloalkyl and heterocycloalkyl;

R^8 and R^9 are independently selected from H, F, C_{1-3}-alkyl, halo-Ci.$_{3}$-alkyl, OH, 0-Ci$_{-3}$-alkyl and O-halo-C^-alkyl,

R^{11} and R^{31} independently selected from H, C^-alkyl, $C_{3.10}$-cycloalkyl, $C_{3.10}$-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 C_{1-6}-alkyl, halo-C^-alky!, OH, 0-Ci.$_{6}$-alkyl, O-halo-C^-alkyl, phenyl, heteroaryl, halogen, NH$_2$, NH^.e-alkyl), N($C_{1.6}$-alkyl)$_2$, C_3-io-heterocycloalkyl and C_{3-10}-cycloalkyl, COOH, S0$_2$-Ci-$_{3}$-alkyl, SOa-C^-fluoroalkyl, oxo and CN,

wherein cycloalkyl and heterocycloalkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of C_{1-6}-alkyl, halo-C_{1-6}-alkyl, OH, 0-C_{1-6}-alkyl, O-halo-d-e-alkyl, phenyl, heteroaryl, halogen, NH$_2$, NH(Ci-$_{6}$-alkyl), N(C_{1-6}-alkyl)$_2$ and $C_{3.10}$-cycloalkyl, wherein phenyl and heteroaryl are unsubstituted or substituted with 1 to 4 substituents independently selected from the group consisting of OH, 0 -C_{1-6}-alkyl, 0-halo -C_{1-6}-alkyl, halogen, d-e-alkyl, halo-C_{1-6}-alkyl, NH_2, NH(d. $_6$-alkyl), N(d- $_6$-alkyl)$_2$ and C_{3-10}-cycloalkyl;

R^{12} and R^{32} are independently selected from H, C_{1-6}-alkyl, halo-d -e-alkyl and C_3-io-cycloalkyl;

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, 0 -C_{1-6}-alkyl, O-halo-d. $_6$-alkyl, d $_{-6}$-alkyl and halo-Ci-e-alkyl;

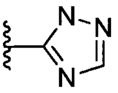
R^{41} is selected from H, d -e-alkyl, C_{3-6}-cycloalkyl and C_{3-6}-heterocycloalkyl,

wherein alkyl, cycloalkyl and heterocycloalkyl is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of OH, oxo, CN, halogen, 0 -C_{1-6}-alkyl, O-halo-Ci-e-alkyl, C_{3-6}-heterocycloalkyl and C_{3-6}-cycloalkyl;

y is independently selected from 0, 1 and 2;

W is selected from C or S=0;

with the proviso that for R^3 the 5-14 membered mono-, bi- or tricyclic heteroaryl containing ring is not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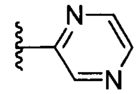
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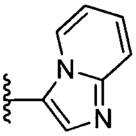
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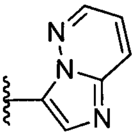
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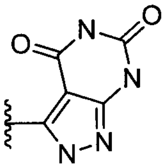
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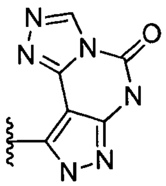
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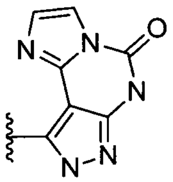

or a 5-membered aromatic heterocyclic group containing at least one oxygen atom.

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};

R^8 is selected from H, F, methyl, trifluoromethyl and O-methyl;

R^9 is selected from H, F and methyl;

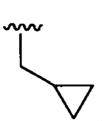
R^{40} is C_{3-8}-cycloalkyl, which is unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of fluoro, methyl and trifluoromethyl.

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

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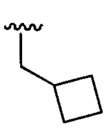
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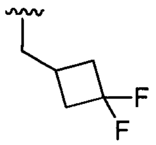

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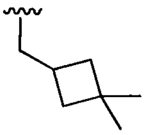
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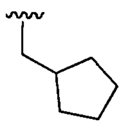
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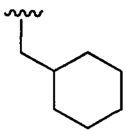
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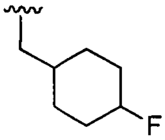

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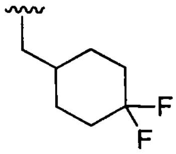

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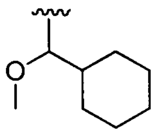

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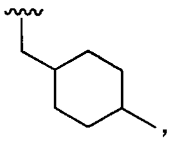
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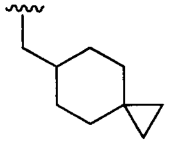
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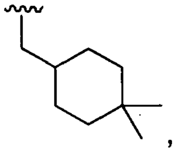
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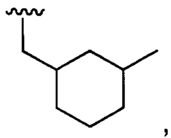
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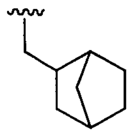
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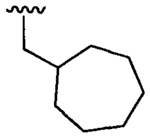
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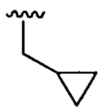
more preferably, R^4 is selected from

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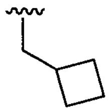
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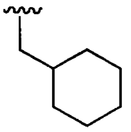
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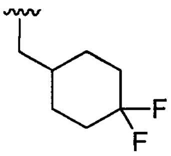

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In a preferred embodiment in combination with any of the above or below embodiments of the third alternative R^1 is selected from H, $C_{1\text{-}10}$-alkyl, $C_{3\text{-}10}$-cycloalkyl, $C_{3\text{-}10}$-heterocycloalkyl, $C_{1\text{-}10}$-alkylene -$C_{3\text{-}10}$-cycloalkyl, Ci-io-alkylene-C3-$_{10}$-heterocycloalkyl, C_1.^-alkylene-iS-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}, 0-$C_{2\text{-}6}$-alkylene -OR^{11}, C^-alkyl, halo-C^-alkyl, halogen, $C0_2R^{11}$, $CONR^{11}R^{12}$, $CONR^{11}S0_2R^{11}$, COR^{11}, SO_xR^{11}, $S0_3H$, $S0_2NR^{11}R^{12}$, $NR^{11}COR^{11}$, $NR^{11}S0_2R^{11}$, NR^{11}-CO-$NR^{11}R^{12}$, NR^{11}-$S0_2$-$NR^{11}R^{12}$, $C_{3\text{-}10}$-cycloalkyl, O-$C_{3\text{-}10}$-cycloalkyl, $C_{3\text{-}10}$-heterocycloalkyl, 0-$C_{3\text{-}10}$-heterocycloalkyl and $NR^{11}R^{12}$;

R^2 is selected from H, Ci.$_6$-alkyl, halo-Ci.$_6$-alkyl and hydroxy -Ci-e-alkyl;

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 substitutents independently selected from halogen, oxo, CN, OR^{11}, SO_xR^{11}, $S0_3H$, $NR^{11}S0_2R^{11}$, $S0_2NR^{11}R^{12}$, $C_{0\text{-}6}$-alkylene-CO_2R^{11}, $CONR^{11}R^{12}$, $CONR^{11}S0_2R^{11}$, COR^{11}, NR^{11}-

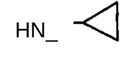
CO-R^{11}, NR^{11}-CO-NR^{11}R^{12}, NR^{11}-S0 $_2$-NR^{11}R^{12}, NR^{11}R^{12}, d -e-alkyl, halo-d -e-alkyl, hydroxy-d-6-alkyl, C$_{3-8}$-cycloalkyl, 0-C $_{3-8}$-cycloalkyl, C$_{3-8}$-heterocycloalkyl and 0-C $_{3-8}$-heterocycloalkyl,

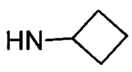
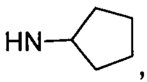
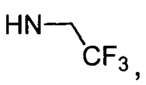
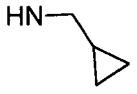
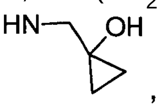
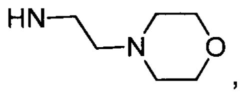
wherein cycloalkyl and heterocycloalkyi are unsubstituted or substituted with 1 to 4 substitutents independently selected from halogen, C$_{1-3}$-alkyl, halo-Ci.$_3$-alkyl, OH, O-C1. 3-alkyl, O-halo-d-a-alkyl, S0 $_2$-d $_{-3}$-alkyl, COOH and oxo.

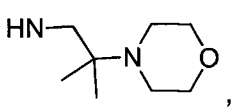
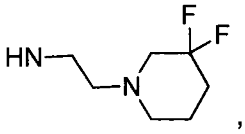
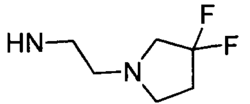
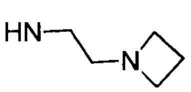
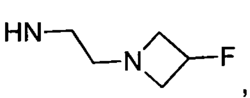
In an alternative preferred embodiment in combination with any of the above or below embodiments of the third alternative R^1 is selected from H, Ci-i $_0$-alkyl, C$_0$-io -alkylene-C $_{3-10}$-cycloalkyl, and C$_0$-io -alkylene-C $_{3-10}$-heterocycloalkyl, wherein alkyl, alkylene, cycloalkyl and heterocycloalkyi is unsubstituted or substituted with 1 to 7 substituents independently selected from oxo, OR^{11}, d-e-alkyl, halo-d-e-alkyl, halogen, C0 $_2$R^{11}, CONR^{11}R^{12}, CONR^{11}S0 $_2$R^{12}, COR^{11}, NR^{11}COR^{11}, NR^{11}S0 $_2$R^{11}, NR^{11}-CO-NR^{11}R^{12}, NR^{11}-S0 $_2$-NR^{11}R^{12}, C$_{3-6}$-cycloalkyl, 0-C $_3$. 6-cycloalkyl, C$_{3-6}$-heterocycloalkyl and 0-C $_{3-6}$-heterocycloalkyl;

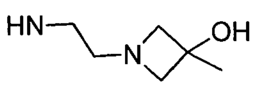
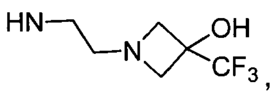
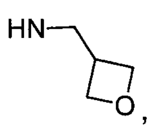
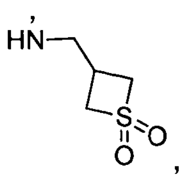
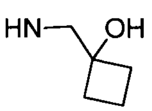
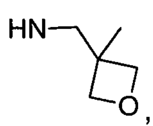
R^2 is selected from the group consisting of H, c $_{1-6}$ alkyl and halo-d. $_6$alkyl;

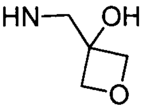
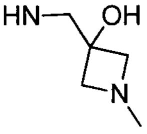
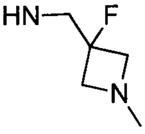
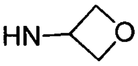
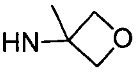
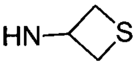
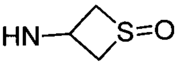
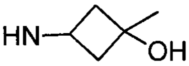
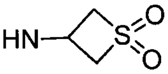
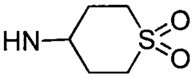
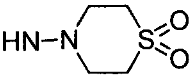
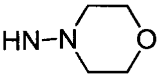
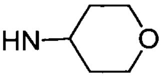
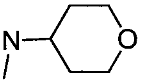
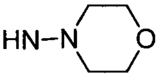
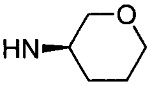
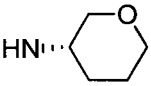
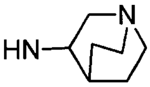
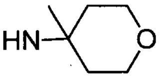
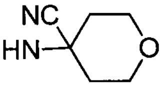
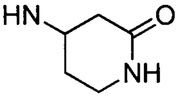
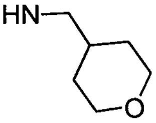
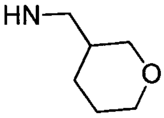
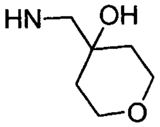
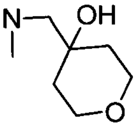
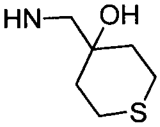
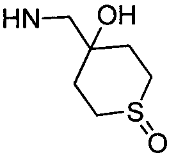
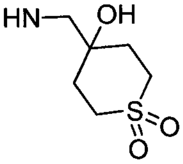
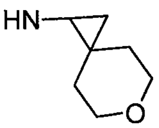
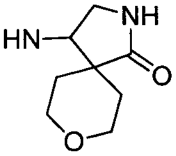
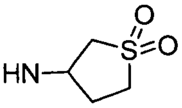
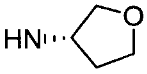
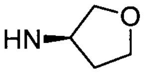
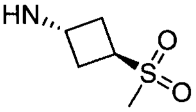
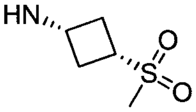
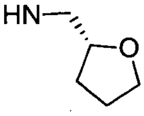
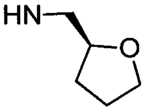
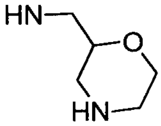
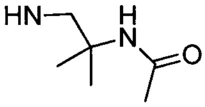
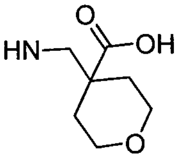
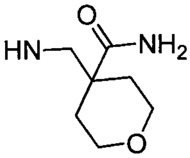
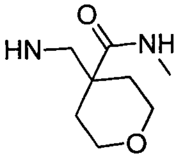
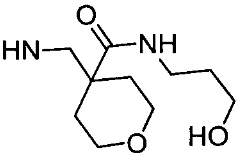
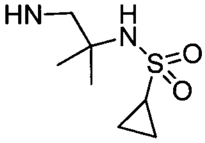
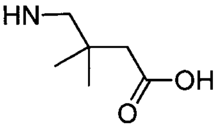
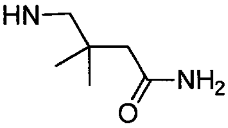
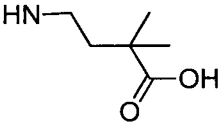
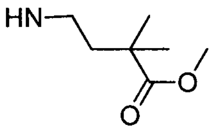
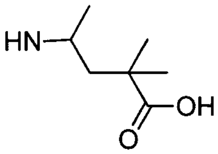
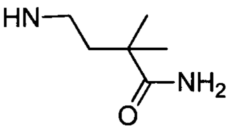
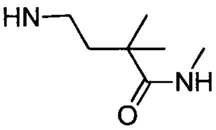
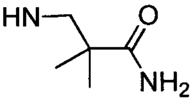
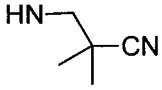
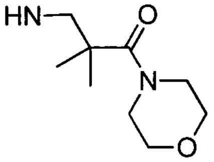
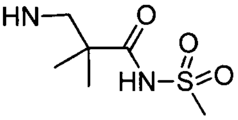
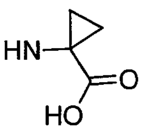
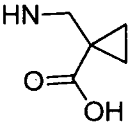
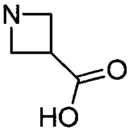
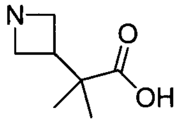
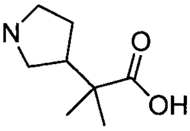
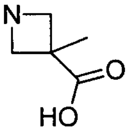
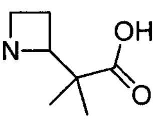
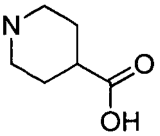
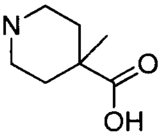
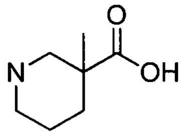
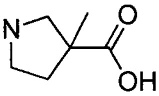
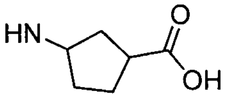
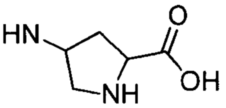
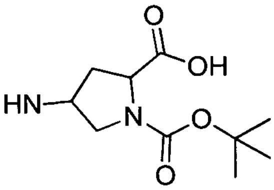
or R^1 and R^2 when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing 1 or 2 heteroatoms selected from O, S or N, wherein the ring is unsubstituted or substituted with 1 to 4 substituents independently selected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

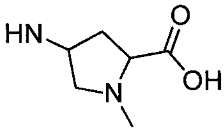
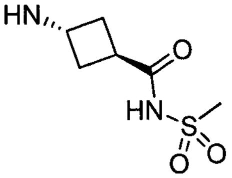
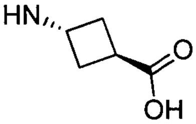
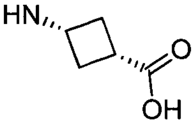
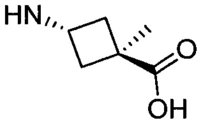
In a preferred embodiment in combination with any of the above or below embodiments of the third alternative NR^{1}R^2 is selected from NHMe, NHEt, NH'Pr, NH'Bu, NHCH$_2$CONH $_2$, NHCH$_2$CONMe$_2$, NHCH$_2$CH$_2$OH, NHCH$_2$CH$_2$OMe, NHCH$_2$CH$_2$S0 $_2$Me, NHCH$_2$CH$_2$S0 $_2$NH$_2$, NH(CH$_2$)$_3$0H, NH(CH$_2$)$_3$OMe, NH(CH2)$_4$OH, NH(CH$_2$)$_4$OMe, NH(CH$_2$)$_5$OH, NH(CH$_2$)$_2$C0 $_2$H, NH(CH$_2$)$_3$C0 $_2$H, NH(CH$_2$)$_4$C0 $_2$H, NH(CH$_2$)$_5$C0 $_2$H, NHCH$_2$CH(CF$_3$)OH, NHCH$_2$C(Me)(CF $_3$)OH, NHCH$_2$CMe$_2$OH, NHCH$_2$CH$_2$CMe$_2$OH, NHCH$_2$CMe$_2$NHCH$_2$CF$_3$, NHCH(Me)CMe $_2$OH, NHCH$_2$CMe$_2$OMe, NHCH$_2$CMe2C0 $_2$H, NHCH$_2$CMe$_2$CONHMe, NHCH$_2$CMe$_2$CONMe $_2$, NHCH$_2$CMe$_2$NHS0 $_2$Me, NH(CH$_2$)$_3$SOMe, NH(CH$_2$)$_5$S0 $_2$Me, NH(CH $_2$)$_5$S0 $_2$NH$_2$, NH(CH$_2$)$_3$NHS0 $_2$Me, NH(CH$_2$)$_2$0(CH $_2$)$_2$OH, NHCH$_2$CHMeOH, NH(CH $_2$)$_5$SOMe, NH(CH$_2$)$_3$S0 $_2$Me, NHC(CH$_2$OH)$_3$, NHCH$_2$CH(OH)CH $_2$OH, N(CH$_2$CH$_2$OH)$_2$, ,

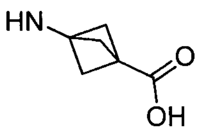
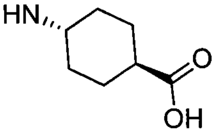
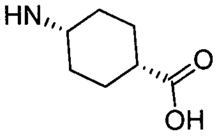
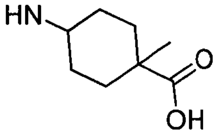
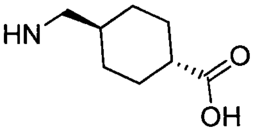
, , , , , ,

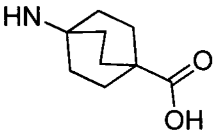
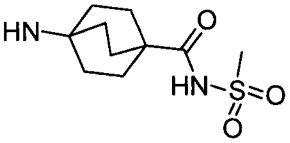
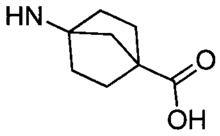
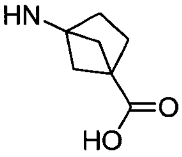
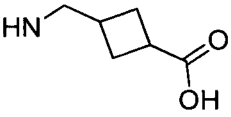
, , , , ,

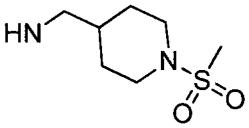
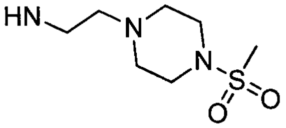
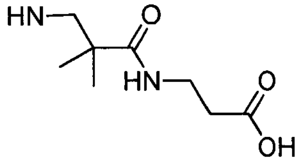
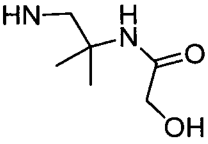
, , , , , ,

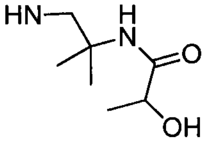
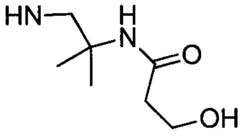
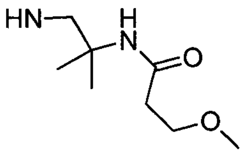
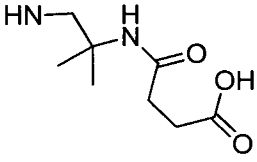
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,

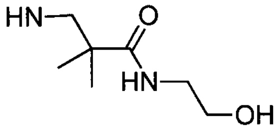
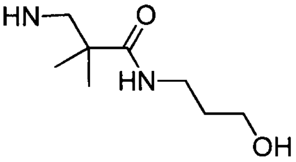
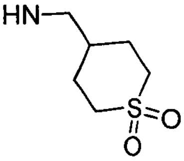
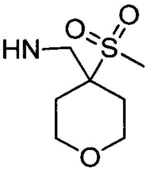
,
,
,
,
,

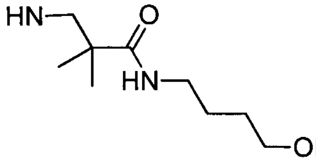
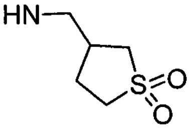
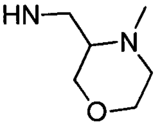
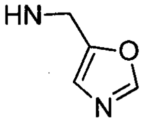
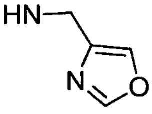
,
,
,
,
,

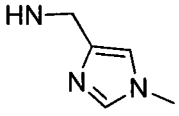
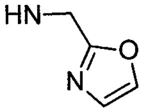
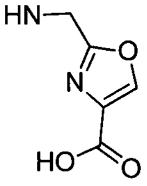
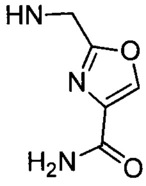
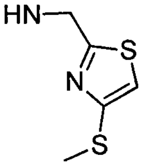
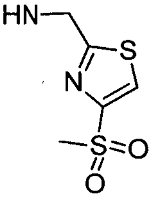
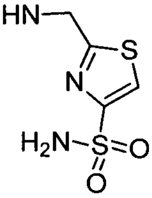
,
,
,
,
,

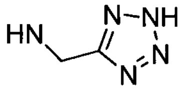
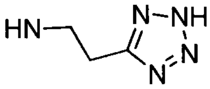
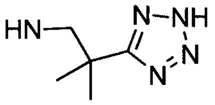
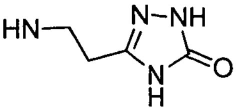
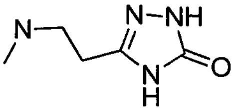
,
,
,
,

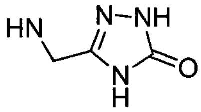
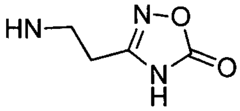
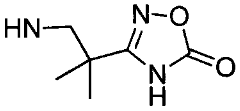
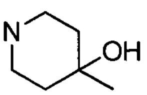
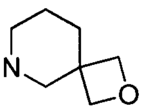
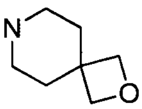
,
,
,
,

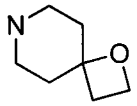
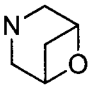
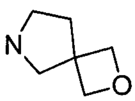
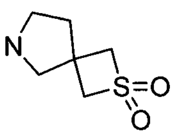
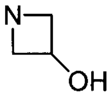
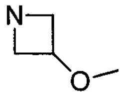
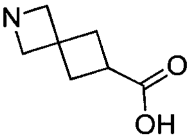
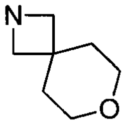
,
,
,
,

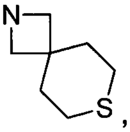
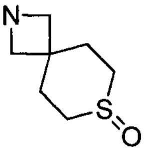
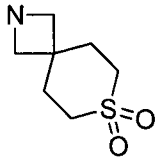
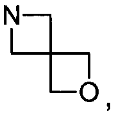
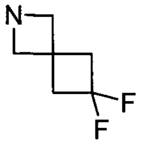
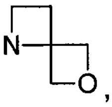
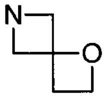
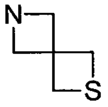
,
,
,
,
,

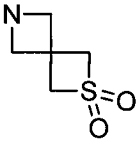
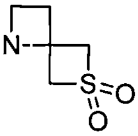
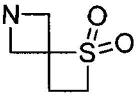
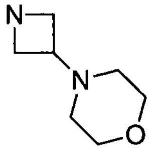
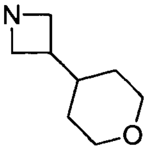
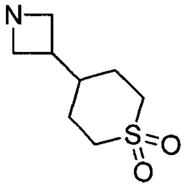
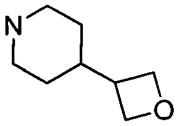
,
,
,
,
,
,
,

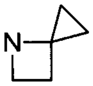
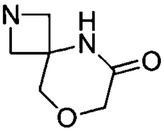
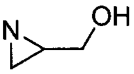
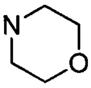
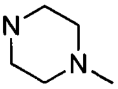
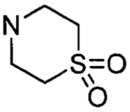
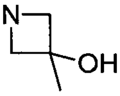
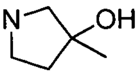
,
,
,
,
,

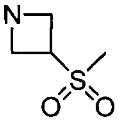
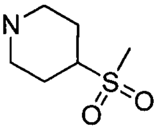
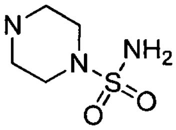
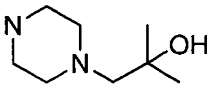
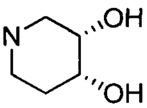
,
,
,
,
,
,

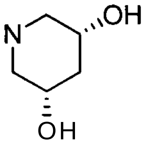
,
,
,
,
,
,
,
,

, , , , , , , ,

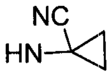
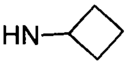
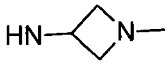
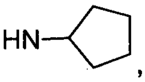
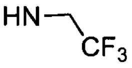
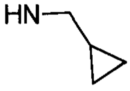
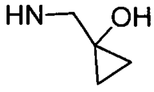
, , , , , , ,

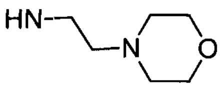
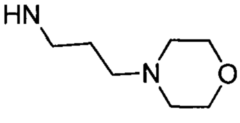
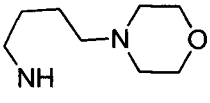
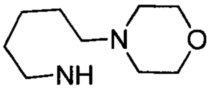
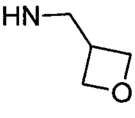
, , , , , , , ,

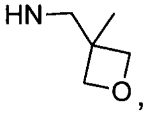
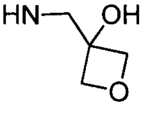
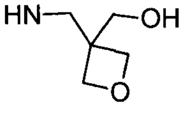
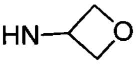
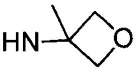
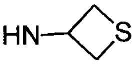
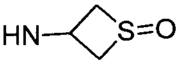
, , , , ,  and

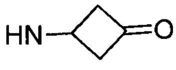
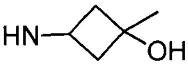
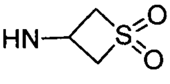
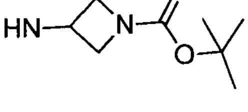
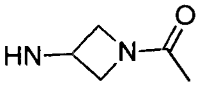
 .

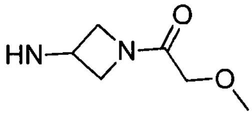
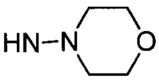
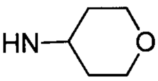
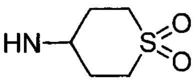
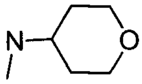
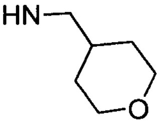
In an alternative preferred embodiment in combination with any of the above or below embodiments of the third alternative NR^1R^2 is selected from NH_2, NHMe, NHEt, NH^iPr, NH^tBu, $NHCH_2CONH_2$, $NHCH_2CONMe_2$, $NHCH_2CH_2OH$, $NHCH_2CH(CF_3)OH$, $NHCH_2C(CF_3)_2OH$, $NHCH_2CH_2OMe$, $NHCH_2CH_2SO_2Me$, $NHCH_2CH_2SO_2NH_2$, $NH(CH_2)_3OH$, $NH(CH_2)_3OMe$, $NH(CH_2)_4OH$, $NH(CH_2)_4OMe$, $NH(CH_2)_5OH$, $NH(CH_2)_2CO_2H$, $NH(CH_2)_3CO_2H$, $NH(CH_2)_4CO_2H$, $NH(CH_2)_5CO_2H$, $NHCH_2CMe_2OH$, $NHCH(Me)CMe_2OH$, $NHCH_2CMe_2OMe$, $NHCH_2CMe_2CO_2H$, $NHCH_2CMe_2CONHMe$, $NHCH_2CMe_2CONMe_2$, $NHCH_2CMe_2NHSO_2Me$, $NH(CH_2)_3SOMe$, $NH(CH_2)_5SO_2Me$, $NH(CH_2)_3NHSO_2Me$, $NH(CH_2)_2O(CH_2)_2OH$, $NHCH_2CHMeOH$, ,

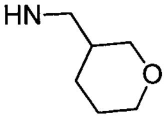
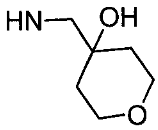
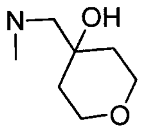
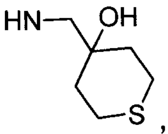
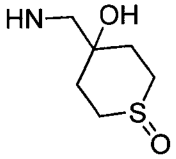
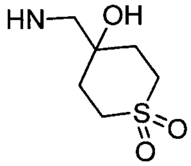
, , , , , , ,

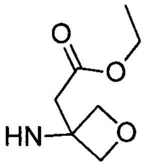
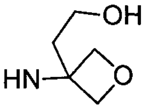
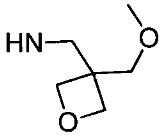
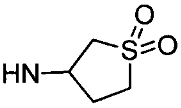
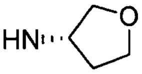
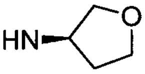
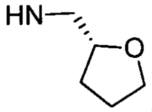
, , , , ,

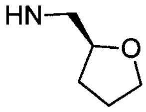
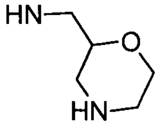
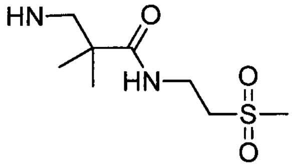
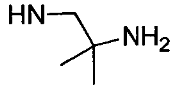
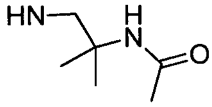
, , , , , , ,

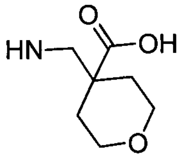
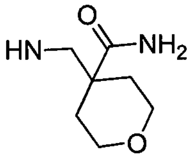
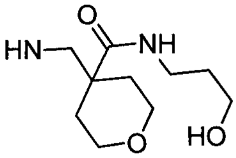
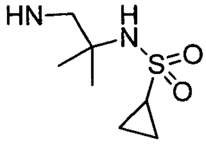
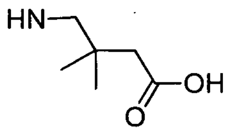
, , , , ,

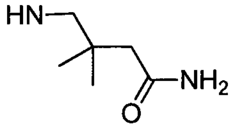
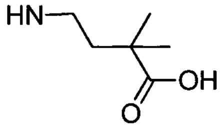
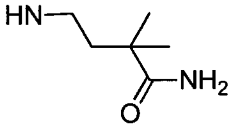
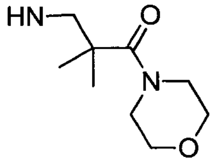
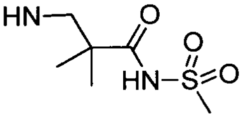
, , , , , ,

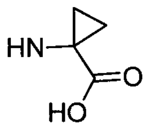
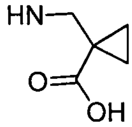
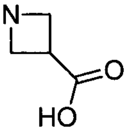
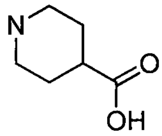
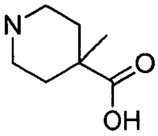
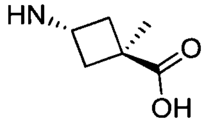
, , , , , ,

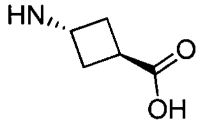
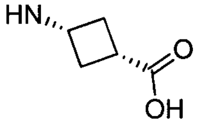
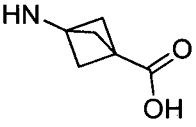
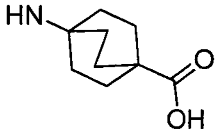
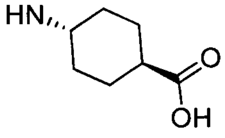
, , , , , , ,

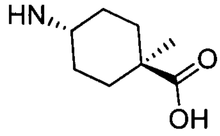
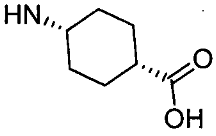
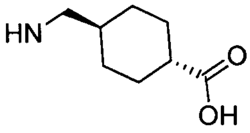
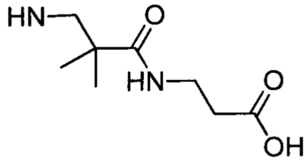
, , , , ,

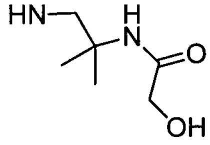
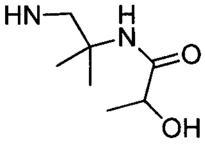
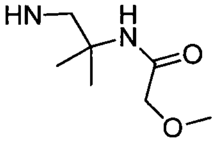
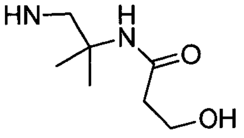
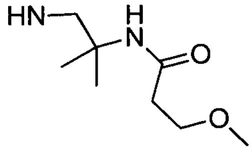
, , , , ,

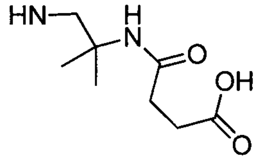
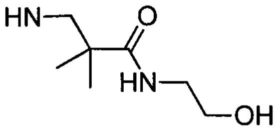
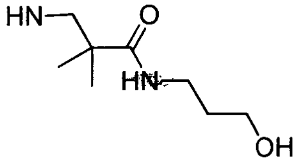
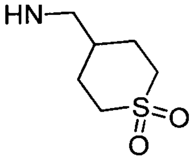
, , , , ,

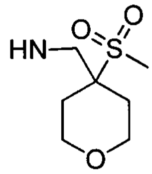
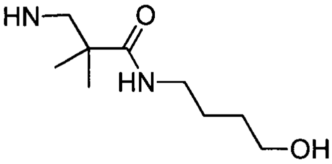
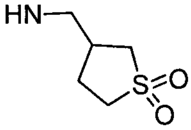
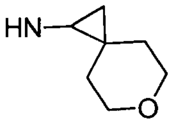
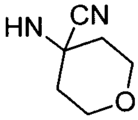
, , , , , ,

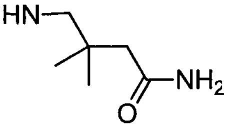
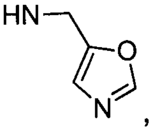
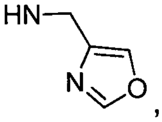
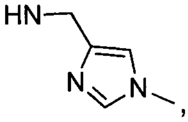
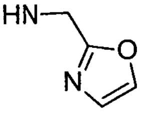
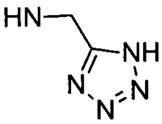
, , , , ,

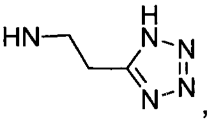
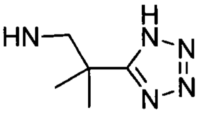
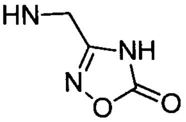
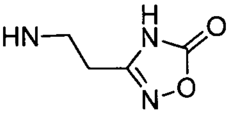
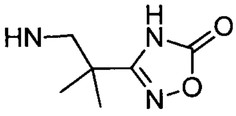
, , , ,

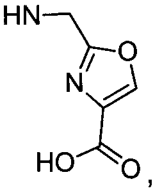
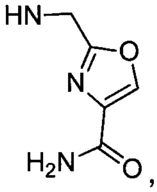
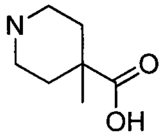
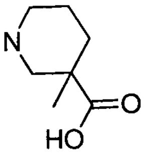
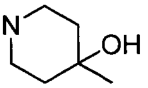
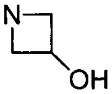
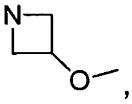
, , , , ,

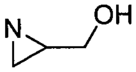
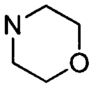
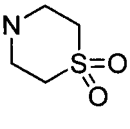
, , , ,

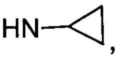
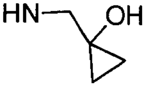
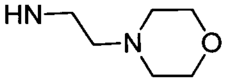
, , , , ,

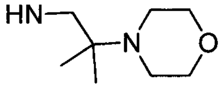
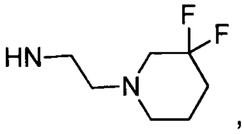
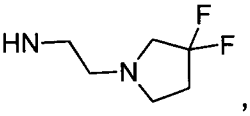
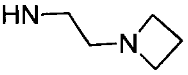
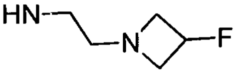
, , , , , ,

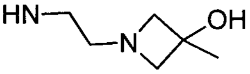
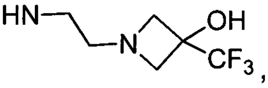
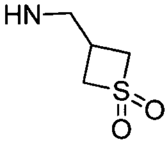
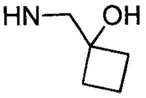
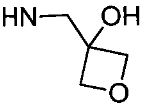
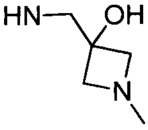
, , , , ,

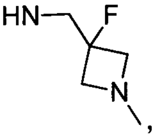
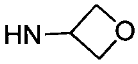
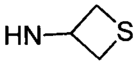
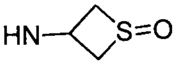
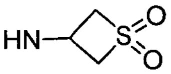
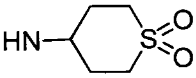
, , , , , , ,

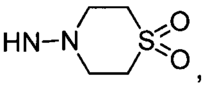
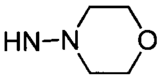
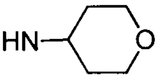
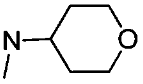
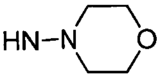
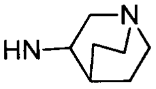
,  and .

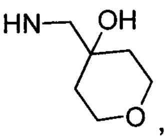
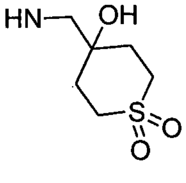
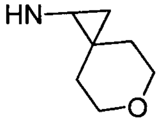
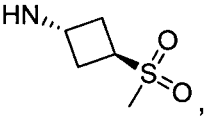
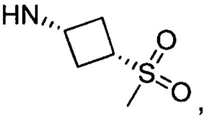
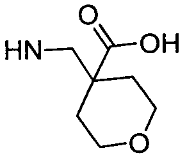
In a more preferred embodiment in combination with any of the above or below embodiments of the third alternative NR^1R^2 is selected from $NHCH_2CH(CF_3)OH$, $NHCH_2C(Me)(CF_3)OH$, $NHCH_2CMe_2OH$, $NHCH_2CH_2CMe_2OH$, $NHCH_2CMe_2NHCH_2CF_3$, $NHC(CH_2OH)_3$, $NHCH_2CH(OH)CH_2OH$, $N(CH_2CH_2OH)_2$, , , ,

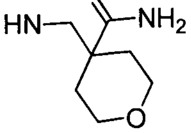
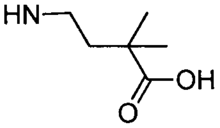
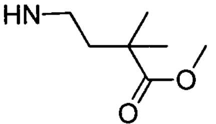
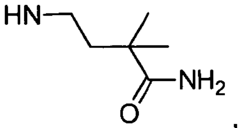
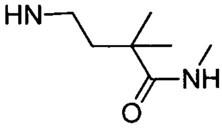
, , , , ,

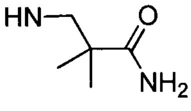
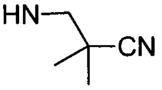
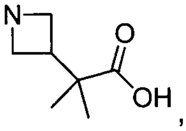
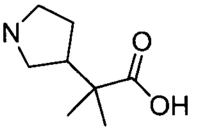
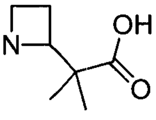
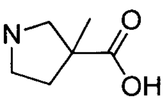
, , , , , ,

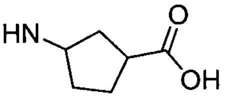
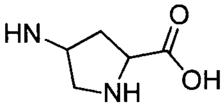
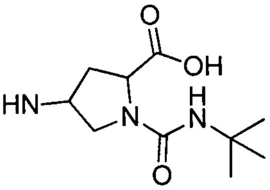
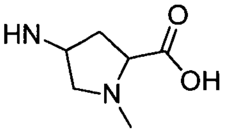
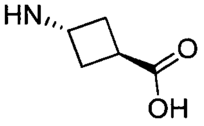
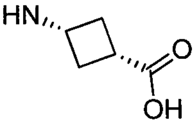
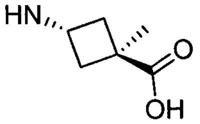
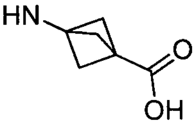
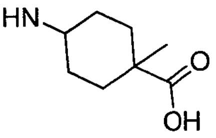
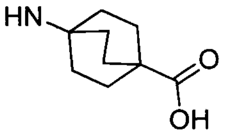
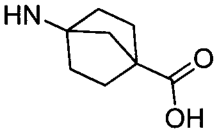
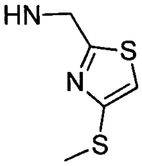
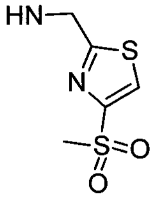
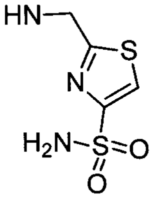
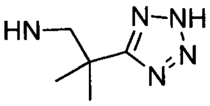
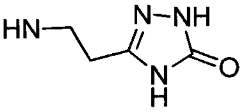
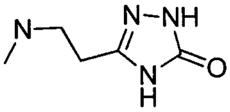
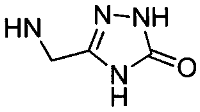
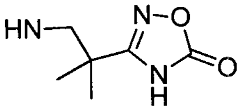
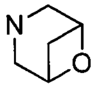
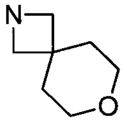
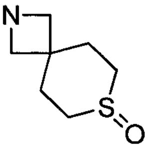
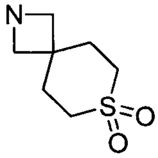
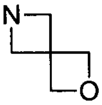
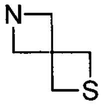
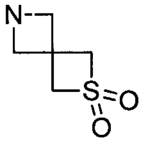
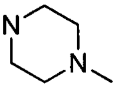
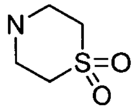
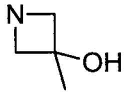
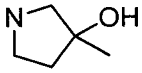
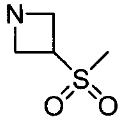
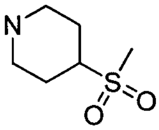
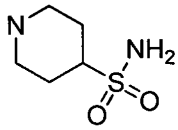
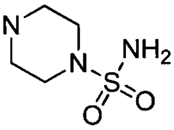
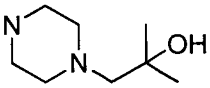
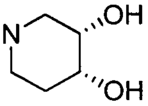
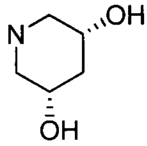
, , , , , ,

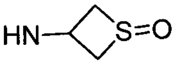
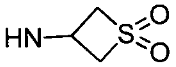
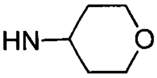
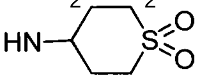
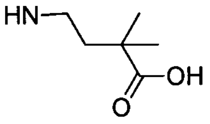
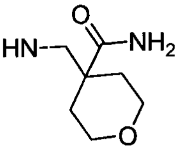
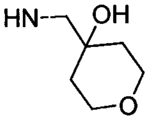
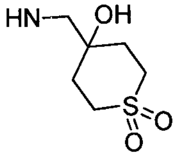
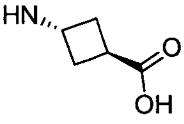
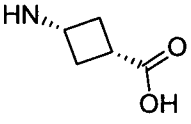
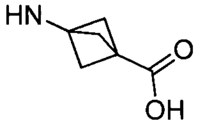
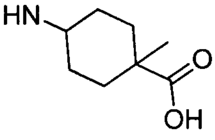
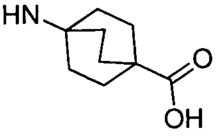
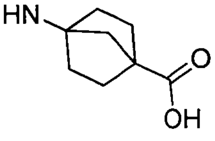
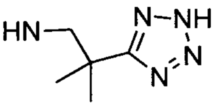
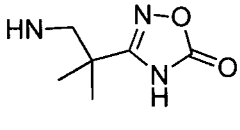
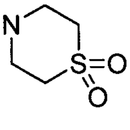
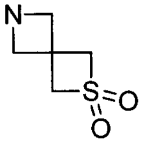
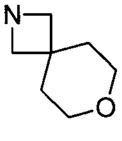
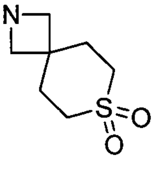
, , , , , ,

, , , , , ,

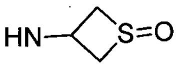
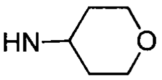
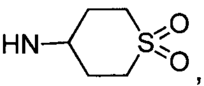
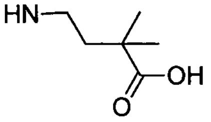
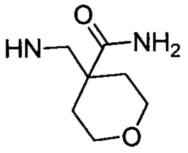
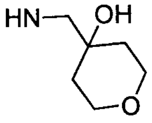
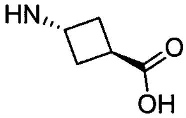
, , , , ,

, , , , , ,

, , , , ,
, , , , ,
, , , , , ,
, , , , , ,
, , , , , , , ,
, , , , ,  and
 .

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

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 $NHCH_2CMe_2OH$, $NHCH_2CMe_2CO_2H$,

, , , , , , and .

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

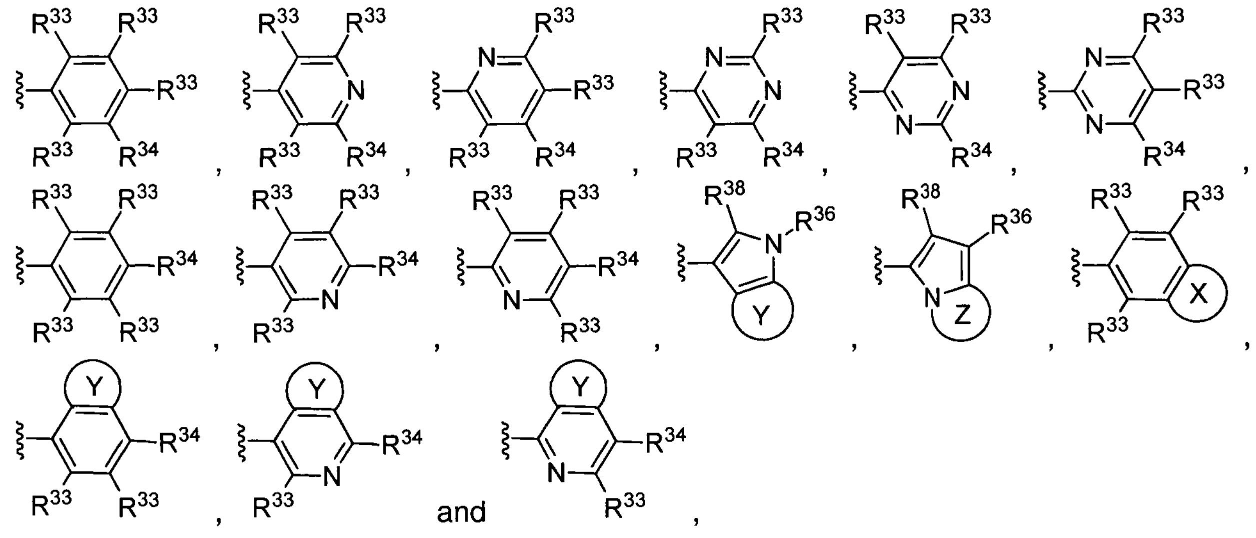
wherein aryl and heteroaryl are unsubstituted or substituted with 1 to 5 substituents independently selected from halogen, **CN,** C_{1-6}-alkyl, halo-d -e-alkyl, **OH,** 0 -C_{1-6}-alkyl, **O-**halo-**Ci-6**-alkyl, C_{0-6}-alkylene -C_{3-10}-cycloalkyl, C_{0-6}-alkylene-0 -C_{3-10}-cycloalkyl, C_{0-6}-alkylene -C_{3-io}-heterocycloalkyl, C_{0-6}-alkylene **-COOR ^{31},** C_{0-6}-alkylene **-C(O)R ^{31},** **C_{0-6}-alkylene-C(0)N(R ^{31})$_2$,** C_{0-6}-alkylene-SO $_2$**-N(R^{31})$_2$,** C_{0-6}-alkylene-SO $_2$**-R^{31},** 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-OR ^{32}, N(R^{31})$_2$,** O-C^-alkyl; **COOH, CON(R ^{31})$_2$, CN, NR^{31}-COR^{31},** C_{3-10}-cycloalkyl, C_{3-10}-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,** $S0_2$ or **NR^{31},** wherein the ring is unsubstituted or substituted with 1 to 4 substituents independently selected from halogen, oxo, **=N-OR ^{32}, OH, O-Ci-6-alkyl**, 0-halo **-**C_{1-6}-alkyl, C_{1-6}-alkyl, C_{3-6}-cycloalkyl and halo-**Ci** $_{-6}$-alkyl.

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.

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



wherein

R^{33} is independently selected from H, halogen, CN, C_{1-6}-alkyl, fluoro-d. $_6$-alkyl, $C_{1\cdot4}$-alkylene-OH, d^-alkylene-O-d-a-alkyl, Ci-$_4$-alkylene-0-fluoro-d. $_3$-alkyl, OH, 0-d. $_6$-alkyl, 0-fluoro-Ci. $_6$-alkyl, NH-d. $_6$-alkyl, NH-fluoro-Ci_$_6$-alkyl, $C_{3\cdot10}$-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-d. $_3$-alkyl;

R^{34} are independently selected from H, halogen, CN, C_{1-6}-alkyl, fluoro-d. $_6$-alkyl, Ci-$_4$-alkylene-OH, C_{1-4}-alkylene-O-C_{1-3}-alkyl, C_{1-4}-alkylene-O-fluoro-C_{1-3}-alkyl, OH, 0-d. $_6$-alkyl, O-fluoro-d-$_6$-alkyl, NH-d. $_6$-alkyl, NH-fluoro-d. $_6$-alkyl, $C_{3\cdot10}$-cycloalkyl, $C_{0\cdot6}$-alkylene-$C_{3\cdot10}$-heterocycloalkyl, 5-membered heteroaryl, 6-membered heteroaryl, C(0)N(R ^{37})$_2$ and S0 $_2$N(R^{37})$_2$,

wherein alkylene is unsubstituted or substituted with 1 to 3 substituents selected from F and cycloalkyl, heterocycloalkyi and heteroaryl is unsubstituted or substituted with 1 to 3 substituents independently selected from F, C_{1-3}-alkyl, fluoro-Ci-$_3$-alkyl, OH, 0-Ci- $_3$-alkyl, fluoro-O-Ci $_{\cdot3}$-alkyl;

R^{35} is selected from halogen, d $_{\cdot6}$-alkyl, halo-d. $_6$-alkyl, C_{3-6}-cycloalkyl, C_{3-6}-heterocycloalkyl, oxo, OH, O-Ci-e-alkyl and O-halo-Ci-e-alkyl;

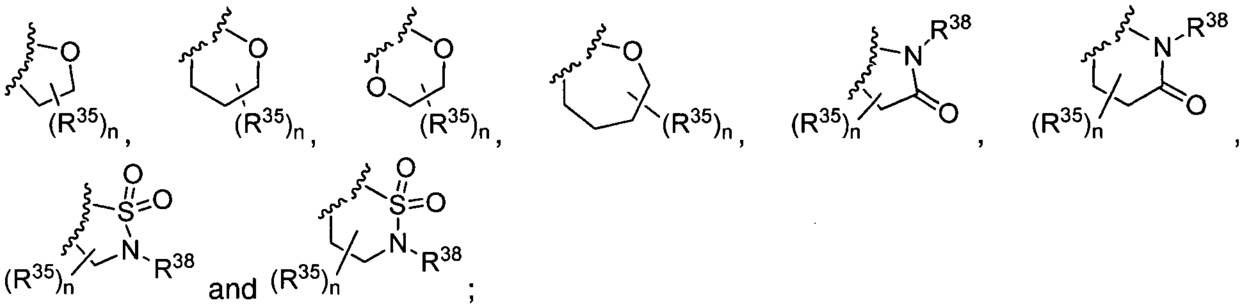
R^{36} is selected from C_{1-6}-alkyl, fluoro-C_{1-6}-alkyl, C(0)N(R ^{37})$_2$, S0 $_2$N(R^{37})$_2$;

R^{37} is independently selected from H, d $_{\cdot6}$-alkyl, halo-Ci-e-alkyl, $C_{0\text{-}4}$-alkylene-$C_{3\cdot6}$-cycloalkyl, $C_{0\cdot4}$-alkylene-$C_{3\cdot6}$-heterocycloalkyl, wherein alkyl and alkylene is unsubstituted or substituted with 1 to 4 substituents selected from halogen, OH, 0-d. $_3$-alkyl, CN, $CONH_2$; and cycloalkyl or heterocycloalkyi is unsubstituted or substituted with 1 to 3 substituents independently selected from F, CN, OH, oxo, C_{1-3}-alkyl and fluoro-Ci. $_3$-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 substitutents independently selected from fluoro, OH, oxo, d-4-alkyl and halo-Ci_$_4$-alkyl;

R^{38} is selected from H, C_{1-3}-alkyl and fluoro-C_1^-alkyl;

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

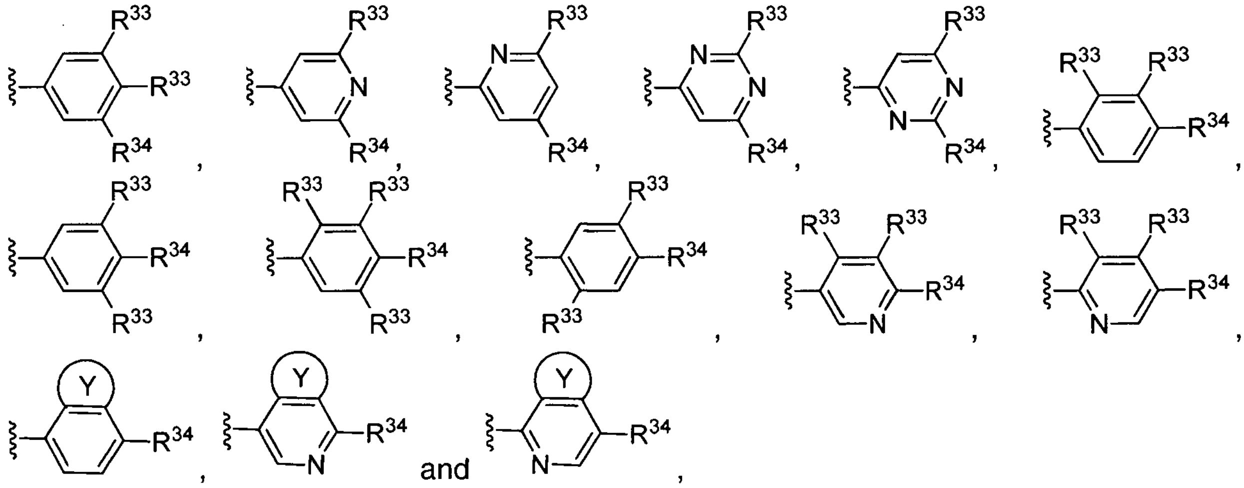


Y is an annelated 5- or 6-membered carbocycle, an annelated 6-membered aryl or an annelated 6-membered heteroaryl containing 1 to 2 nitrogen atoms, wherein the carbocycle, aryl or heteroaryl is unsubstituted or substituted with 1 to 3 substituents selected from halogen, C_{1-3}-alkyl and fluoro-Ci.$_3$-alkyl;

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, Ci-3-alkyl and fluoro-Ci.$_3$-alkyl;

n is selected from 1 to 4.

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



wherein

R^{33} is independently selected from H, halogen, CN, C_{1-6}-alkyl, fluoro-C^e-alkyl, ^-alkylene - OH, d^-alkylene-O-d-a-alkyl, d-4-alkylene-0-fluoro-d. $_3$-alkyl, OH, 0-Ci. $_6$-alkyl, O-fluoro-d . $_6$-alkyl, NH-d. $_6$-alkyl, NH-fluoro-d-e-alkyl, C_{3-10}-cycloalkyl, C(0)N(R ^{37})$_2$, 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-**Ci-3**-alkyl;

R^{34} is selected from C_{1-4}-alkylene-**OH**, $C_{1.4}$-alkylene-0 -**Ci** $_{.3}$-alkyl, $C_{1.4}$-alkylene-0-fluoro -C_{1-3}-alkyl, (Wcycloalkyl, C(0)**N**(R^{37})$_2$, S0 $_2$N(R^{37})$_2$,

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-**Ci** $_{-3}$-alkyl;

R^{37} is independently selected from H, C_{1-e}-alkyl, halo-d $_{-e}$-alkyl, C_{0-4}-alkylene-C_{3-6}-cycloalkyl, C_{0-4}-alkylene-C_{3-6}-heterocycloalkyl,

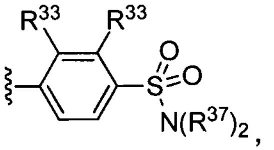
wherein alkyl and alkylene is unsubtituted or substituted with 1 to 4 substituents selected from halogen, **OH**, 0 -**Ci** $_{-3}$-alkyl, **CN**, **CONH** $_2$; and

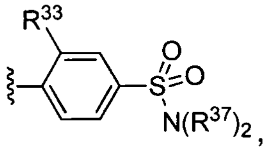
wherin cycloalkyl or heterocycloalkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from **F**, **CN**, **OH**, oxo, 0 -**Ci** $_{.3}$-alkyl, C_{1-3}-alkyl and fluoro-C_{1-3}-alkyl;

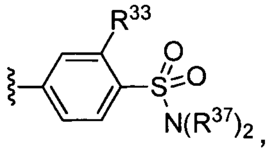
or wherein two R^{37} when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing 1 or 2 heteroatoms selected from **O**, **S** or **N**, wherein the ring is unsubstituted or substituted with 1 to 4 substitutents independently selected from fluoro, **OH**, oxo, C_{1-4}-alkyl and halo-C_{1-4}-alkyl;

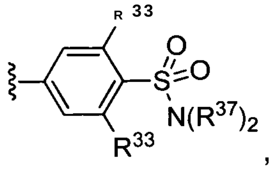
Y is selected from an annelated 5- or 6-membered carbocycle, an annelated 6-membered aryl or an annelated 6-membered heteroaryl containing 1 to 2 nitrogen atoms, wherein the carbocycle, aryl or heteroaryl is unsubstituted or substituted with 1 to 3 substituents selected from fluoro, methyl or CF_3.

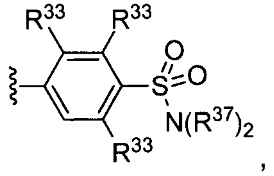
In an even more preferred embodiment in combination with any of the above or below embodiments of the third alternative R^3 is selected from

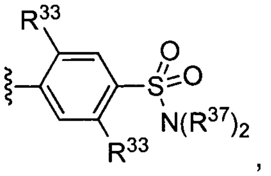


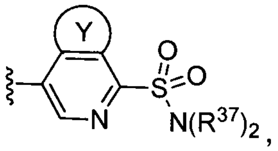


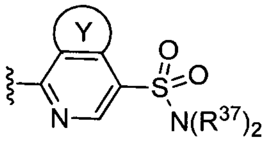












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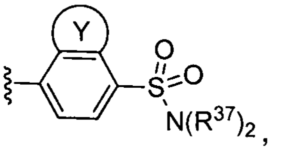


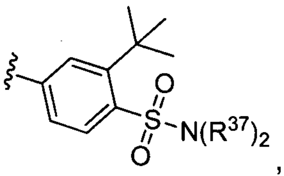
wherein R^{33} is independently selected from H, halogen, C_{1-6}-afkyl, fluoro-C!-6-alkyl, $C_{1\cdot4}$-alkylene-OH, C_{1-4}-alkylene-O-C_{1-3}-alkyl, 0-C $_{1-6}$-alkyl, and 0-fluoro-Ci. $_{6}$-alkyl, more preferably R^{33} is independently selected from fluoro, chloro, CF_3, CHF_2, OCF_3, $OCHF_2$, methyl, 'butyl and CMe_2OH;

one R^{37} is selected from H, C_{1-6}-alkyl, fluoro-Ci-$_{6}$-alkyl and the other R^{37} is selected from Ci-$_{6}$-alkyl, fluoro-$C_{1\cdot6}$-alkyl, C_{0-4}-alkylene-C_{3-6}-cycloalkyl, C o4-alkylene-C $_{3\bar{}6}$-heterocycloalkyl, wherein alkyl and alkylene is unsubtituted or substituted with a substituent selected from halogen, OH, 0 -C_{1-3}-alkyl, CN, $CONH_2$; and cycloalkyl or heterocycloalkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from F, CN, $CONH_2$, OH, oxo, Ci.$_3$-alkyl and fluoro-C!-3-alkyl,

or wherein two R^{37} 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 substitutents independently selected from fluoro, OH, oxo, C!-4-alkyl and halo-Ci $_{\cdot4}$-alkyl;

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 a most 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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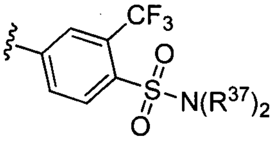
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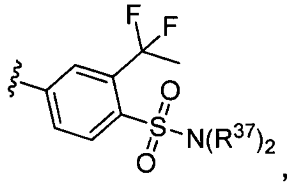
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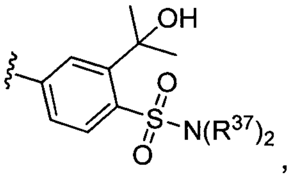
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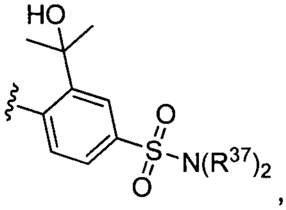
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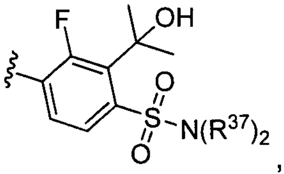
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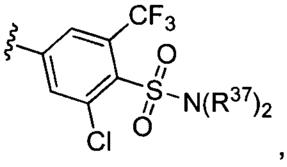
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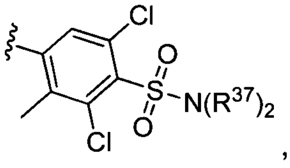
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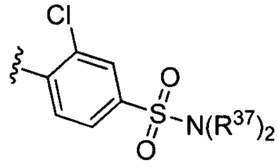
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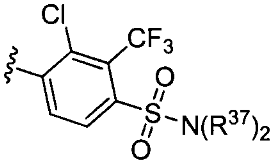
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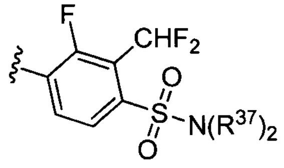
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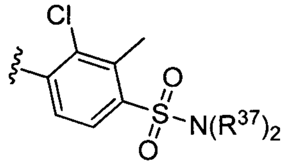
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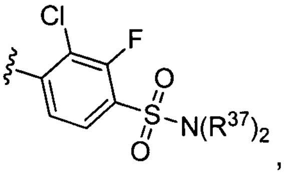
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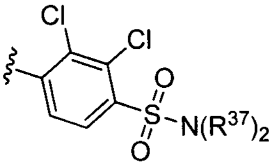
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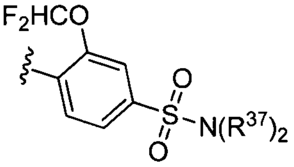
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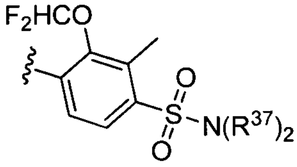
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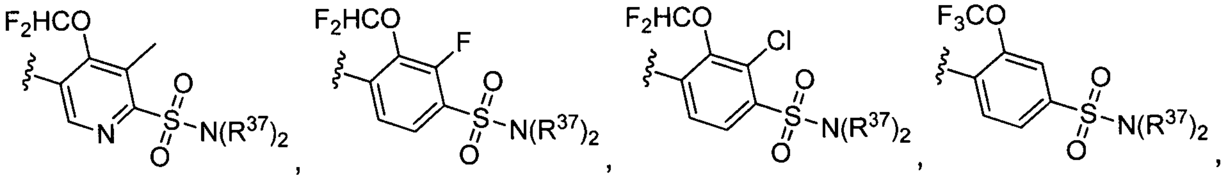
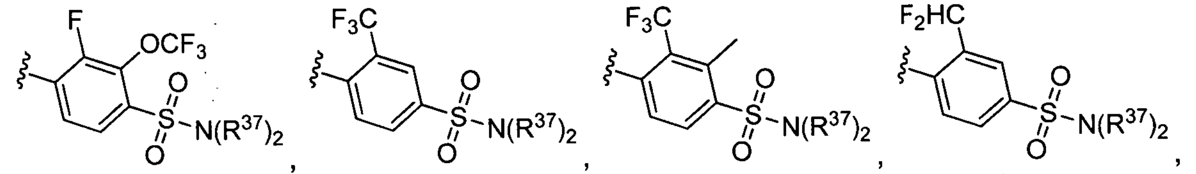
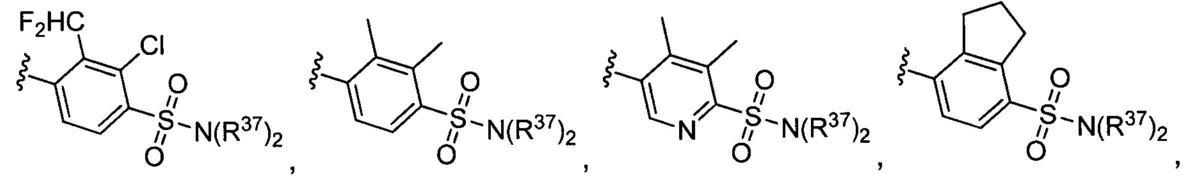
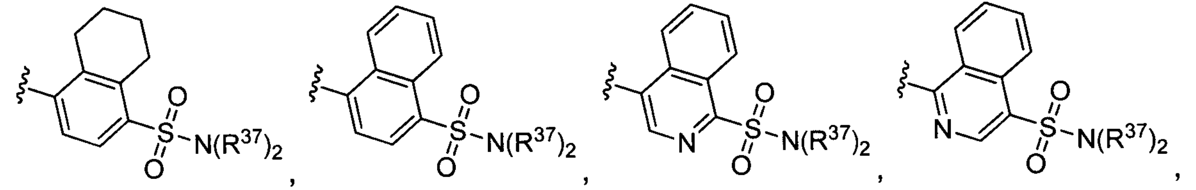
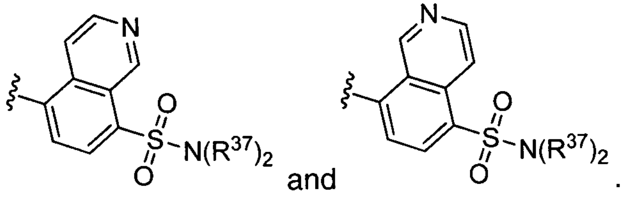


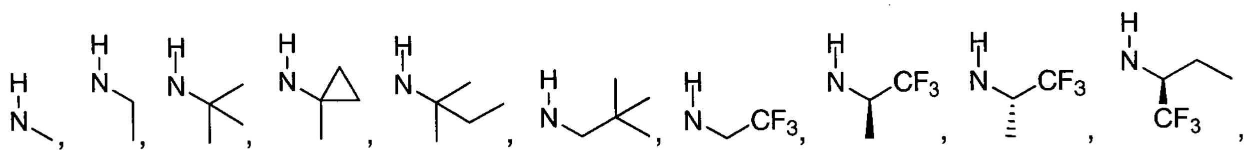


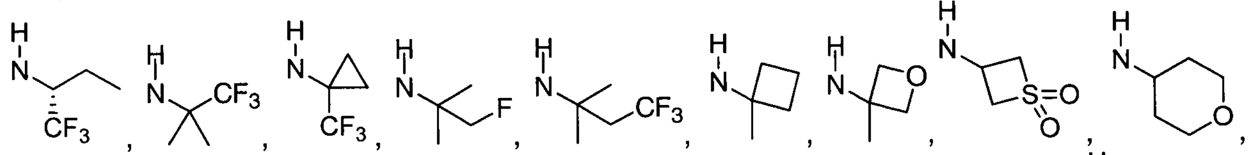


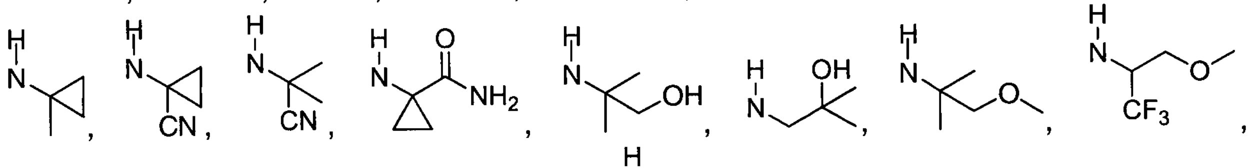


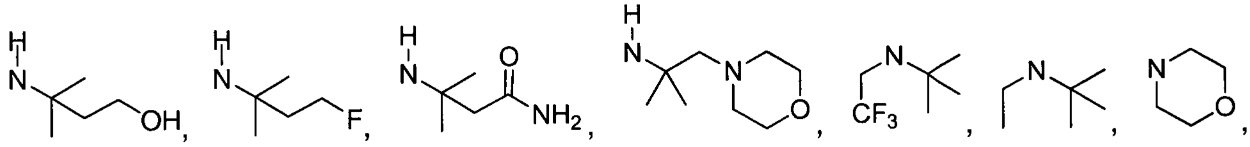


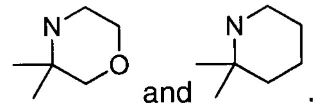
In another preferred embodiment in combination with any of the above or below embodiments of the third alternative $N(R^{37})_2$ is selected from



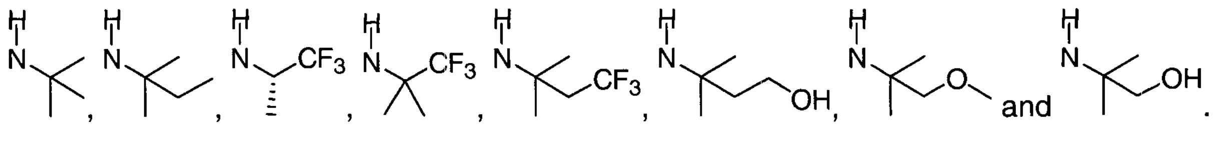




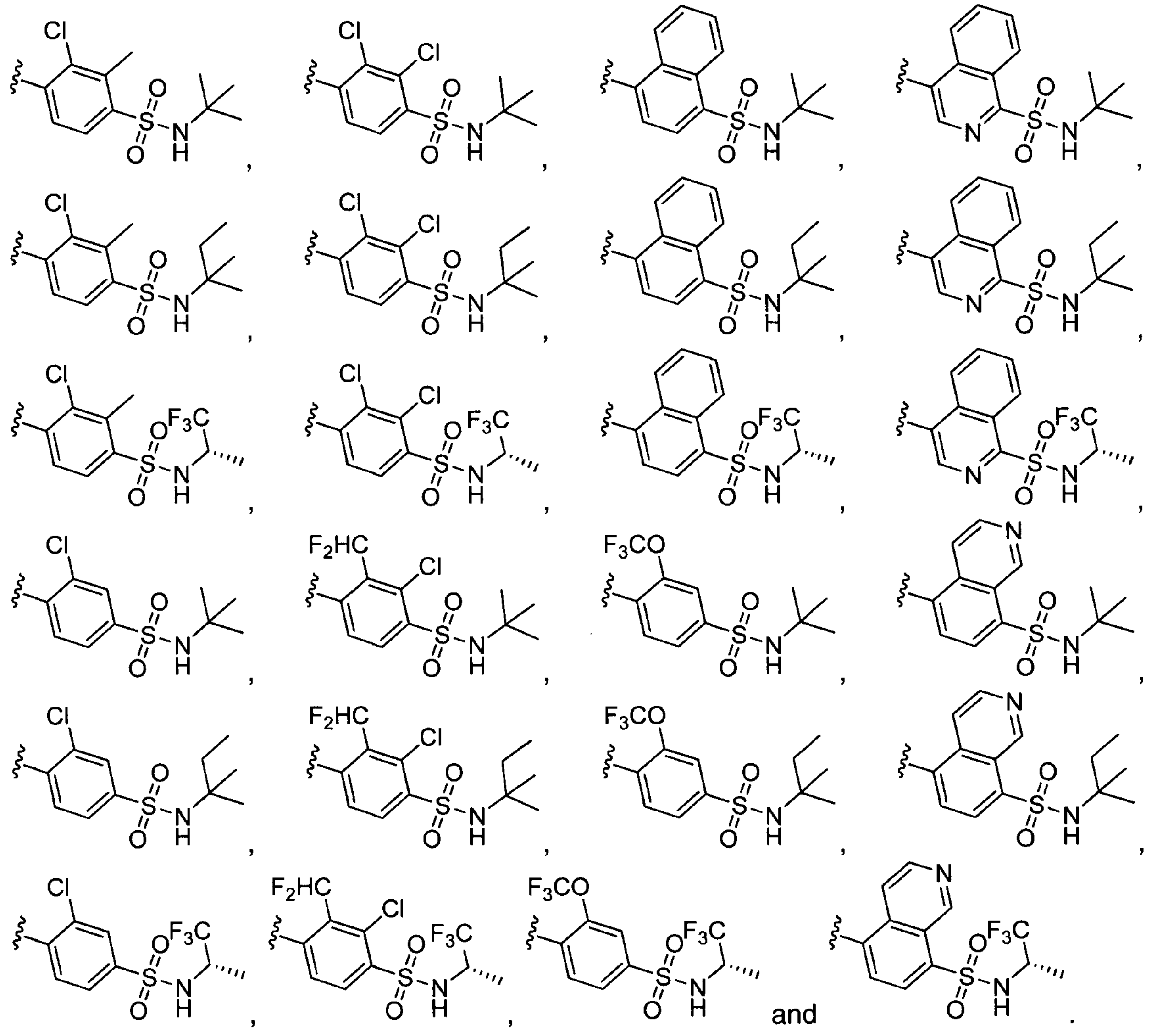




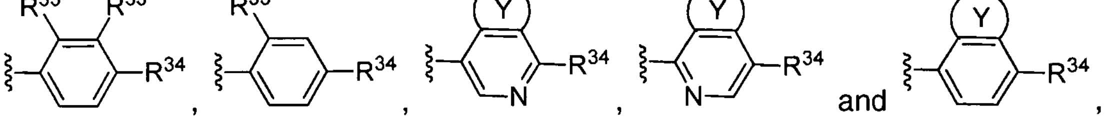
In a more preferred embodiment in combination with any of the above or below embodiments of the third alternative $N(R^{37})_2$ is selected from



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



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



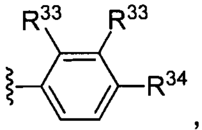
wherein R^{33} is independently selected from H, halogen, d-e-alkyl, fluoro-Ci-$_6$-alkyl, C_{1-4}-alkylene-OH, C_{1-4}-alkylene-O-C_{1-3}-alkyl, O-C_{1-6}-alkyl, and O-fluoro-C_{1-6}-alkyl, more preferably R^{33} is independently selected from fluoro, chloro, CF_3, CHF_2, OCF_3, $OCHF_2$, methyl, 'butyl and CMe_2OH;

R^{34} is selected from $C_{1\text{-}6}$-alkyl, halo-Ci $_{.6}$-alkyl and Co-6-alkylene-$C_{3\text{-}1}$o-heterocycloalkyl,

wherein alkyl, alkylene and heterocycloalkyl are unsubstituted or substituted by 1 to 3 substituents independently selected from the group consisting of halogen, $C_{1\text{-}6}$-alkyl, halo-$C_{1\text{-}e}$-alkyl, OH, oxo, $N(R^{31})_2$, 0-$C_{1\text{-}6}$-alkyl, $C_{3\text{-}i0}$-cycloalkyl, $C_{3\text{-}10}$-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 CF_3.

In more 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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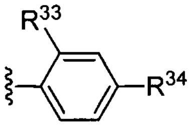
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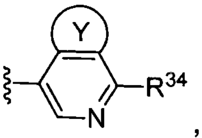
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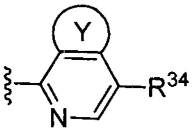
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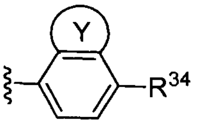
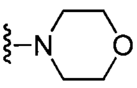

,

wherein R^{33} is independently selected from H, halogen, $C_{1\text{-}6}$-alkyl, fluoro-$C_{1\text{-}6}$-alkyl, $C_{1\text{-}4}$-alkylene-OH, Ci-4-alkylene-0-$C_{1\text{-}3}$-alkyl, 0-$C_{1\text{-}6}$-alkyl, and 0-fluoro-Ci $_{\text{-}6}$-alkyl, more preferably R^{33} is independently selected from fluoro, chloro, CF_3, CHF_2, OCF_3, $OCHF_2$, methyl, 'butyl and CMe_2OH;

R^{34} is selected from

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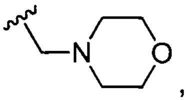
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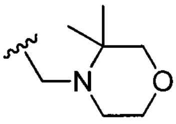
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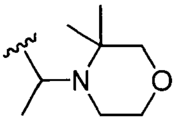
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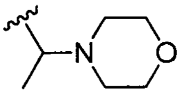
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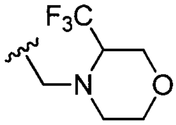
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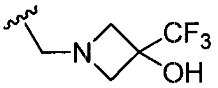
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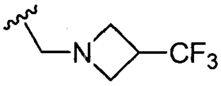
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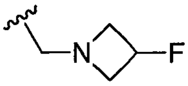
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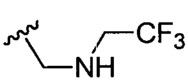
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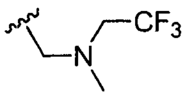
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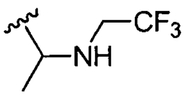
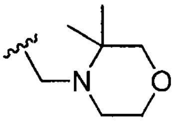
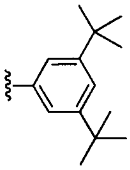
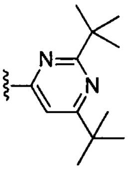
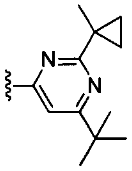
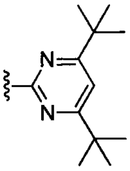
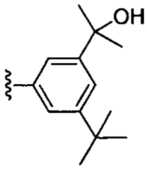
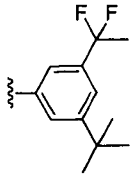
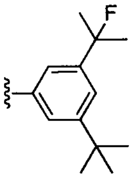
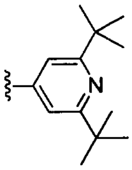
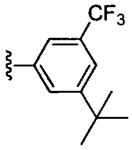
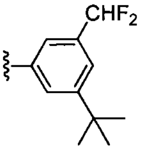
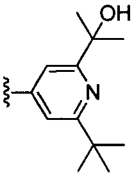
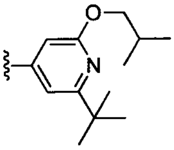
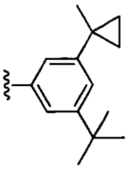
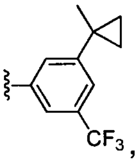
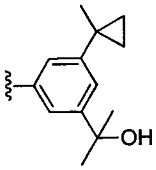
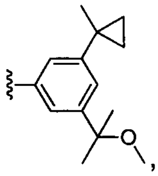
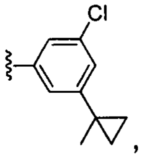
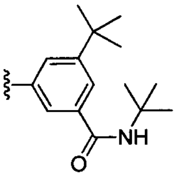
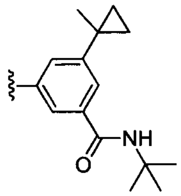
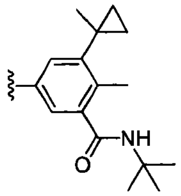
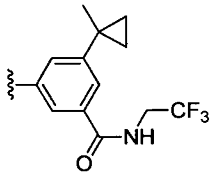

; more preferably R^{34} is

;

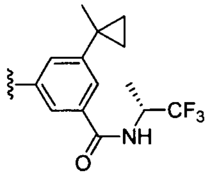
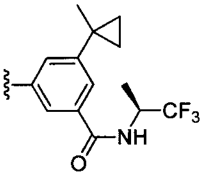
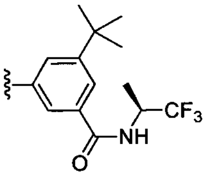
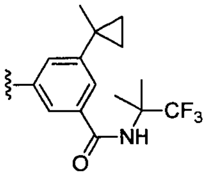
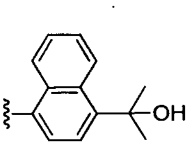
Y is selected from an annelated 5- or 6-membered carbocycle, an annelated 6-membered aryl or an annelated 6-membered heteroaryl containing 1 to 2 nitrogen atoms, wherein the carbocycle, aryl or heteroaryl is unsubstituted or substituted with 1 to 3 substituents selected from fluoro, methyl or CF_3.

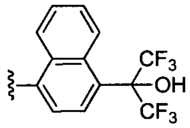
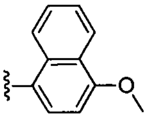
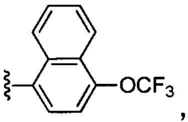
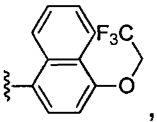
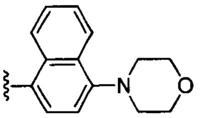
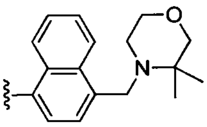
In an alternative preferred embodiment in combination with any of the above or below embodiments of the third alternative R^3 is selected from

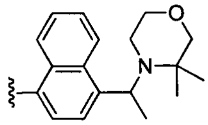
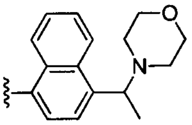
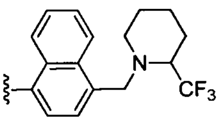
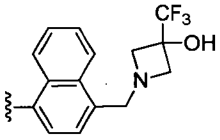
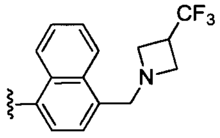
 ,  ,  ,  ,  ,  ,  ,  ,

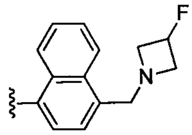
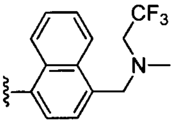
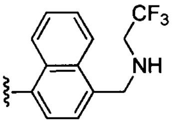
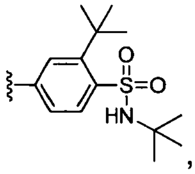
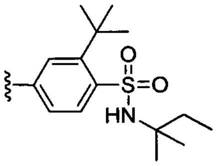
 ,  ,  ,  .  ,  ,  ,

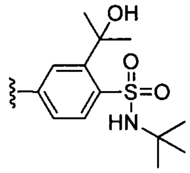
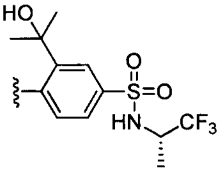
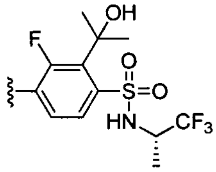
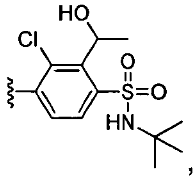
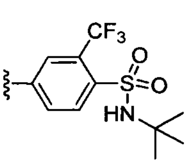
 ,  ,  ,  ,  ,  ,

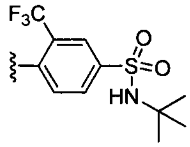
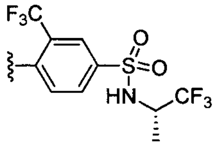
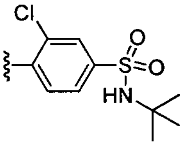
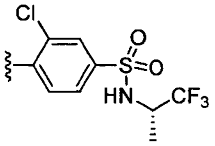
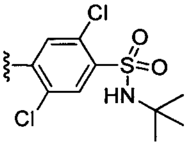
 ,  ,  ,  ,  ,

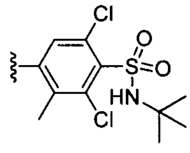
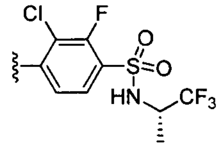
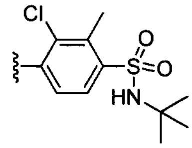
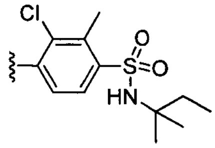
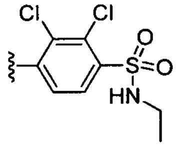
 ,  ,  ,  ,  ,  ,

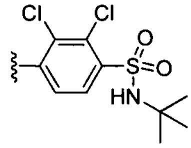
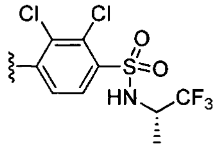
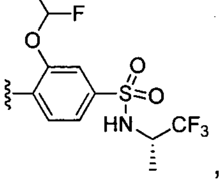
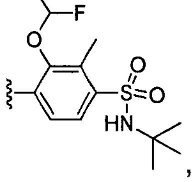
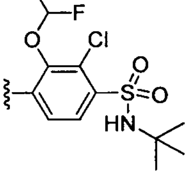
 ,  ,  ,  ,  ,

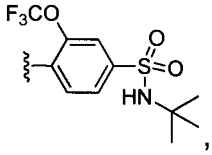
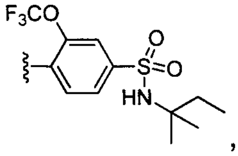
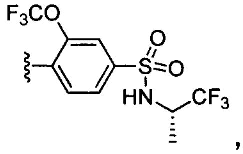
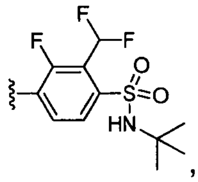
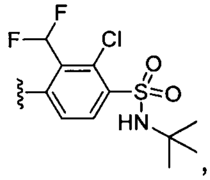
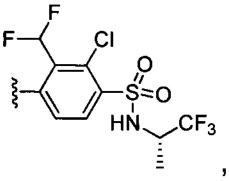
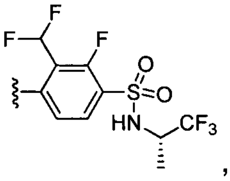
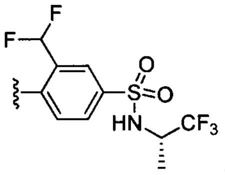
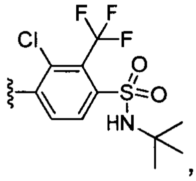
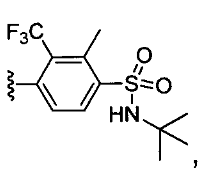
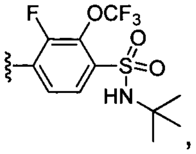
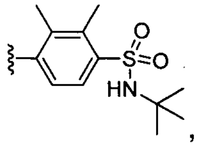
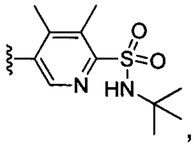
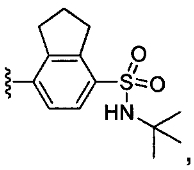
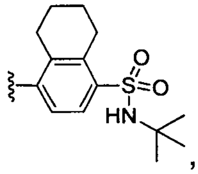
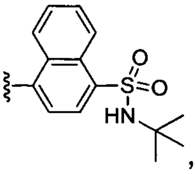
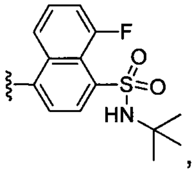
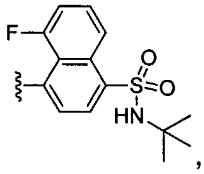
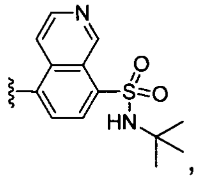
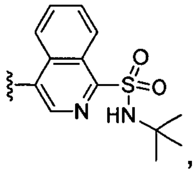
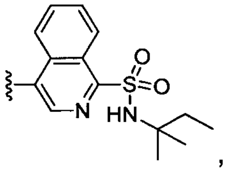
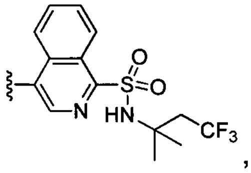
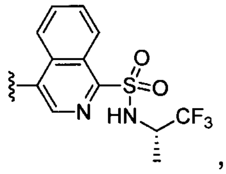
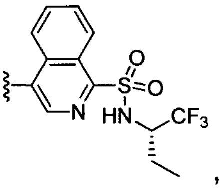
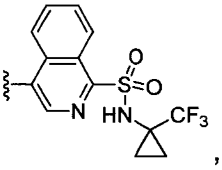
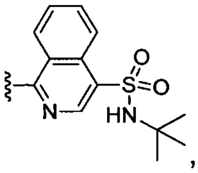
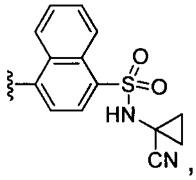
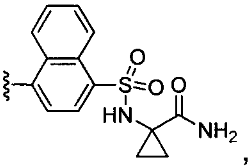
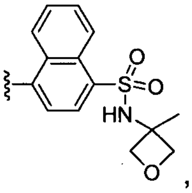
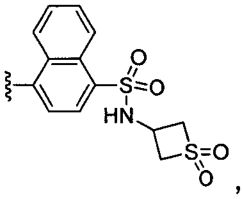
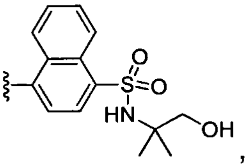
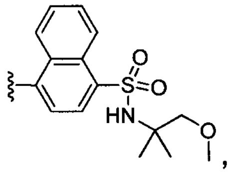
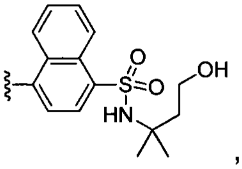
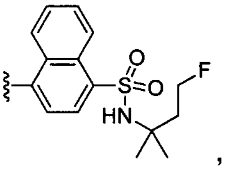
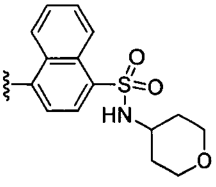
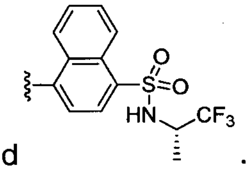
 ,  ,  ,  ,  ,  ,

 ,  ,  ,  ,  ,

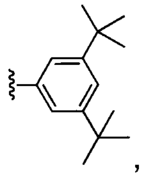
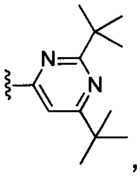
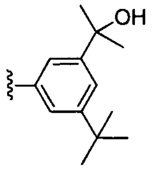
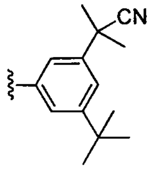
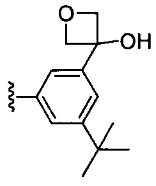
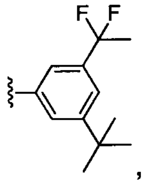
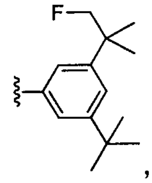
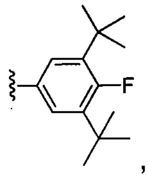
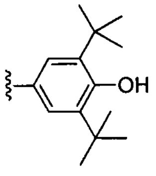
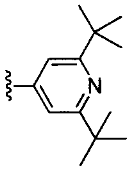
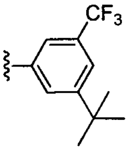
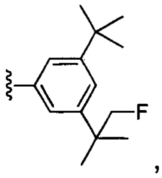
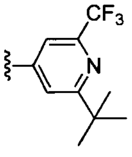
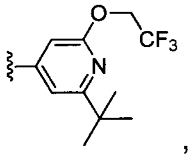
 ,  ,  ,  ,  ,

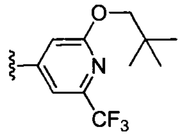
 ,  ,  ,  ,  ,

 ,  ,  ,  ,  ,

 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 and
 .

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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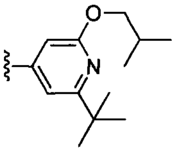
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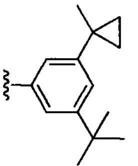
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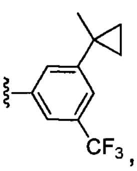
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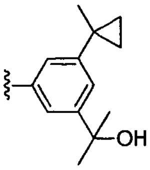
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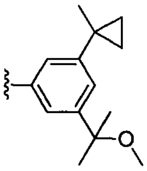
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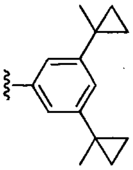
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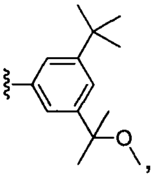
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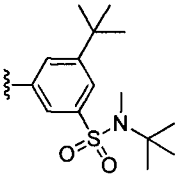
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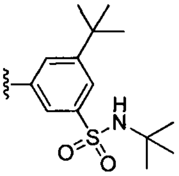
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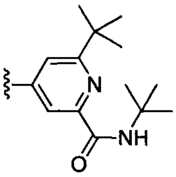
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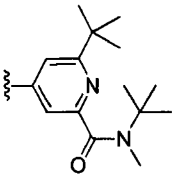
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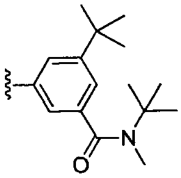
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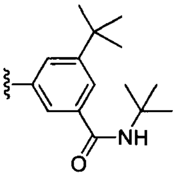
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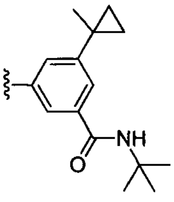
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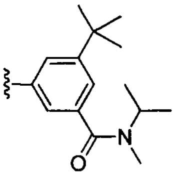
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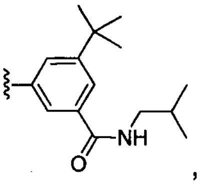
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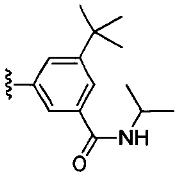
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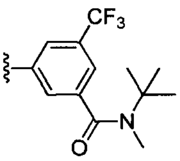
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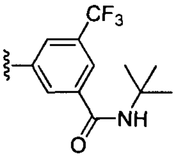
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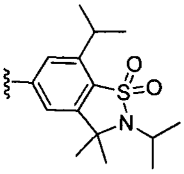
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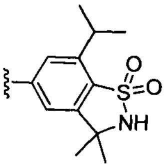
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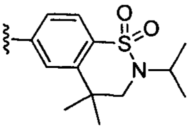
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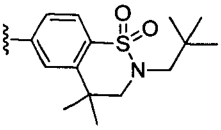
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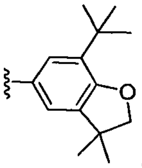
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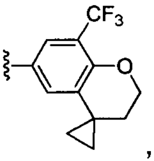
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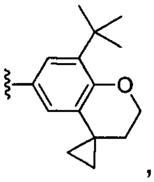
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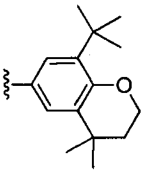
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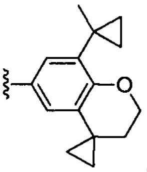
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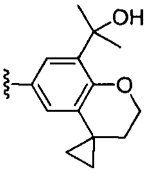
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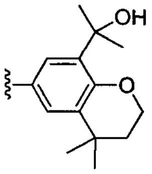
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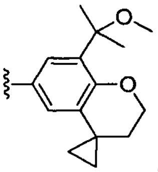
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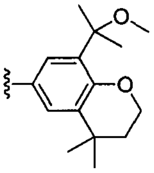
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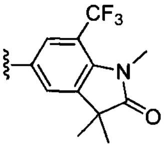
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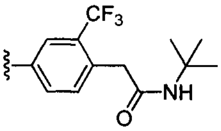
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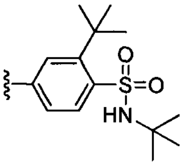
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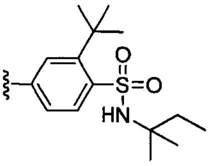
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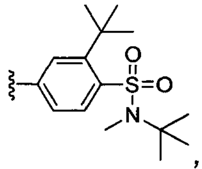
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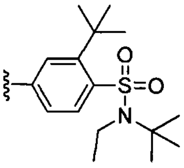
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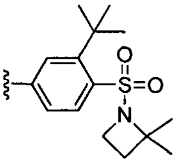
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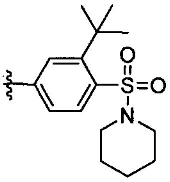
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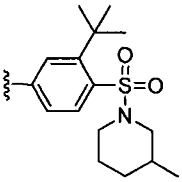
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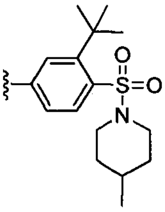
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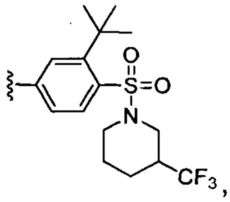
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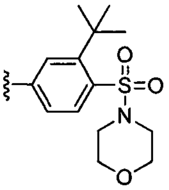
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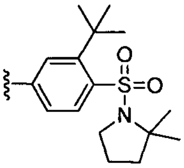
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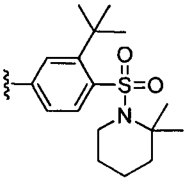
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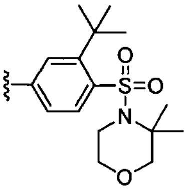
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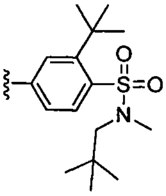
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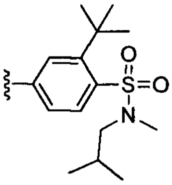
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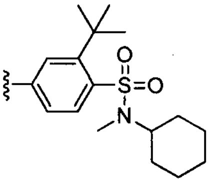
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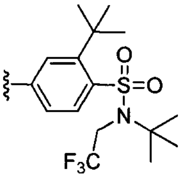
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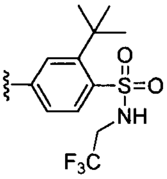
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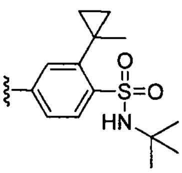
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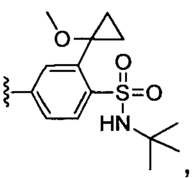
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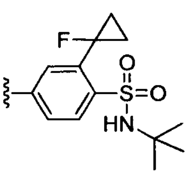
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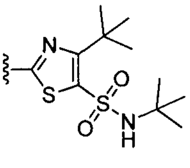
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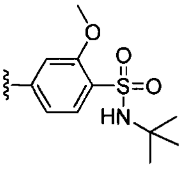
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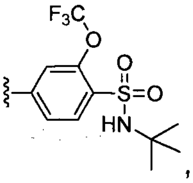
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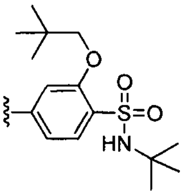
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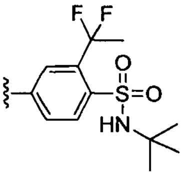
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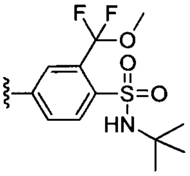
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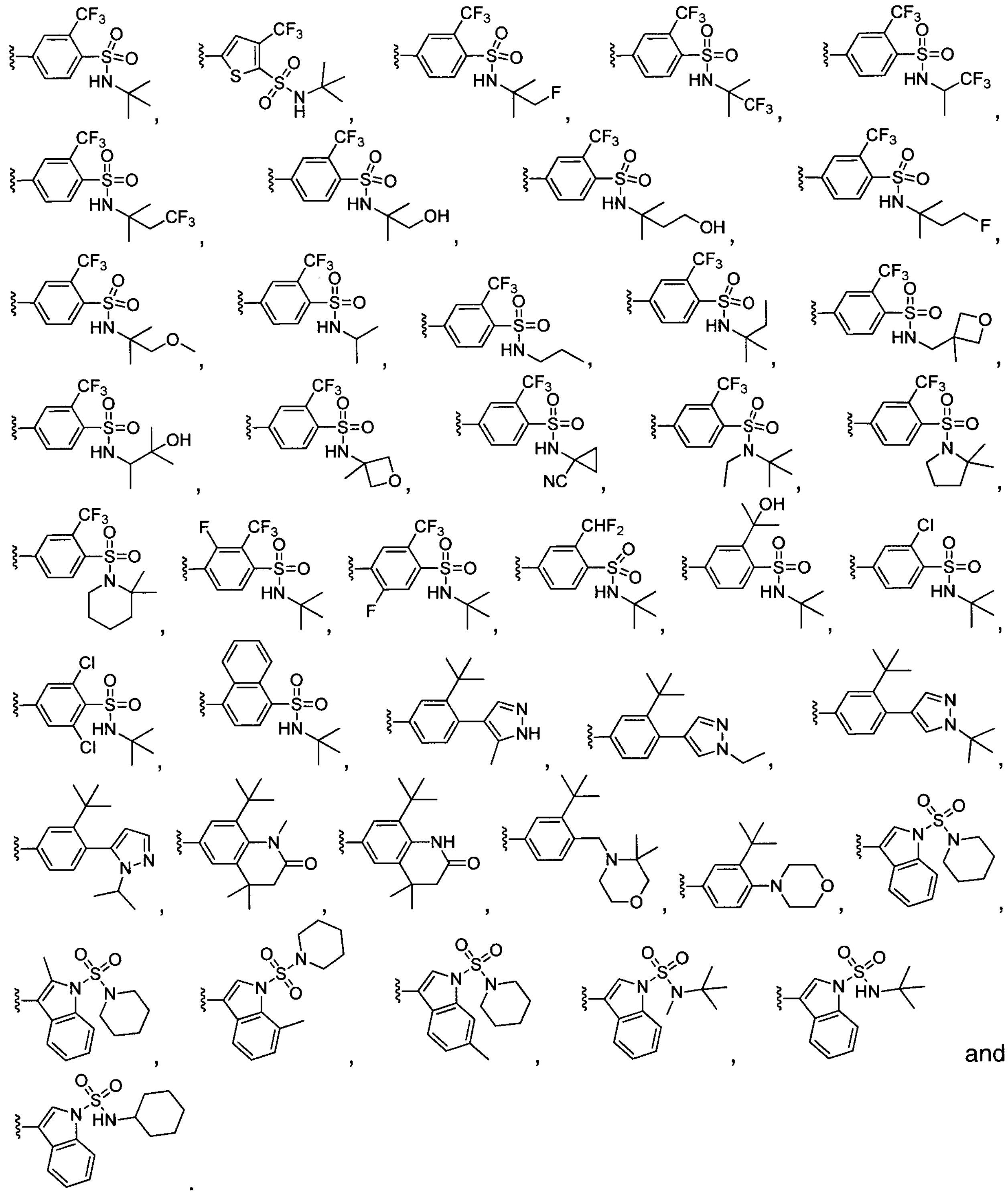
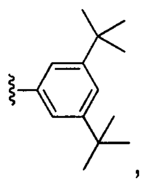


In a preferred embodiment in combination with any of the above or below embodiments of the third alternative R^3 is selected from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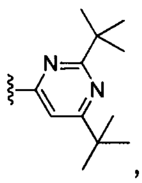
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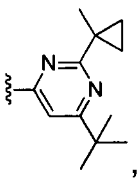
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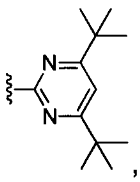
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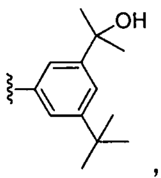
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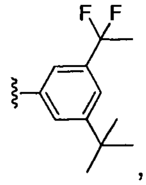
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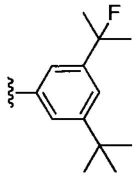
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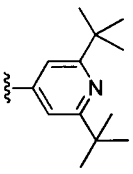
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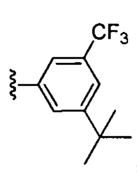
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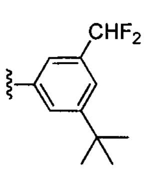
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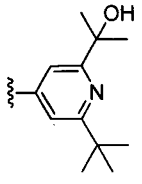
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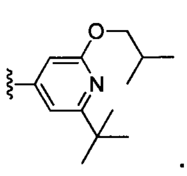
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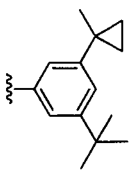
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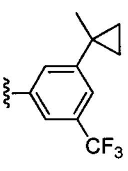
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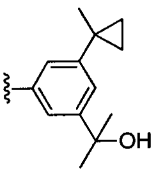
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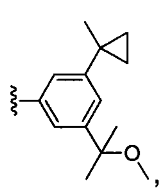
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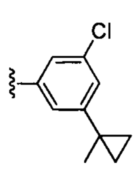
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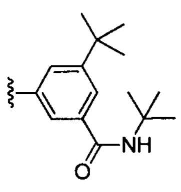
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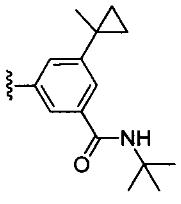
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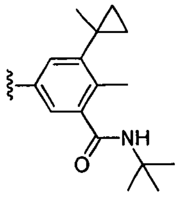
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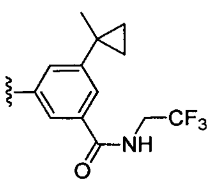
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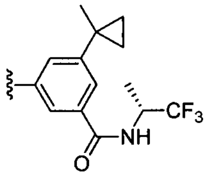
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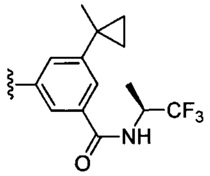
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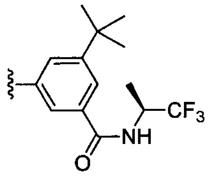
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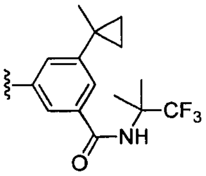
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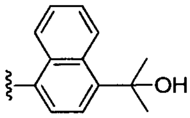
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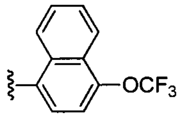
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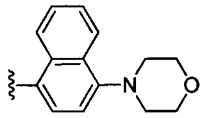
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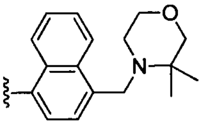
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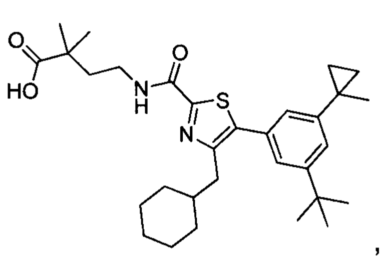
In another preferred embodiment in combination with any of the above or below embodiments of the third alternative the compound is represented by Formula **(1)**.

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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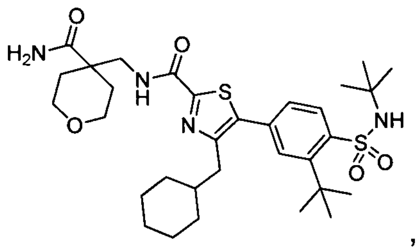
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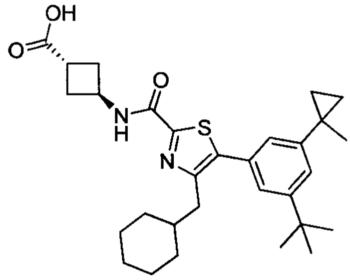
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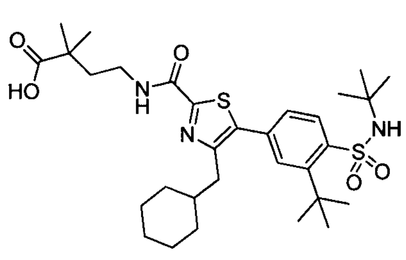
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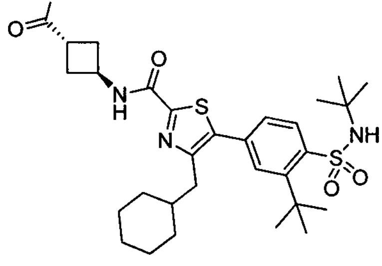
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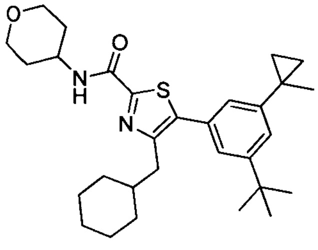
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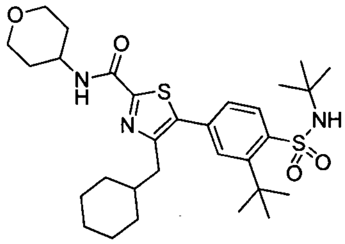
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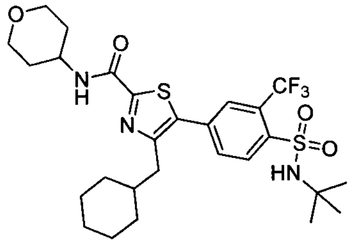
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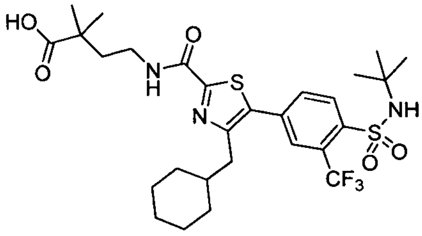
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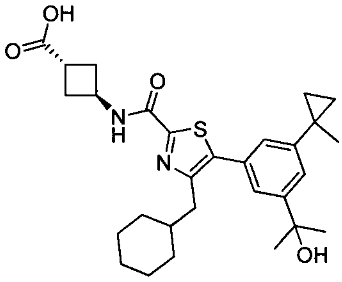
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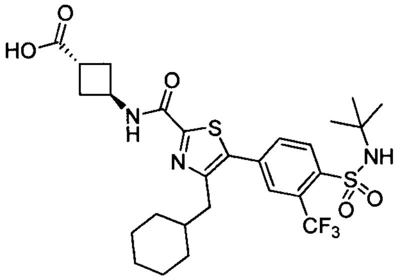
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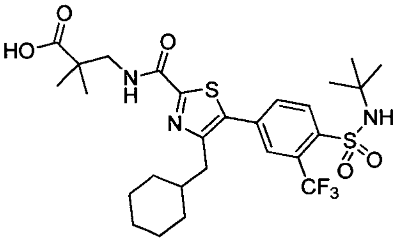
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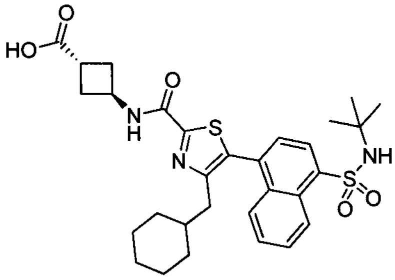
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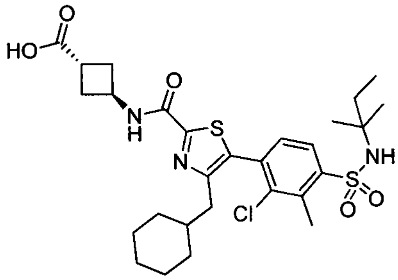
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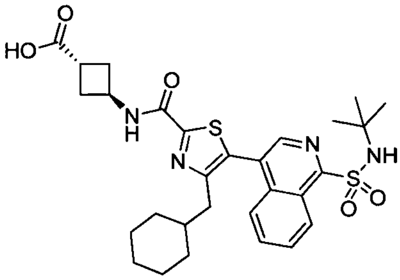
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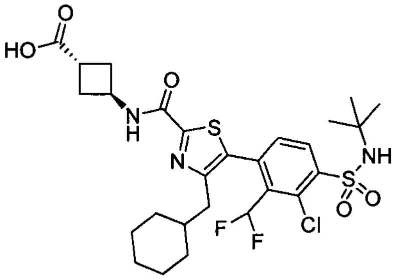
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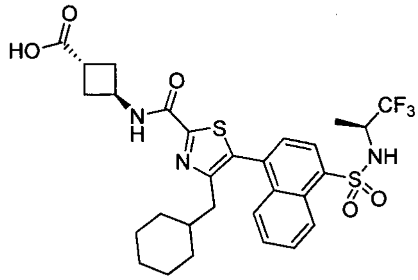
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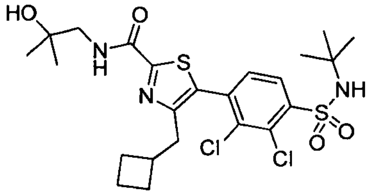
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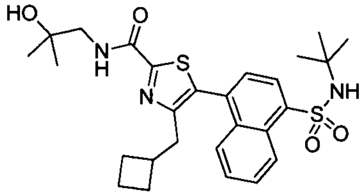
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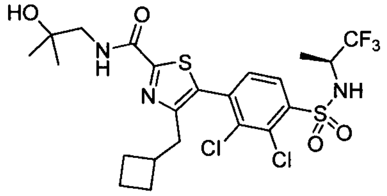
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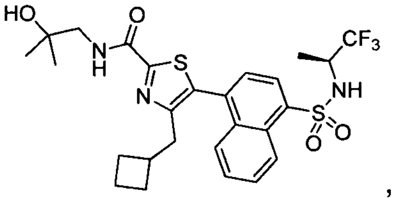
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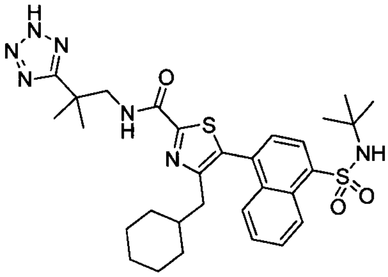
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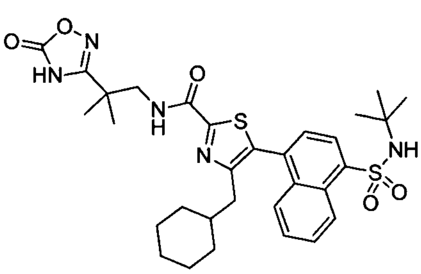
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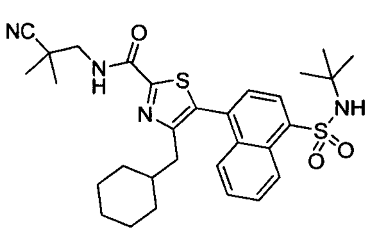
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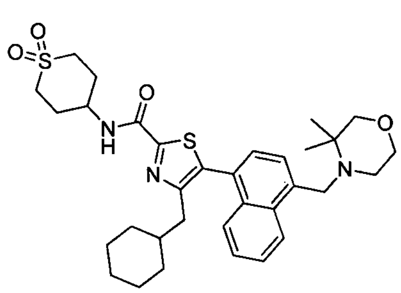

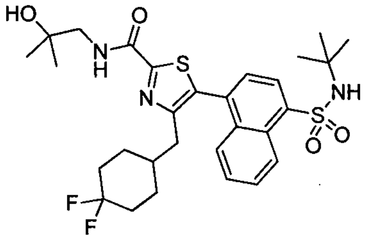

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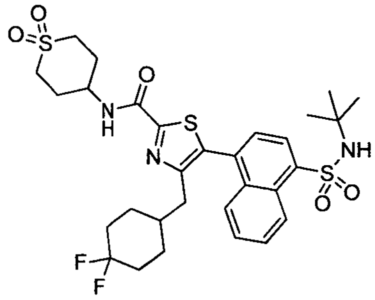

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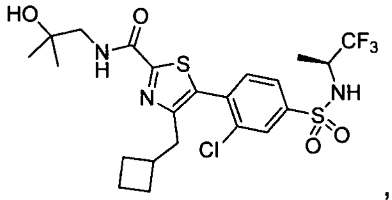

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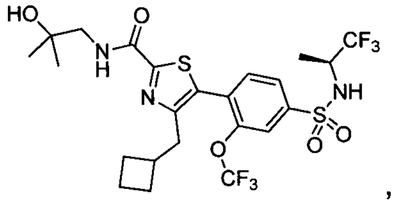

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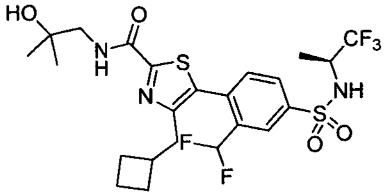

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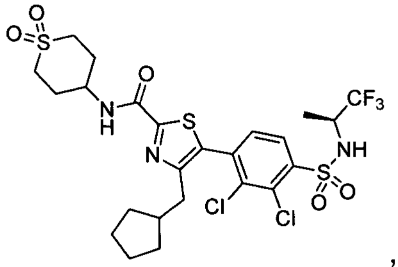

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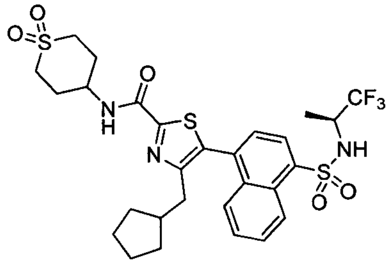

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and an enantiomer, diastereomer, tautomer, /V-oxide, solvate and pharmaceutically acceptable salt thereof.

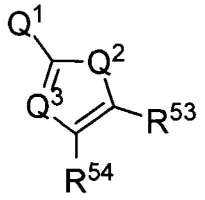
The invention also provides the compound of the third alternative of the invention for use as a medicament.

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 RORy receptor.

Also provided is the compound of the third alternative of the invention in treating RORy 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 thromobotic 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')**



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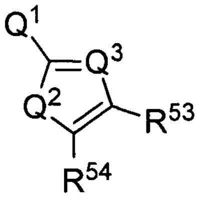


(2')

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

wherein

Q^1 is selected from CO-N$R^{51}R^{52}$, CO-R^{52}, C0 $_2R^{51}$, S0 $_2$-N$R^{51}R^{52}$, S0 $_2$-R^{52}, NR^{52}CO-R^{51} and NR^{52}S0 $_2$-R^{51};

Q^2 is selected from -0-, -S-, -CR^{55}=CR^{56}-, -N=CR^{56}-, -CR^{55}=N- and -N=N-;

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

R^{51} and R^{52} are independently selected from H, $C_{1\text{-}10}$-alkyl, $C_{2\text{-}10}$-alkenyl, $C_{2\text{-}10}$-alkynyl, **C_0-io-**alkylene-C $_{3\text{-}10}$-cycloalkyl, C_0-io-alkylene-C $_3$-io-heterocycloalkyl, C_0-io-alkylene-heteroaryl, **C_0-i $_0$-**alkylene-aryl, 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^{61}, 0-C $_{2\text{-}6}$-alkylene-OR ^{61}, **C_1**-e-alkyl, halo-d. $_6$-alkyl, halogen, C0 $_2R^{61}$, CONR $^{61}R^{62}$, CONR^{61}S0 $_2R^{62}$, COR^{61}, SO$_x$$R^{61}$, S0 $_3$H, S0 $_2$N$R^{61}R^{62}$, NR^{61}COR^{61}, NR^{61}S0 $_2R^{61}$, NR^{61}-CO-N$R^{61}R^{62}$, NR^{61}-S0 $_2$-N$R^{61}R^{62}$, $C_{3\text{-}6}$-cycloalkyl, 0-C $_{3\text{-}6}$-cycloalkyl, $C_{3\text{-}6}$-heterocycloalkyl, 0-C $_{3\text{-}6}$-heterocycloalkyl and N$R^{61}R^{62}$;

or R^{51} and R^{52} 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^{61}, SO$_x$$R^{61}$, S0 $_3$H, NR^{61}S0 $_2R^{61}$, S0 $_2$N$R^{61}R^{62}$, C0 $_2R^{61}$, CONR $^{61}R^{62}$, CONR ^{61}S0 $_2R^{62}$, COR^{61}, NR^{61}-CO-R ^{61}, NR^{61}-CO-NR $^{61}R^{62}$, NR^{61}-S0 $_2$-N$R^{61}R^{62}$, N$R^{61}R^{62}$, C^-alkyl, halo-C^-alky!, hydroxy-d-e-alkyl, $C_{3\text{-}6}$-cycloalkyl, 0-C $_{3\text{-}6}$-cycloalkyl, $C_{3\text{-}6}$-heterocycloalkyl and 0-C $_{3\text{-}6}$-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 independently selected from halogen, **CN, $C_{1\text{-}6}$**-alkyl, **$C_{1\text{-}6}$**-alkenyl, **$C_{1\text{-}6}$**-alkynyl, **halo-Ci $_{-6}$-**alkyl, **OH,** 0 **-$C_{1\text{-}6}$**-alkyl, 0-halo **-Ci $_{.6}$**-alkyl, **$C_{0\text{-}6}$**-alkylene **-$C_{3\text{-}10}$**-cycloalkyl, $C_{0\text{-}6}$-alkylene **-O-**C_3_io-cycloalkyl, $C_{0.6}$-alkylene-C $_{3\text{-}10}$-heterocycloalkyl, $C_{0\text{-}6}$-alkylene-COOR ^{81}, **$C_{0\text{-}6}$-**alkylene-C(0)R ^{81}, $C_{0\text{-}6}$-alkylene-C(O)N(R ^{81})$_2$, $C_{0\text{-}6}$-alkylene-SO $_2$-N(R^{81})$_2$, $C_{0\text{-}6}$-alkylene-

S0 $_2$-R^{81}, Co-6-alkylene-(6-10-membered mono- or bicyclic aryl), $C_{0\text{-}6}$-alkylene-(6-10-membered mono- or bicyclic heteroaryl),

wherein alkyl, alkenyl, alkynyl, alkylene, cycloalkyi, heterocycloalkyi and heteroaryl are unsubstituted or substituted by 1 to 3 substituents independently selected from the group consisting of $C_{1\text{-}6}$-alkyl, halo-$C_{1\text{-}6}$-alkyl, halogen, OH, oxo, =N-OR ^{82}, N(R ^{81})$_2$, O-d-e-alkyl, O-halo-d-e-alkyl, COOH, CON(R ^{81})$_2$, CN, NR^{81}-COR ^{81}, $C_{3\cdot10}$-cycloalkyl, $C_{3\text{-}10}$-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, S0 $_2$ or NR^{81}, wherein the ring is unsubstituted or substituted with one to four substituents independently selected from halogen, oxo, =N-OR^{82}, OH, O-d-e-alkyl, 0-halo -$C_{1\cdot6}$-alkyl, d $_{\cdot6}$-alkyl, $C_{3\text{-}6}$-cycloalkyl and halo-d. $_6$-alkyl;

R^{54} is selected from $C_{0\text{-}6}$-alkylene-R^{57}, C_3-cycloalkyl-R^{57}, O-C $_{0\text{-}5}$-alkylene-R^{57}, NR^{91}-$C_{0\text{-}5}$-alkylene-R^{57} and SO$_x$-$C_{0\text{-}5}$-alkylene-R^{57},

wherein alkylene is optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, OH, oxo, =N-OR ^{82}, N(R ^{81})$_2$, O-d-e-alkyl, COOH, CON(R ^{81})$_2$, CN, NR^{81}-COR ^{81}, $C_{3\text{-}6}$-cycloalkyl and $C_{3\cdot6}$-heterocycloalkyl;

R^{55} and R^{56} are independently selected from H, halogen, CN, $C_{1\text{-}6\text{-}}$alkyl and 0 -Ci $_{\text{-}6\cdot}$alkyl,

wherein alkyl is optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, OH, oxo, 0 -$C_{1\text{-}3}$-alkyl; 0-halo-d. $_3$-alkyl and $C_{3\cdot6}$-cycloalkyl;

R^{57} is selected from d $_{\cdot10}$-alkyl, $C_{3\text{-}10}$-cycloalkyl, $C_{3\text{-}10}$-heterocycloalkyl, 6-10-membered mono- or bicyclic aryl and 6-10-membered mono- or bicyclic heteroaryl,

wherein alkyl, cycloalkyi, heterocycloalkyi, aryl and heteroaryl are unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of halogen, OH, oxo, O-Ci-6 -alkyl, O-halo-Ci-e-alkyl, $C_{1\text{-}6}$-alkyl, halo-d -e-alkyl, cycloalkyi and heterocycloalkyi;

R^{61} and R^{81} independently selected from H, d $_{\cdot6}$-alkyl, $C_{3\text{-}10}$-cycloalkyl, $C_{3\text{-}10}$-heterocycloalkyl, phenyl, 5-6-membered heteroaryl containing 1 to 4 heteroatoms independently selected from N, O and S

wherein alkyl, cycloalkyi and heterocycloalkyi is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of $C_{1\text{-}6}$-alkyl, halo-d. $_6$-alkyl, OH, O-d-e-alkyl, O-halo-Ci-e-alkyl, phenyl, heteroaryl, halogen, NH$_2$, NH(d. $_6$-alkyl), N(Ci $_{\text{-}6}$-alkyl)$_2$, C_3-io-heterocycloalkyl and $C_{3\text{-}10}$-cycloalkyl, S0 $_2$-Ci $_{\cdot3}$-alkyl, oxo, CN, wherein cycloalkyl and heterocycloalkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of d-e-alkyl, halo-Ci-e-alkyl, OH, O-d -e-alkyl, 0-halo-d. $_6$-alkyl, phenyl, heteroaryl, halogen, NH_2, NH(d. $_6$-alkyl), N($C_{1\text{-}6}$-alkyl) $_2$ and $C_{3\text{-}10}$-cycloalkyl,

wherein phenyl and heteroaryl are unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of OH, 0 -Ci $_{.6}$-alkyl, O-halo -Ci -e-alkyl, halogen, d-e-alkyl, halo-d .e-alkyl, NH_2, NH(d. $_6$-alkyl), N($C_{1\text{-}6}$-alkyl)2 and $C_{3\text{-}10}$-cycloalkyl;

R^{62} and R^{82} are independently selected from H, d .6-alkyl, halo-d- $_6$-alkyl and $C_{3\text{-}10}$-cycloalkyl;

R^{91} is selected from H, d $_{-6}$-alkyl, $C_{3\text{-}6}$-cycloalkyl and $C_{3\text{-}6}$-heterocycloalkyl,

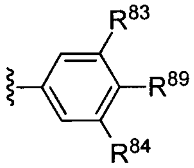
wherein alkyl, cycloalkyl and heterocycloalkyl is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of OH, oxo, CN, halogen, O-Ci-6-alkyl, O-halo-d -6-alkyl, $C_{3\text{-}6}$-heterocycloalkyl ^{anc} ' $C_{3\text{-}6}$-cycloalkyl;

x is independently selected from 0, 1 and 2; for use in the treatment or prophylaxis of a disease or disorder associated with the inhibition or activation of the RORy receptor; with the proviso that compounds of Formula (2') with Q^1 is NHCO-R^{51}, Q^2 is sulfur, Q^3 is nitrogen, R^{53} and R^{57} are optionally substituted aryl and R^{54} is COR^{57} are excluded.

In a preferred embodiment in combination with any of the above or below embodiments of the fourth alternative Q^1 is selected from CO-$NR^{51}R^{52}$ and NR^{52}CO-R^{51}; Q^2 is selected from -O- and -S-; and Q^3 is N.

In a further preferred embodiment in combination with any of the above or below embodiments of the fourth alternative R^{51} is selected from H, d $_{-10}$-alkyl, C_0-io-alkylene-$C_{3\text{-}10}$-cycloalkyl, and C_0-io-alkylene-$C_{3\text{-}1}$o-heterocycloalkyl, wherein alkyl, alkylene, cycloalkyl and heterocycloalkyl is unsubstituted or substituted with 1 to 7 substituents independently selected from oxo, OR^{61}, d-e-alkyl, halo-d-e-alkyl, halogen, C0 $_2R^{61}$, $CONR^{61}R^{62}$, $CONR^{61}$S0 $_2R^{62}$, COR^{61}, $NR^{61}COR^{61}$, NR^{61}S0 $_2R^{61}$, NR^{61}-CO-$NR^{61}R^{62}$, NR^{61}-S0 $_2$-$NR^{61}R^{62}$, $C_{3\text{-}6}$-cycloalkyl, 0-C $_{3\text{-}6}$-cycloalkyl, $C_{3\text{-}6}$-heterocycloalkyl and 0-C $_{3\text{-}6}$-heterocycloalkyl; R^{52} is selected from the group consisting of H, **Ci-6** alkyl and halo-d. $_6$ alkyl; or R^{51} and R^{52} 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^{61}, SO_xR^{61}, S0 $_3$H, NR^{61}S0 $_2R^{61}$, S0 $_2NR^{61}R^{62}$, C0 $_2R^{61}$, $CONR^{61}R^{62}$, $CONR^{61}$S0 $_2R^{62}$, COR^{61}, NR^{61}-CO-R^{61}, NR^{61}-CO-$NR^{61}R^{62}$, NR^{61}-S0 $_2$-$NR^{61}R^{62}$, $NR^{61}R^{62}$, d-e-alkyl, halo-d .e-alkyl, hydroxy-d. $_6$-alkyl, $C_{3\text{-}6}$-cycloalkyl, 0-C $_{3\text{-}6}$-cycloalkyl, $C_{3\text{-}6}$-heterocycloalkyl and 0-C $_{3\text{-}6}$-heterocycloalkyl.

In another preferred embodiment in combination with any of the above or below embodiments of the fourth alternative R^{53} is selected from



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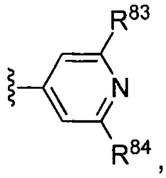

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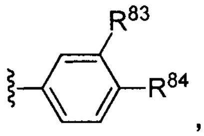

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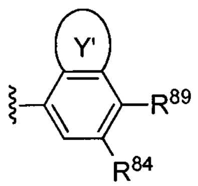

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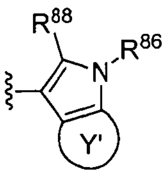

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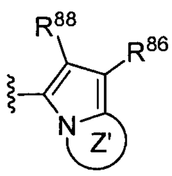

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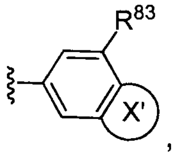

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wherein

R^{83} is selected from halogen, $C_{1\text{-}6}$-alkyl, fluoro-d -e-alkyl, $C_{1\text{-}4}$-alkylene-OH, $C_{1\text{-}4}$-alkylene -CN, $C_{1\text{-}4}$-alkylene-O-$C_{1\text{-}3}$-alkyl, $C_{1\text{-}4}$-alkylene-O-fluoro-$C_{1\text{-}3}$-alkyl, O-$C_{1\text{-}6}$-alkyl, O-fluoro-$C_{1\text{-}6}$-alkyl, $C_{3\text{-}10}$-cycloalkyl, C(0)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, $C_{1\text{-}3}$-alkyl and fluoro-C^-alkyl;

R^{84} is selected from $C_{1\text{-}4}$-alkylene-OH, $C_{1\text{-}4}$-alkylene-0 -$C_{1\text{-}3}$-alkyl, $C_{1\text{-}4}$-alkylene-O-fluoro-$C_{1\text{-}3}$-alkyl, $C_{3\text{-}i0}$-cycloalkyl, C(0)N(R^{87})$_2$, S(0 $_2$)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, $C_{1\text{-}3}$-alkyl and fluoro-d. $_3$-alkyl;

R^{86} is selected from $C_{1\text{-}6}$-alkyl, fluoro-$C_{1\text{-}6}$-alkyl, C(0)N(R^{87})$_2$, S(0 $_2$)N(R^{87})$_2$,

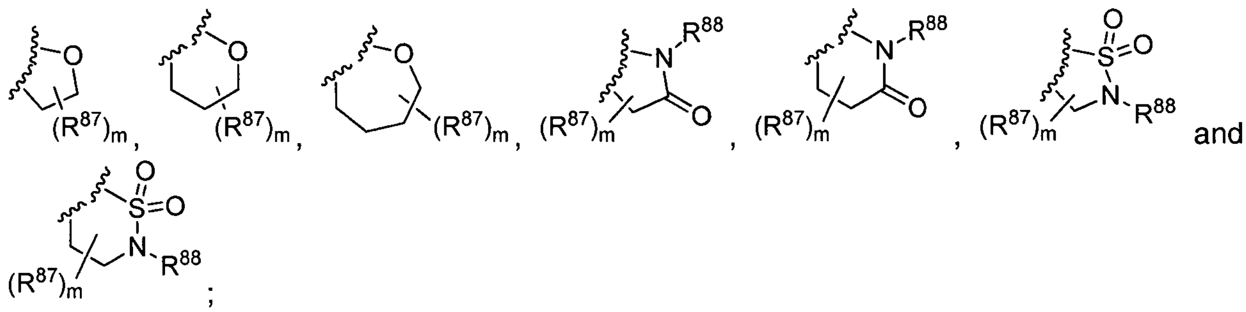
R^{87} is independently selected from H, $C_{1\text{-}6}$-alkyl, fluoro-$C_{1\text{-}6}$-alkyl, (-Walkylene-d -e-cycloalkyl, $C_{1\text{-}6}$-alkylene-OH, d $_{\text{-}6}$-alkylene-0 -Ci $_{\text{-}3}$-alkyl, $C_{1\text{-}6}$-alkylene-CN, wherein alkylene and cycloalkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from F, d $_{\text{-}3}$-alkyl and fluoro-d. $_3$-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, $C_{1\text{-}4}$-alkyl and halo-Ci $_{\text{-}4}$-alkyl;

R^{88} is selected from H, $C_{1\text{-}3}$-alkyl and fluoro-d .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, C_{1-3}-alkyl and fluoro-C^-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, Ci-3-alkyl and fluoro-Ci $_{-3}$-alkyl; and m is selected from 1 to 4.

In yet another preferred embodiment in combination with any of the above or below embodiments of the fourth alternative R^{54} is selected from d-e-alkylene-R ^{57}, O-R^{57}, and S0 $_2$-R^{57},

wherein alkylene is optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, OH, oxo, 0-C $_{1-6}$-alkyl, CN and C_{3-6}-cycloalkyl;

R^{57} is selected from C_{1-10}-alkyl, C_3-io-cycloalkyl, C_{3-10}-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, 0-C $_{1-3}$-alkyl, 0-halo -C_{1-3}-alkyl, C_{1-3}-alkyl, halo-Ci $_{-3}$-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 RORy 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 "$C_{1\cdot10}$-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.

The term "halo-d $_{-10}$-alkyl" means that one or more hydrogen atoms in the alkyl chain are replaced by a halogen. A preferred example thereof is CF_3.

"C_2-io-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£,4£)-hexa-2,4-dienyl.

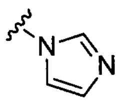
"$C_{2\text{-}10}$-alkynyl" means an alkyl chain having 1 to 10 carbon atoms which may be straight chained or branched, containing at least one carbon to carbon triple bond. Examples thereof include ethynyl, propynyl and decynyl.

A "Co-$_{10}$-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 invention, "C_0-alkylene" is meant to be represent a bond. The same applies to the divalent C_3-cycloalkylene.

A $C_{3\cdot1}$o-cycloalkyl group or $C_{3\cdot10}$-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, adamantyl and pentacyclo[4.2.0.0$^{2'5}$.0$^{3'8}$.0$^{4'7}$]octyl.

A C_3.io-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 $S0_2$. Examples thereof include epoxidyl, oxetanyl, pyrrolidinyl, tetrahydrofuranyl, piperidinyl, piperazinyl tetrahydropyranyl, 1,4-dioxanyl, morpholinyl, 4-quinuclidinyl, 1,4-dihydropyridinyl and 3,6-dihydro-2H-thiopyranyl. The $C_{3\cdot10}$-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 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, 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 /V-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 /V-linked heterocycles are



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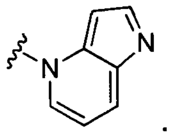

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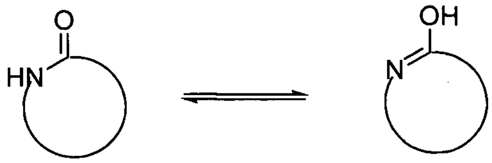
A 6-10-membered mono- or bicyclic aromatic ring system (within the application also referred to as aryl) means an aromatic carbon cycle such as phenyl or naphthalenyl.

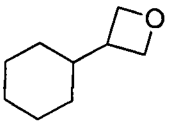
The term "/V-oxide" denotes compounds, where the nitrogen in the heteroaromatic system (preferably pyridinyl) is oxidized. Such compounds can be obtained in a known manner by reacting a compound of the present invention (such as in a pyridinyl group) with H_20_2 or a peracid in an inert solvent.

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:



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:



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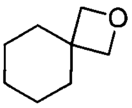

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It will be appreciated by the skilled person that when lists of alternative substituents include members which, because of their valency requirements or other reasons, cannot be used to substitute a particular group, the list is intended to be read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

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 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 RORγ-mediated conditions for which compounds of Formula **(1)**, **(V)**, **(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 RORγ receptor. Surprisingly, it has been found that compounds of Formula **(1)**, **(1')**, **(2)**, **(2')**, **(100)**, **(100')**, **(200)** and **(200')** act as modulators of the RORγ receptor.

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

The RORγ 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 RORγ 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 erythomatosis, 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 RORγ 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 RORγ 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 RORγ.

The identification of high affinity ligands for RORγ 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 RORγ ligands from libraries of small molecules. The identification of ligands which bind to and modulate the activity of RORγ1 and RORγ2 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 RORyl or ROR^. 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 erythomatosis, inflammatory bowel disease (Crohn 's disease), ulcerative colitis, inflammatory skin diseases such as atopic eczema or psoriasis, multiple sclerosis or similar diseases.

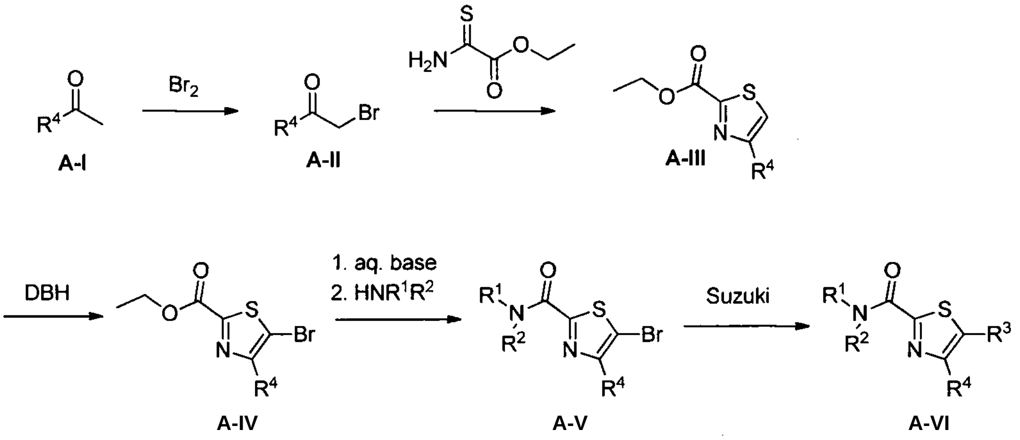
Another aspect of the invention provides for combination therapy. Thiazoles and related compounds (e.g. a compound of Formula **(1)**, (**1'**), **(2)**, **(2')**, **(100)**, **(100')**, **(200)** and **(200')**) or their pharmaceutically acceptable salts may be used in combination with additional therapeutic 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-cc 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-lg, or a mimetic of CTLA-4-lg; (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 Hi receptor antagonist; (9) an α1- and a2-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, pirprofen, pranoprofen, suprofen, tiaprofenic acid and tioxaprofen), acetic acid derivatives (indomethacin, acemetacin, alclofenac, 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 tenoxican), 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.

The amount thiazole or related compound (e.g. a compound of Formula **(1),** (V), **(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 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 in the art including the procedures described in Schemes I to V below.

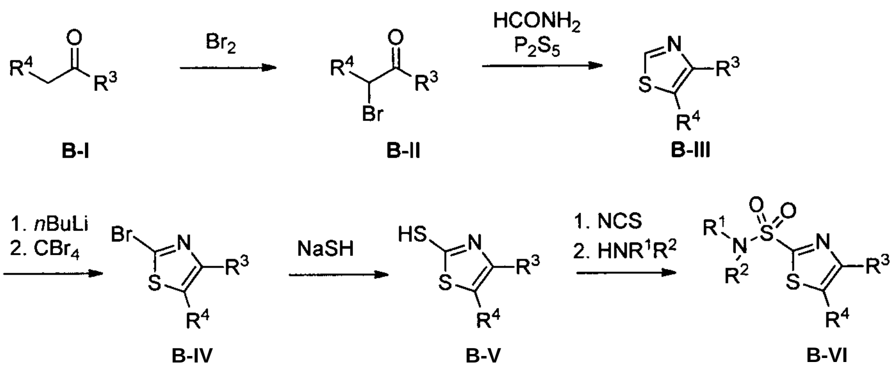
Scheme I depicts the cc-bromination of ketone **A-I** ($R^4 = (CR^8R^8)R^{40}$) or ester **A-I** ($R^4 = OR^{40}$) to afford compound **A-II.** Subsequent cyclisation as previously described in US2005/065189 or WO2007/079186 using ethyl 2-amino-2-thioxoacetate furnished thiazole **A-III,** which can be brominated (e.g. with 1,3-dibromo-5,5-dimethylhydantoin) to afford bromide **A-IV.** 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



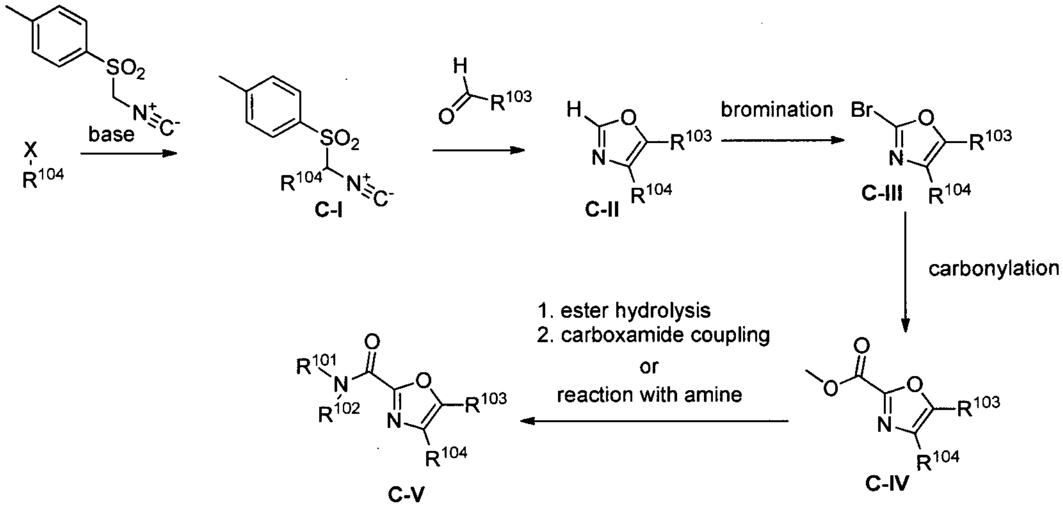
The sulfonamide derivatives can be prepared as shown in Scheme II. Again, a-bromination of a ketone gives intermediate **B-II,** which can be cyclisized to thiazole **B-III** by use of formamide and phosphorus sulfide. Incorporation of the sulfonamide moiety can be accomplished via bromination (→ **B-IV)**, Br-SH-exchange (→ **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.

Scheme II



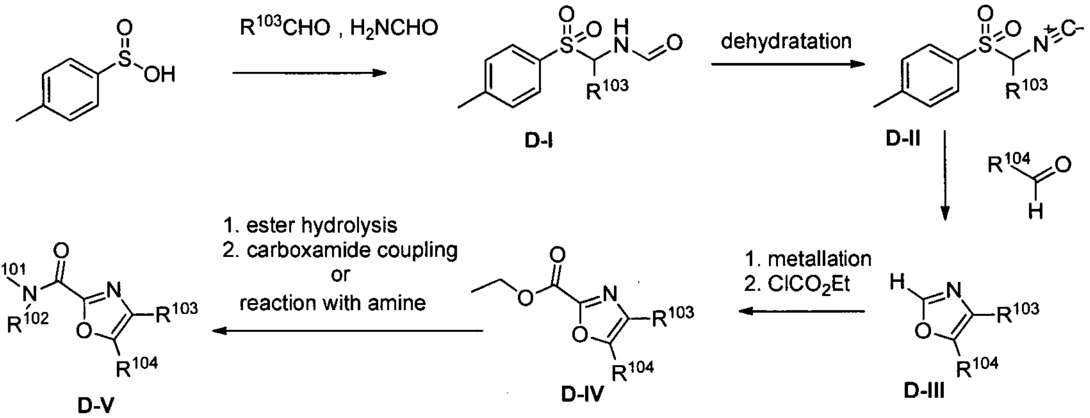
In Scheme III is depicted a synthetic route for oxazoles of the present invention where R^{104} is in the 4-position and R^{103} in the 5-position of the oxazole ring. The synthesis starts with an alkylation of (p-tolylsulfonyl)methyl isocyanide (TosMIC) to obtain intermediate **C-I.** A subsequent cylocondensation 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.

Scheme III



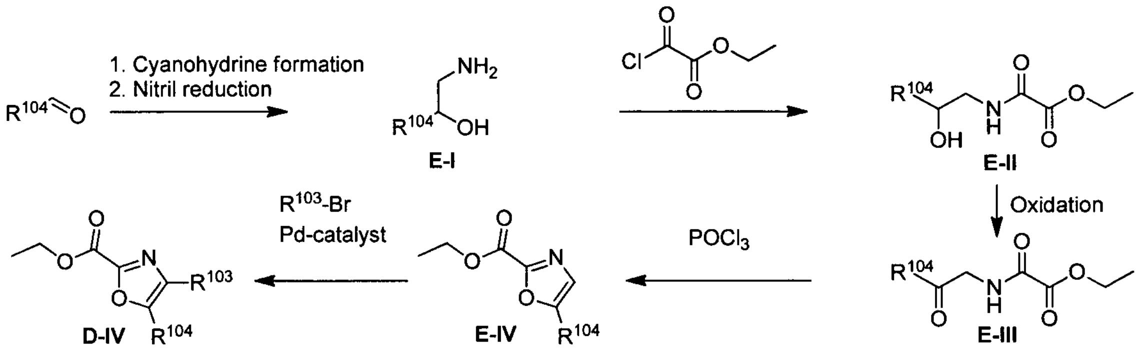
In Scheme IV is depicted the synthesis for oxazoles of the present invention where R^{103} is in the 4-position and R^{104} in the 5-position. The aromatic aldehyde $R^{103}CHO$ is reacted with formamide in the presence of TMSCl and then with tosylsulfinic acid to form intermediate **D-I** which is dehydrated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

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. /V-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.

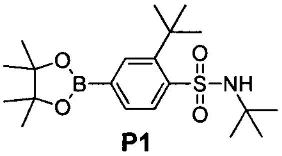
Abbreviations

Ac	acetyl
ACN	acetonitrile
AIBN	azobisisobutyronitrile

aq.	aqueous
B_2Pin_2	4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxaborolane
m-CPBA	mefa-chloroperbenzoic acid
CC	chromatography on silica gel
Cy	cyclohexyl
DAST	diethylaminosulfur trifluoride
dba	dibenzylideneacetone
DBH	1,3-Dibromo-5,5-dimethylhydantoin
DCM	dichloromethane
DIPEA	diisopropylethylamine
DMA	dimethyl acetamide
DMF	N,N-dimethylformamide
dppf	1,1'-bis(diphenylphosphino)ferrocene
DPPP	1,3-bis(diphenylphosphino)propane
DTBPy	2,6-di-tert-butylpyridine
EA	ethyl acetate
HATU	0-(7-azabenzotriazole-1 -yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
MTBE	tert-butylmethylether
NBS	N-bromosuccinimide
NCS	N-chlorosuccinimide
PCC	pyridinium chlorochromate
Pin	pinacolato ($OCMe_2CMe_20$)
PivOH	pivalic acid
PE	petroleum ether
prep.	preparative
sat.	saturated
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography

Experimental Section

Preparative Example P1



P1

Step 1: 4-Bromo-2-te/t-butylaniline (P1a)

To a solution of NBS (218 mg, 1 mmol) in DMF was added a solution of 2-te/?-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 Na_2S0_4, concentrated and purified by CC (hexane/EA = 3/1) to give compound **P1a** (180 mg, 79%).

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

4-Bromo-2-ierf-butylaniline **P1a** (20 mmol) was added to a mixture of cone. HCI (11.2 mL) and AcOH (2.24 mL) at -10°C. To this mixture, a solution of $NaN0_2$ (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. $S0_2$ gas was bubbled into AcOH (22.4 mL) in a three-neck flask until saturation (30 min). Then CuCI (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-/V,2-di-tert-butylbenzenesulfonamide (P1c)

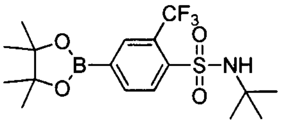
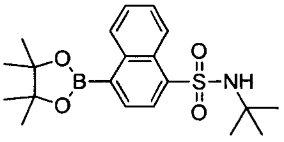
Compound **P1b** (1.0 mmol) and NEt_3 (2.0 mmol) were added into a solution of 2-methylpropan-2-amine (88 mg, 1.2 mmol) in toluene (20 mL). The mixture was stirred for 4 h at reflux, evaporated, poured into water and extracted with EA. The combined organic layers were washed with brine, dried over Na_2S0_4, filtered and evaporated to give compound **P1c** as a solid (330 mg, 85%)

Step 4: /V,2-Di-tert-butyl-4-(4,4,5,5-tetramethyl-1 ,3,2-dioxaborolan-2-yl)benzenesulfonamide (PI)

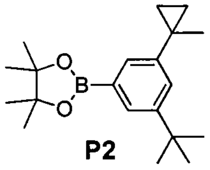
A flask charged with $Pd(dppf)Cl_2$ (30 µmol), KOAc (294 mg, 3.0 mmol) and compound **P1c** (279 mg, 1.0 mmol) was flushed with N_2, then 1,4-dioxane (6 mL) and B_2Pin_2 (1.2 mmol) were added. After being stirred at 80°C for an appropriate period, the product was extracted with benzene, washed with water and dried over $MgS0_4$. 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:

#	Structure	#	Structure
P1/1		**P1/2**	

Preparative Example P2



P2

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

To a solution of 1,3-dibromo-5-(terf-butyl)benzene (2.92 g, 10 mmol) in dioxane (20 mL) was added $Pd(PPh_3)_4$ (3.0 g, 2.6 mmol), prop-1-en-2-ylboronic acid (1.0 g, 12 mmol), K_2C0_3 (2.8 g, 20 mmol) and H_20 (1 mL) under N_2. 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.

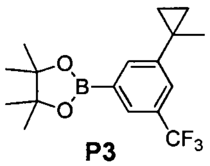
Step 2: 1-Bromo-3-(tert-butyl)-5-(1-methylcvclopropyl)benzene **(P2b)**

To a solution of Et_2Zn (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 CH_2I_2 (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. NH_4Cl (50 mL) and extracted with hexanes. The combined organic layers were dried over $MgS0_4$. Evaporation and purification by CC (hexane) afforded compound **P2b** (1.6 g, 60%) as a colorless oil.

Step 3: 2-(3-(ferf-Butyl)-5-(1-methylcvclopropyl)phenyl)-4.4.5.5-tetramethyl-1 .3.2-dioxaborolane **(P2)**

To a suspension of compound **P2b** (1.6 g, 70 mmol), B_2Pin_2 (3.0 g, 15 mmol), KOAc (2.32 g, 24 mmol) in dioxane (40 mL) was added $Pd(dppf)Cl_2$ (0.16 g) under N_2. 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



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 $Pd(PPh_3)_4$ (300 mg, 0.26 mmol), prop-1-en-2-ylboronic acid (1.0 g, 12 mmol), K_2C0_3 (2.8 g, 20 mmol) and water (1 mL) under N_2. 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.

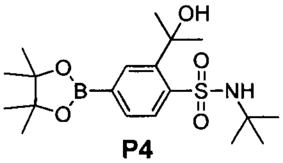
Step 2: 1-Bromo-3-(1-methylcvclopropyl)-5-(trifluoromethyl)benzene **(P3b)**

To a solution of Et_2Zn (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 CH_2I_2 (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. NH_4Cl (5 mL) and extracted with hexanes. The combined organic layers were dried ($MgS0_4$), 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-methylcvclopropyl)-5-(trifluoromethyl)phenyl)-1 ,3.2-dioxaborolane **(P3)**

To a suspension of compound **P3b** (300 mg, 1.0 mmol), B_2Pin_2 (380 mg, 1.5 mmol), KOAc (290 mg, 3 mmol) in dioxane (5 mL) was added $Pd(dppf)Cl_2$ (20 mg) under N_2. 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



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 Et_20 (3 x 250 mL). The organic layer was washed with brine, dried over Na_2S0_4, concentrated and purified by CC to give compound **P4a** (19 g, 83%).

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

Compound **P4a** (10 g, 51 mmol) was added to a mixture of cone. HCl (28 mL) and AcOH (5.6 mL) at -10°C. Then a solution of $NaN0_2$ (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. $S0_2$ gas was bubbled into AcOH (56 mL) until saturation (60 min). Then $CuCl_2$ (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-A/-(tert-butyl)-2-cvanobenzenesulfonamide **(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 N_2, 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.

Step 4: 2-Acetyl-4-bromo-A*/*-(te *rt*-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 Et_20 , 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 Na_2C0_3 and extracted with EA. The combined organic phases were dried over Na_2S0_4, evaporated and purified by CC (n-heptan/EA = 100/0 to 60/40) to give compound **P4d** (0.6 g, 34%).

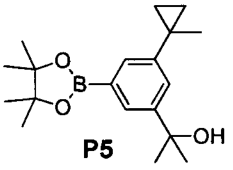
Step 5: 4-Bromo-A/-(fe^-butyl)-2-(2-hvdroxypropan-2-yl)benzenesulfonamide **(P4e)**

Compound **P4d** (200 mg, 0.60 mmol) was dissolved in THF (15 mL) at 0°C. A 3M solution of MeMgBr in Et_20 (1 mL, 3.0 mmol) was added slowly and the reaction mixture was stirred at rt for 3 h, then another portion of a MeMgBr in Et_20 (1 mL, 3.0 mmol) was added. The mixture was evaporated, diluted with water (20 mL) and extracted with Et_20 . The organic layer was dried over $MgS0_4$, filtered, evaporated and purified by HPLC (DCM/MeOH = 100/0 to 70/30) to give compound **P4e** (100 mg, 39%; 47% purity).

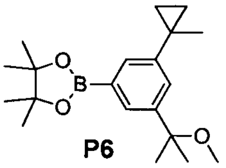
Step 6: A/-(feft-Butyl)-2-(2-hvdroxypropan-2-yl)-4-(4.4,5.5-tetramethyl-1 ,3.2-dioxaborolan-2-vDbenzenesulfonamide **(P4)**

To a solution of compound **P4e** (200 mg, 0.57 mmol), Pin_2B_2 (290 mg, 1.14 mmol) and KOAc (160 mg, 1.7 mmol) in dioxane (10 mL) at rt under N_2 was added Pd(dppf)Cl_2 (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 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



P5



P6

Step 1: 3,5-Dibromo-/V-methoxy-A/-methylbenzamide **(P5a)**

The solution of 3,5-dibromobenzoic acid (26 g, 93 mmol) in $SOCl_2$ (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 EtN_3 (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 Na_2SO_4, 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 Et_2O, 1 mL, 3.0 mmol) dropwise at 0°C and the solution was stirred for 4 h at rt, then quenched with aq. $NHCl_4$ and extracted with tert-butylmethylether. The organic layer was washed with water and brine consecutively, dried over Na_2SO_4, 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 PPh_3CH_3Br (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. $NHCl_4$ and extracted with Et_2O. 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-methylcvclopropyl)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 CH_2N_2 (487 mg, 11.6 mmol) in Et_2O (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-methylcvclopropyl)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. $NHCl_4$ 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-methylcvclopropyl)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 N_2 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 Et_2O. The organic layer was washed with brine, dried over Na_2SO_4, filtered, concentrated and purified by CC (PE) to give compound **P5f** (1.6 g, 100%) as a colorless oil.

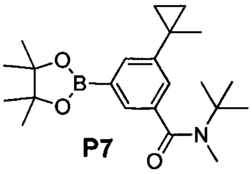
Step 7: 2-(3-(1-Methylcvclopropyl)-5-(4.4.5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propan-2-ol **(P5)**

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-methylcvclopropynphenyl)-4,4,5,5-tetramethyl-1 ,3,2-dioxaborolane **(P6)**

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

Preparative Example P7



P7

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 $Pd(PPh_3)_4$ (300 mg, 0.26 mmol), prop-1-en-2-yl boronic acid (1.0 g, 12 mmol), K_2C0_3 (2.8 g, 20 mmol) and H_20 (1 mL) under N_2 atmosphere. The mixture was stirred overnight at 90°C. Then the mixture was concentrated and purified by CC (PE/EA = 6/1) to afford compound **P7a** (1.9 g, 71%) as a solid.

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

To a solution of Et_2Zn (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 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. NH_4Cl (5 mL) and the layers were separated. The aq. layer was extracted with hexane (2 x) and dried over $MgS0_4$. 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-methylcvclopropyl)benzoic acid **(P7c)**

Compound **P7b** (270 mg, 1.0 mmol) and LiOH (50 mg, 2.0 mmol) were mixed in THF (3 mL) and H_20 (3 mL). The mixture was stirred for 10 h, then the pH was adjusted to pH 3 with aq. 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-/V-(rerf-butyl)-A/-methyl-5-(1-methylcvclopropyl)benzamide **(P7d)**

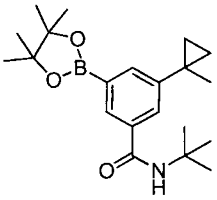
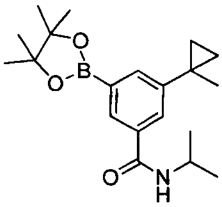
To a solution of compound **P7c** (250 mg, 1.0 mmol) in DMF (5 mL) was added HATU (380 mg, 1.0 mmol) and Et_3N (202 mg, 2.0 mmol) and the mixture was stirred overnight. After removal of the solvents the crude product was purified with prep. HPLC to afford compound **P7d** (300 mg, 95%).

Step 5: A/-(terf-Butyl)-/V-methyl-3-(1-methylcvcloDropyl)-5-(4.4.5.5-tetramethyl-1 .3.2-dioxaborolan-2-yl)benzamide **(P7)**

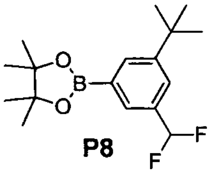
To a suspension of compound **P7d** (323 mg, 1.0 mmol), B_2Pin_2 (380 mg, 1.5 mmol), KOAc (290 mg, 3.0 mmol) in dioxane (5 mL) was added $Pd(dppf)Cl_2$ (20 mg) under N_2 atmosphere. The mixture was heated to 100°C for 16 h. The mixture was purified by CC (PE/EA = 4/1) to afford compound **P7** (200 mg,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

Preparative Example P7/1 to P7/2

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

#	Structure	#	Structure
P7/1		**P7/2**	

Preparative Example P8



P8

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

To a solution of 1,3-dibromo-5-(fert-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_2S0_4, filtered, concentrated and purified by CC (PE) to give compound **P8a** (40 g, 82%) as a colorless oil.

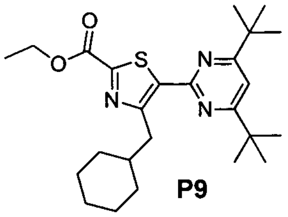
Step 2: 1-Bromo-3-(tert-butyl)-5-(difluoromethyl)benzene **(P8b)**

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. $NaHC0_3$, water and brine consecutively, dried over Na_2S0_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.

Step 3: 2-(3-(*teA*-Butyl)-5-(difluoromethyl)Dhenyl)-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.

Preparative Example P9



P9

Step 1: 4,6-Di-tert-butyl-2-chloropyrimidine **(P9a)**

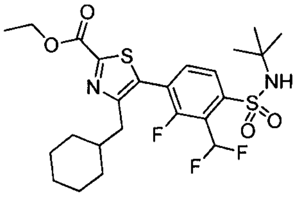
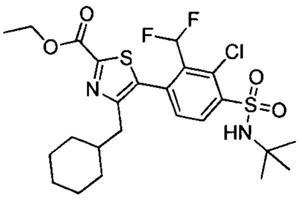
A mixture of 2,4,6-trichloropyrimidine (46 mg, 250 μητιοl) and CuI (3 mg, 12 μηηοl) in dry THF (10 mL) was cooled to -20°C and purged with N_2 for 10 min. Then a iert-BuMgCI solution (2M in THF, 64 mg, 0.55 mmol) was added dropwise at a rate such that the reaction solution did not exceed 0°C. After the 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_2S0_4), concentrated and purified by CC (PE/EA = 100/1) to give compound **P9a** (45 mg, 80%) as yellow solid.

Step 2: Ethyl 4-(cvclohexylmethyl)-5-(4.6-di-terf-butylpyrimidin-2-vnthiazole-2-carboxylate **(P9)**

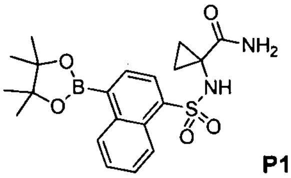
The solution of **P9a** (45 mg, 0.2 mmol), methyl 4-(cyclohexylmethyl)thiazole-2-carboxylate (50 mg, 0.2 mmol), K_2C0_3 (46 mg, 0.33 mmol), $Pd(OAc)_2$ (2 mg, 4 μηηοl), PCy_3-HBF_4 (4 mg, 8 μηιοl) and PivOH (6 mg, 0.06 mmol) in a solution of DMA (2 mL) was heated under Ar at 100°C overnight, cooled to rt, partitioned between EA and water and separated. The organic phase was washed with water and brine, dried over Na_2S0_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:

#	Structure	#	Structure
P9/1		**P9/2**	

Preparative Example P10



P10

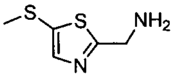
Step 1: 1-(4-Bromonaphthalene-1-sulfonamido)cvclopropanecarboxamide **(P10a)**

The solution of 4-bromo-A/-(1-cyanocyclopropyl)naphthalene-1 -sulfonamide (200 mg, 0.57 mmol), 2N NaOH (0.6 mL, 1.20 mmol) and 30% aq. H_2O_2 (0.5 mL) in MeOH (3 ml_) was heated at 60°C for 3 h, cooled 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 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)cvclopropanecarboxamide **(P1 0)**

The solution of compound **P10a** (188 mg, 0.51 mmol), $(Bpin)_2$ (153 mg, 0.60 mmol), KOAc (196 mg, 2.0 mmol) and $Pd(dppf)Cl_2$ (20 mg) in dioxane (5 mL) was heated for 16 h at 95°C under N_2, cooled, filtered, diluted 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 (PE/EA = 10/1) to give compound **P10** (60 mg, 28%) as a white solid.

Preparative Example P11



P11

Step 1: 5-Bromo-/V-(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 rert-buytlamine (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. Na_2CO_3. The organic layer was washed with 1N HCl and brine, dried over Na_2SO_4, filtered, concentrated and purified by CC (PE/EA = 4/1) to give compound **P11a** (3.42 g, 100%) as a yellow solid.

Step 2: /V-(ferf-Butvn-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 Me_2S (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 Na_2SO_4, filtered, concentrated and purified by CC (PE/EA = 5/1) to give compound **P11b** (2.50 g, 90%) as a brown solid.

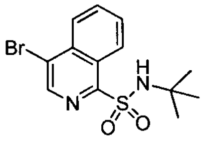
Step 3: 5-(Methylthio)thiazole-2-carboxamide **(P11c)**

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 Na_2S0_4, filtered and concentrated to give compound **P11c** (1.77 g, 93%) as a yellow solid.

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 $LiAlH_4$ 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 H_20, 15% aq. NaOH and H_20. The suspension was stirred until all $LiAlH_4$ was neutralized and a white precipitate was formed, filtered and the precipitate was washed with Et_20. The combined organic layers were dried over Na_2S0_4, filtered, concentrated and purified by prep-HPLC to give compound **P11** (410 mg, 25%) as a brown oil.

Preparative Example P12



P12

Step 1: 4-Bromoisoquinolin-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 Br_2 (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 Et_20 to give compound **P12a** (5.0 g, 62%) as a yellow solid.

Step 2: 4-Bromoisoquinoline-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** (600 mg, 56%) as pale yellow crystal.

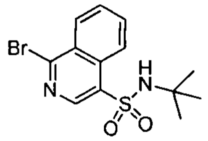
Step 3: 4-Bromoisoquinoline-1-sulfonyl chloride **(P12c)**

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 organic layer was dried over Na_2S0_4, 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-A/-(fert-butyl)isoquinoline-1-sulfonamide **(P12)**

To a solution of f-$BuNH_2$ (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 Na_2S0_4, filtered, concentrated and purified by CC (PE/EA = 6/1) to give compound **P12** (800 mg, 65%) as a yellow solid.

Preparative Example P13



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 NH_4Cl (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 Na_2S0_4 and concentrated to give compound **P13b** (6.1 g, 90%) as a brown solid.

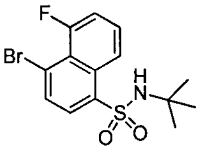
Step 3: 1-Bromoisoquinolin-4-amine **(P13c)**

A solution of compound **P13b** (6.1 g, 38.1 mmol) and PBr_3 (28.7 g, 100 mmol) was stirred at 135°C for overnight, cooled to rt, diluted with water, adjusted to pH = 8 with Na_2C0_3 (solid) and extracted with EA (3x). The combined organic layers were washed with sat. $NaHC0_3$ and brine, dried over Na_2S0_4, 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-A/-(te *rt*-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 $NaN0_2$ (1.12 g, 16.2 mmol) in water (20 mL) at 0°C. After stirring 20 min, $S0_2$ gas was bubbled in over 20 min, keeping the reaction temperature <0°C. A solution of $CuCl_2$-$2H_20$ (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 terf-$BuNH_2$ (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 Na_2S0_4, 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



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 cone. 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 Na_2S0_4> 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 $NaN0_2$ (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 Et_20 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 $MgS0_4$, 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 Na_2S0_4, filtered, concentrated and purified by CC (PE/EA = 4/1) to give compound **P14d** (6.5 g, 62%) as an off-white solid.

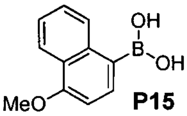
Step 5: 4-Bromo-5-fluoronaphthalene-1-sulfonyl chloride **(P14e)**

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 $NaN0_2$ (2.45 g, 35.5 mmol) in water (50 mL) at 0°C. After stirring 20 min, $S0_2$ gas was bubbled in over 1 h, keeping the reaction temperature <0°C. A solution of $CuCl_2$-$2H_20$ (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.

Step 6: 4-Bromo-/V-(ferf-butyl)-5-fluoronaphthalene-1 -sulfonamide **(P14)**

To a solution of compound **P14e** (3.0 g, 9.27 mmol) in pyridine (15 mL) was added terf-$BuNH_2$ (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.

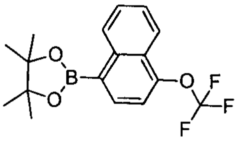
Preparative Example P15



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

A mixture of 1-bromo-4-methoxynaphthalene (2.0 g, 8.44 mmol) in Et_20 (10 mL) was cooled down to -70°C under N_2 and then n-BuLi in hexane (3.37 mL, 8.44 mmol) was added dropwise. The solution was stirred under N_2 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 N_2. Then 2M HCl (10 mL) and Et_20 (10 mL) was added to the mixture which was washed by brine till it turned neutral. The organic layer was dried over Na_2S0_4, filtered, concentrated and the residue was washed with EA to give compound **P15** (500 mg, 29%) as a colorless solid.

Preparative Example P16


P16

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

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 Na_2S0_4, 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)**

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 CF_2Br_2 (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 Na_2SO_4, filtered, concentrated and purified by CC (PE) to give compound **P16b** (1.6 g, 43%) as a colorless oil.

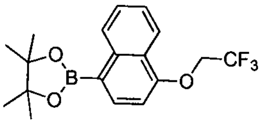
Step 3: 1-Bromo-4-(trifluoromethoxy)naphthalene **(P16c)**

A solution of compound **P16b** (3.5 g, 10.0 mmol) in DCM (70 mL) was cooled to -78°C under N_2, then $AgBF_4$ (4.3 g, 22.0 mmol) was added and the solution was warmed to rt slowly and stirred overnight. $NaHCO_3$ 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 Na_2SO_4, filtered and concentrated to give compound **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), Pin_2B_2 (1.75 g, 6.9 mmol), AcOK (1.0 g, 10.4 mmol) and $Pd(dppf)Cl_2$-CH_2Cl_2 (282 mg, 0.35 mmol) in 1,4-dioxane (20 mL) was bubbled with N_2 for 10 min and the mixture was stirred at 80°C for 16 h under N_2, cooled to rt and diluted 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



P17

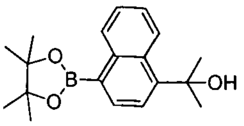
Step 1: 1-Bromo-4-(2,2,2-trifluoroethoxy)naphthalene **(P17a)**

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 Cs_2CO_3 (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.

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), B_2Pin_2 (835 mg, 3.29 mmol) and KOAc (483 mg, 4.93 mmol) in dioxane (30 mL) was bubbled with N_2 for 10 min, then $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (134 mg, 0.164 mmol) was added and the mixture was stirred at 80°C for 16 h under N_2, 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



P18

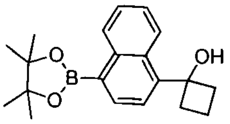
Step 1: 2-(4-Bromonaphthalen-1-yl)propan-2-ol **(P18a)**

To a solution of 1,4-dibromonaphthalene (2.0 g, 7.0 mmol) in dry Et_2O (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 Et_2O (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, 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), B_2Pin_2 (690 mg, 2.7 mmol), KOAc (450 mg, 4.6 mmol) and $Pd(dppf)Cl_2$ (150 mg, 0.2 mmol) in dioxane (10 mL) was heated overnight at 85°C under N_2, 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 Na_2SO_4, filtered, concentrated and purified by CC (PE/EA = 20/1) to give compound **P18** (600 mg, 83%) as a colorless solid.

Preparative Example P19



P19

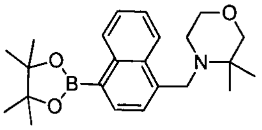
Step 1: 3-(4-Bromonaphthalen-1-yl)oxetan-3-ol **(P19a)**

To a solution of 1,4-dibromonaphthalene (2.0 g, 7.0 mmol) in dry Et_2O (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 Et_2O (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, 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-vnoxetan-3-ol **(P19)**

The solution of compound **P19a** (500 mg, 1.8 mmol), B_2Pin_2 (559 mg, 2.2 mmol), KOAc (353 mg, 3.6 mmol) and $Pd(dppf)Cl_2$ (145 mg, 0.2 mmol) in dioxane (10 mL) was heated overnight at 85°C under N_2, 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 Na_2SO_4, filtered, concentrated and purified by CC (PE/EA = 20/1) to give compound **P19** (110 mg, 15%) as a colorless solid.

Preparative Example P20



P20

Step 1: 4-Bromo-1-naphthaldehvde (P20a)

To a solution of 1,4-dibromonaphthalene (2.0 g, 7.0 mmol) in dry Et_20 (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 Et_20 (3x). The combined organic layers were washed with brine, dried over Na_2S0_4, 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 $NaBH_4$ (378 mg, 10 mmol) slowly and the suspension was stirred at rt for 1 h, was quenched with sat. NH_4Cl, concentrated and diluted with EA and water. The organic layer was washed with brine, dried over Na_2S0_4, filtered and concentrated to give a residue. To this residue was added DCM (10 mL), NEt_3 (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 Na_2S0_4, filtered and concentrated to give crude compound **P20b** (700 mg, 52%) as a colorless oil.

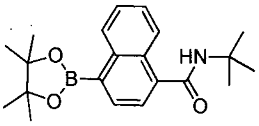
Step 3: 4-((4-Bromonaphthalen-1-yl)methyl)-3,3-dimethylmorpholine (P20c)

A suspension of compound **P20b** (700 mg, 2.2 mmol), 3,3-dimethyl-morpholine (512 mg, 4.4 mmol) and K_2C0_3 (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-vDmethvDmorpholine (P20)

A solution of compound **P20c** (460 mg, 1.38 mmol), B_2Pin_2 (953 mg, 3.75 mmol), KOAc (368 mg, 3.75 mmol) and $Pd(dppf)Cl_2$ (51 mg, 0.06 mmol) in dioxane (10 mL) was heated overnight at 90°C under N_2, 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 Na_2S0_4, filtered, concentrated and purified by CC (PE/EA = 5/1) to give compound **P20** (110 mg, 21%) as a colorless solid.

Preparative Example P21



P21

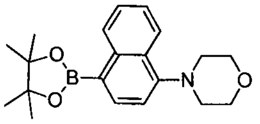
Step 1: 4-Bromo-A/-(te^butyl)-1-naphthamide **(P21a)**

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 f-BuNH$_2$ (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 Na$_2$S0$_4$, concentrated and purified by CC (PE≡/ EA = 8/1) to give compound **P21a** (3.8 g, 78%) as a colorless solid.

Step 2: A/-(re/t-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), B$_2$Pin$_2$ (1.5 g, 6.0 mmol), KOAc (980 mg, 10.0 mmol) and Pd(dppf)Cl$_2$ (366 mg, 0.5 mmol) in dioxane (15 mL) was heated overnight at 90°C under N$_2$, 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 Na$_2$S0$_4$, filtered, concentrated and purified by CC (PE/EA = 10/1) to give compound **P21** (1.7 g, 96%) as a colorless solid.

Preparative Example P22



P22

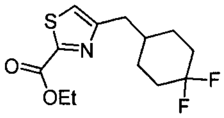
Step 1: 4-(4-Bromonaphthalen-1-yl)morpholine **(P22a)**

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 Na$_2$S0$_4$, 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), B$_2$Pin$_2$ (945 mg, 3.7 mmol), KOAc (608 mg, 6.2 mmol) and Pd(dppf)Cl$_2$ (220 mg, 0.3 mmol) in dioxane (10 mL) was heated overnight at 90°C under N$_2$, 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 Na$_2$S0$_4$, filtered, concentrated and purified by CC (PE/EA = 4/1) to give compound **P22** (770 mg, 73%) as a colorless solid.

Preparative Example P23


P23

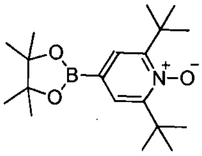
Step 1: l-Bromo-S-^^-difluorocvclohexyDpropan^-one **(P23a)**

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_20 (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-difluorocvclohexyl)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


P24

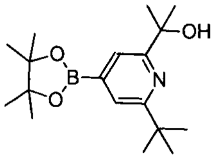
Step 1: 2,6-Di-tert-butylpyridine 1-oxide **(P24a)**

To a solution of 2,6-di-terf-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. $NaHC0_3$ and sat. NaS_20_3 consecutively, dried over Na_2S0_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-fe/t-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 pmol), $[Ir(COD)(OMe)]_2$ (13 mg, 20 pmol), DTBPy (11 mg, 40 µηηοl) and $(BPin)_2$ (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


P25

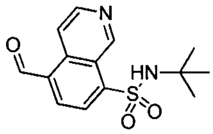
Step 1: 2-(6-(tert-Butyl)pyridin-2-yl)propan-2-ol (P25a)

A solution of 1-(6-(fert-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_2S0_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), $[Ir(COD)(OMe)]_2$ (100 mg, 0.16 mmol), DTBPy (83 mg, 0.31 mmol) and $(BPin)_2$ (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


P26

Step 1: 5-Bromoisoquinoline-8-sulfonic acid (P26a)

A solution of 5-bromoisoquinoline (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-A/-(terf-butyl)isoguinoline-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_20 and dried in vacuum to give compound **P26b** (22g, 63%) as a yellow solid.

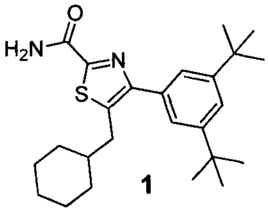
Step 3: A/-(fert-Butyl)-5-formylisoauinoline-8-sulfonamide (P26)

A solution of n-butyllithium (46 mL, 114mmol) in hexane was added dropwise to a solution of **P26b** (15 g, 52 mmol) in THF/Et_20 (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 NH_4Cl and extracted with EA. The organic layer was washed with brine, dried with Na_2S0_4, concentrated and purified by CC (PE/E =6/1) to give compound **P26** (5.5 g, 36%) as a yellow solid.

Additonal Preparative Examples

The synthesis of additonal Preparative Examples (e.g. boronic esters) is described in WO201 2/1 39775 and in PCT/EP201 2/004977.

Example 1


1

Step 1: 3-Cvclohexyl-1-(3,5-di-ten'-butylphenyl)propan-1-one (1a)

A solution of 1,3-di-terf-butylbenzene (4.36 g, 22.9 mmol) in dry CH_2Cl_2 (20 mL) was sequentially treated at 0°C with 3-cyclohexylpropanoyl chloride (4.00 g, 22.9 mmol) and $AlCl_3$ (3.35 g, 25.2 mmol) and the solution was stirred at 0°C for 2 h. The resulting solution was poured into 0.1 N HCl and the organic layer was separated. The aq. phase was extracted with EA. The combined organic layers were washed with sat. $NaHC0_3$ and brine consecutively, dried over Na_2S0_4, filtered, concentrated and purified by CC (DCM/PE = 1/6) to give compound **1a** (2.3 g, 30%) as a light yellow oil.

Step 2: 2-Bromo-3-cvclohexyl-1-(3,5-di-te/t-butylphenyl)propan-1-one (1b)

To a solution of compound **1a** (2.0 g, 6.02 mmol) in AcOH (20 mL) was added Br_2 (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. Na_2S0_3 and extracted with EA twice. The combined organic layers were washed with water and brine consecutively, dried over Na_2S0_4, filtered, concentrated and purified by CC (DCM/PE = 1/8) to give compound **1b** (2.2 g, 89%) as a colorless oil.

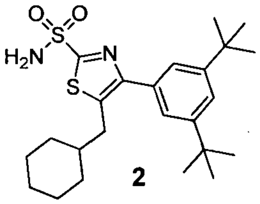
Step 3: Ethyl 5-(cvclohexylmethyl)-4-(3,5-di-ten>butylphenyl)thiazole-2-carboxylate (1c)

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 Na_2S0_4, 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-(Cvclohexylmethyl)-4-(3.5-di-ferf-butylphenyl)thiazole-2-carboxamide **(1)**

To a solution of compound **1c** (0.15 g, 0.34 mmol) in methanol (5 mL) was bubbled NH_3 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. ^{1}H-NMR ($CDCl_3$, 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).

Example 2



2

Step 1: 5-(Cvclohexylmethyl)-4-(3.5-di-te/t-butylphenyl)thiazole **(2a)**

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. Na_2C0_3, dried over Na_2S0_4, filtered, concentrated and purified by CC (DCM/PE = 1/3) to give compound **2a** (0.9 g, 59%) as a colorless sticky oil.

Step 2: 2-Bromo-5-(cvclohexylmethyl)-4-(3,5-di-te/t-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. CBr_4 (0.33 g, 1.0 mmol) in dry THF (1 mL) was added at -78°C and the solution was stirred at rt for 1 h. The resulting solution was quenched with sat. NH_4Cl and extracted with EA twice. The combined organic layers were washed with water and brine consecutively, dried over Na_2S0_4, filtered, concentrated and purified by CC (DCM/PE = 1/4) to give compound **2b** (0.36 g, 86%) as a white solid.

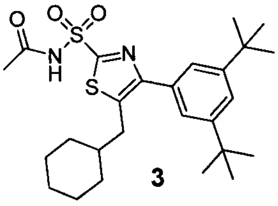
Step 3: 5-(Cvclohexylmethyl)-4-(3.5-di-terf-butylphenvnthiazole-2-thiol **(2c)**

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 Na_2S0_4, filtered, concentrated and purified by CC (EA/PE = 1/4) to give compound **2c** (80 mg, 26%) as a white solid.

Step 4: 5-(Cvclohexylmethyl)-4-(3.5-di-re/f-butylphenyl)thiazole-2-sulfonamide **(2)**

To a solution of compound **2c** (45 mg, 0.1 1 mmol) in CH_2Cl_2 (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 CH_2Cl_2 twice. The combined organic layers were washed with sat. $NaHC0_3$ and brine consecutively, dried over Na_2S0_4, filtered and concentrated. The residue was dissolved in a mixture of acetone (3 mL) and NH_4OH (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 Na_2S0_4, filtered, concentrated and purified by CC (EA/PE = 1/4) to give compound **2** (27 mg, 55%) as a white solid. ^{1}H-NMR ($CDCl_3$, 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

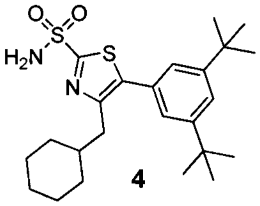


3

yV-((5-(Cvclohexylmethyl)-4-(3,5-di-terf-butylphenyl)thiazol-2-yl)sulfonyl)acetamide **(3)**

To a solution of compound **2** (20 mg, 45 μιηοl) in CH_2Cl_2 (2 mL) was added NEt_3 (50 μL) and Ac_20 (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 Na_2S0_4, filtered, concentrated and purified by CC (EA/PE = 1/3) to give compound **3** (18 mg, 81%) as a white solid. ^{1}H-NMR ($CDCl_3$, 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



4

Step 1: 1-Allyl-3,5-di-terf-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 K_2C0_3 (27.6 g, 200 mmol), $Pd_2(dba)_3$ (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 CH_2Cl_2 (70 mL) was added m-CPBA (6.6 g, 38 mmol) at rt and the solution was stirred for 2 h, quenched with aq. $Na_2S_20_3$ and the organic layer was separated, washed with water and brine consecutively, dried over Na_2S0_4, filtered, concentrated and CC (PE) to give compound **4b** (6.0 g, 76%) as a colorless oil.

Step 3: 1-Cvclohexyl-3-(3,5-di-tertbutylphenyl)propan-2-ol **(4c)**

To a solution of CuBr (150 mg) and cyclohexylmagnesium chloride (2M in Et_20 , 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. NH_4Cl 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-Cvclohexyl-3-(3,5-di-terf-butylphenyl)propan-2-one **(4d)**

A solution of H_5I0_6 (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-cvclohexyl-1-(3.5-di -te *rt*-butylphenyl)propan-2-one **(4e)**

To a solution of compound **4d** (6.0 g, 18.3 mmol) in CCl_4 (100 mL) was added a solution of Br_2 (1M in CH_2Cl_2, 2.93 g, 18.3 mmol) at -15°C and the solution was stirred at 0°C for 1 h, then poured into sat. Na_2S0_3 and extracted with EA twice. The combined organic layers were washed with water and brine consecutively, dried over Na_2S0_4, filtered, concentrated and purified by CC (PE) to give compound **4e** (6.5 g, 87%) as a colorless oil.

Step 6: 4-(Cvclohexylmethyl)-5-(3,5-di-feff-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. $NaHC0_3$ was added. The formed solid was collected by filtration and dried in vaccuo to give compound **4f** (6.0 g, 98%) as a light yellow solid.

Step 7: 2-Bromo-4-(cvclohexylmethyl)-5-(3,5-di-terf-butylphenyl)thiazole **(4q)**

The solution of $CuBr_2$ (4.05 g, 18 mmol) and tert-butyl nitrite (2.1 g, 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_2C0_3. The organic layer was dried over $MgS0_4$, filtered, concentrated and purified by CC (DCM/PE = 2/1) to give compound **4g** (4.4 g, 67%) as a light yellow solid.

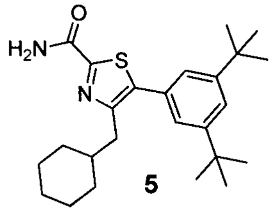
Step 8: 4-(Cvclohexylmethyl)-5-(3.5-di-ferf-butylphenyl)thiazole-2-thiol **(4h)**

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_2S0_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-(Cvclohexylmethvh-5-(3,5-di-terf-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. $NaHC0_3$ and brine consecutively, dried over Na_2S0_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_2S0_4, filtered, concentrated and purified by CC (EA/PE = 1/4) to give compound **4** (70 mg, 41%) as a white solid. ^{1}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



5

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

A solution of 1,3-di-ie/f-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_2S0_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-fert-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 extracted with EA three times. The combined organic layers were washed with brine, dried over Na_2S0_4, 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-terf-butylphenyl)-A/-methoxy-/V-methylacetamide **(5c)**

A solution of compound **5b** (6.4 g, 25.7 mmol) in $SOCl_2$ (5 mL) was heated at reflux for 1 h, concentrated under reduced pressure and diluted in dry CH_2Cl_2 (40 mL). This solution was slowly added to a solution of *N,O*-dimethyhydroxylamine hydrochloride (2.52 g, 25.7 mmol) and DIEA (9.9 g, 77 mmol) in dry CH_2Cl_2 (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. Na_2C0_3 and brine consecutively, dried over Na_2S0_4, 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-Cvclohexyl-3-(3,5-di-terf-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 Et_20, 15 mL, 8.6 mmol) at 0°C and the solution was stirred at rt for 3 h, quenched with sat. NH_4Cl and extracted with EA twice. The combined organic layers were washed with water and brine consecutively, dried over Na_2S0_4, 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-cvclohexyl-1-(3,5-di-fe/t-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 Br_2 (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. Na_2S0_3 and extracted with EA. The combined organic layers were washed with water and brine consecutively, dried over Na_2S0_4, filtered, concentrated and purified by CC (DCM/PE = 1/8) to give compound **5e** (0.50 g, 59%) as a yellow oil.

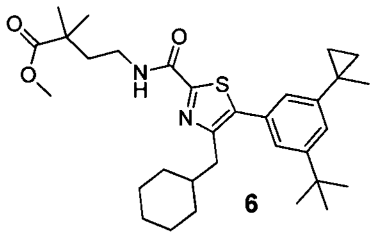
Step 6: Ethyl 4-(cvclohexylmethyl)-5-(3.5-di-terf-butylphenyl)thiazole-2-carboxylate **(5f)**

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 Na_2S0_4, filtered, concentrated and purified by CC (DCM/PE = 1/5) to give compound **5f** (60 mg, 67%) as a light yellow sticky oil.

Step 7: 4-(Cvclohexylmethyl)-5-(3,5-di-fe/†-butylphenyl)thiazole-2-carboxamide **(5)**

To a solution of compound **5f** (60 mg, 0.14 mmol) in MeOH (10 mL) was bubbled NH_3 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. ^{1}H-NMR (400 MHz, $CDCl_3$) 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



6

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

To an ice-cooled solution of 1-cyclohexylpropan-2-one (19.6 g, 140 mmol) in MeOH (150 mL) was added Br_2 (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. H_20 was added and the solution was extracted with Et_20 (3x). The combined organic layers were combined, washed with 10% aq. K_2C0_3 (3x), dried over Na_2S0_4, filtered and concentrated to give crude compound **6a** (22 g) as a yellowish liquid.

Step 2: Ethyl 4-(cvclohexylmethyl)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 NH_4OH. The aq. layer was extracted with EA (3x). The combined organic layers were dried over Na_2S0_4, 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-(cvclohexylmethyl)thiazole-2-carboxylate **(6c)**

To a solution of compound **6b** (14.5 g, 57.3 mmol) in CH_2Cl_2 (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 Na_2C0_3 solution and then washed with water, dried over $MgS0_4$, 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.

Step 4: Ethyl 5-(3-(fe/t-butyl)-5-(1-methylcvclopropyl)phenyl)-4-(cvclohexylmethyl)thiazole-2-carboxylate **(6d)**

A solution of compound **6c** (2.0 g, 6.0 mmol), 2-(3-(terf-butyl)-5-(1-methylcyclopropyl)phenyl)-4,4,5,5-tetramethyl-1 ,3,2-dioxaborolane (2.3 g, 7.2 mmol), Na_2C0_3 (2.5 g, 24 mmol) and

Pd(dppf)Cl_2 (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 Na_2S0_4, 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-(te/t-Butyl)-5-(1 -methylcvclopropyl)phenyl)-4-(cvclohexylmethyl)thiazole-2-carboxylic acid **(6e)**

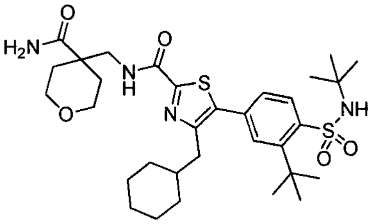
To a solution of compound **6d** (1.5 g, 3.4 mmol) in a solution of MeOH (50 mL) and H_20 (10 mL) was added KOH (765 mg, 13.6 mmol) and then the solution was stirred for 4 h at 90°C, then concentrated and diluted with H_20 . 1N HCI solution was added to adjust pH to 5, which was then extracted with DCM. The organic layer was washed with brine, dried over Na_2S0_4, filtered and concentrated to give compound **6e** (1.2 g, 86%) as a white solid.

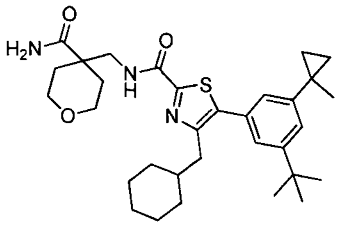
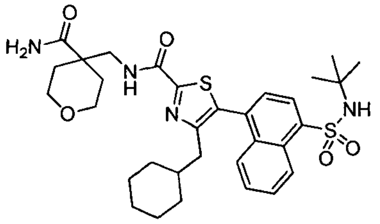
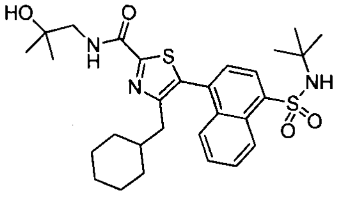
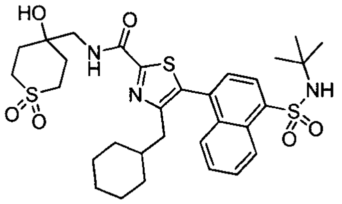
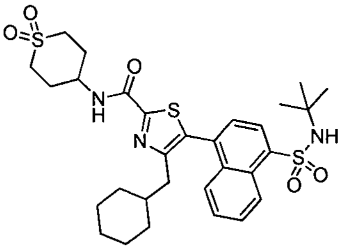
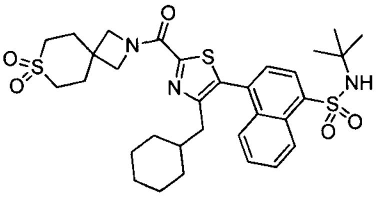
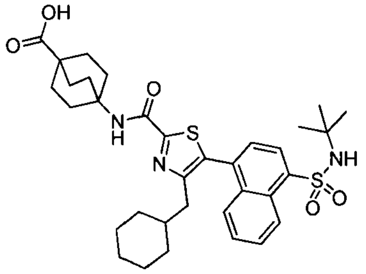
Step 6: Methyl 4-(5-(3-(te/t-butvh-5-(1-methylcvclopropyl)phenyl)-4-(cvclohexylmethyl)thiazole-2-carboxamido)-2,2-dimethylbutanoate **(6)**

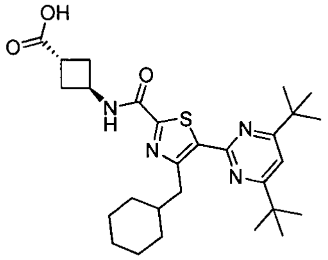
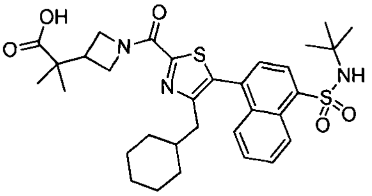
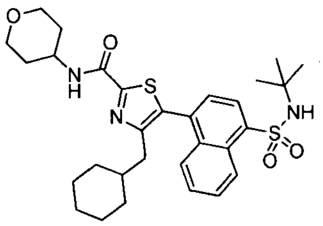
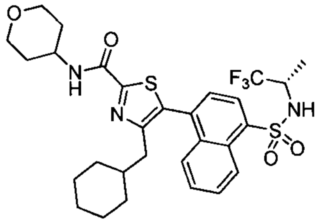
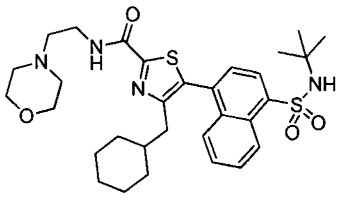
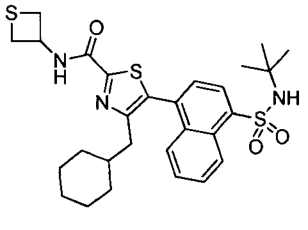
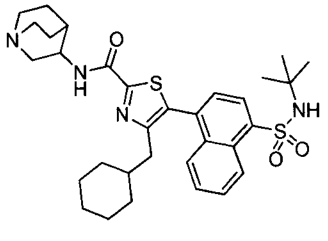
To a solution of compound **6e** (300 mg, 0.73 mmol) in DMF (3 mL) was added HATU (416 mg, 1.09 mmol), DIEA (283 mg, 2.2 mmol) and methyl 4-amino-2,2-dimethylbutanoate hydrochloride (125 mg, 0.87 mmol) and the solution was stirred for 20 min, then H_20 and EA was added. The organic layer was washed with brine, dried over Na_2S0_4, filtered, concentrated and purified by CC (PE/EA = 5/1) to give compound **8** (300 mg, 76%) as white powder. ^{1}H-NMR (300 MHz, $CDCl_3$) 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 $(M+1)^+$.

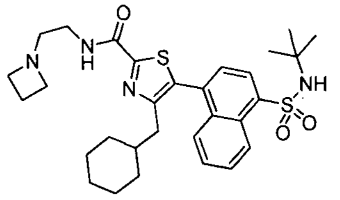
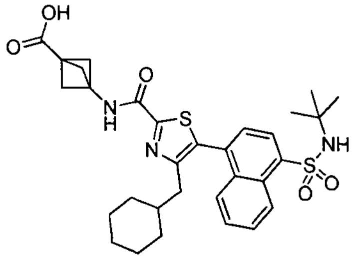
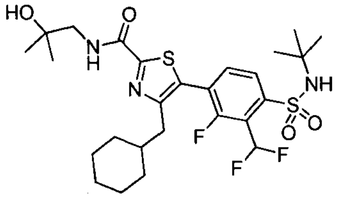
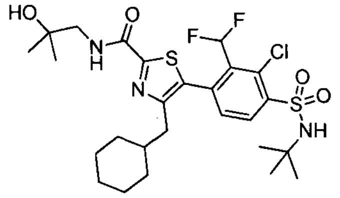
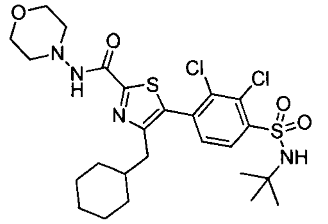
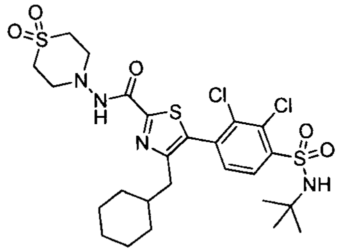
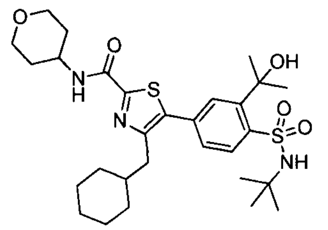
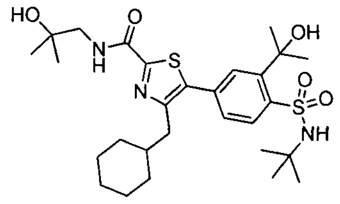
Example 6/1 to 6/64

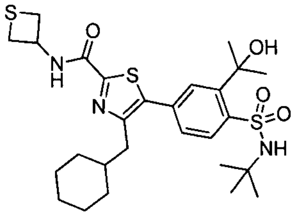
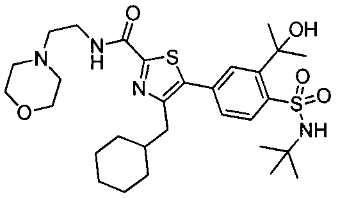
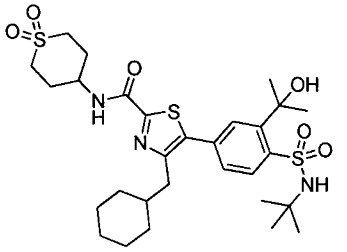
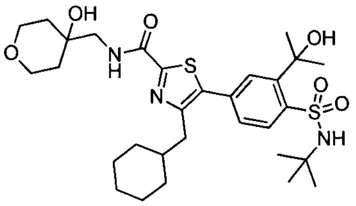
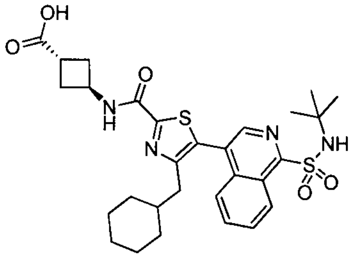
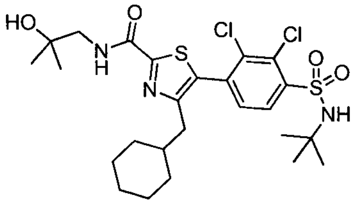
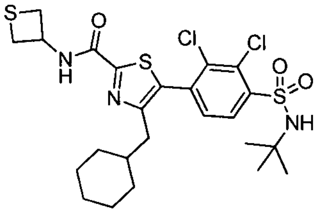
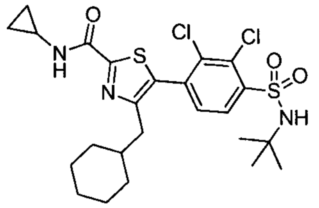
The following Examples were prepared similar as in Example **6**. Due to some extent of decarboxylation upon storage it is preferred not to neutralize the reaction mixture in Step **6e** above but to use the potassium salt for the amide coupling.

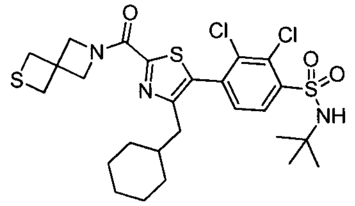
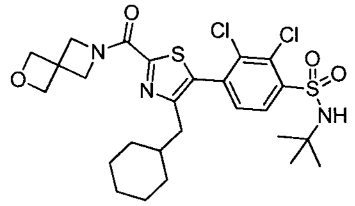
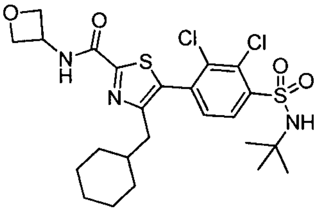
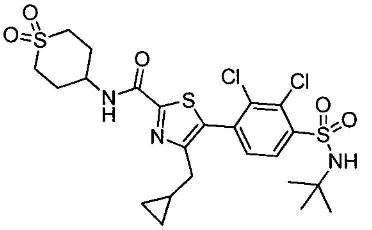
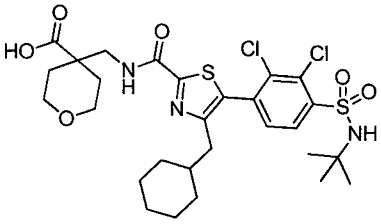
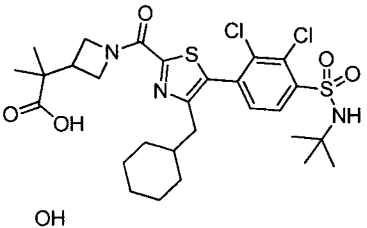
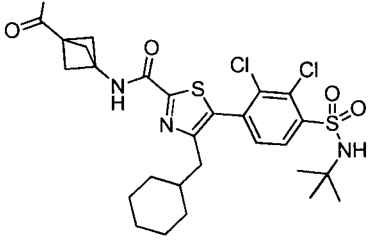
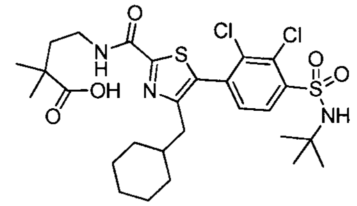
#	Structure	Analytical data
6/1		^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.22 (d, J = 7.6 Hz, 1H), 7.64-7.67 (m, 2H), 7.32-7.35 (m. 1H), 5.93 (br s, 1H), 5.65 (br s, 1H), 4.66 (s, 1H), 3.86 (br s, 2H), 3.72-3.76 (m, 4H), 2.65 (d, J = 5.2 Hz, 2H), 1.89-2.00 (m, 2H), 1.69-1.78 (m, 3H), 1.62 (s, 15H), 1.34 (s, 9H), 1.07-1.28 (m, 3H), 0.85-0.91 (m, 2H). MS 633.3 $(M+1)^+$

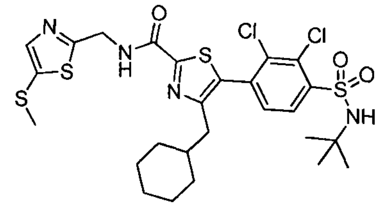
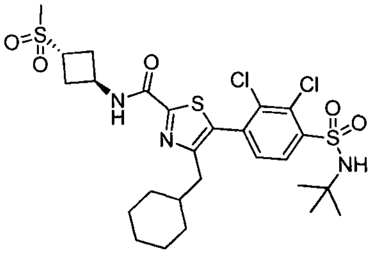
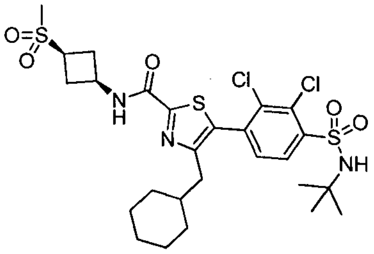
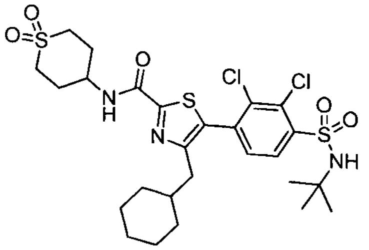
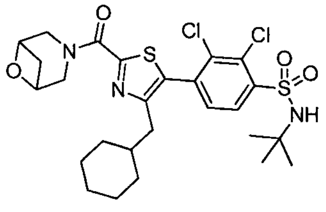
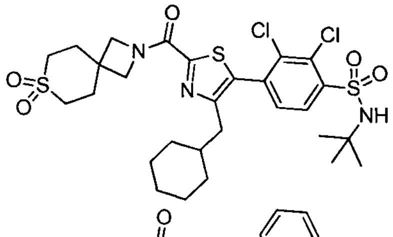
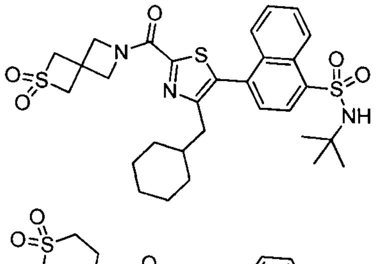
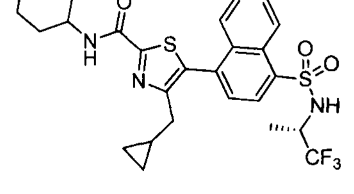
#	Structure	Analytical data
6/2		^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.58-7.61 (m, 1H), 7.30 (s, 1H), 7.22 (s, 1H), 7.09 (s, 1H), 5.91 (br s, 1H), 5.53 (br s, 1H), 3.86-3.92 (m, 2H), 3.68-3.74 (m, 4H), 2.63 (d, J = 6.8 Hz, 2H), 1.99-2.03 (m, 2H), 1.58-1.83 (m, 9H), 1.43 (s, 3H), 1.34 (s, 9H), 1.10-1.27 (m, 3H), 0.87-0.93 (m, 3H), 0.75-0.77 (m, 2H). MS 552.3 $(M+1)^+$
6/3		^{1}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 $(M+1)^+$
6/4		^{1}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 $(M+1)^+$
6/5		^{1}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 $(M+1)^+$
6/6		^{1}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-.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 $(M-1)^-$
6/7		^{1}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 $(M+1)^+$
6/8		^{1}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 $(M+1)^+$

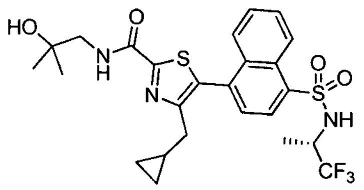
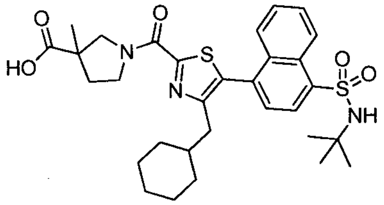
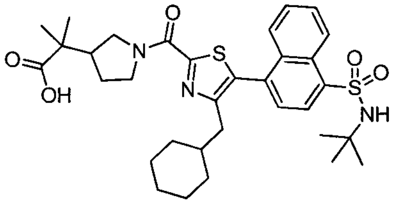
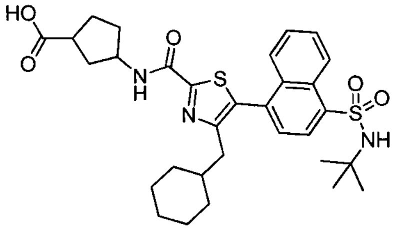
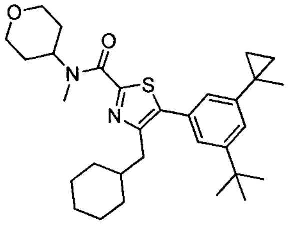
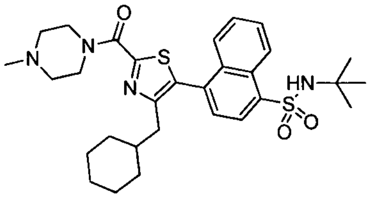
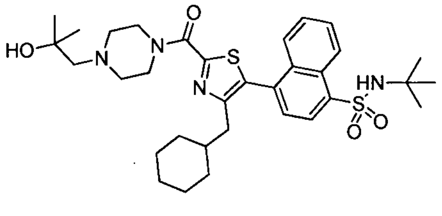
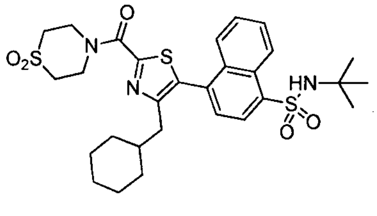
#	Structure	Analytical data
6/9		^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.58 (d, 1H, J = 7.6 Hz), 7.14 (s, 1H), 4.86-4.79 (m, 1H), 3.37 (d, 2H, J = 7.6 Hz), 3.22-3.17 (m, 1H), 2.85-2.79 (m, 2H), 2.55-2.47 (m, 2H), 1.92-1.68 (m, 6H), 1.37 (s, 18H), 1.30-1.06 (m, 5H). MS 513.3 $(M+1)^+$
6/10		^{1}H-NMR ($CDCl_3$, 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 $(M+1)^+$
6/11		^{1}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, 2.4 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 $[M+1]^+$
6/12		^{1}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 $[M+1]^+$
6/13		^{1}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 $(M+1)^+$
6/14		^{1}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 $(M+1)^+$
6/15		^{1}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 $(M+1)^+$

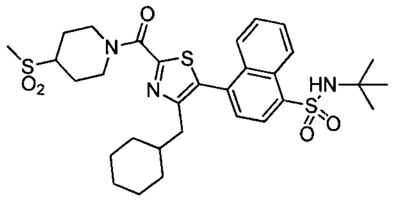
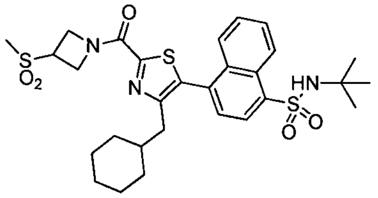
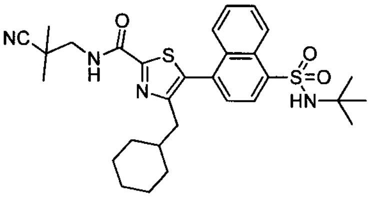
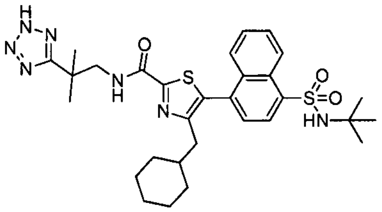
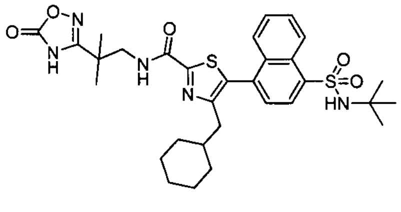
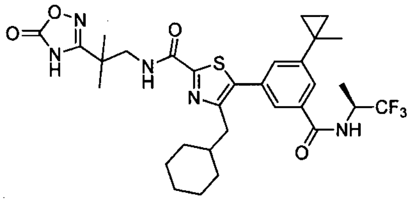
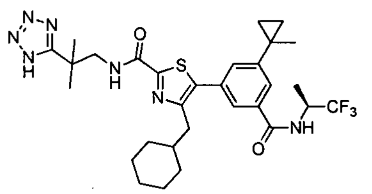
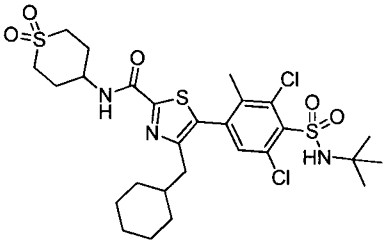
#	Structure	Analytical data
6/16		^{1}H-NMR (CDCl$_{3}$> 300 MHz) δ: 0.59-0.65 (m, 2H), 0.98-1.16 (m, 3H), 1.21 (s, 9H), 1.45-1.69 (m, 3H), 2.32-2.44 (m, 3H), 2.74-2.81 (m, 1H), 3.45-3.48 (m, 3H), 3.78-3.97 (m, 6H), 4.52 (br s, 2H), 4.79 (s, 1H), 7.50 (d, J = 7.2 Hz, 1H), 7.56-7.59 (m, 1H), 7.68-7.73 (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 (M+1)$^+$
6/17		^{1}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 (M+1)$^+$
6/18		^{1}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 (M+1)$^+$
6/19		^{1}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 = 53 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 (M+1)$^+$
6/20		^{1}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 [M+1]$^+$
6/21		^{1}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 [M+1]$^+$
6/22		^{1}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 (M+1)$^+$
6/23		^{1}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 (M+1)$^+$

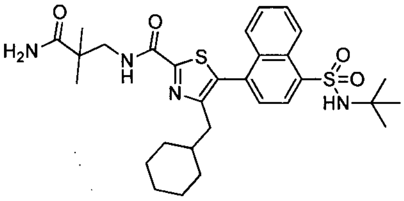
#	Structure	Analytical data
6/24		^{1}H-NMR (CDCl$_3$, 300 MHz) δ: 0.83-0.89 (m, 2H), 1.12-1.27 (m, 3H), 1.27 (s, 11H), 1.54-1.67 (m, 4H), 1.70 (s, 6H), 1.73-1.83 (m, 1H), 2.64 (d, J = 7.2 Hz, 2H), 3.42-3.58 (m, 4H), 4.38-4.39 (m, 1H), 5.39-5.47 (m, 1H), 6.23-6.24 (m, 1H), 7.27-7.39 (m, 2H), 7.60-7.64 (m, 1H), 8.22-8.25 (m, 1H). MS 566.2 (M+1)$^+$
6/25		^{1}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 (M+1)$^+$
6/26		^{1}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 (M+1)$^+$
6/27		^{1}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 (M+1)$^+$
6/28		^{1}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 [M+1]$^+$
6/29		^{1}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 [M+1]$^+$
6/30		^{1}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 (M+1)$^+$
6/31		^{1}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 (M+1)$^+$

#	Structure	Analytical data
6/32		^{1}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 $(M+1)^+$
6/33		^{1}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 $(M+1)^+$
6/34		^{1}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 $(M+1)^+$
6/35		^{1}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 $[M+1]^+$
6/36		^{1}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 $[M+1]^+$
6/37		^{1}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 $[M+1]^+$
6/38		^{1}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 $[M+1]^+$
6/39		^{1}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 $[M+1]^+$

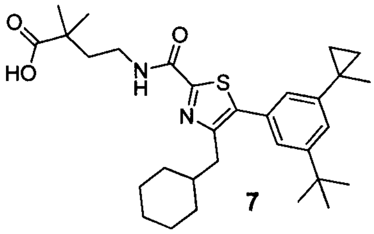
#	Structure	Analytical data
6/40		^{1}H-NMR (300 MHz, CDCl$_3$) δ: 0.73-0.77 (m, 2H), 1.10-1.18 (m, 3H), 1.28 (s, 9H), 1.52-1.61 (m, 6H), 2.40 (d, J = 6.9 Hz, 2H), 2.47 (s, 3H), 4.91 (d, J = 6.0 Hz, 2H), 5.12 (s, 1H), 7.37 (d, J = 8.1 Hz, 1H), 7.62 (s, 1H), 7.96 (t, 1H), 8.12 (d, J = 8.4 Hz, 1H). MS 647.1 [M+1]$^+$
6/41		^{1}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 (M+1)$^+$
6/42		^{1}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 (M+1)$^+$
6/43		^{1}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 (M+1)$^+$
6/44		^{1}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 (M+1)$^+$
6/45		^{1}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 (M+1)$^+$
6/46		^{1}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 [M+1]$^+$
6/47		^{1}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 [M+1]$^+$

#	Structure	Analytical data
6/48		^{1}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 $[M+1]^+$
6/49		^{1}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 $[M+1]^+$
6/50		^{1}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 $[M+1]^+$
6/51		^{1}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 $(M+1)^+$
6/52		^{1}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 (M+1)
6/53		^{1}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 $(M+1)^+$
6/54		^{1}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 $(M+1)^+$
6/55		^{1}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 $(M+1)^+$

#	Structure	Analytical data
6/56		^{1}H-NMR (400 MHz, CD$_3$OD) 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 (M+1)$^+$
6/57		^{1}H-NMR (400 MHz, CD$_3$OD) 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 (M+1)$^+$
6/58		^{1}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, 2 H). MS 567.2 (M+1)$^+$
6/59		^{1}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 (M+1)$^+$
6/60		^{1}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, 12 H), 0.60-0.51 (m, 2H). MS 626.2 (M+1)$^+$
6/61		^{1}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 (M+1)$^+$
6/62		^{1}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 (M+1)$^+$
6/63		^{1}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 (M+1)$^+$

#	Structure	Analytical data
6/64		^{1}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 (M+1)$^+$.

Example 7



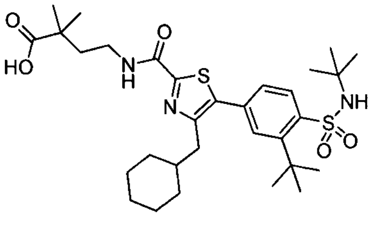
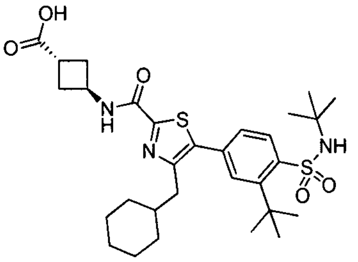
7

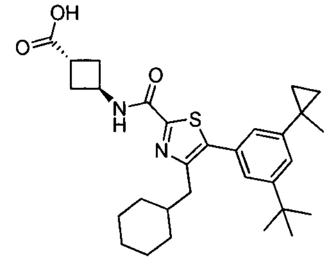
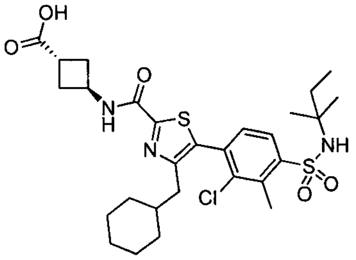
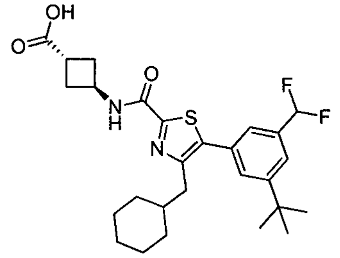
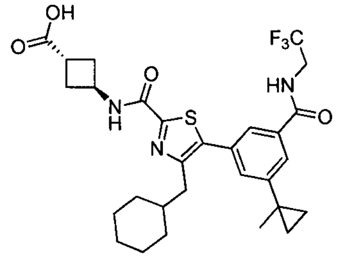
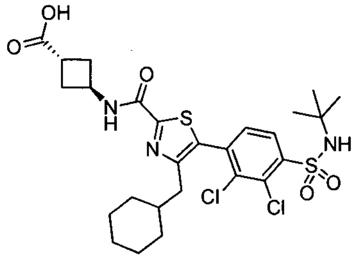
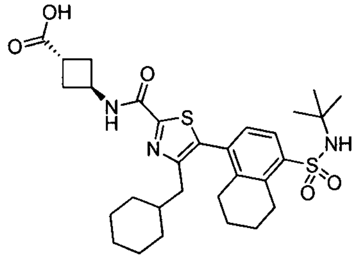
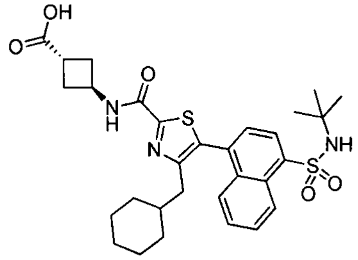
4-(5-(3-(tert-Butyl)-5-(1-methylcyclopropyl)phenyl)-4-(cyclohexylmethyl)thiazole-2-carboxamido)-2,2-dimethylbutanoic acid **(7)**

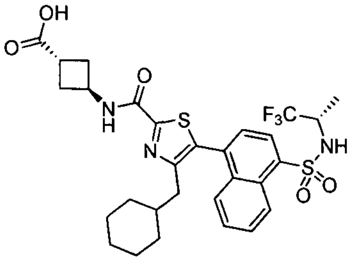
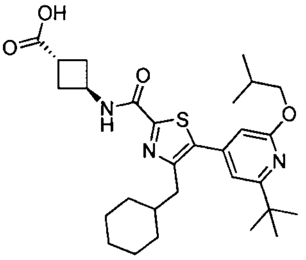
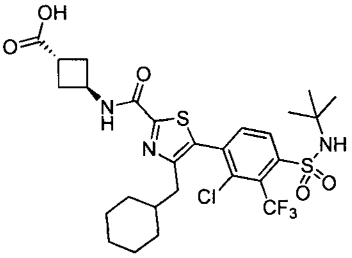
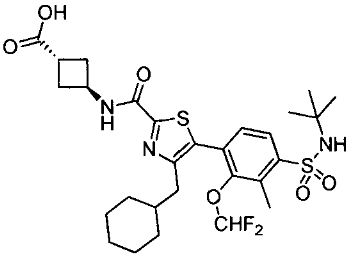
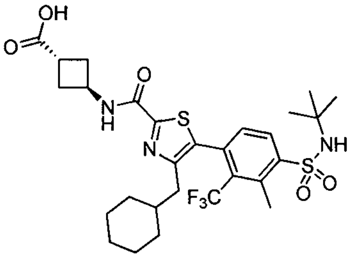
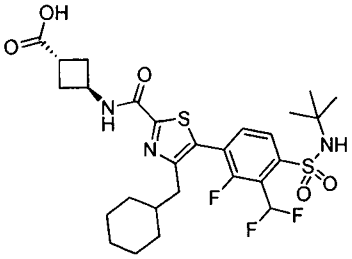
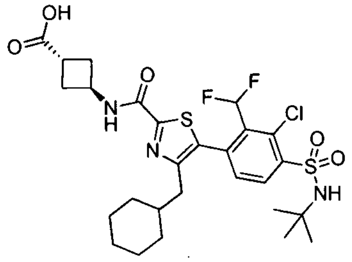
To a solution of compound **6** (300 mg, 0.55 mmol) in a solution of MeOH (10 mL) and H_20 (2 mL) was added KOH (125 mg, 2.23 mmol) and the solution was stirred for 4 h at 50°C, concentrated under reduced pressure, diluted with H_20 and adjusted to pH = 5 with 1N HCl. The solution was extracted with DCM and the organic layer was washed with brine, dried over Na_2S0_4, filtered, concentrated and purified by prep-HPLC to give compound **7** (40 mg, 14%) as a white solid. ^{1}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 (M+1)$^+$.

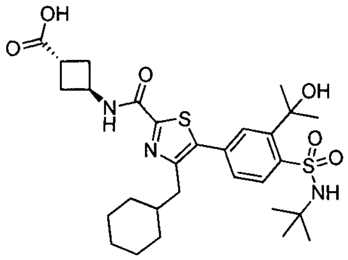
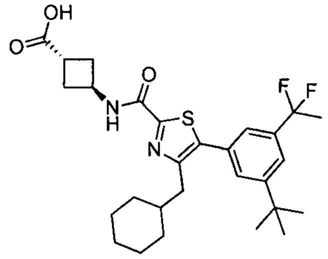
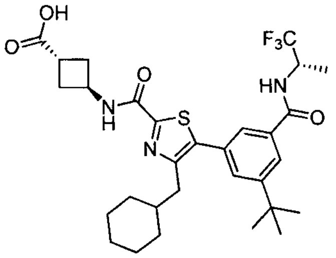
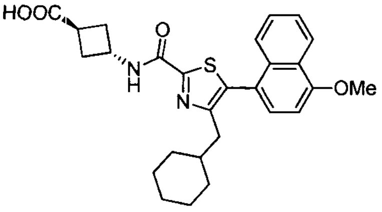
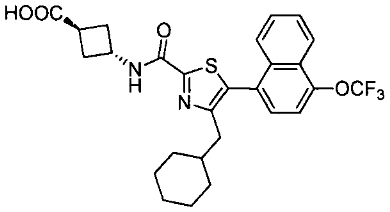
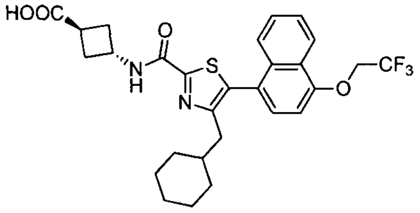
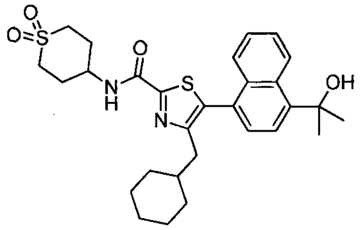
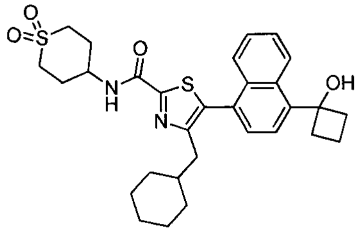
Example 7/1 to 7/27

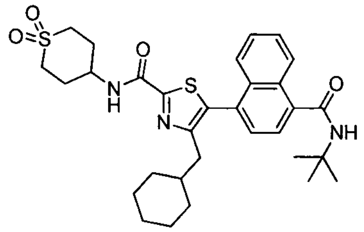
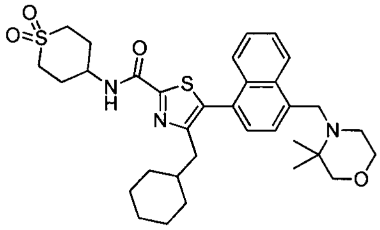
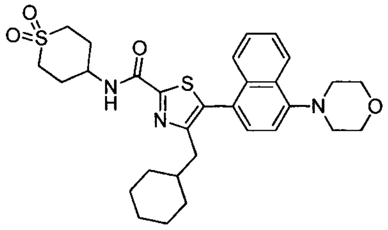
The following Examples were prepared similar as in Example **7**:

#	Structure	Analytical data
7/1		^{1}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 (M+1)$^+$
7/2		^{1}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 (M+1)$^+$

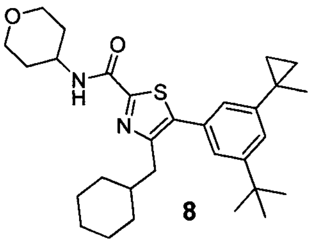
#	Structure	Analytical data
7/3		^{1}H-NMR (300 MHz, CDCl$_3$) δ: 7.55 (d, J = 6.9 Hz, 1H), 7.31 (s, 1H), 7.23 (s, 1H), 7.11 (s, 1H), 4.80-4.86 (m, 1H), 3.18-3.21 (br s, 1H), 2.80-2.83 (m, 2H), 2.65 (d, J = 6.9 Hz, 2H), 2.51-2.53 (m, 2H), 1.79-1.84 (m, 1H), 1.67-1.70 (m, 5H), 1.44 (s, 3H), 1.35 (s, 9H), 1.07-1.29 (m, 3H), 0.87-0.93 (m, 4H), 0.75-0.77 (m, 2H). MS 509.3 (M+1)$^+$
7/4		^{1}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 [M+1]$^+$
7/5		^{1}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 (M+1)$^+$
7/6		^{1}H-NMR (400 MHz, CD$_3$OD) 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 [M+1]$^+$
7/7		^{1}H-NMR (300 MHz, CD$_3$OD) 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 [M+1]$^+$
7/8		^{1}H-NMR (300 MHz, CD$_3$OD) 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 [M+1]$^+$
7/9		^{1}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 [M+1]$^+$

#	Structure	Analytical data
7/10		^{1}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 $[M+1]^+$
7/11		^{1}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 $(M+1)^+$
7/12		^{1}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 $(M+1)^+$
7/13		^{1}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 = 74 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 $(M+1)^+$
7/14		^{1}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 $(M+1)^+$
7/15		^{1}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 $(M+1)^+$
7/16		^{1}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 = 53 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 $(M+1)^+$

#	Structure	Analytical data
7/17		^{1}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 (M+1)$^+$
7/18		^{1}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 [M+1]$^+$
7/19		^{1}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 [M+1]$^+$
7/20		^{1}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 [M+1]$^+$
7/21		^{1}H-NMR (400 MHz, CD$_3$OD) 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 [M+1]$^+$
7/22		^{1}H-NMR (400 MHz, CD$_3$OD) 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 [M+1]$^+$
7/23		^{1}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 [M+1]$^+$
7/24		^{1}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



8

Step 1: 5-Bromo-4-(cvclohexylmethyl)-/V-(tetralivdro-2H-pyran-4-yl)thiazole-2-carboxamide (8a)

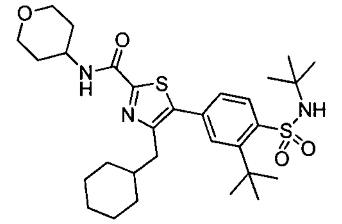
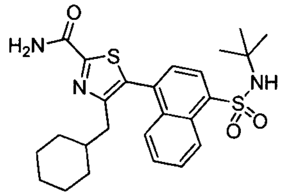
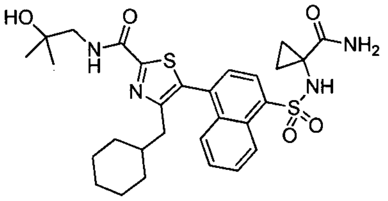
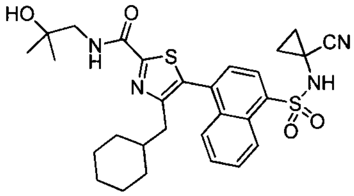
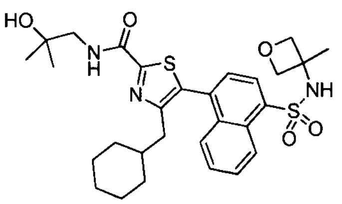
To a solution of **6c** (0.20 g, 0.60 mmol) in toluene (0.6 mL) was added tetrahydro-2H-pyran-4-amine (182 mg, 1.8 mmol) and the resulting solution was heated at 130°C for 15 h. The reaction mixture was then cooled to rt and purified by CC (PE/EA = 10/1 to 5/1) to afford compound **8a** (0.21 g, 91%)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

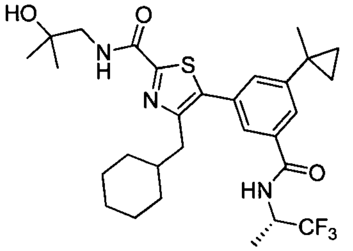
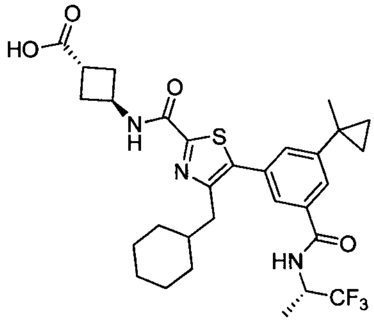
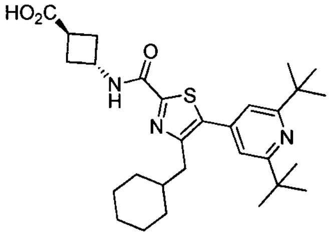
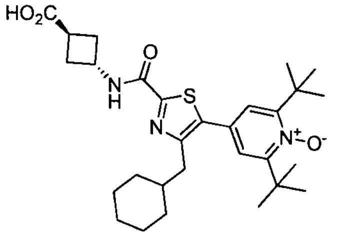
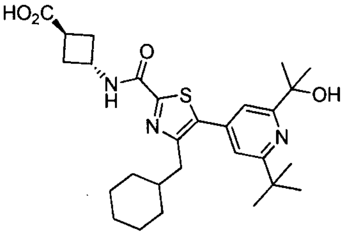
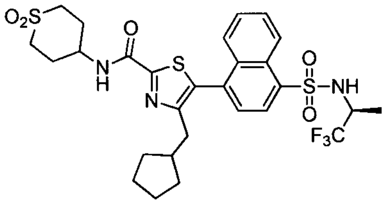
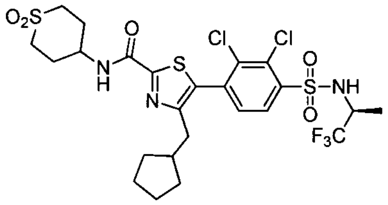
Step 2: 5-(3-(te rt-Butvl)-5-(1-methylcvclopropyl)phenyl)-4-(cvclohexylmethyl)-/V-(tetrahvdro-2H-pyran-4-yl)thiazole-2-carboxamide (8)

Compound **8a** (210 mg, 540 µηιοl), 2-(3-(te^butyl)-5-(1-methylcyclopropyl)phenyl)-4,4,5,5-tetramethyl-1 ,3,2-dioxaborolane (180 mg, 560 µηιοl), Na_2C0_3 (180 mg, 1.69 mmol), Pd(dppf)Cl_2-CH_2Cl_2 (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 mL) and water (10 mL) and the layers were separated. The organic phase was washed with water and brine, dried over Na_2S0_4, concentrated and purified by CC (PE/EA = 10/1 to 5/1) to give compound **8** (189 mg, 75%). ^{1}H-NMR (400 MHz, $CDCl_3$) 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 $(M+1)^+$.

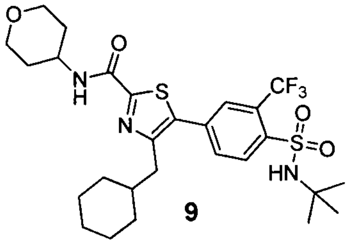
Example 8/1 to 8/12

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}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 [M+1]$^+$
8/7		^{1}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 [M+1]$^+$
8/8		^{1}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 (M+1)$^+$
8/9		^{1}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 (M+1)$^+$
8/10		^{1}H-NMR (400 MHz, CD$_3$OD) 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 (M+1)$^+$
8/11		MS 644.1.3 (M+1)$^+$
8/12		MS 662.0 (M+1)$^+$

Example 9



9

Step 1: 5-Bromo-4-(cvclohexylmethyl)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 Na_2S0_4. After filtration, the filtrate was evaporated to give compound **9a** (60 mg, 87%) as a white solid.

Step 2: 5-Bromo-4-(cvclohexylmethyl)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-(cvclohexylmethyl)-/V-(tetrahvdro-2/-/-pyran-4-yl)thiazole-2-carboxamide **(9c)**

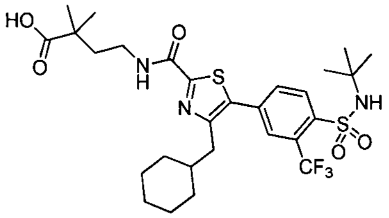
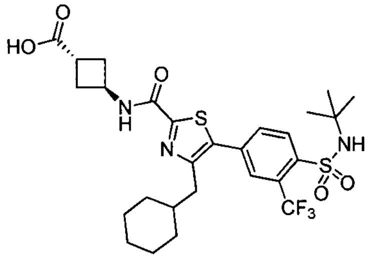
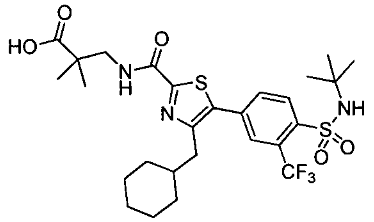
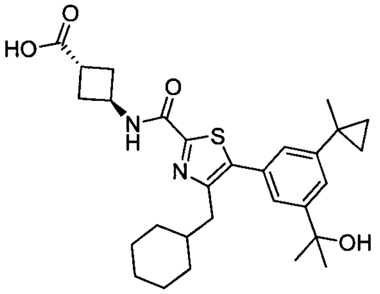
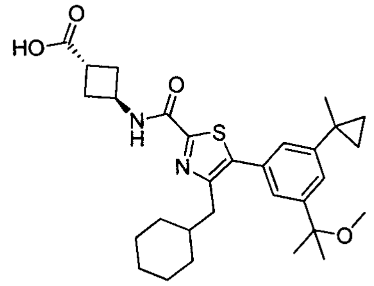
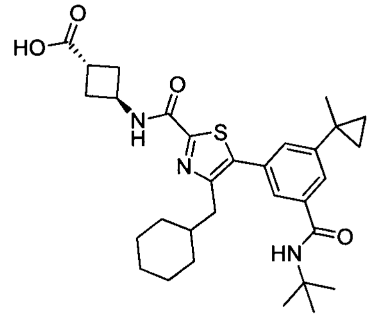
To a solution of compound **9b** (50 mg, 0.16 mmol) in DCM (2.5 mL) was added TEA (33 mg, 0.32 mmol) and tetrahydro-2/-/-pyran-4-amine (20 mg, 0.19 mmol). The mixture was stirred overnight, quenched with water and extracted with EA. The organic layer was separated and washed with brine, dried over Na_2S0_4, filtered and evaporated to give compound **9c** (51 mg, 85%) as a yellow solid.

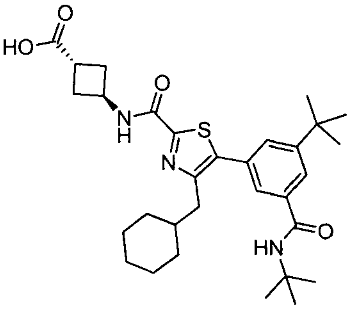
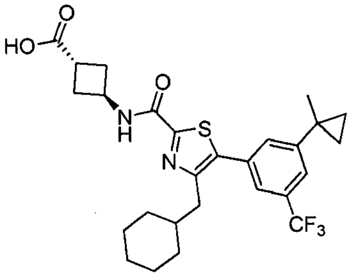
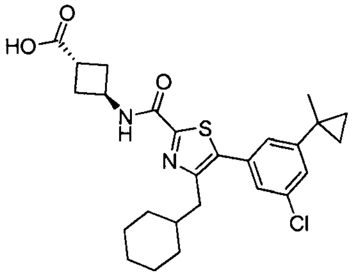
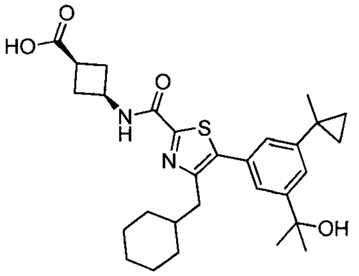
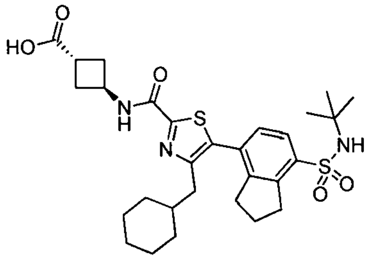
Step 4: 5-(4-(A/-(te/t-Butyl)sulfamoyl)-3-(trifluoromethyl)phenyl)-4-(cvclohexylmethyl)-/V-(tetrahvdro-2H-pyran-4-yl)thiazole-2-carboxamide **(9)**

A suspension of compound **9c** (46 mg, 0.12 mmol), Na_2C0_3 (32 mg, 0.32 mmol), A/-(tert-butyl)-4-(4,4,5,5-tetramethyl-1 ,3,2-dioxaborolan-2-yl)-2-(trifluoromethyl)benzenesulfonamide (59 mg, 0.14 mmol), $Pd(dppf)Cl_2$ (30 mg) in DMF/H_20 (10:1, 10 mL) was heated overnight under N_2 at 90°C, cooled, concentrated and extracted with EA. The organic layer was washed with brine, dried over $MgS0_4$, filtered, evaporated and purified by prep-HPLC to give compound **9** (41 mg, 59%) as a white solid. ^{1}H-NMR (400 MHz, DMSO-d_6) 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 $(M+1)^+$.

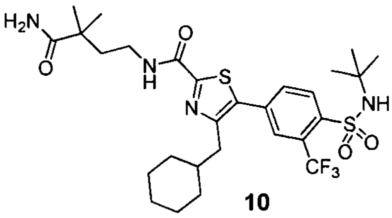
Example 9/1 to 9/11

The following Examples were prepared similar as in Example **9**:

#	Structure	Analytical data
9/1		^{1}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 $(M+1)^+$
9/2		^{1}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 $(M+1)^+$
9/3		^{1}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 $(M+1)^+$
9/4		^{1}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 $(M+1)^+$
9/5		^{1}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 $(M+1)^+$.
9/6		^{1}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 $(M+1)^+$

#	Structure	Analytical data
9/7		^{1}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 (M+1)$^+$
9/8		^{1}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 (M+1)$^+$.
9/9		^{1}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 (M+1)$^+$
9/10		^{1}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 (M+1)$^+$
9/11		^{1}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 [M+1]$^+$

Example 10



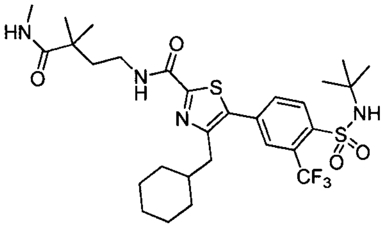
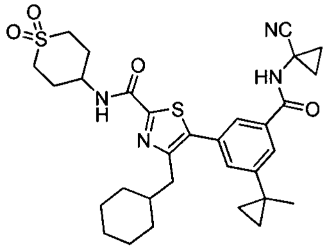
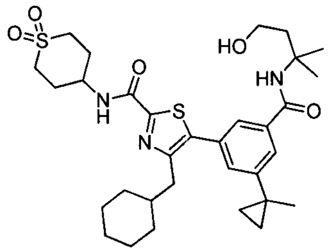
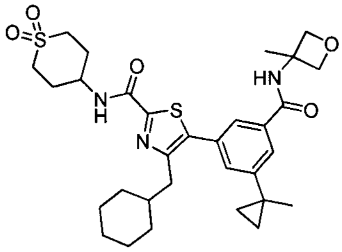
10

A/-(4-Amino-3,3-dimethyl-4-oxobutyl)-5-(4-(AH^ert-butyl)sulfamoyl)-3-(trifluoromethyl)phenyl)-4-(cvclohexylmethyl)thiazole-2-carboxamide (10)

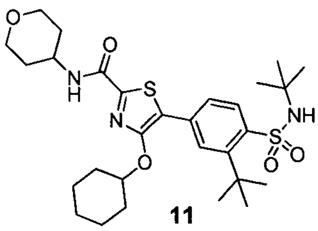
To a solution of compound **9/1** (90 mg, 0.15 mmol) in dry DMF (2 mL) was added HATU (86 mg, 0.23 mmol) and DIPEA (48 mg, 0.38 mmol). The mixture was stirred for 60 min and then NH_4Cl (10 mg, 0.18 mmol) was added. The reaction mixture was stirred overnight, quenched with water and extracted with EA. 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}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 $(M+1)^+$.

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}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 $(M+1)^+$
10/2		^{1}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 $(M+1)^+$
10/3		^{1}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 $(M+1)^+$
10/4		^{1}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 $(M+1)^+$

Example 11



11

Step 1: Cyclohexyl 2-bromoacetate **(11a)**

If one were to treat cyclohexyl acetate with Br$_2$ in MeOH, compound **11a** can be obtained.

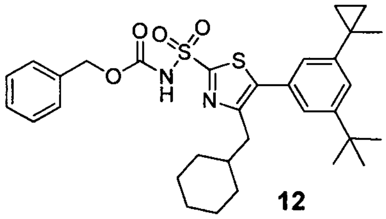
Step 2: Ethyl 4-(cvclohexyloxy)thiazole-2-carboxylate **(11b)**

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.

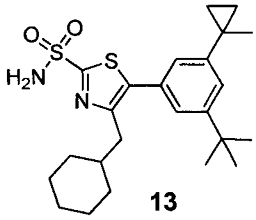
Step 3: 5-(3-(ferf-Butyl)-4-(A/-(tert-butyl)sulfamoyl)phenyl)-4-(cvclohexyloxy)-A/-(tetrahvdro-2/-/-pyran-4-yl)thiazole-2-carboxamide **(11)**

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

Example 12



12



13

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

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. NaHC0$_3$. The organic layer was washed with brine, dried over Na$_2$S0$_4$, filtered, concentrated and purified by CC (PE/EA = 3/1) to give compound **12a** (1.1 g, 44%) as a yellow solid.

Step 2: 5-Bromo-4-(cvclohexylmethyl)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. NaHC0$_3$ and extracted with EA. The organic layer was washed water and brine consecutively, dried over Na$_2$S0$_4$, filtered and concentrated to give crude compound **12b** (1.14 g, 81%) as a pale yellow solid.

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

To a solution of compound **12b** (1.14 g, 4.1 mmol) in MeCN (15 mL) was added CuBr$_2$ (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 Na_2SO_4, 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-(cvclohexylmethyl)thiazole-2-sulfonamide **(12d)**

The solution of compound **12c** (3.1 g, 9.14 mmol), BnSH (1.7 g, 13.7 mmol) and K_2CO_3 (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 Na_2SO_4, filtered and concentrated to give a residue. To this residue was added CCl_4 (15 mL) and water (1.5 mL) and the solution was stirred for 1 min. Cl_2 was bubbled through the system for 30 min. The organic layer was separated, washed with water, dried over Na_2SO_4, filtered and concentrated to give a residue. This residue was dissolved in THF (10 mL) and then 20% aq. NH_4OH (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 Na_2SO_4, filtered, concentrated and purified by CC (PE/EA = 2/1) to give compound **12d** (1.3 g, 42%) as a brown solid.

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

To a solution of compound **12d** (550 mg, 2.0 mmol) and NEt_3 (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 twice. The combined organic layers were washed with water and brine consecutively, dried over Na_2SO_4, 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-(fe/t-butyl)-5-(1-methylcvclopropyl)phenyl)-4-(cvclohexylmethyl)thiazol-2-vDsulfonylcarbamate **(12)**

A solution of compound **12e** (400 mg, 0.98 mmol), compound **P2** (458 mg, 1.46 mmol), K_2CO_3 (552 mg, 4.0 mmol) and $Pd(PPh_3)Cl_2$ (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 Na_2SO_4, filtered, concentrated and purified by CC (PE/EA = 1/1) to give compound **12** (200 mg, 35%) as a white solid. ^{1}H-NMR ($CDCl_3$, 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 $(M+1)^+$.

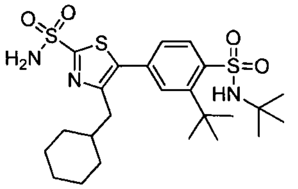
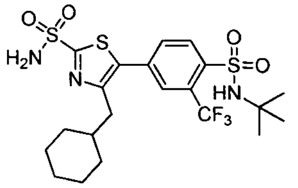
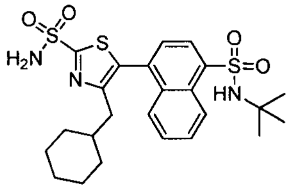
Step 6: 5-(3-(tert-Butyl)-5-(1-methylcvclopropyl)phenyl)-4-(cvclohexylmethyl)thiazole-2-sulfonamide **(13)**

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 H_2 atmosphere, concentrated and purified by prep-HPLC to give compound **13** (25 mg, 25%) as a white solid. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.33

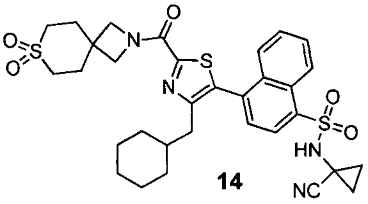
(t, 1H, J = 1.7 Hz), 7.21 (t, 1H, J = 1.7 Hz), 7.09 (t, 1H, J = 1.7 Hz), 5.56 (s, 2H), 2.66 (d, 2H, J = 6.9 Hz), 1.76-1.81 (m, 1H), 1.63-1 .68 (m, 5H), 1.43 (s, 3H), 1.34 (s, 9H), 1.13-1.22 (m, 3H), 0.76-0.96 (m, 6H). MS 447.1 $(M+1)^+$.

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



14

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

To a suspension of naphthalene-1 -thiol (40 g, 0.25 mol) and K_2C0_3 (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.

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

To a solution of compound **14a** (59 g, 236 mmol) in CCl_4 (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 Na_2S0_4, filtered, concentrated and purified by CC (PE) to give crude compound **14b** (18 g, 23%) as a pale red solid.

Step 3: Ethyl 5-(4-(benzylthio)naphthalen-1-yl)-4-(cvclohexylmethyl)thiazole-2-carboxylate i!4c)

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), PPh_3 (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 Na_2S0_4, 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-(cvclohexylmethyl)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 Cl_2 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 Et_20 twice. The combined organic layers were washed with water and brine, dried over Na_2S0_4, 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-(A/-(1-cvanocvclopropyl)sulfamoyl)naphthalen-1-yl)-4-(cvclohexylmethyl)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 Na_2S0_4, filtered, concentrated and purified by CC (PE/EA = 6/1) to give compound **14e** (101 mg, 61%) as a white solid.

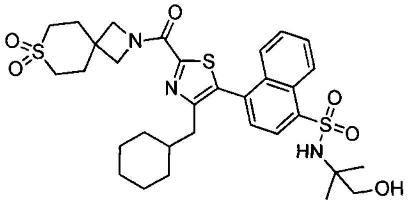
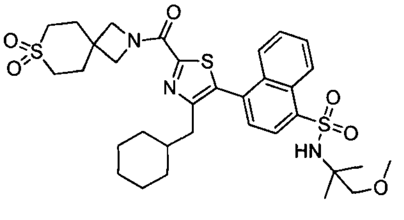
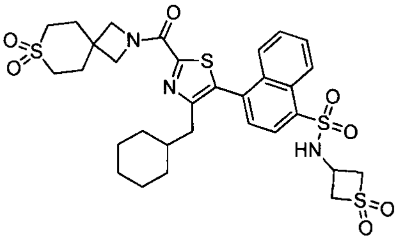
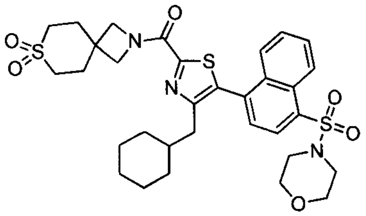
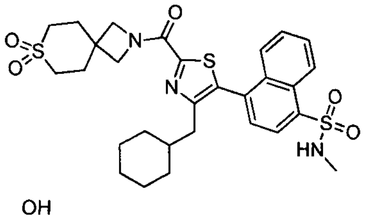
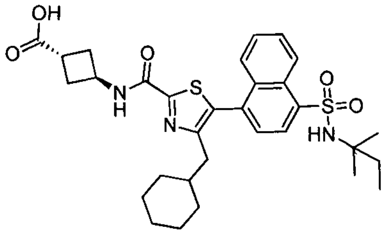
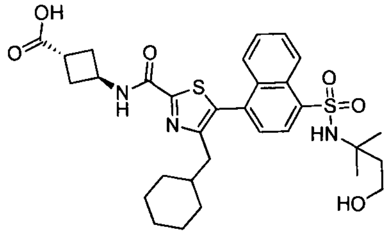
Step 6: *N*-(1-Cvanocvclopropyl)-4-(4-(cvclohexylmethyl)-2-(7,7-dioxido-7-thia-2-azaspirof3.51nonane-2-carbonyl)thiazol-5-yl)naphthalene-1 -sulfonamide (14)

Compound **14e** was saponified and then coupled with the appropriate amine 7-thia-2-aza-spiro[3.5] nonane 7,7-dioxide to give compound **14** (27%) as a white solid. ^{1}H-NMR ($CDCI_3$, 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 $(M+1)^+$.

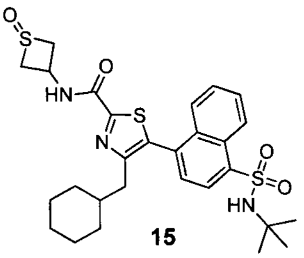
Example 14/1 to 14/7

The following Examples were prepared similar as in Example **14:**

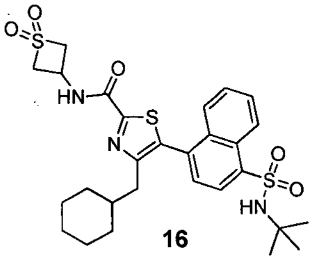
#	Structure	Analytical data

#	Structure	Analytical data
14/1		^{1}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 (M+1)$^+$
14/2		^{1}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 (M+1)$^+$
14/3		^{1}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 (M+1)$^+$
14/4		^{1}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 (M+1)$^+$
14/5		^{1}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 (M+1)$^+$
14/6		^{1}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 (M+1)$^+$
14/7		^{1}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 (M+1)$^+$

Example 15 and Example 16



15

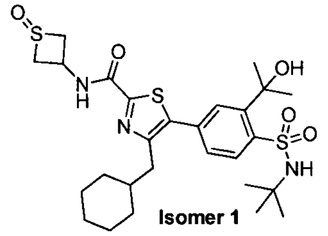
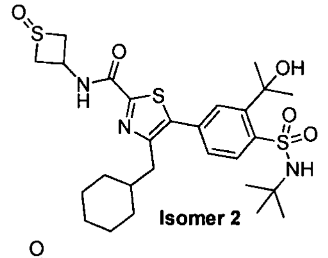
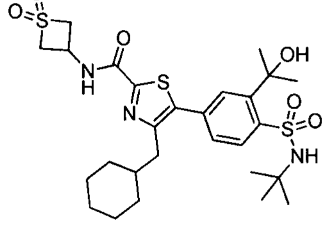


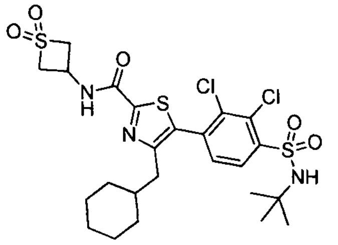
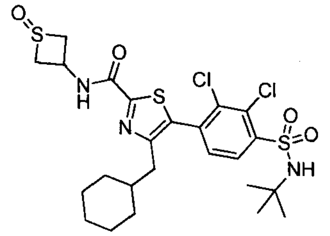
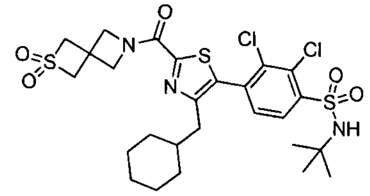
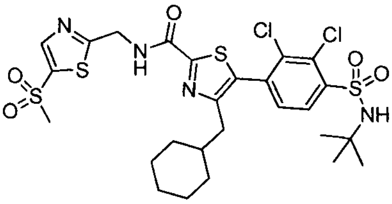
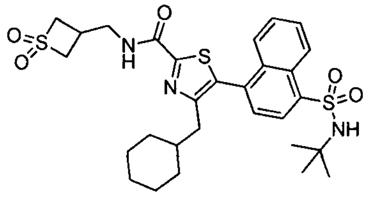
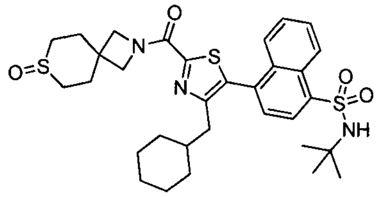
16

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. Na_2S0_3 and extracted with EA (3x). The combined organic layers were washed with water and brine, dried over Na_2S0_4, 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:** ^{1}H-NMR ($CDCl_3$, 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:** ^{1}H-NMR ($CDCl_3$, 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]$^+$.

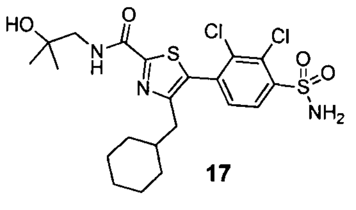
Example 15/1 to 15/9

The following Examples were prepared similar as in Example **15:**

#	Structure	Analytical data
15/1		^{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		^{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), 4.1 9-4.25 (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}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 (M+1)$^+$
15/5		^{1}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 (M+1)$^+$
15/6		^{1}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 (M+1)$^+$
15/7		^{1}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 [M+1]$^+$
15/8		^{1}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 [M+1]$^+$
15/9		^{1}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 (M+1)$^+$

Example 17



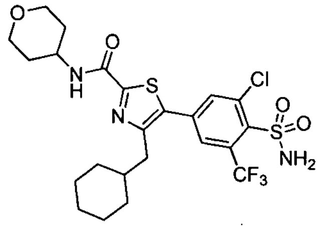
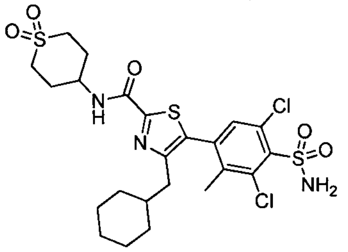
17

4-(Cvclohexylmethyl)-5-(2,3-dichloro-4-sulfamoylphenyl)-/V-(2-hvdroxy-2-methylpropyl)thiazole-2-carboxamide (17)

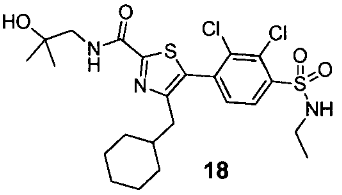
A solution of compound **6/29** (260 mg, 0.45 mmol) in TFA (2 mL) was stirred for 2 h at 55°C, concentrated, diluted with EA, washed with brine, dried over Na_2S0_4, filtered, concentrated and purified by prep-HPLC to give compound **17** (90 mg, 39%) as a white solid. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 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), 8.1 1 (d, J = 8.1 Hz, 1H). MS 520.1 $(M+1)^+$.

Example 17/1 to 17/2

The following Examples were prepared similar as in Example **17:**

#	Structure	Analytical data
17/1		^{1}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 $(M+1)^+$
17/2		^{1}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 $(M+1)^+$

Example 18

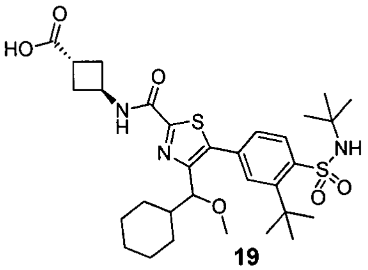


18

4-(Cvclohexylmethyl)-5-(2,3-dichloro-4-(A/-ethylsulfamoyl)phenyl)-A/-(2-hvdroxy-2-methylpropyl)thiazole-2-carboxamide (18)

The solution of compound **17** (40 mg, 0.07 mmol) and aq. CH_3CHO (0.5 mL) in MeOH (5 mL) was stirred for 10 min at rt. Then $NaBH_3CN$ (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 Na_2SO_4, filtered, concentrated and purified by prep-HPLC to give compound **18** (26 mg, 62%) as a white solid. ^{1}H-NMR (300 MHz, CD_3OD) 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), 8.1 1 (d, J = 7.8 Hz, 1H). MS 548.2 $(M+1)^+$.

Example 19



19

Step 1: 2-Cvclohexyl-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 $CHCI_3$ (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_20. The aq. layer was adjusted pH to 1 with cone. HCI and extracted with Et_20 twice. The combined organic layers were washed with water and brine, dried over Na_2S0_4, filtered and concentrated to give crude compound **19a** (12.9 g, 42%) as a brown oil.

Step 2: 2-Cvclohexyl-A/,2-dimethoxy-A/-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_2S0_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-Cvclohexyl-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_20, 30 mL, 90 mol) under ice cooling and the solution was stirred at rt for 3 h, quenched carefully with saturated aq. NH_4CI. The organic phase was separated and concentrated, diluted with EA, washed with water and brine, dried over Na_2S0_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-cvclohexyl-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_20 was added and the solution was extracted with in Et_20 (3x). The combined organic layers were washed with 10% aq. K_2C0_3 (3x), dried over Na_2S0_4, filtered and concentrated to give compound **19d** (8.5 g, 95%) as a yellowish liquid.

Step 5: Ethyl 4-(cvclohexyl(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 NH_4OH. The aq. layer was extracted with EA (3x). The combined organic layers were dried over Na_2S0_4, 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-(ferf-butyl)-4-(/V **-(ŧ t** -butyl)sulfamoyl)phenyl)-4-(cvclohexyl(methoxy)methvDthiazole-2-carboxylate (**19f)**

A solution of compound **19e** (2.2 g, 7.78 mmol), 4-bromo-A/,2-di-tert-butylbenzenesulfonamide (3.24 g, 9.32 mmol), $Pd(OAc)_2$ (200 mg) and PPh_3 (2.24 g, 8.54 mmol) in DMF (80 mL) was bubbled with N_2 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 Na_2S0_4, filtered, concentrated and purified by CC (PE/EA = 15/1) and then prep-HPLC to give compound **19f** (280 mg, 6.5%) as a pale yellow solid.

Step 7: Potassium 5-(3-(fert-butyl)-4-(A **/-(ŧ ri**-butyl)sulfamoyl)phenyl)-4-(cvclohexyl(methoxy)methyl)thiazole-2-carboxylate **(19q)**

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 white solid.

Step 8: frans-Methyl 3-(5-(3-(fe/t-butyl)-4-(A/-(ferf-butvnsulfamoyl)phenyl)-4-(cvclohexyl(methoxy)methyl)thiazole-2-carboxamido)cvclobutanecarboxylate **(19h)**

The solution of compound **19g** (250 mg, 0.364 mmol), *trans* methyl 3-aminocyclo butanecarboxylate hydrochloride (93 mg, 0.56 mmol), DIEA (867 mg, 6.72 mmol) and HATU (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 Na_2S0_4, filtered, concentrated and purified by CC (PE/EA = 6/1) to give compound **19h** (91 mg, 39%) as a yellow solid.

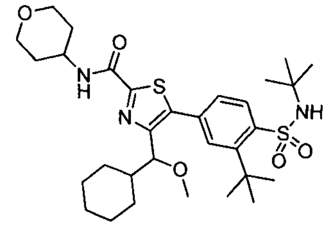
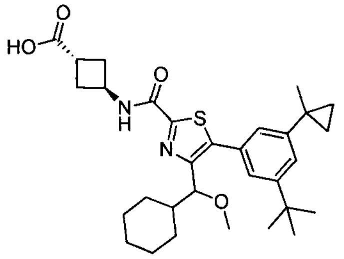
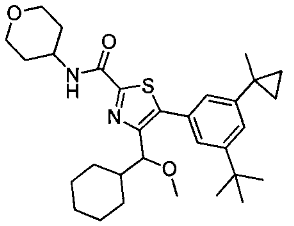
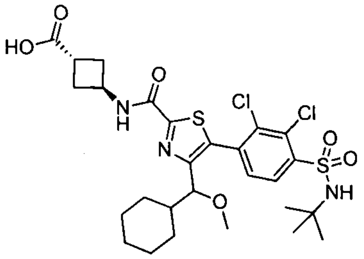
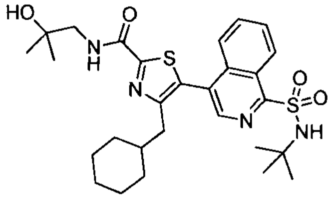
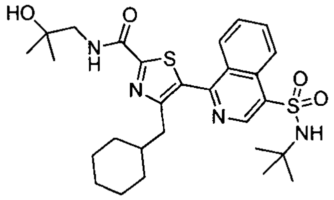
Step 9: frans-3-(5-(3-(fert-Butyl)-4-(/V-(ferf-butvnsulfamovnphenyl)-4-(cvclohexyl(methoxy)methyl)thiazole-2-carboxamido)cvclobutanecarboxylic acid (**19)**

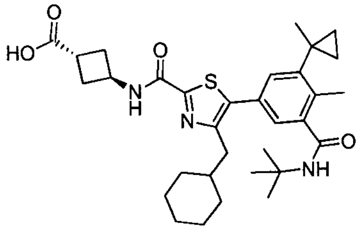
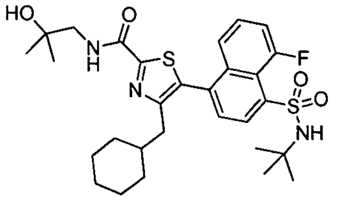
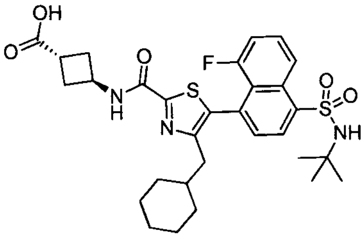
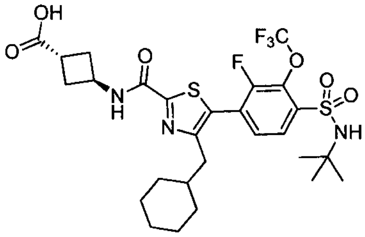
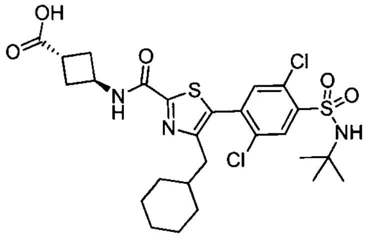
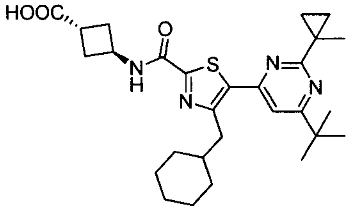
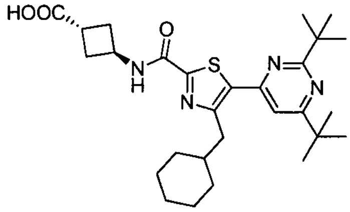
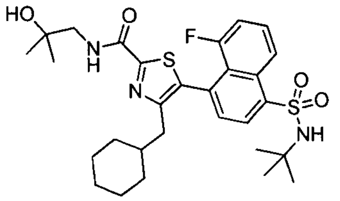
To a solution of compound **19h** (91 mg, 0.14 mmol) in a mixture of THF/MeOH/water (2 mL/2 mlJ 1 mL) was added $LiOH{\cdot}H_20$ (11 mg, 0.26 mmol) and the solution was stirred at rt for 2 h, diluted with water and extracted with EA. The aq. layer was adjusted with 1N HCl to pH = 2 and then extracted with DCM. The combined organic phase was washed with brine, dried over Na_2S0_4, filtered, concentrated and purified by prep-HPLC to give compound **19** (45 mg, 52%) as a white solid. ^{1}H-NMR (400 MHz, $CDCl_3$) 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

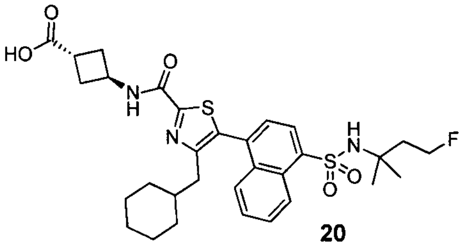
The following Examples were prepared similar as in Example **19:**

#	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}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 $(M+1)^+$
19/8		^{1}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 $[M+1]^+$
19/9		^{1}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 $[M+1]^+$
19/10		^{1}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 $[M-1]^-$
19/11		^{1}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 $[M-1]^-$
19/12		^{1}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 $(M+1)^+$
19/13		^{1}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 $(M+1)^+$
19/14		^{1}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 $[M+1]^+$

Example 20

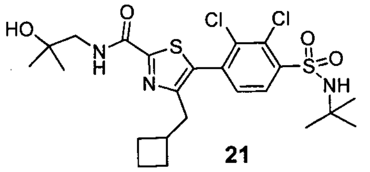
frans-3-(4-(Cvclohexylmethyl)-5-(4-(M-(4-fluoro-2-m ethylbutan-2-yl)sulfamoyl)naphthalen-1-yl)thiazole-2-carboxamido)cvclobutanecarboxylic acid **(20)**



20

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 CH_2Cl_2. The organic layer was dried with $MgS0_4$, filtered, concentrated and purified by CC (DCIWMeOH = 10/1) to give compound **20** (170 mg, 84%) as a white solid. ^{1}H-NMR ($CDCl_3$, 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



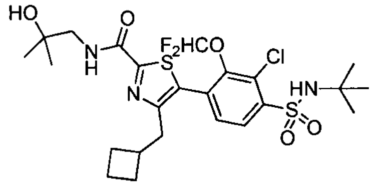
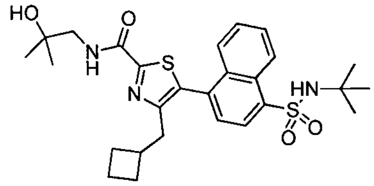
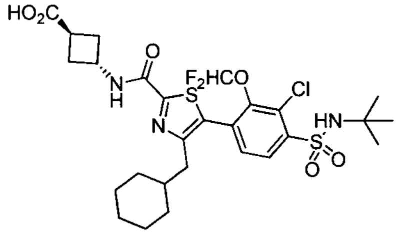
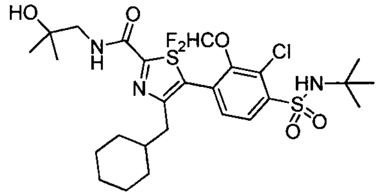
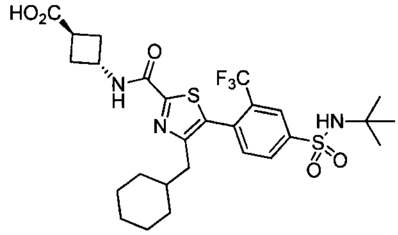
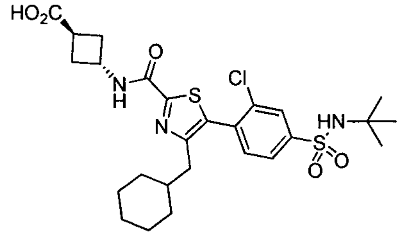
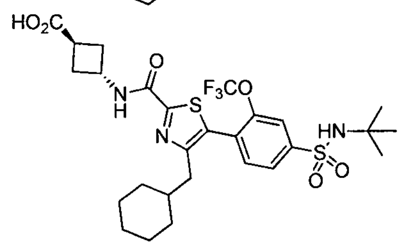
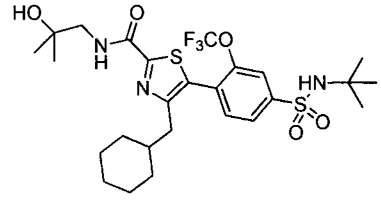
21

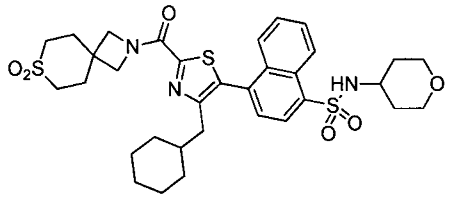
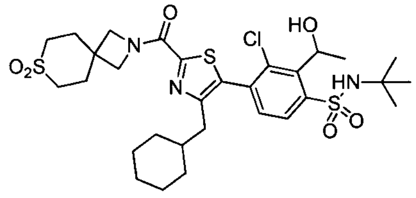
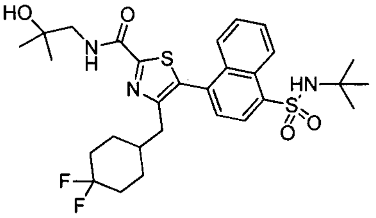
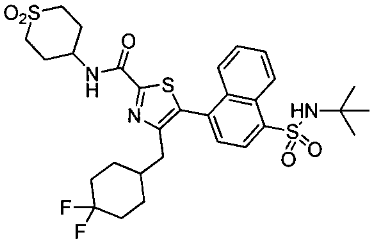
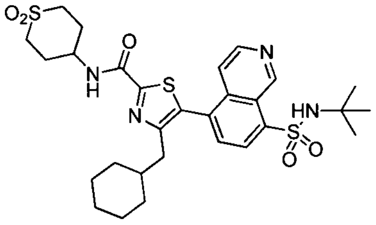
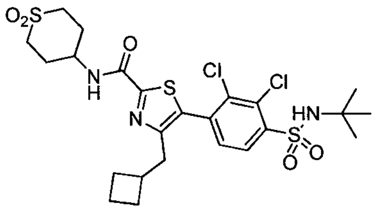
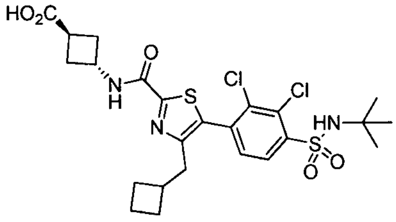
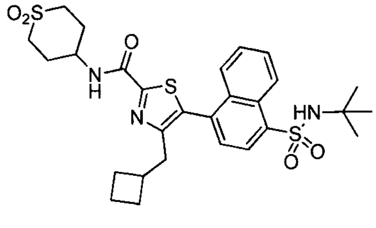
5-(4-(A/-(fe/t-butyl)sulfamoyl)-2,3-dichlorophenyl)-4-(cvclobutylmethyl)-A/-(2-hvdroxy-2-methylpropyl)thiazole-2-carboxamide **(21)**

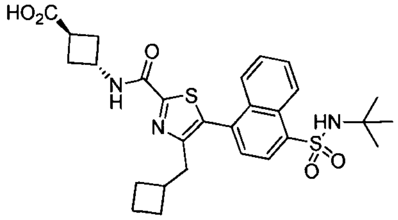
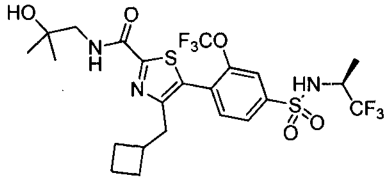
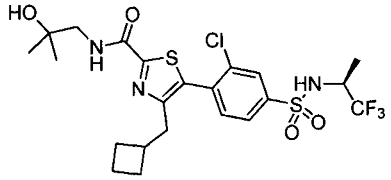
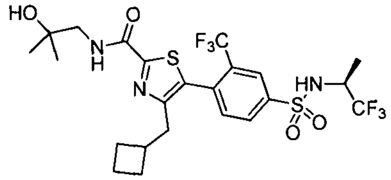
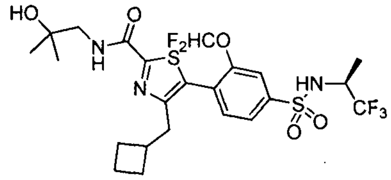
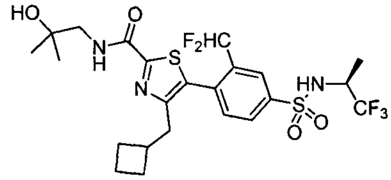
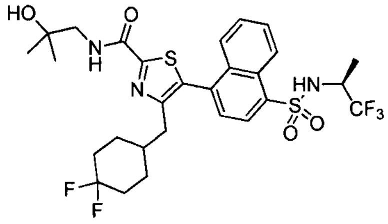
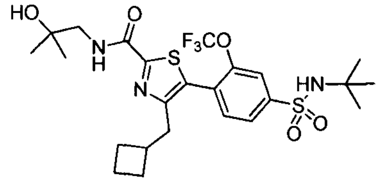
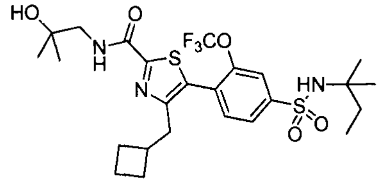
A solution of 4-(cyclobutylmethyl)-/V-(2-hydroxy-2-methylpropyl)thiazole-2-carboxamide (27 mg, 0.1 mmol, prepared using similar procedures as described above), 4-bromo-/V-(terf-butyl)-2,3-dichlorobenzenesulfonamide (36 mg, 0.1 mmol), K_2C0_3 (21 mg, 0.15 mmol), $Pd(OAc)_2$ (1 mg, 2 µιτιοl), $PCy_3 \cdot HBF_4$ (2 mg, 4 µιηοl) 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 Na_2S0_4, filtered, concentrated and purified by CC (PE/EA = 10/1 to 5/1) to give compound **21** as a white solid (33 mg, 64%). ^{1}H-NMR (400 MHz, $CDCl_3$) 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

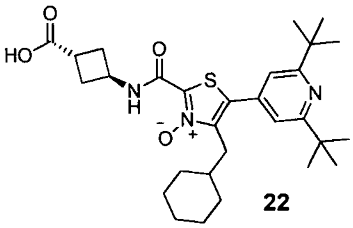
The following examples were prepared according to Example **21**.

#	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 = 8Hz, 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		^{11}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)$^+$

#	Structure	Analytical data
21/17		^{1}H-NMR (400 MHz, DMSO-d_6) δ: 9.16 (d, 1H, J = 8.4 Hz), 8.81 (d, 1H, J = 8.8 Hz), 8.26 (d, 1H, J = 7.6 Hz), 7.81 (m, 2H), 7.70 (m, 3H), 4.60 (m, 1H), 2.92 (m, 1H), 2.56 (m, 3H), 2.45 (m, 4H), 1.79 (m, 2H), 1.64 (m, 2H), 1.31 (m, 2H), 1.09 (s, 9H). MS 556.2 (M+H)$^+$
21/18		MS 604.1 (M+H)$^+$
21/19		MS 554.1 (M+H)$^+$
21/20		MS 588.1 (M+H)$^+$
21/21		MS 586.1 (M+H)$^+$
21/22		MS 570.1 (M+H)$^+$
21/23		MS 634.1 (M+H)$^+$
21/24		^{1}H-NMR (400 MHz, DMSO-d_6) δ: 8.24 (m, 1H), 7.99-7.82 (m, 4H), 4.73 (s, 1H), 3.28 (m, 2H), 2.73 (m, 2H), 2.62 (m, 1H), 1.95-1.86 (m, 2H), 1.75-1.60 (m, 2H), 1.55-1.42 (m, 4H), 1.18-1.09 (m, 16H). MS 564.1 (M+H)$^+$
21/25		^{1}H-NMR (400 MHz, DMSO-d_6) δ: 8.23 (m, 1H), 7.98-7.92 (m, 2H), 7.87-7.82 (m, 1H), 7.79 (s, 1H), 4.71 (s, 1H), 3.28 (m, 2H), 2.73 (m, 2H), 2.62 (m, 1H), 1.95-1 .86 (m, 2H), 1.75-1.60 (m, 2H), 1.55-1.42 (m, 4H), 1.13 (s, 6H), 1.08 (s, 6H), 0.74 (t, J = 7.6 Hz, 3H). MS 578.1 (M+H)$^+$

Example 22



22

Step 1: 4-(Cvclohexylmethyl)-5-(2,6-di-r^ butylpyridin-4-yl)-2-(((*trans*)-3-(methoxycarbonyl)-cvclobutvDcarbamovDthiazole 3-oxide **(22a)**

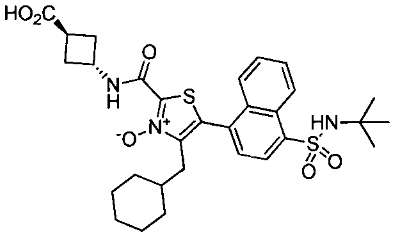
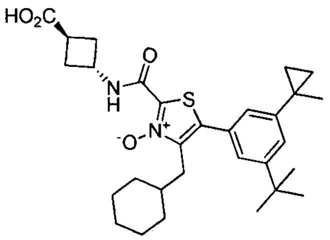
To a solution of *(trans)*-methy\ 3-(4-(cyclohexylmethyl)-5-(2,6-di-ferf-butylpyridin-4-yl)thiazole-2-carboxamido)cyclobutanecarboxylate (60 mg, 0.1 1 mmol) in DCM (2 mL) was added *m*-CPBA (35 mg, 0.17 mmol) and the solution was stirred at rt overnight, washed with sat. $NaHC0_3$ and sat. aq. NaS_20_3 consecutively, dried over Na_2S0_4, filtered, concentrated and purified by CC (PE/EA = 3/1) to give compound **22a** (38 mg, 62%) as a pale yellow solid.

Step 2: 2-(((^ans)-3-Carboxycvclobutyl)carbamoyl)-4-(cvclohexylmethyl)-5-(2,6-di -*tert*-butyl-Pyridin-4-yl)thiazole 3-oxide **(22)**

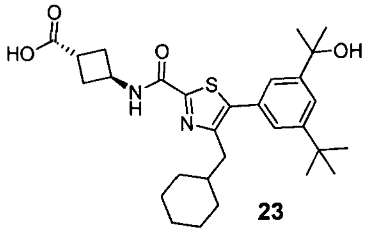
A solution of compound **22a** (36 mg, 0.066 mmol) and $LiOH•H_20$ (6 mg, 0.1 mmol) in a mixture of MeOH (2 mL) and H_20 (1 mL) was stirred at rt overnight, diluted with aq. HCl to adjust the pH to ca. 5 and extracted with EA. The organic layer was washed with water and brine, dried over Na_2S0_4, filtered, 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-d_6) 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 $(M+1)^+$.

Example 22/1 to 22/2

The following examples were prepared similar to Example **22.**

#	Structure	Analytical data
22/1		^1H-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		^1H-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



23

Step 1: (*tr*ans)-Methvl 3-(5-(3-acetyl-5-(terf-butyl)phenyl)-4-(cvclohexylmethyl)thiazole-2-carboxamido)cvclobutanecarboxylate **(23a)**

A mixture of (*trans*)-methyl 3-(5-bromo-4-(cyclohexylmethyl)thiazole-2-carboxamido)cyclobutanecarboxylate (415 mg, 1.00 mmol), 1-(3-(fert-butyl)-5-(4,4,5,5-tetramethyl-1 ,3,2-dioxaborolan-2-yl)phenyl)ethanone (362 mg, 1.20 mmol) and K_2C0_3 (500 mg, 3.62 mmol) in dry DMF (10 mL) was purged with N_2 for 10 min. Pd(dppf)Cl_2 (50 mg) was added and degassing with N_2 was continued for 10 min. The mixture was stirred at 100 °C for 14 h under N_2, cooled to rt, concentrated and purified by CC (PE/EA = 5/1) to give compound **23a** (465 mg, 91%) as a white solid.

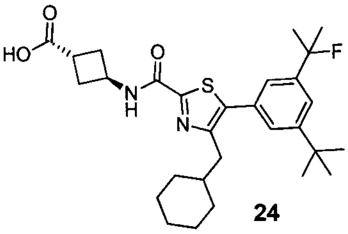
Step 2: (*trans*)-Methvl 3-(5-(3-(ferf-butyl)-5-(2-hvdroxypropan-2-yl)phenyl)-4-(cvclohexylmethyl)-thiazole-2-carboxamido)cvclobutanecarboxylate **(23b)**

To a solution of compound **23a** (465 mg, 0.91 mmol) in dry THF (10 mL) was added MeMgBr (3M in Et_20 , 0.30 mL, 0.90 mmol) at 0°C under N_2 and the solution was stirred at rt for 2.5 h, quenched with sat. NH_4Cl and extracted with EA. The organic layer was washed with water and brine, dried over Na_2S0_4, filtered, concentrated and purified by CC (PE/EA = 5/1) to give compound **23b** (240 mg, 50%) as a white solid.

Step 3: (*trar7s*)-3-(5-(3-(te/t-Butyl)-5-(2-hvdroxypropan-2-yl)phenyl)-4-(cvclohexylmethyl)-thiazole-2-carboxamido)cvclobutanecarboxylic 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•H_20 (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 Na_2S0_4, filtered, concentrated and purified by prep-HPLC to give compound **23** (20 mg, 41%) as a white solid. ^{1}H-NMR (300 MHz, CD_3OD) 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), 3.05-3.1 1 (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


24

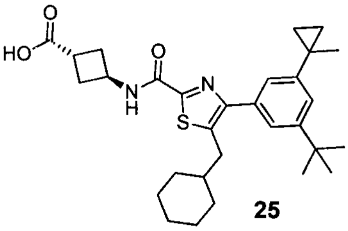
Step 1: *(trans)*-Methyl 3-(5-(3-(teff-butyl)-5-(2-fluoropropan-2-yl)phenyl)-4-(cvclohexylmethyl)-thiazole-2-carboxamido)cyclobutanecarboxylate **(24a)**

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 N_2 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 Na_2S0_4, filtered, concentrated and purified by prep-TLC (PE/EA = 5/1) to give compound **24a** (90 mg, 50%) as a white solid.

Step 2: (frans)-3-(5-(3-(te/t-Butyl)-5-(2-fluoropropan-2-yl)phenyl)-4-(cvclohexylmethyl)thiazole -2-carboxamido)cvclobutanecarboxylic acid **(24)**

A similar procedure as described for Example **23** was applied to afford compound **24** (50 mg, 52%) as a white solid. ^{1}H-NMR (300 MHz, CD_3OD) 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


25

Step 1: 2,4-Dibromothiazole-5-carbaldehvde **(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 N_2 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. NH_4Cl and extracted with EA twice. The combined organic layers were washed with water and brine, dried over Na_2S0_4, filtered, concentrated and purified by CC (PE/EA = 15/1) to give compound **25a** (14.5 g, 35%) as a yellow solid.

Step 2: Cvclohexyl(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 cominbed organic layers were washed with water and brine, dried over Na_2S0_4, 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-(cvclohexylmethyl)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 quenched with water. The organic layer was washed with water and brine, dried over Na_2S0_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-(cvclohexylmethyl)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 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_2S0_4, filtered, concentrated and purified by CC (PE/EA = 30/1) to give compound **25d** (2.54 g, 40%) as a light yellow oil.

Step 5: Ethyl 4-(3-(terf-butyl)-5-(1-methylcvclopropyl)phenyl)-5-(cvclohexylmethyl)thiazole-2-carboxylate **(25e)**

The suspension of compound **25d** (500 mg, 1.50 mmol), K_2C0_3 (690 mg, 5.00 mmol), 2-(3-(rerf-butyl)-5-(1-methylcyclopropyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (471 mg, 1.50 mmol) and $Pd(dppf)Cl_2$ (150 mg) in DMF (10 mL) was stirred at 100°C for overnight, 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-methylcvclopropyl)phenyl)-5-(cvclohexylmethyl)thiazole-2-carboxylate **(25f)**

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: ?rans-3-(4-(3-(rerf-Butyl)-5-(1-methylcvclopropyl)phenyl)-5-(cvclohexylmethyl)thiazole-2-carboxamido)cvclobutanecarboxylic acid **(25)**

The solution of compound **25f** (305 mg, 0.68 mmol), frans-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 byEA (3x).

The combined organic layers were washed by water (3x) and brine consecutively, dried over Na_2S0_4, filtered, concentrated and purified by prep-HPLC and then prep-TLC to give compound **25** (37 mg, 11%) as a white solid. ^{1}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 $(M+1)^+$.

Example 25/1 to 25/2

The following examples were prepared similar to Example **25.**

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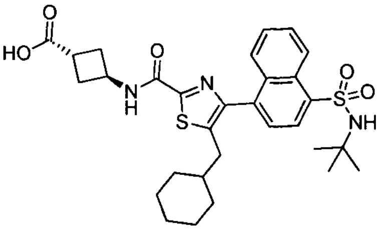
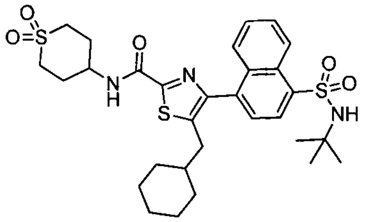
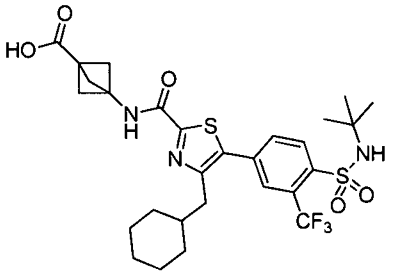
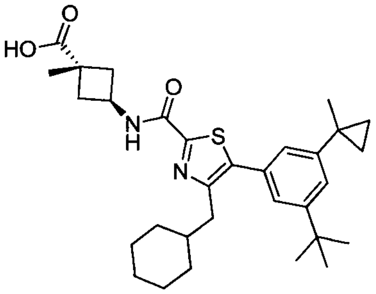
25/1		^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 0.63-0.66 (m, 2H), 0.98-1.20 (m, 3H), 1.22 (s, 9H), 1.48-1.67 (m, 6H), 2.37 (br s, 2H), 2.53-2.57 (m, 2H), 2.84-2.86 (m, 2H), 3.20-3.21 (m, 2H), 4.67 (s, 1H), 4.81-4.83 (m, 1H), 7.48-7.51 (m, 3H), 7.70-7.75 (m, 1H), 8.36 (d, J = 10.8 Hz, 1H), 8.69 (d, J = 8.4 Hz, 1H). MS 584.2 $(M+1)^+$
25/2		^{1}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 $(M+1)^+$

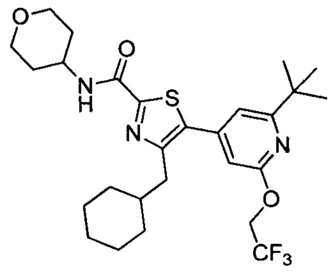
Additional Examples

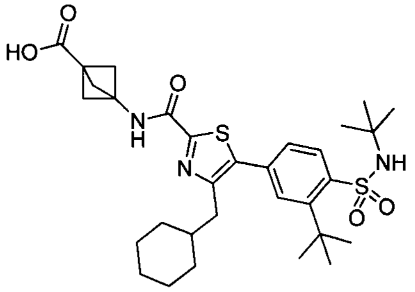
The following compounds can be prepared in the same manner by using the procedures as described above:

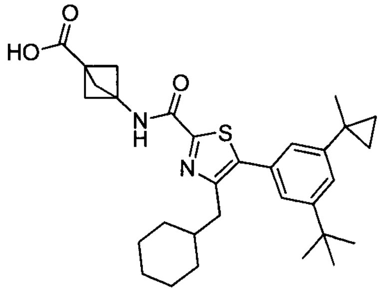
Structure Structure Structure

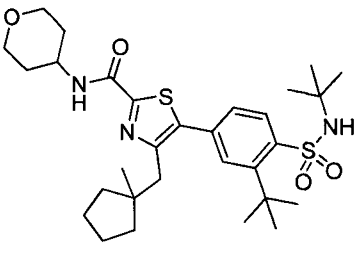












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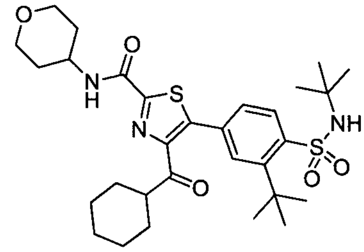	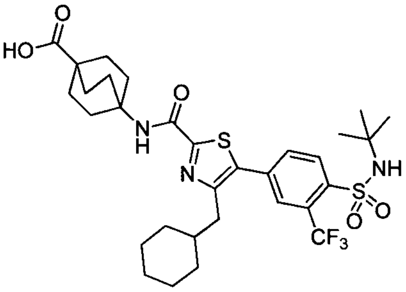	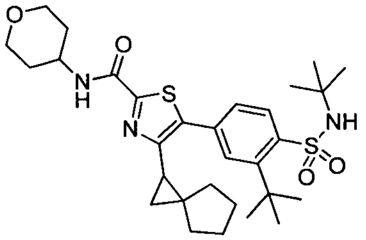
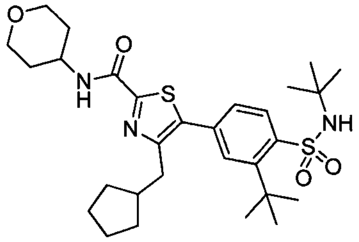	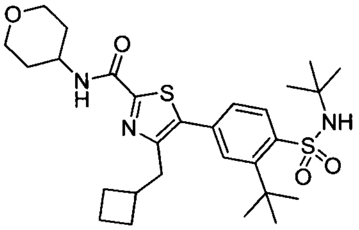	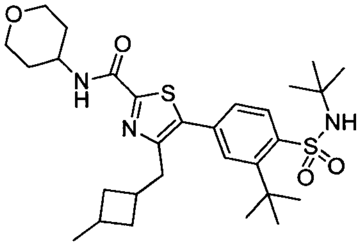
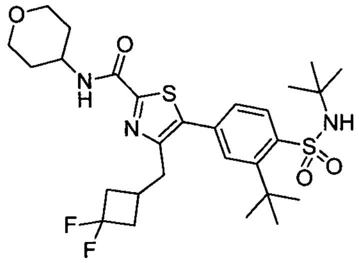	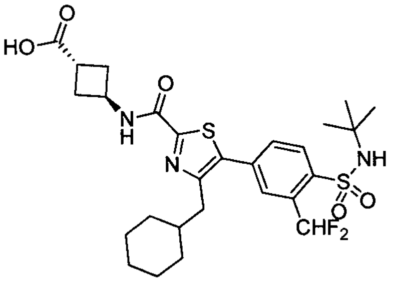	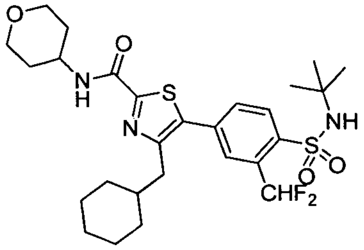
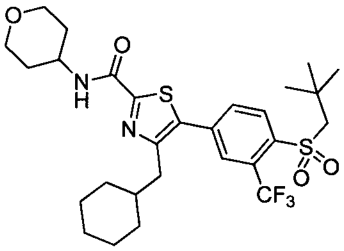	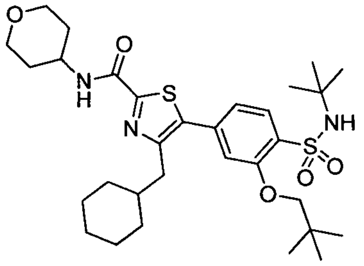	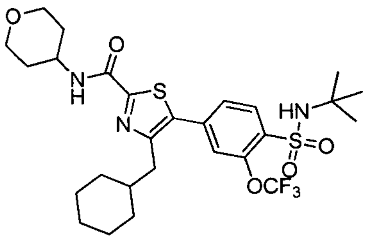
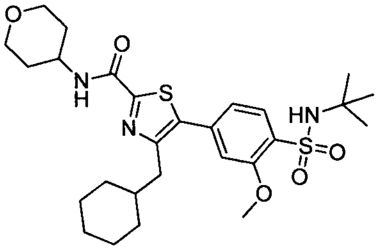	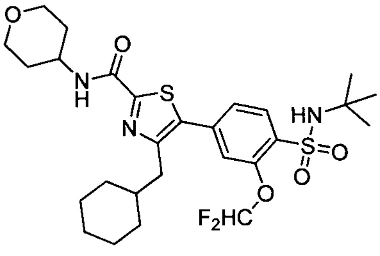	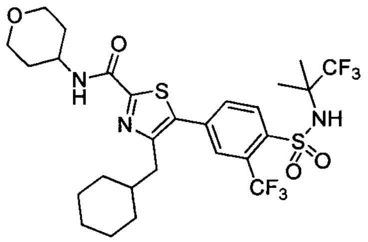
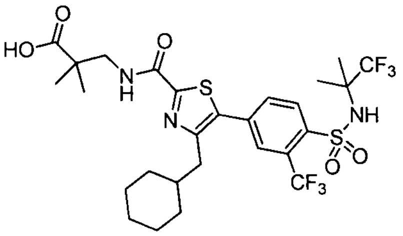	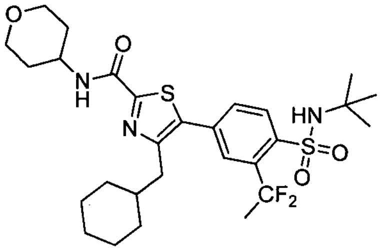	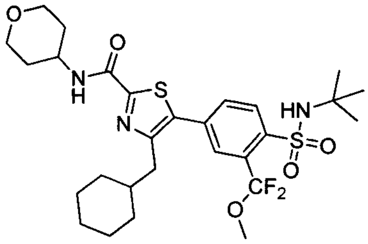

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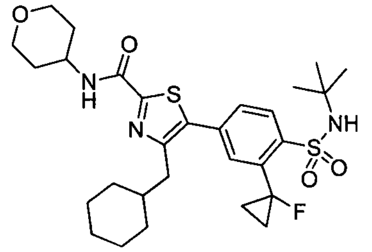	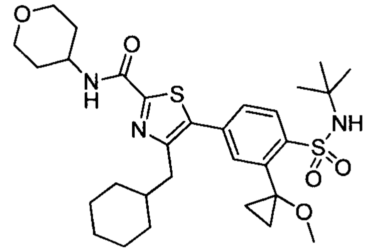	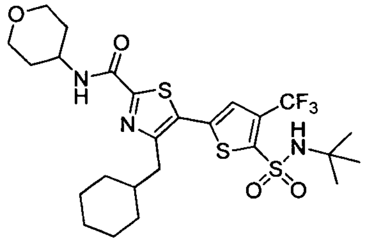
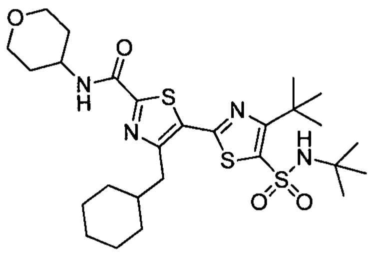	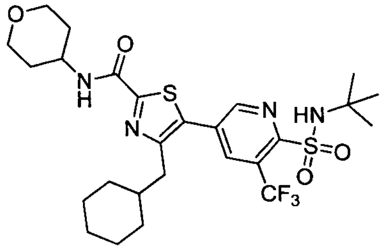	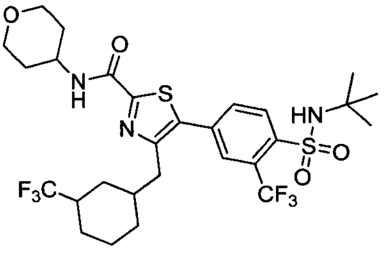
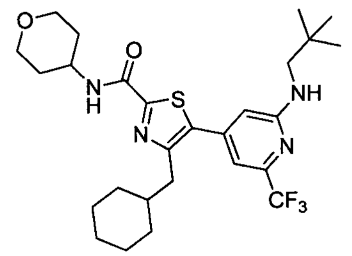	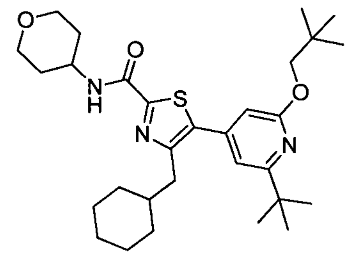	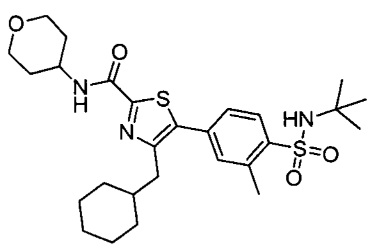
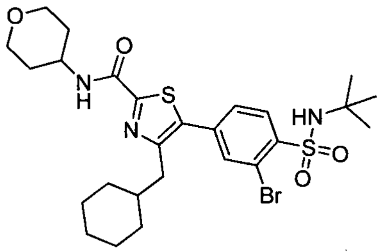	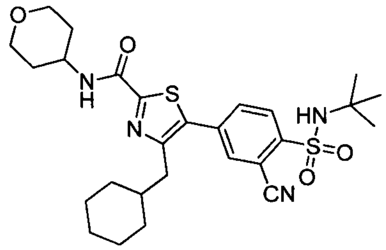	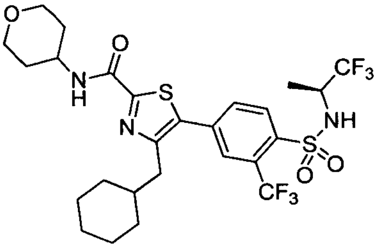
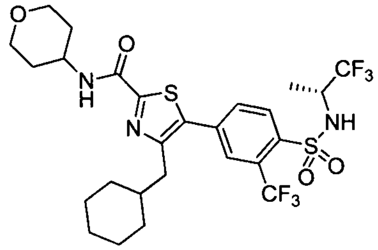	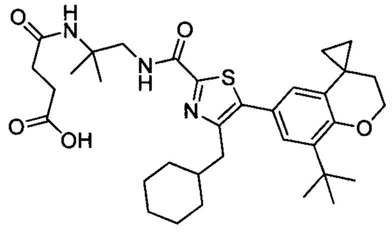	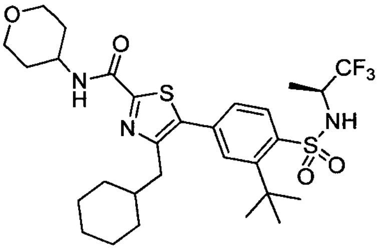
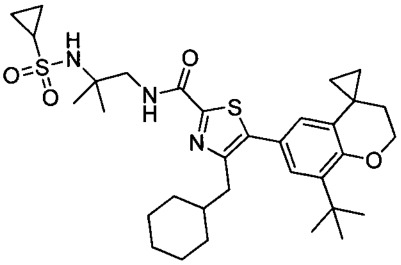	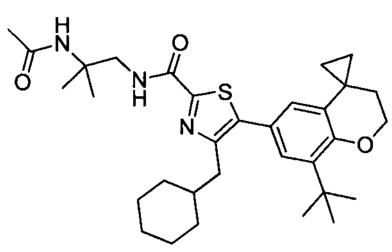	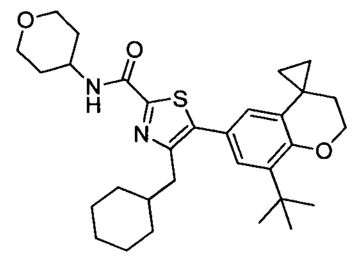

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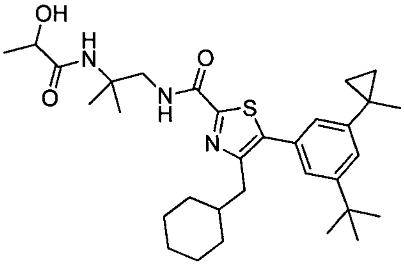	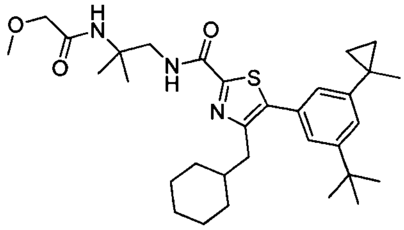	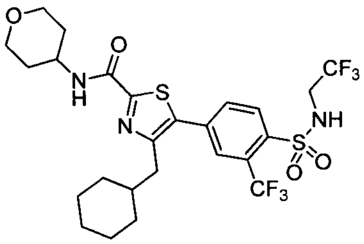
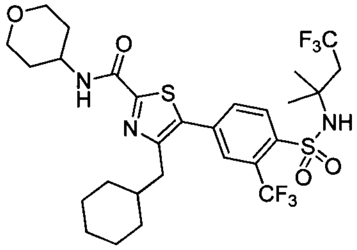	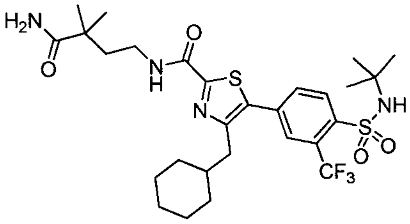	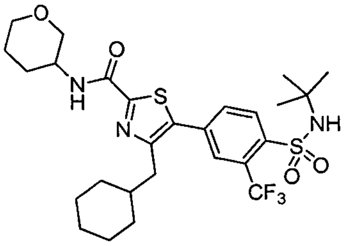
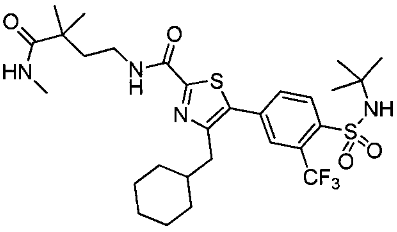	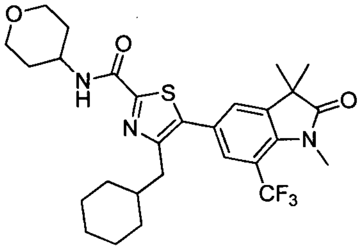	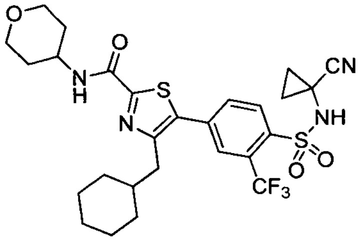
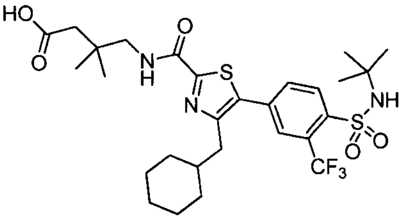	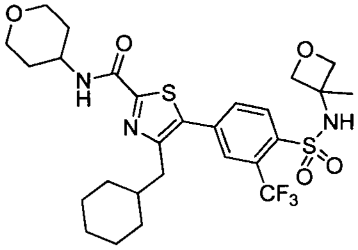	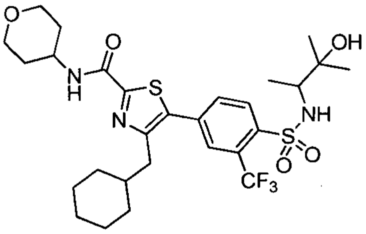
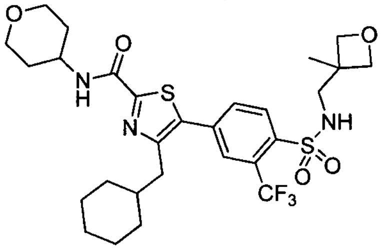	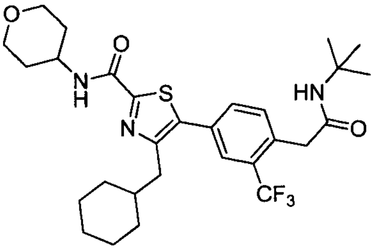	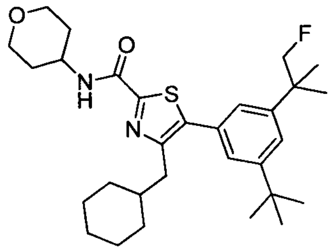
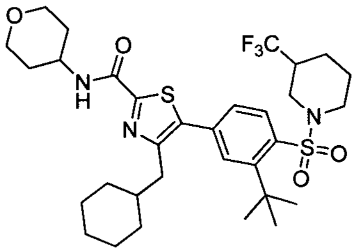	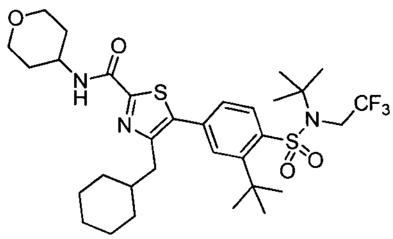	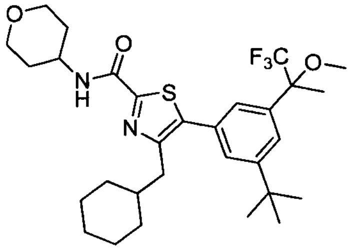

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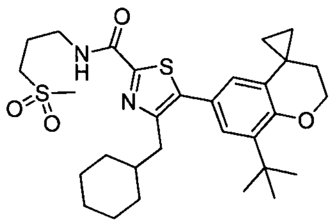	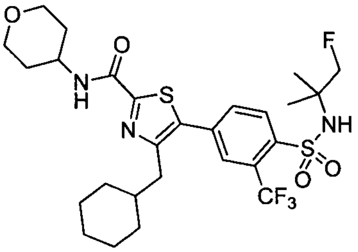	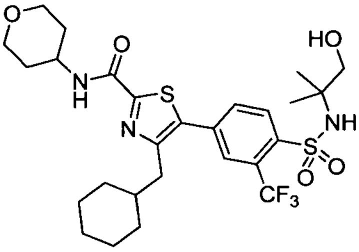
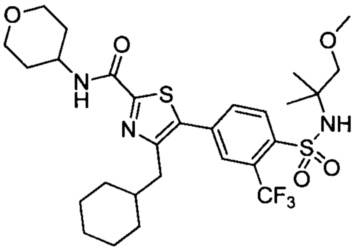	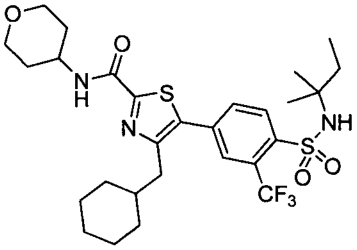	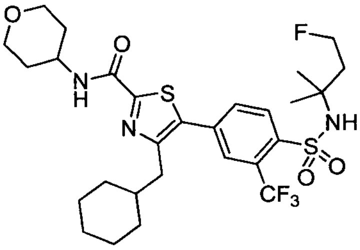
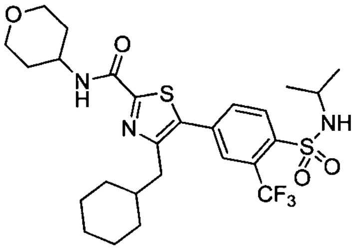	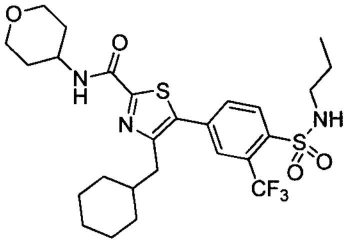	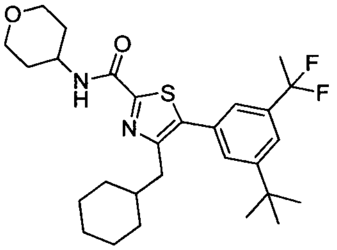
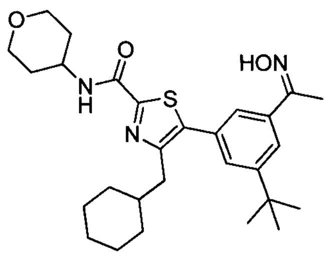	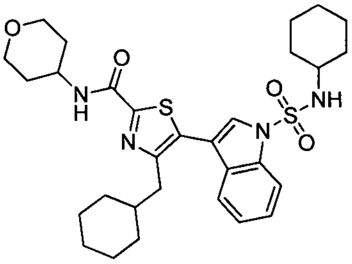	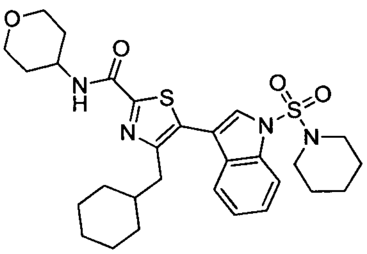
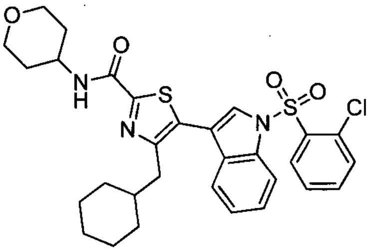	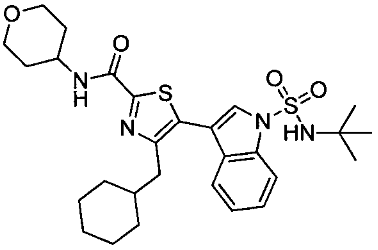	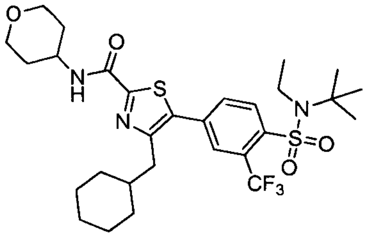
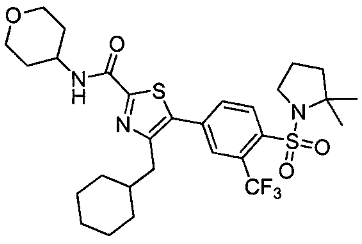	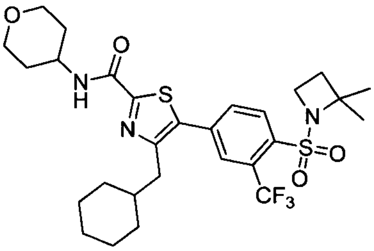	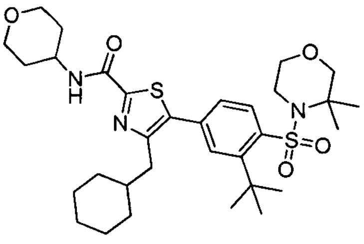

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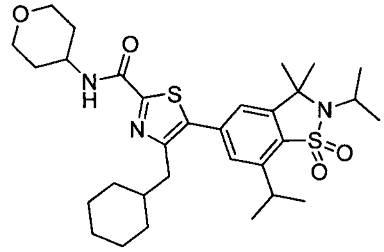	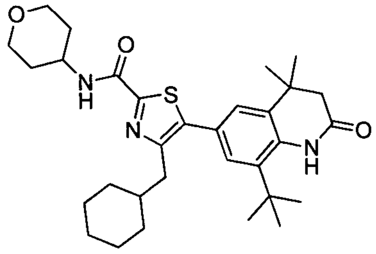	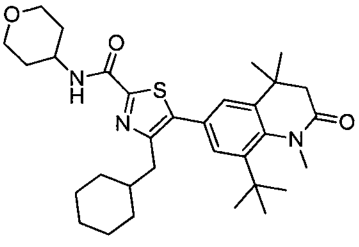
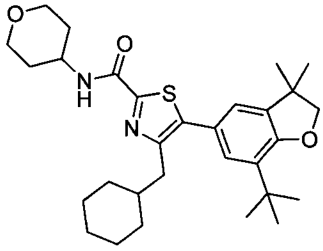	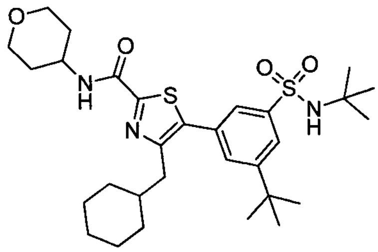	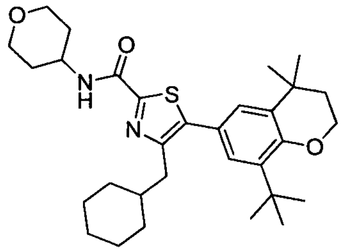
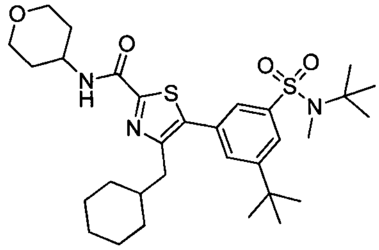	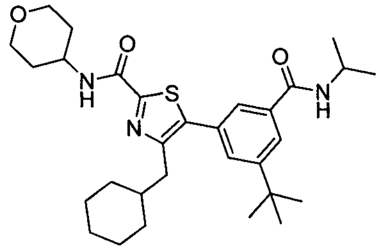	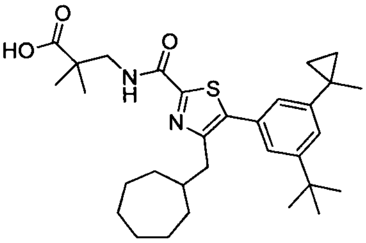
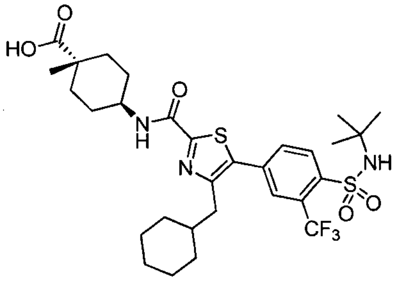	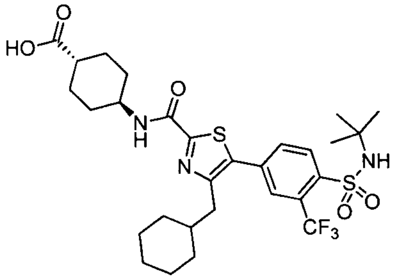	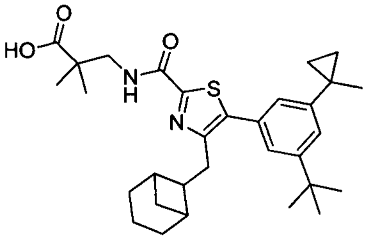
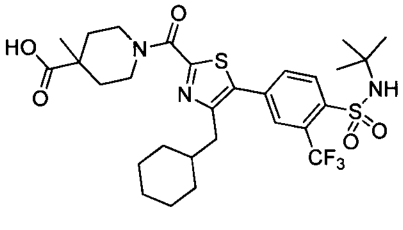	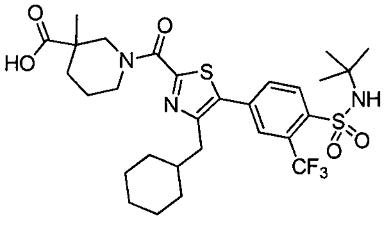	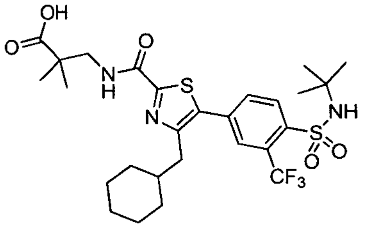
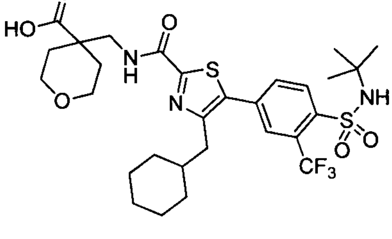	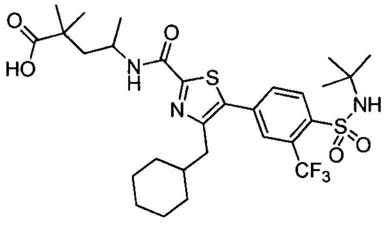	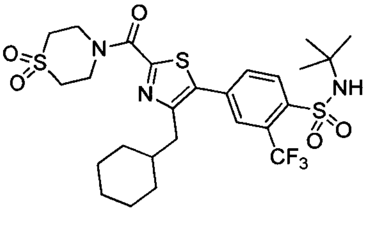

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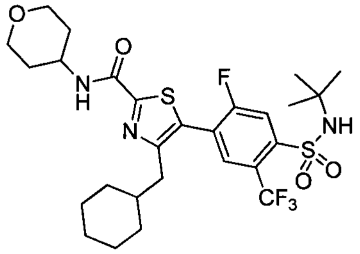	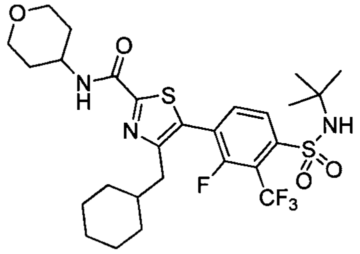	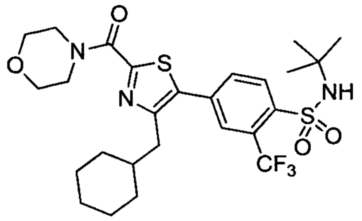
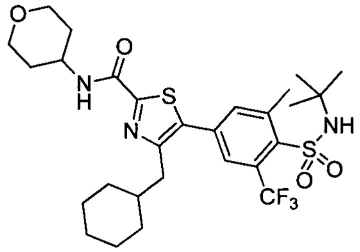	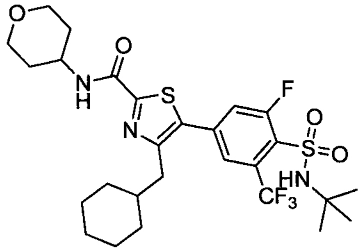	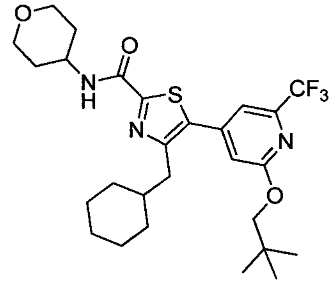
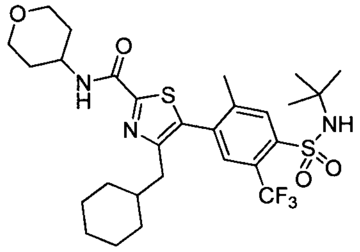	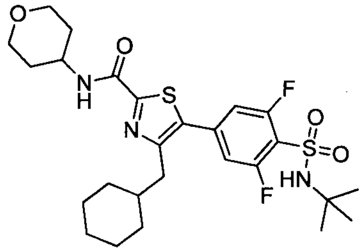	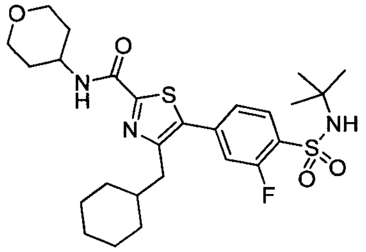
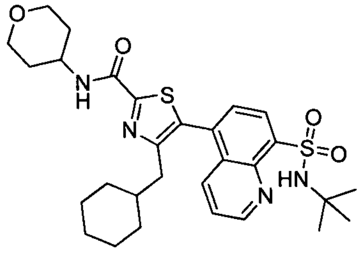	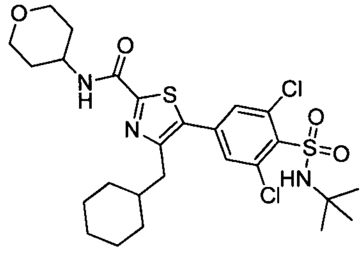	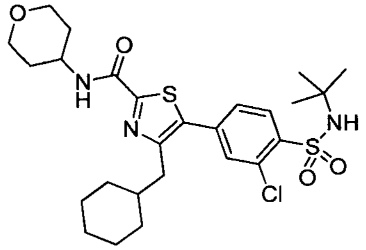
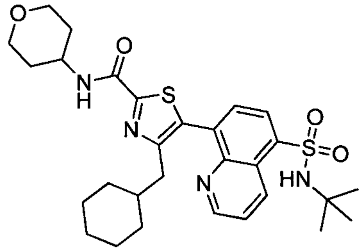	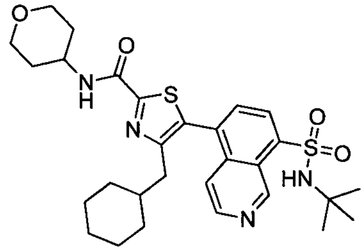	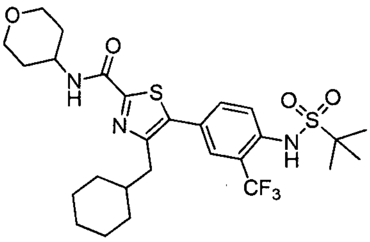
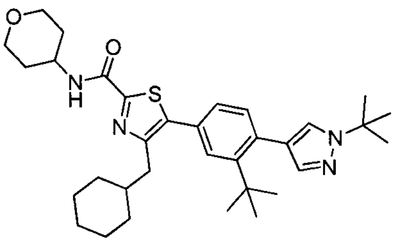	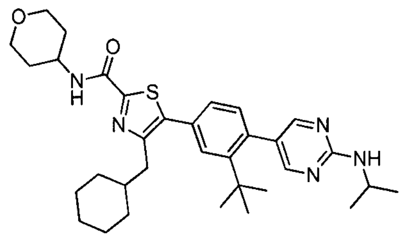	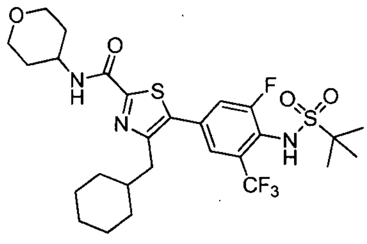

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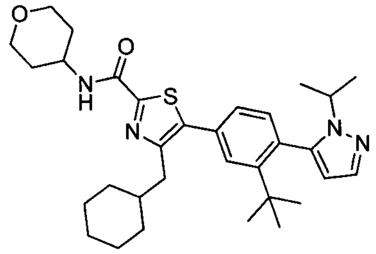	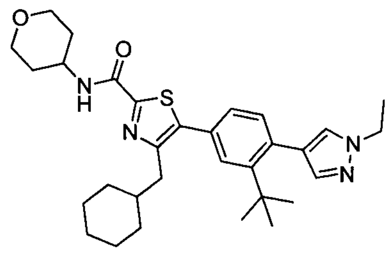	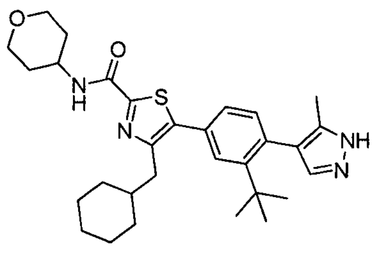
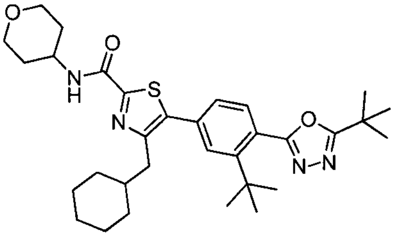	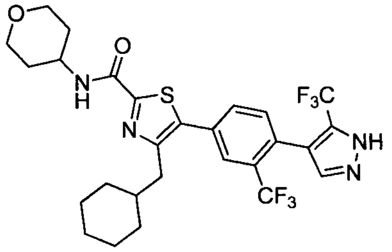	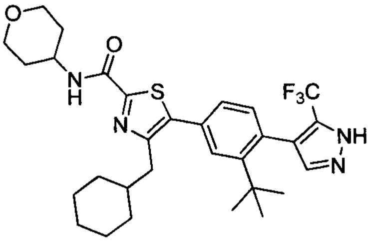
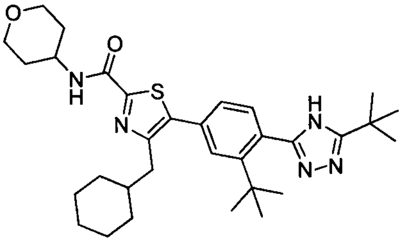	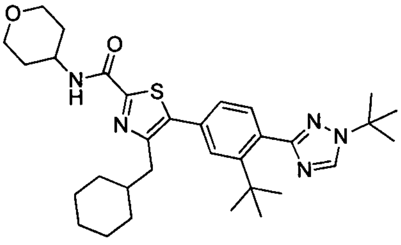	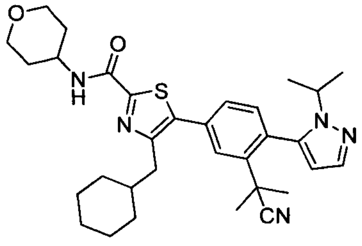
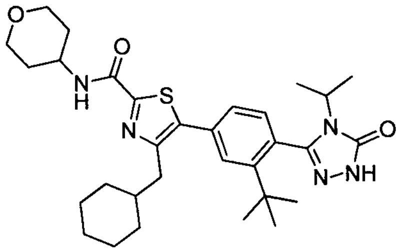	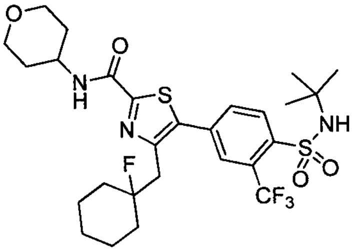	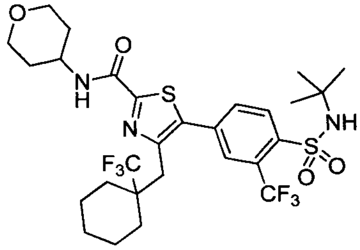
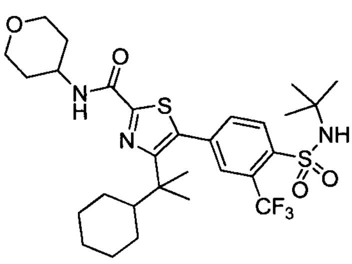	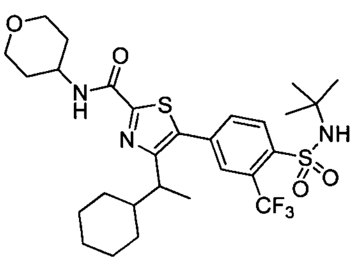	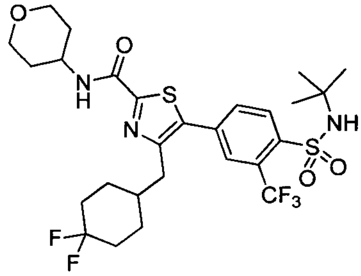
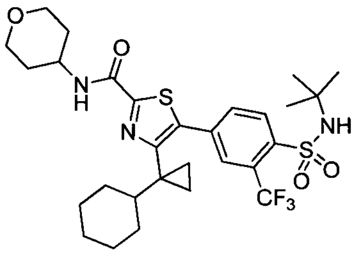	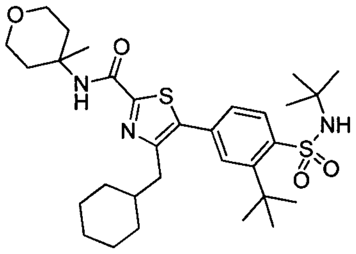	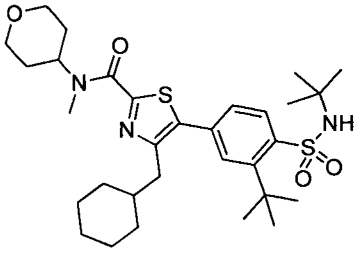

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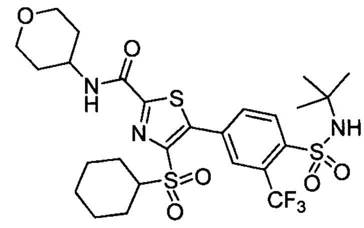	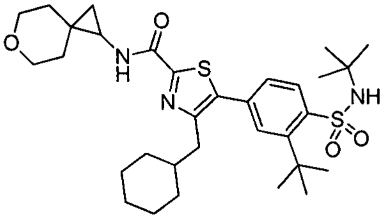	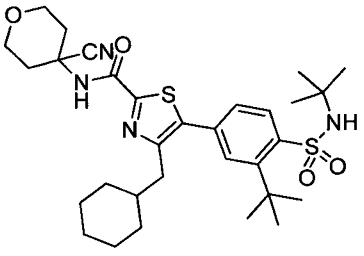
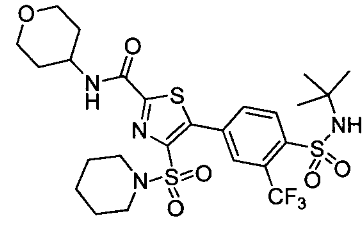	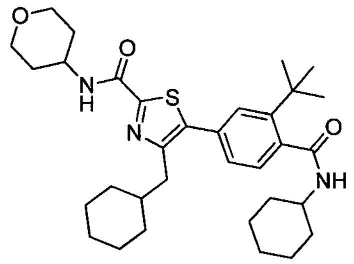	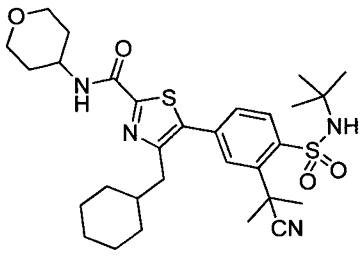
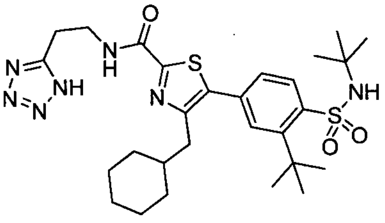	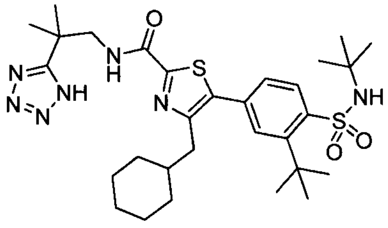	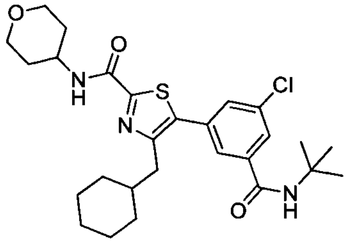
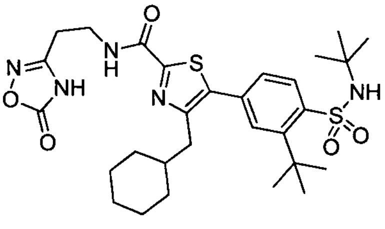	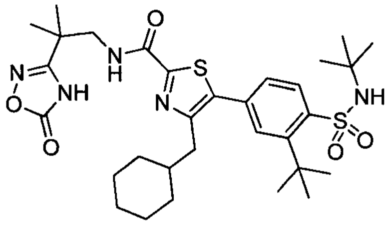	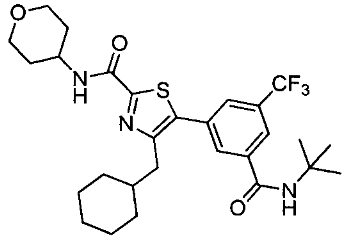
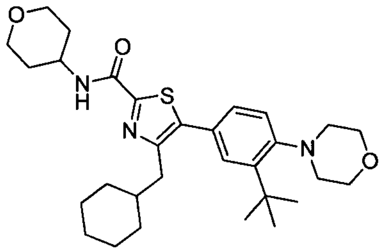	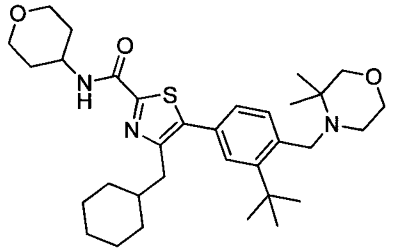	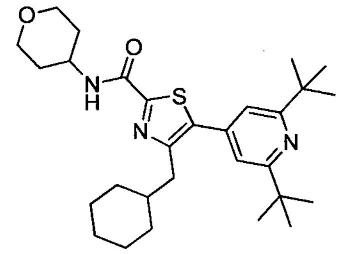
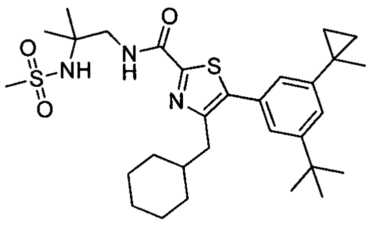	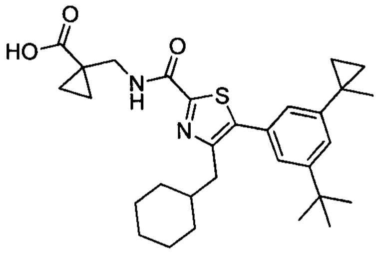	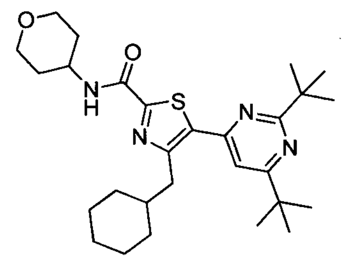

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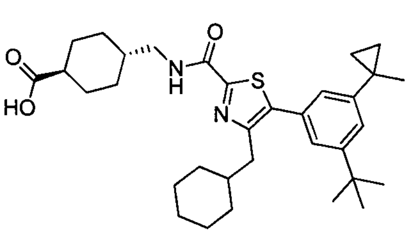	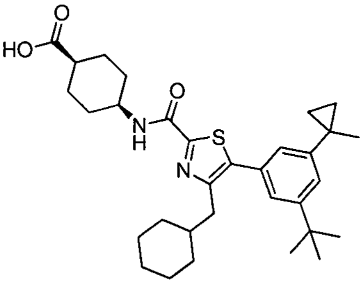	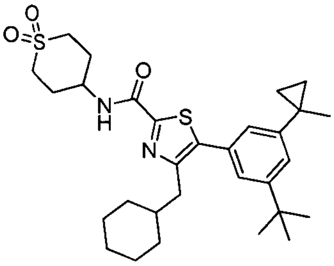
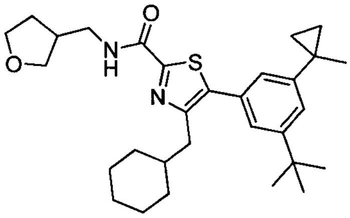	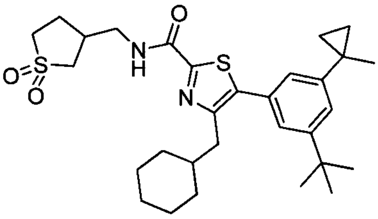	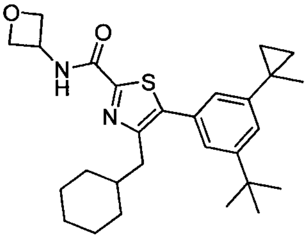
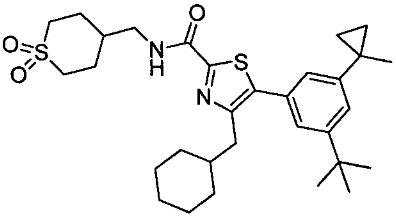	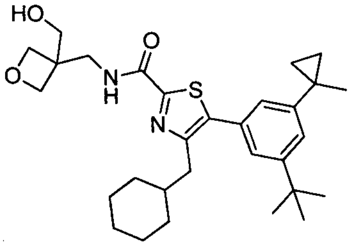	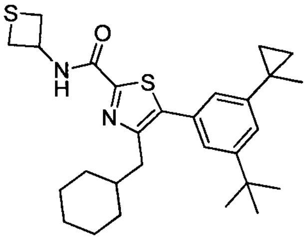
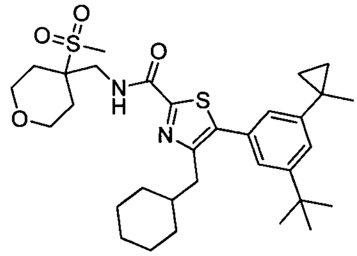	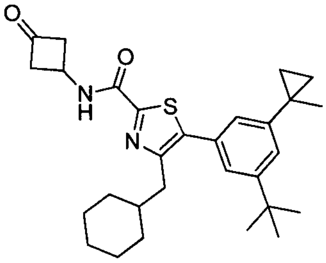	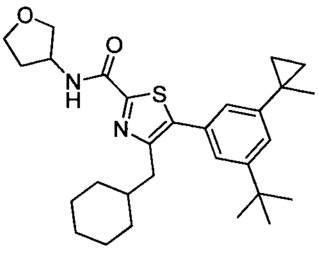
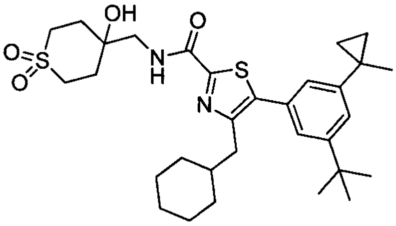	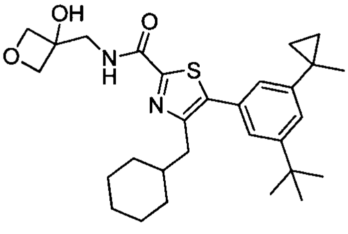	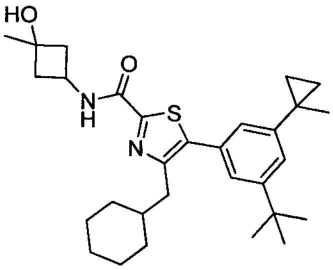
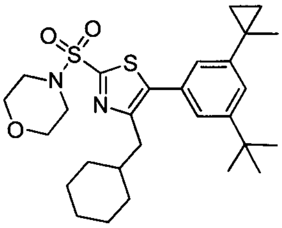	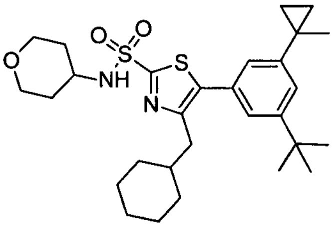	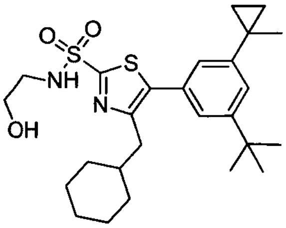

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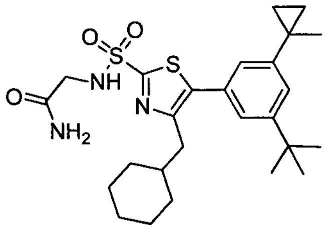	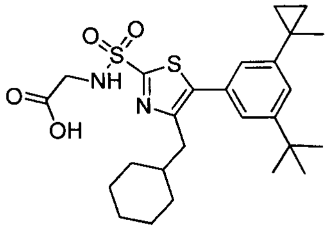	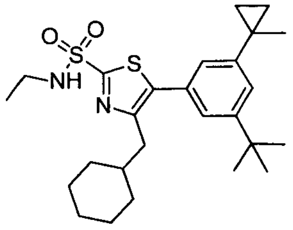
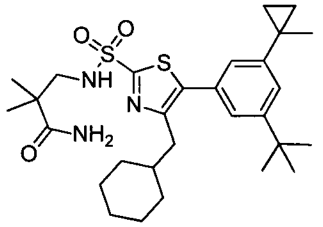	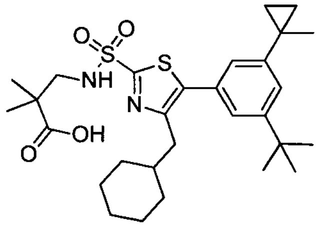	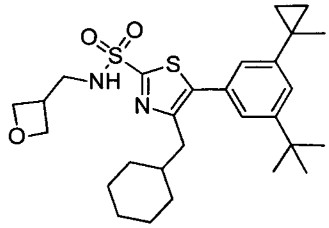
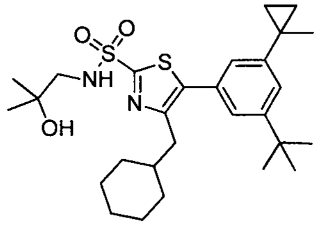	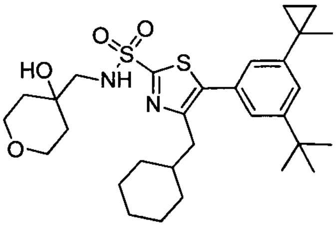	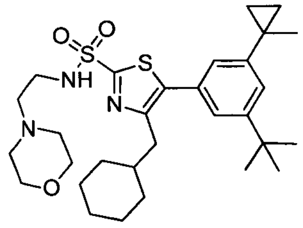
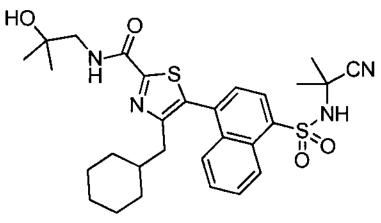	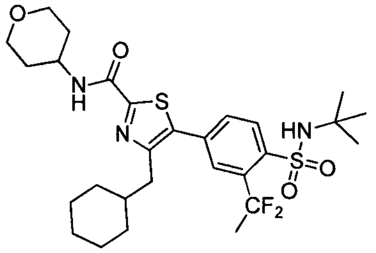	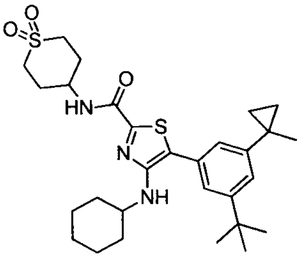
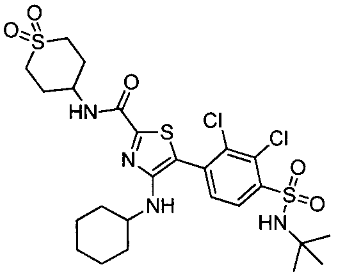	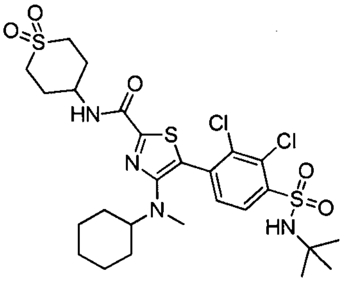	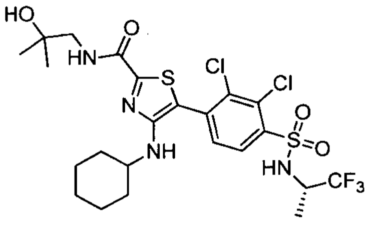
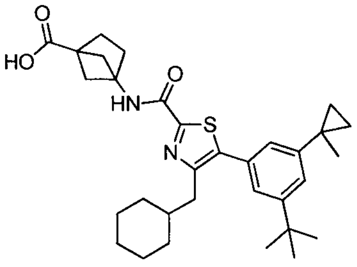	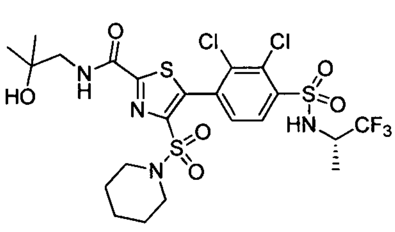	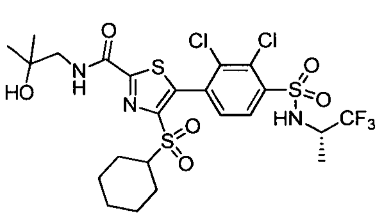
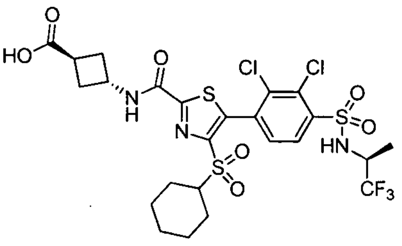	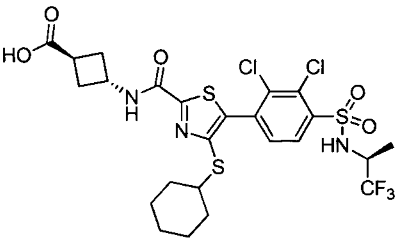	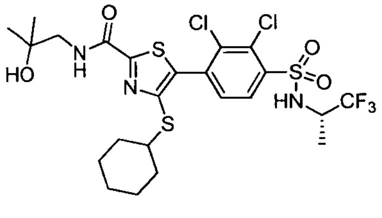

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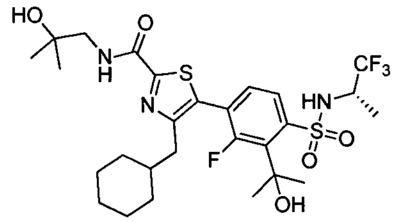	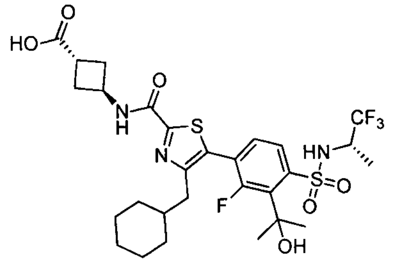	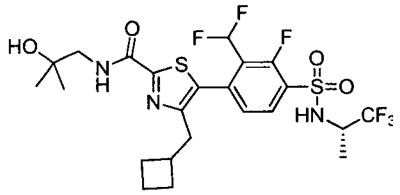
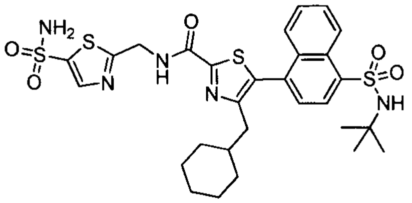	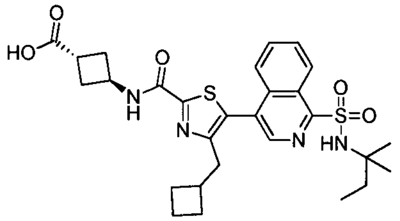	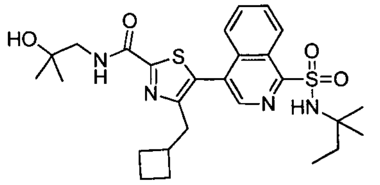
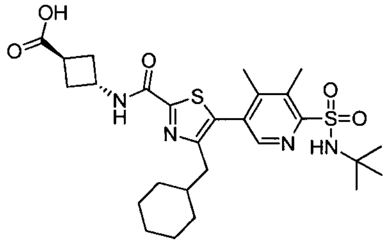	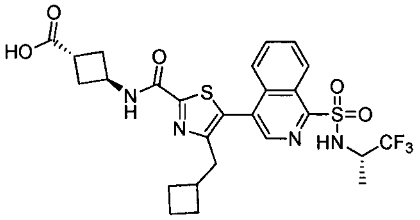	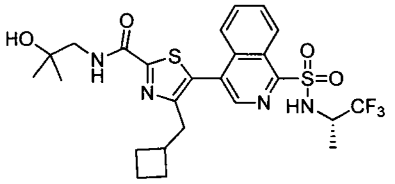
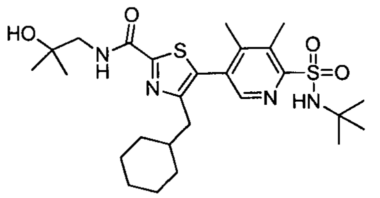	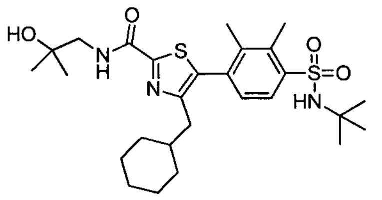	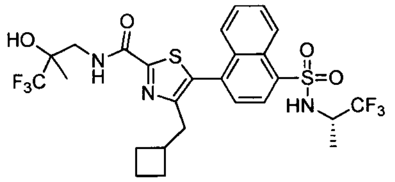
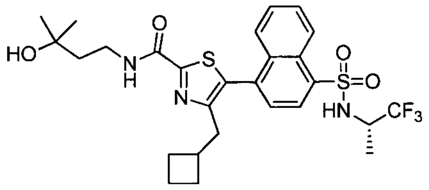	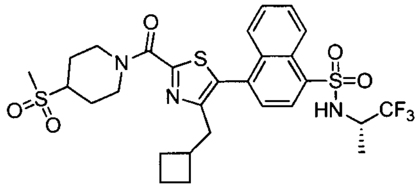	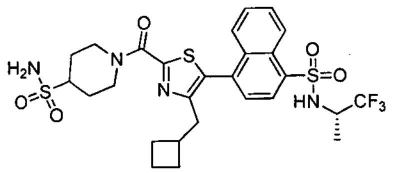
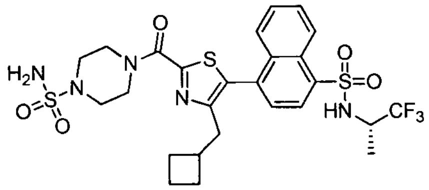	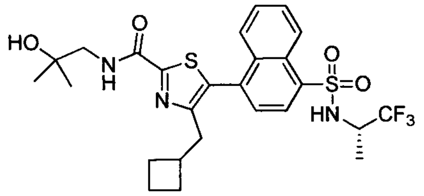	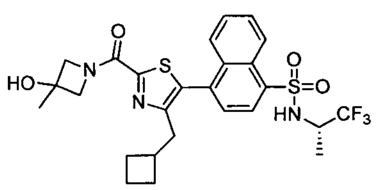
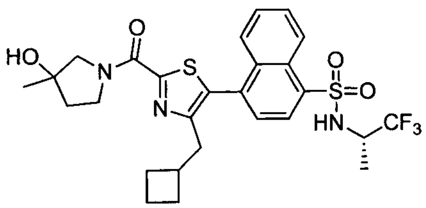	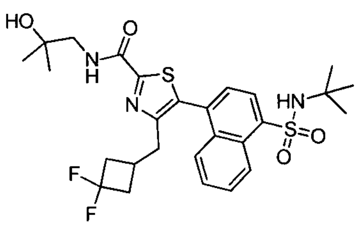	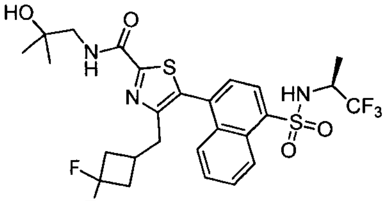

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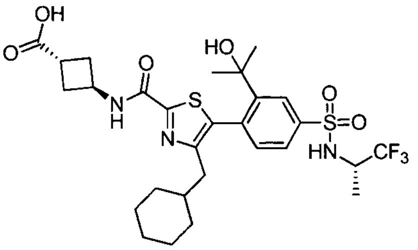	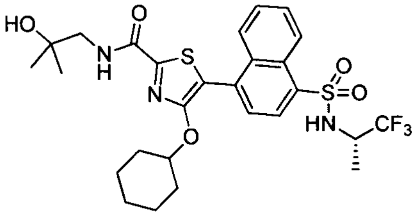	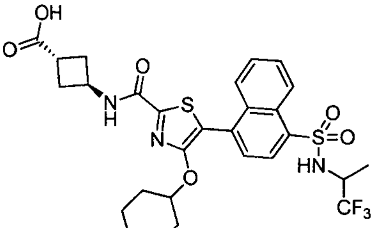
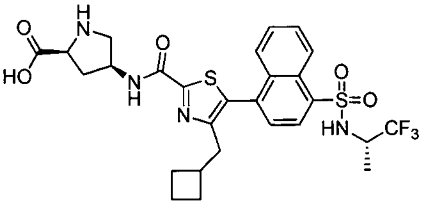	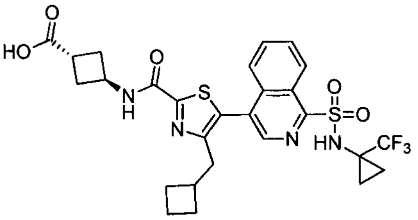	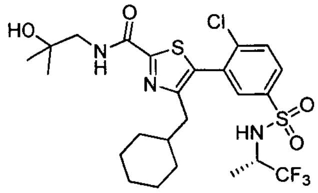
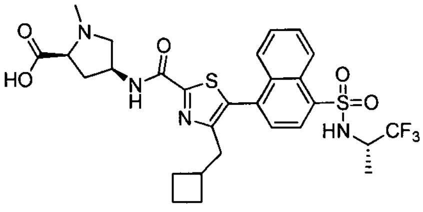	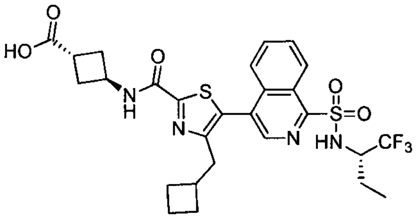	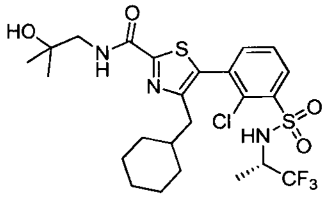
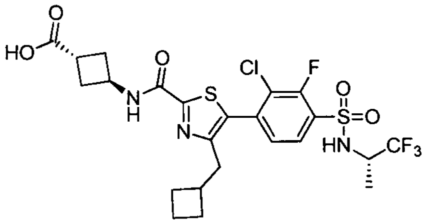	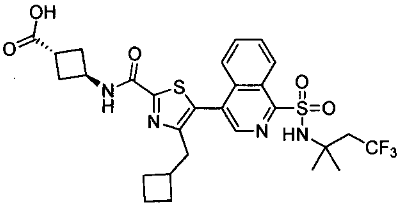	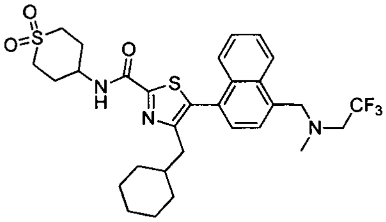
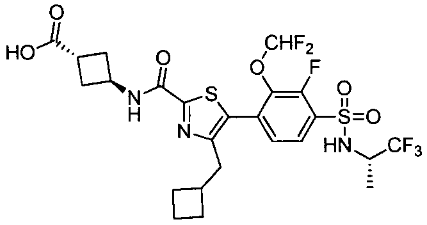	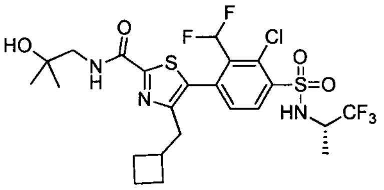	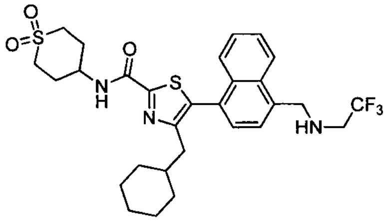
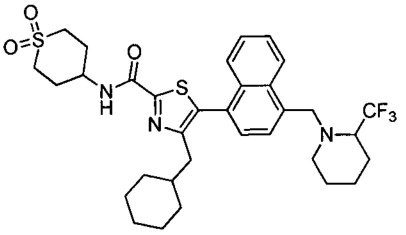	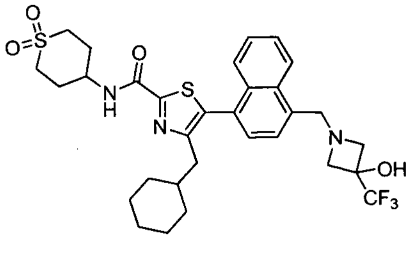	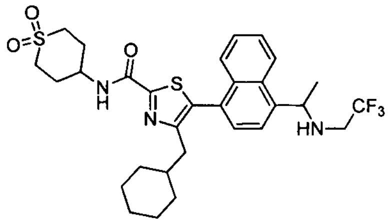

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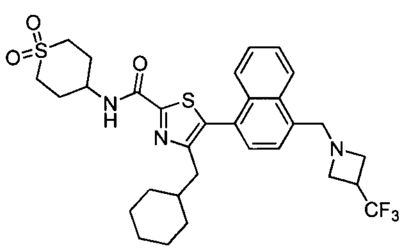	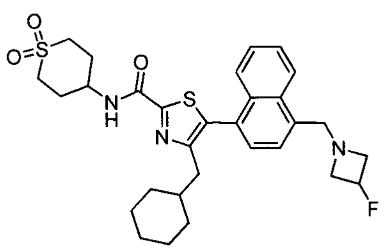	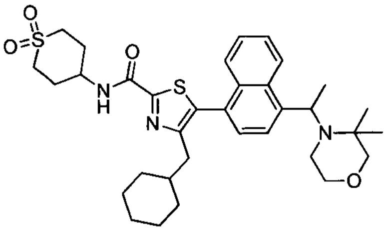
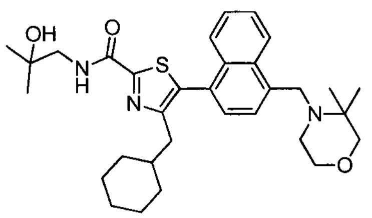	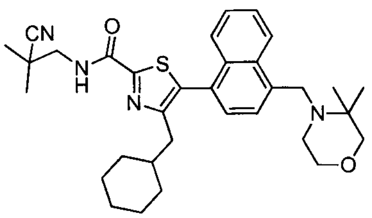	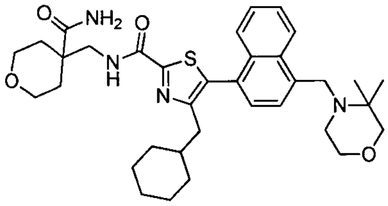
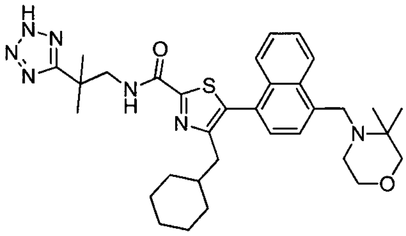	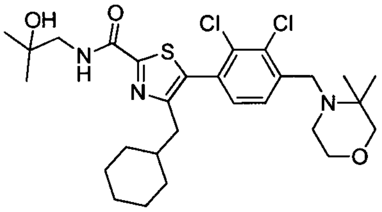	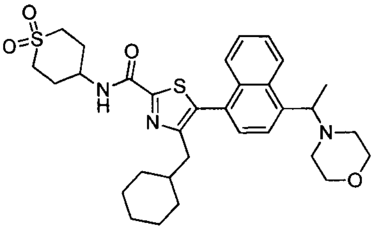
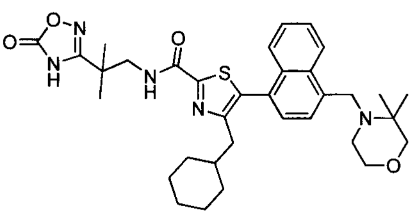	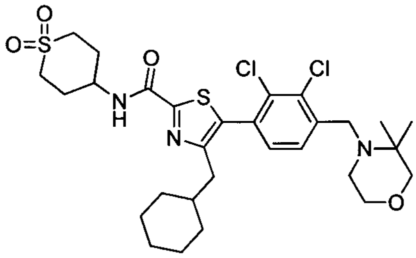	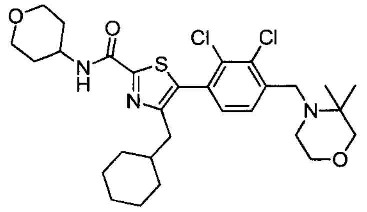
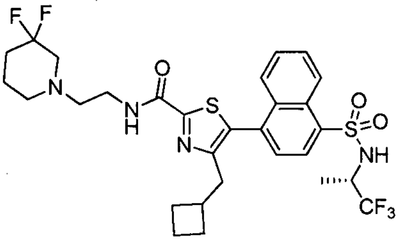	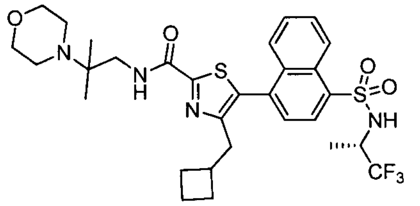	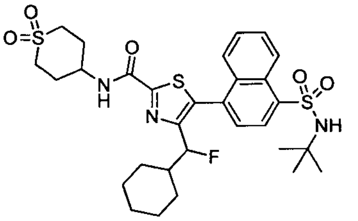
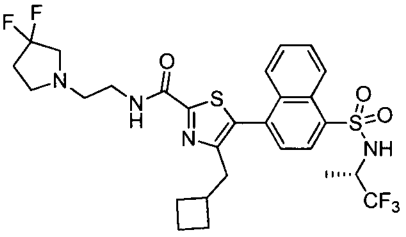	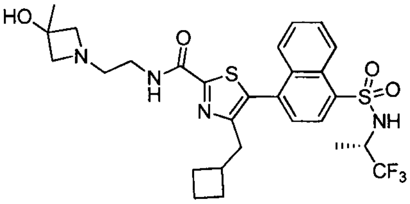	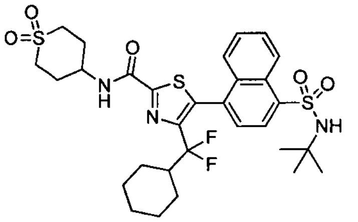
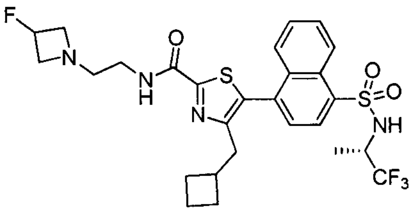	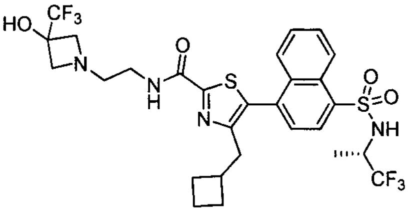	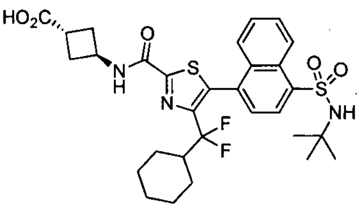

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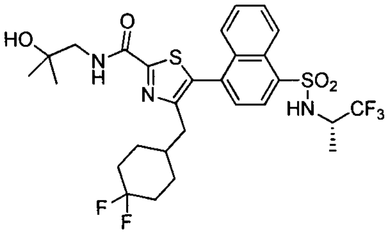
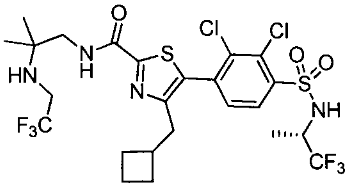
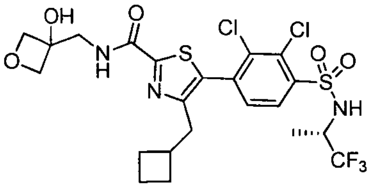
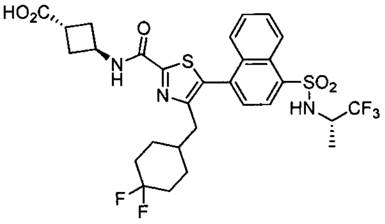
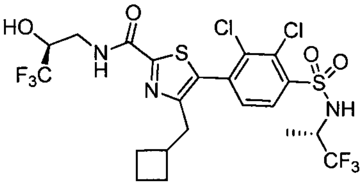
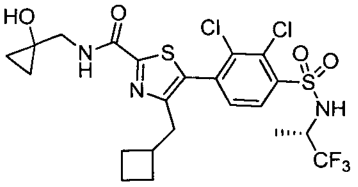
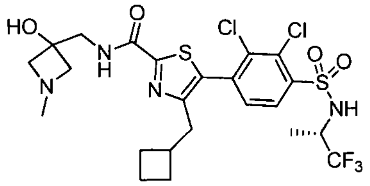
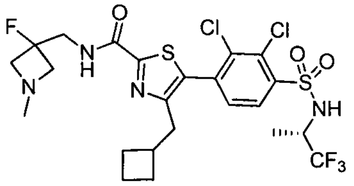
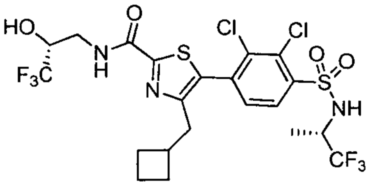
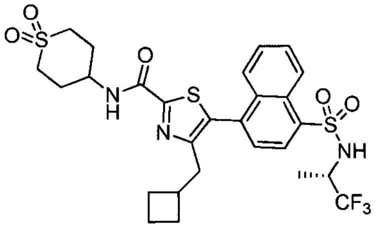
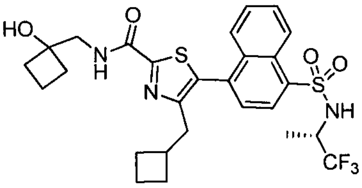
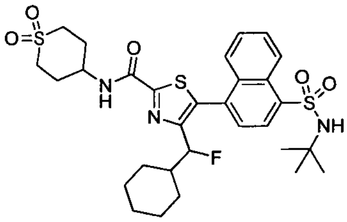
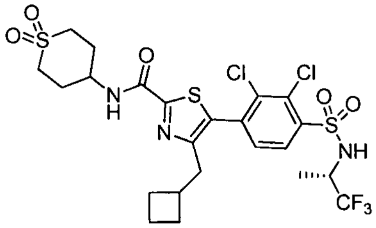
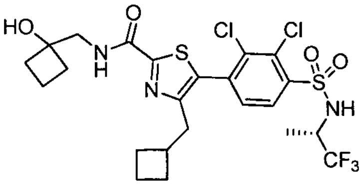
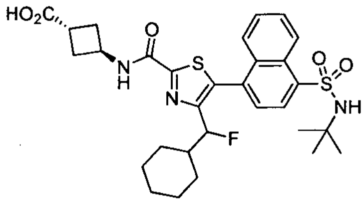
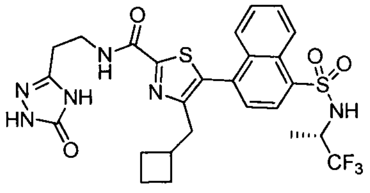
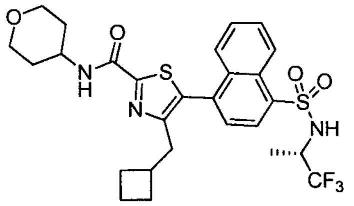
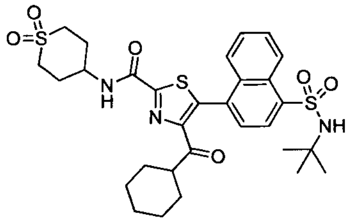
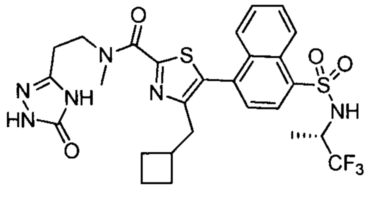
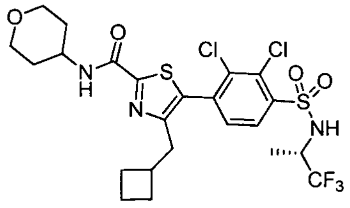
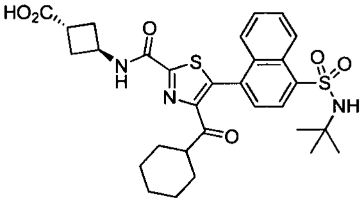
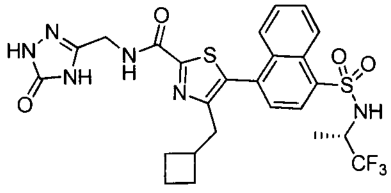
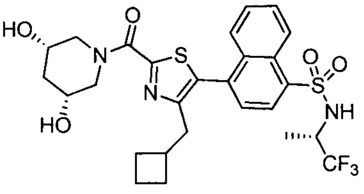
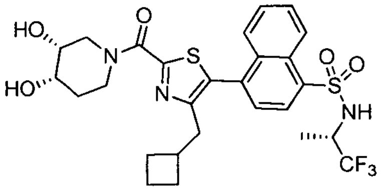
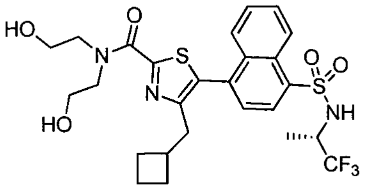
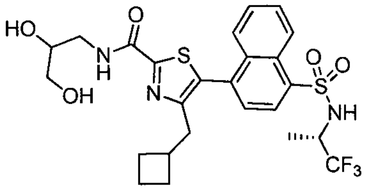
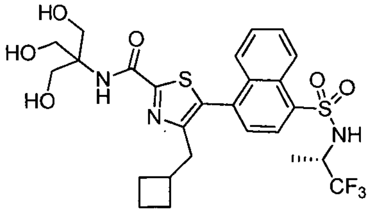
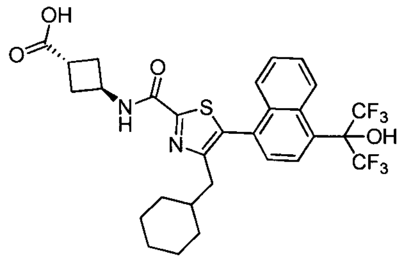
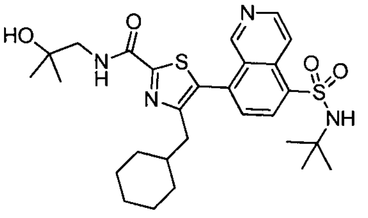
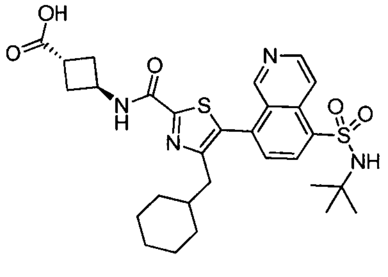
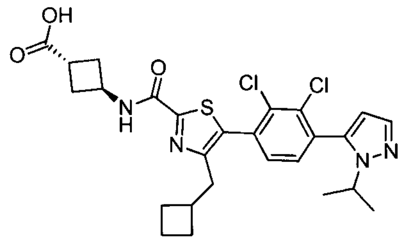
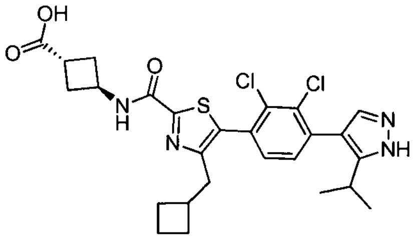
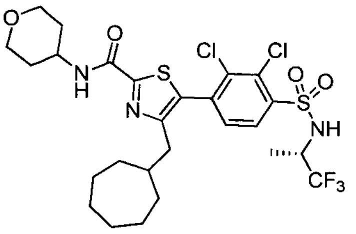
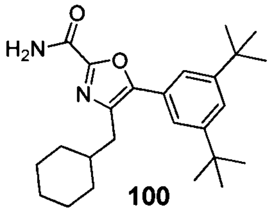
		
		
		
		
		
		
		
		

Structure	Structure	Structure
		
		
		

Example 100



100

Step 1: ((2-Cvclohexyl-1-isocvanoethyl)sulfonyl)benzene **(100a)**

To a solution of 1-((isocyanomethyl)sulfonyl)-4-methylbenzene (8.0 g, 80 mmol) in dry DMF (180 mL) was added K_2C0_3 (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 Na_2S0_4, concentrated and purified by CC (PE/EA = 10/1) to give compound **100a** (2.2 g, 10%) as a white solid.

Step 2: 4-(Cvclohexylmethyl)-5-(3.5-di-fe/t-butylphenyl)oxazole **(100b)**

To a solution of compound **100a** (1.0 g, 3.4 mmol) in dry MeOH (20 mL) was added K_2C0_3 (1.0 g, 6.8 mmol) and 3,5-di-terf-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 (3 x). The combined organic layers were washed with brine, dried over Na_2S0_4, 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-(cvclohexylmethyl)-5-(3,5-di-te/t-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 Na_2S0_4, concentrated and purified by CC (PEΞ/EA = 20/1) to givecompound **100c** (0.5 g, 63%) as a white solid.

Step 4: Methyl 4-(cvclohexylmethyl)-5-(3,5-di -te At-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)Cl_2 (50 mg) and Et_3N (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-(Cvclohexylmethyl)-5-(3,5-di-ferf-butylphenyl)oxazole-2-carboxylic acid **(100e)**

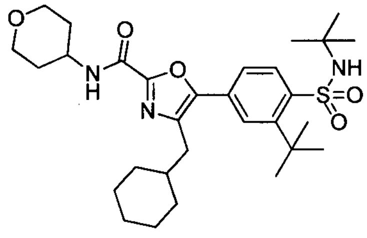
To a solution of compound **100d** (300 mg, 0.7 mmol) in THF (10 mL) and H_20 (2 mL) was added LiOH·H_20 (110 mg, 2.6 mmol) and then the mixture was stirred overnight at rt, concentrated, diluted with H_20, adjusted to pH 5 with 1N HCl and extracted with DCM. The organic layer was washed with brine, dried over Na_2S0_4, filtered and concentrated to give compound **100e** (270 mg, 97%) as a white solid.

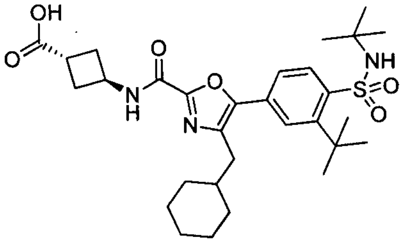
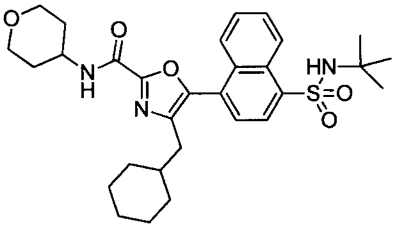
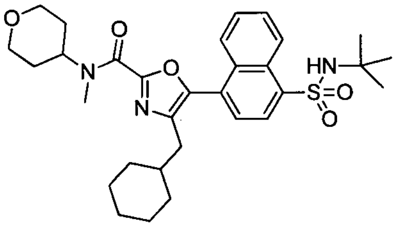
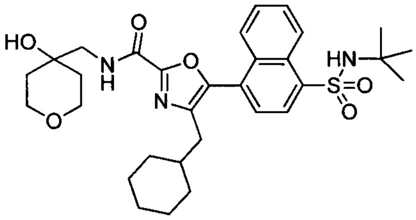
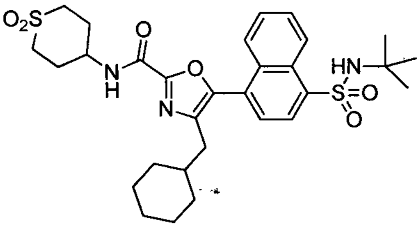
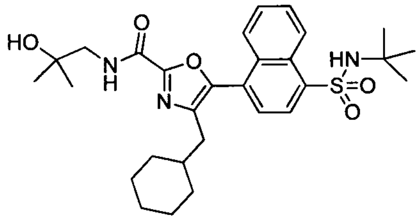
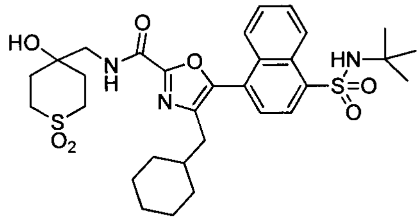
Step 6 : 4-(Cvclohexylmethyl)-5-(3.5-di-rerf-butylphenyl)oxazole-2-carboxamide **(100)**

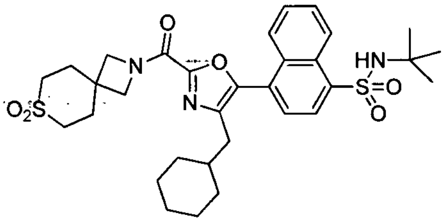
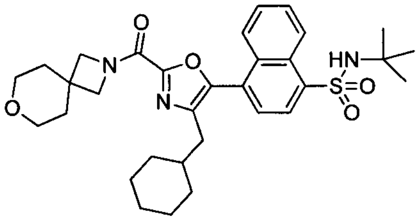
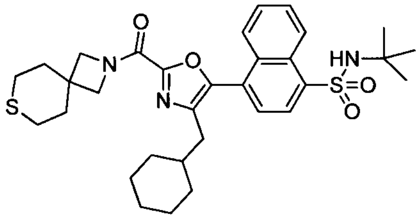
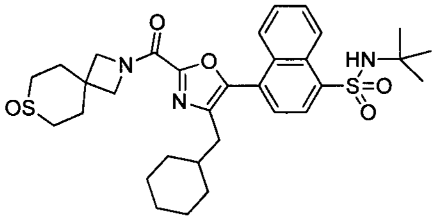
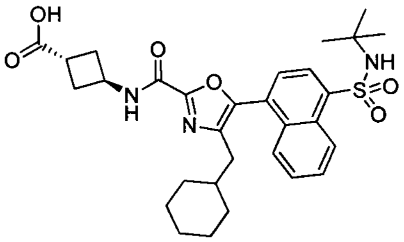
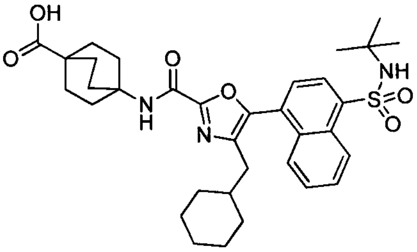
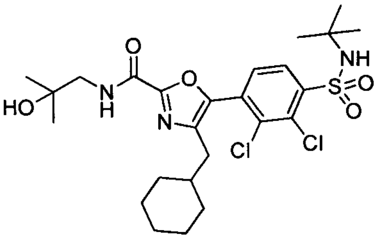
To a solution of compound **100e** (270 mg, 0.7 mmol) and 1 drop of DMF in DCM (10 mL) at 0°C was added dropwise oxalyl chloride (0.15 mL, 1.5 mmol). The reaction mixture was stirred at rt for 0.5 h and concentrated. A solution of the crude carbonyl chloride in dry THF (5 mL) was added to a **NH_3/THF** solution (20 mL) and the mixture stirred at rt for 1 h, quenched with aq. $NaHC0_3$ (30 mL) and extracted with EA (3 x). The combined organic layers were washed with brine, dried over Na_2S0_4, concentrated and purified by CC (PE/EA = 4/1) to give the compound **100** (75 mg, 22%) as a white solid. ^{1}H-NMR ($CDCl_3$, 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$^+$).

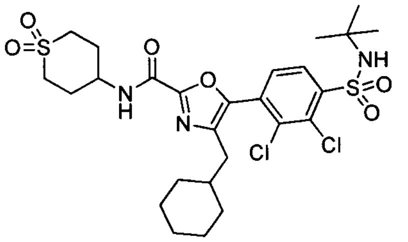
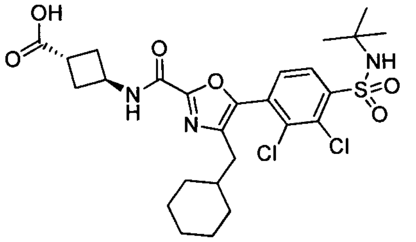
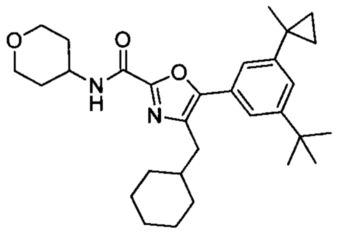
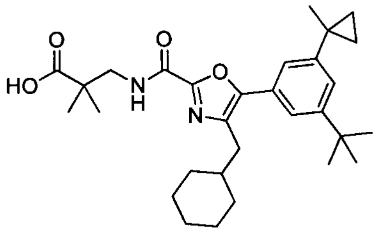
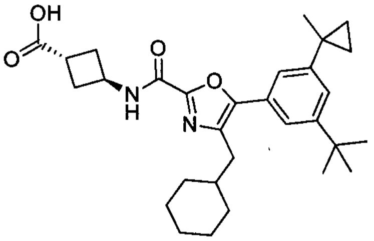
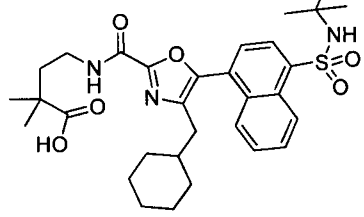
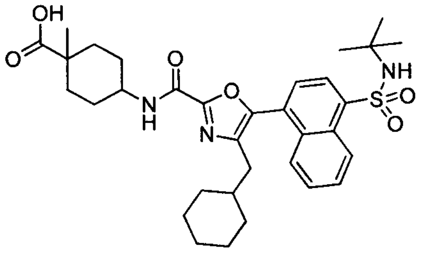
Example 100/1 to 100/20

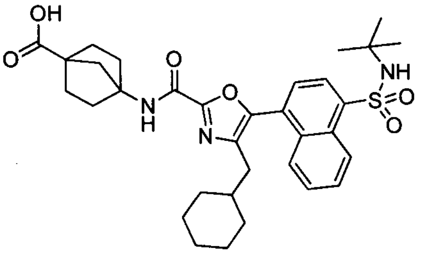
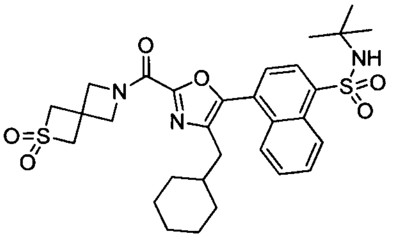
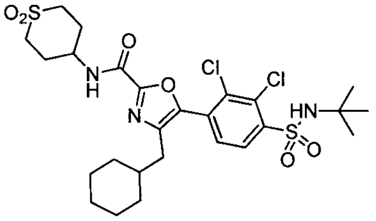
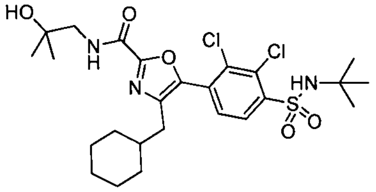
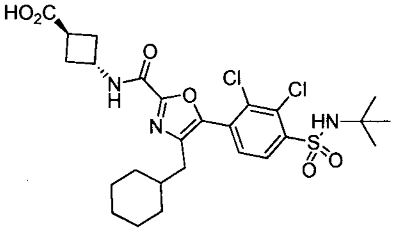
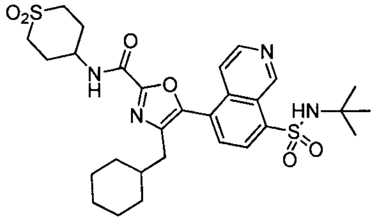
The following Examples were prepared similar as described above:

#	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), 4.25-4.1 4 (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)$^+$**

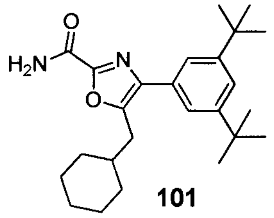
#	Structure	Analytical data
100 /2		^{1}H-NMR (400 MHz, DMSO-d_6) δ: 9.23 (d, J = 7.6 Hz, 1H), 8.25 (d, J = 8.0 Hz, 1H), 7.86 (s, 2H), 7.78 (d, J = 8.0 Hz, 1H), 4.59-4.54 (m, 1H), 2.93-2.89 (m, 1H), 2.71 (d, J = 6.4 Hz, 2H), 2.49-2.43 (m, 4H), 1.80-1.64 (m, 6H), 1.58 (s, 9H), 1.20-1.15 (m, 12H), 1.03-1.00 (m, 2H). MS 574.3 $(M+1)^+$
100 /3		^{1}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}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, ½H), 4.86-4.79 (m, ½H), 4.15-4.05 (m, 2H), 3.60-3.43 (m, 2H), 3.38 (s, 1½H), 3.07 (s, 1½H), 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}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}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}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}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}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 $(M+1)^+$
100 /10		^{1}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 $(M+1)^+$
100 /11		^{1}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 $(M+1)^+$
100 /12		^{1}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 $(M+1)^+$
100 /13		^{1}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 $(M+1)^+$
100 /14		^{1}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 $(M+1)^+$
100 /15		MS 560.2 $(M+1)^+$

#	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}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 $(M+1)^+$
100/24		^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 0.69-0.73 (m, 2H), 1.04-1.16 (m, 3H), 1.18 (s, 9H), 1.58-1.72 (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 $(M+1)^+$
100/25		^{1}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,1 H). MS 620.1 $(M+1)^+$.
100/26		^{1}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 $(M+1)^+$.
100/27		^{1}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 $(M+1)^+$.
100/28		^{1}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 $(M+1)^+$.

Example 101



101

Step 1: 4-Methylbenzenesulfinic acid **(101a)**

To a mixture of sodium 4-methylbenzenesulfinate (1.0 g, 5.0 mmol) in TBME (30 mL) was added cone. 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 Na_2S0_4 and concentrated to give compound **101a** (0.8 g, 93%) as a white solid.

Step 2: /N/-((3,5-Di-terf-butylphenyl)(tosyl)methyl)formamide **(101b)**

To a solution of 3,5-di-terf-butylbenzaldehyde (873 mg, 4 mmol) in toluene (6 mL) and MeCN (6 mL) was added formamide (540 mg, 12 mmol) and TMSCI (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-(isocvano(tosyl)methyl)benzene **(101c)**

To a solution of compound **101b** (0.20 g, 0.49 mmol) in THF (1.5 mL) was added $POCI_3$ (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. $NaHC0_3$ (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-(Cvclohexylmethyl)-4-(3.5-di-fe/t-butylphenyl)oxazole **(101d)**

A solution of compound **101c** (0.20 g, 0.50 mmol), 2-cyclohexylacetaldehyde (64 mg, 0.50 mmol) and K_2C0_3 (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.

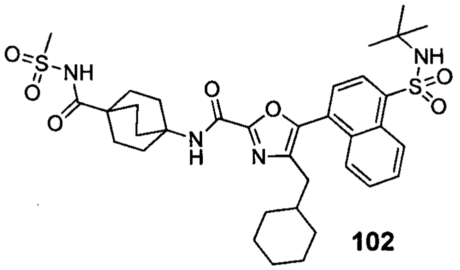
Step 5: Ethyl 5-(cvclohexylmethyl)-4-(3,5-di-te/t-butylphenyl)oxazole-2-carboxylate **(101e)**

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. NH_4CI 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-(Cvclohexylmethyl)-4-(3,5-di-terf-butylphenyl)oxazole-2-carboxamide **(101)**

A mixture of compound **101e** (300 mg, 0.70 mmol) and THF/NH_3 (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. ^{1}H-NMR ($CDCI_3$, 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

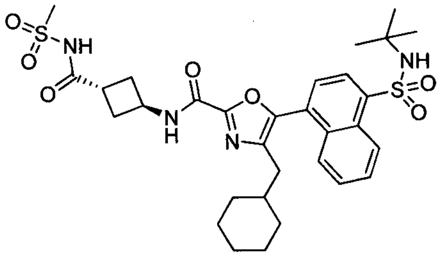


5-(4-(A/-(te/i-Butyl)sulfamoyl)naphthalen-1-yl)-4-(cvclohexylmethyl)-A/-(4-((methylsulfonyl)carbamoyl)bicvclor2.2.2loctan-1-yl)oxazole-2-carboxamide **(102)**

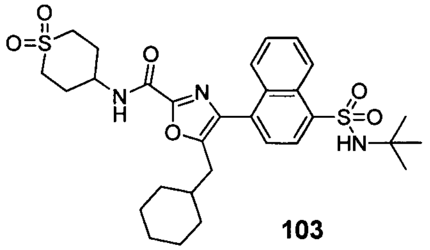
A solution of compound **100/14** (94 mg, 0.15 mmol), EDCI (105 mg, 0.53 mmol), DMAP (110 mg, 0.85 mmol) and $MeS0_2NH_2$ (45 mg, 0.44 mmol) in DCM (5 mL) were stirred at 30°C overnight, diluted with EA, washed with H_20 and brine, dried over Na_2S0_4, concentrated and purified by prep-HPLC to give compound **102** (31 mg, 30%) as a white solid. ^{1}H-NMR (300 MHz, $CDCl_3$) 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

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 103



Step 1: 2-Cvclohexylacetaldehvde **(103a)**

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 Et_20 , 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-Cvclohexyl-2-hvdroxypropanenitrile **(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. Trimethysilyl 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 Na_2S0_4, 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.

Step 3: 1-Amino-3-cvclohexylpropan-2-ol **(103c)**

A solution of compound **103b** (24.1 g, 144 mmol) in dry THF (250 mL) was added $LiAlH_4$ (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 $LiAlH_4$ was neutralized by addition of H_20 (8 mL), 15% aq. NaOH (8 mL) and H_20 (24 mL). The suspension was stirred until all $LiAlH_4$ was neutralized and a white precipitate was formed, filtered and the precipitate was washed with Et_20. The combined organic layers were dried over Na_2S0_4, filtered and concentrated to give compound **103c** (21.6 g, 95%) as a colorless oil.

Step 4: Ethyl 2-((3-cvclohexyl-2-hvdroxypropyl)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. $NaHC0_3$ and extracted with EA. The organic layer was washed with brine, dried over Na_2S0_4, filtered, concentrated and purified by CC (PE/EA = 1/1) to give compound **103d** (12.4 g, 35%) as a colorless oil.

Step 5: Ethyl 2-((3-cvclohexyl-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 Na_2S0_4, filtered, concentrated and purified by CC (PE/EA = 1/1) to give compound **103e** (10.1 g, 82%) as colorless solid.

Step 6: Ethyl 5-(cvclohexylmethyl)oxazole-2-carboxylate **(103f)**

A solution of compound **103e** (10.1 g, 39.6 mmol) and $POCl_3$ (6.1 g, 39.6 mmol) in dry toluene (100 mL) was heated at reflux overnight, cooled to rt, concentrated uand then partitioned between DCM and 5% aq. Na_2C0_3. The layers were separated and the aq. layer was extracted with DCM. The combined organic layers were dried over Na_2S0_4, 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-(A/-(te/t-butyl)sulfamoyl)naphthalen-1-yl)-5-(cvclohexylmethvhoxazole-2-carboxylate (103q)

The solution of compound **103f** (500 mg, 2.10 mmol), 4-bromo-A/-(tert-butyl)naphthalene-1-sulfonamide (791 mg, 2.30 mmol), PPh_3 (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 Na_2S0_4, 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-(A/-(te ri-butyl)sulfamoyl)naphthalen-1-yl)-5-(cvclohexylmethyl)oxazole-2-carboxylate (103h)

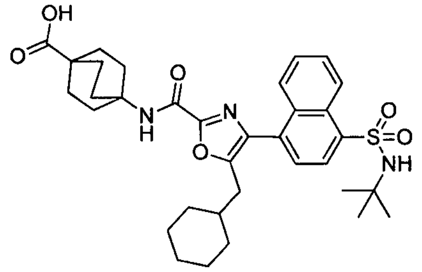
To a solution of compound **103g** (350 mg, 0.70 mmol) in a mixture of MeOH (10 mL) and H_20 (1 mL) was added KOH (56 mg, 1.0 mmol) and the mixture was stirred at rt for 5 h and concentrated to give crude compound **103h** (365 mg) as an off-white solid.

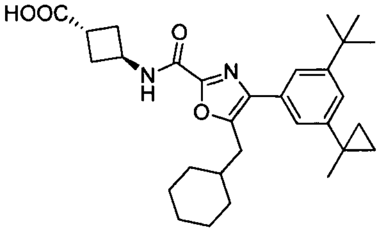
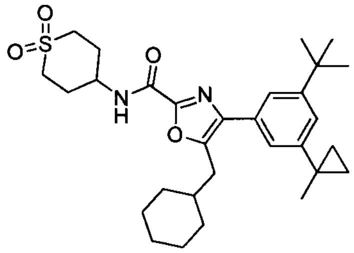
Step 9: 4-(4-(/V-(te/Y-Butyl)sulfamoyl)naphthalen-1-yl)-5-(cvclohexylmetriyl)-/V-(1,1-dioxidotetrahvdro-2H-thiopyran-4-yl)oxazole-2-carboxamide (103)

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 H_20 and EA. The organic layer was washed with brine, dried over Na_2S0_4, filtered, concentrated and purified by prep-HPLC to give compound **103** (31 mg, 18%) as a colorless solid. ^{1}H-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 $[M+1]^+$.

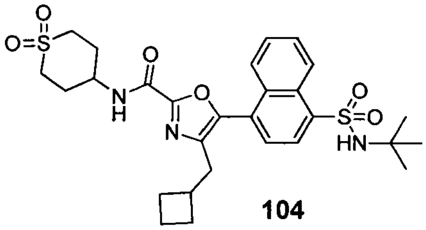
Example 103/1 to 103/3

The following Examples were prepared similar as described in Example **103** above:

#	Structure	Analytical data
103 /1		^{1}H-NMR (300 MHz, DMSO-d_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, J = 6.9 Hz, 2H), 7.62-7.72 (m, 3H), 7.86 (s, 1H), 7.94-7.97 (m, 2H), 8.23 (d, J = 7.5 Hz, 1H), 8.75 (d, J = 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



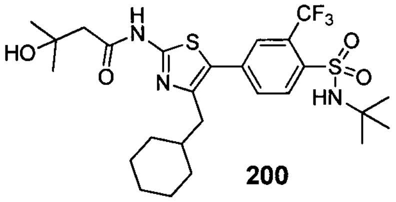
Step 1: Ethyl 5-(4-(/V-(terf-butyl)sulfamoyl)naphthalen-1-yl)-4-(cvclobutylmethyl)oxazole-2-carboxylate **(104a)**

To a solution of /V-(fert-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_2S0_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-(A/-(te/t-Butyl)sulfamoyl)naphthalen-1 **-vn**-4-(cvclobutylmethyl)-/V-(1 ,1-dioxidotetrahvdro-2H-thiopyran-4-yl)oxazole-2-carboxamide **(104)**

Example **104** was prepared from intermediate **104a** similar as described for Example **6** from intermediate **6e.** ^{1}H-NMR (300 MHz, $CDCl_3$) 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



200

Step 1: 4-(Cvclohexylmethyl)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. $NaHC0_3$. The organic layer was washed with brine, dried over Na_2S0_4, 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-(cvclohexylmethyl)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 cobined organic layer was washed with brine, dried over Na_2S0_4 and evaporated to obtain compound **200b** (7.5 g, 71%) as yellowish solid.

Step 3: /V-(5-Bromo-4-(cvclohexylmethyl)thiazol-2-yl)-3-hvdroxy-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 cobined organic layer was washed with brine, dried over Na_2S0_4 and evaporated to obtain compound **200c** (220 mg, 29%) as yellowish solid.

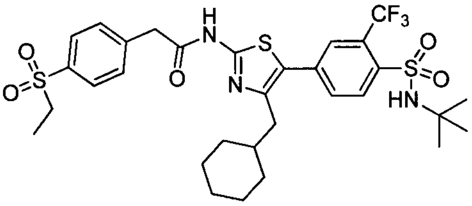
Step 4: A/-(5-(4-(A/-(terf-Butyl)sulfamoyl)-3-(trifluoromethyl)phenyl)-4-(cvclohexylmethyl)thiazol-2-yl)-3-hvdroxy-3-methylbutanamide **(200)**

A suspension of compound **200c** (75 mg, 0.2 mmol), Cs_2C0_3 (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), $Pd(PPh_3)_4$ (23 mg, 20 pmol) in toluene/H_20 (10:1, 10mL) was heated overnight under N_2 at 100°C, concentrated and extracted with EA. The organic layer was washed with brine, dried over $MgS0_4$, filtrered, evaporated and purified by prep-HPLC to give compound **200** (30 mg, 25%) as yellowish solid. ^{1}H-NMR (DMSO-d_6, 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 $(M+1)^+$.

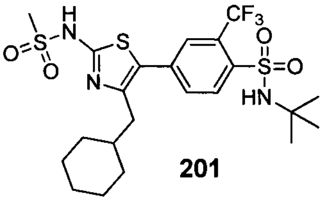
Example 200/1

The following Example was prepared similar as in Example **200:**

#	Structure	Analytical data

#	Structure	Analytical data
200/1		^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.25 (d, J = 8.4 Hz, 1H), 7.87 (d, J = 8.4 Hz, 2H), 7.79 (s, 1H), 7.61 (d, J = 8.4 Hz, 1H), 7.50 (d, J = 8.4 Hz, 2H), 4.68 (s, 1H), 3.87 (s, 2H), 3.1 1-3.05 (m, 2H), 2.49 (d, J = 7.2 Hz, 2H), 1.59-1.53 (m, 6H), 1.26-1.20 (m, 12H), 1.12-0.79 (m, 5H). MS 686.1 $(M+1)^+$.

Example 201



201

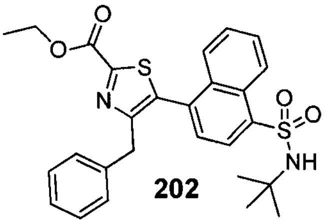
Step 1: A/-(5-Bromo-4-(cvclohexylmethyl)thiazol-2-yl)methanesulfonamide **(201a)**

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_2S0_4, filtered and concentrated to give compound **201a** (640 mg, 91%) as a yellowis solid.

Step 2: *N-(*fe/†-Butyl)-4-(4-(cvclohexylmethyl)-2-(methylsulfonamido)thiazol-5-yl)-2-(trif luoromethvDbenzenesulfonamide **(201)**

A suspension of compound **201a** (90 mg, 0.25 mmol), Cs_2C0_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), Pd $(PPh_3)_4$ (35 mg, 0.03 mmol) in toluene/H_20 (10:1, 10 mL) was heated overnight under N_2 at 100°C, cooed, concentrated and extracted with EA. The organic layer was washed with brine, dried over $MgS0_4$, filtered, evaporated and purified by prep-HPLC to give compound **201** (35 mg, 25%) as yellowish solid. ^{1}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 $(M+1)^+$.

Example 202

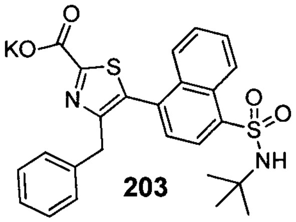


202

Ethyl 4-benzyl-5-(4-(/V-(terf-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 (2.1 1 g, 5.43 mmol), Na_2C0_3 (1.90 g, 18.0 mmol) and Pd(dppf)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 Na_2S0_4, 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. ^{1}H-NMR (400 MHz, $CDCI_3$) 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 $[M+1]^+$.

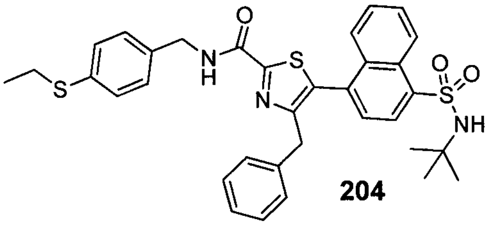
Example 203


203

Potassium 4-benzyl-5-(4-(A/-(te^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 H_20 (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 Et_20 and dried in vacuum to give compound **203** (1.32 g, 96%) as a yellow solid. ^{1}H-NMR (400 MHz, CD_3OD) 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 $[M-K+1]^+$.

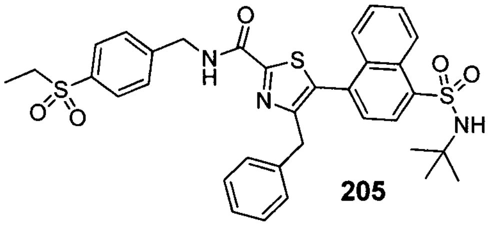
Example 204


204

4-Benzyl-5-(4-(A/-(ferf-butyl)sulfamoyl)naphthalen-1-yl)-/V-(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 H_20 and extracted with EA (3x). The combined organic layers were washed with water (3x) and brine consecutively, dried over Na_2S0_4, filtered, concentrated and purified by prep-HPLC to give compound **204** (117 mg, 48%) as a white powder.

Example 205

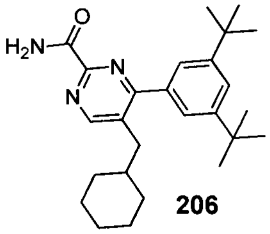


205

4-Benzyl-5-(4-(A/-(tetf-butyl)sulfamo yl)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. Na_2S0_3 and extracted with EA. The organic layer was washed with water and brine, dried over Na_2S0_4, filtered, concentrated and purified by prep-HPLC to give compound **205** (67 mg, 56%) as a white solid. ^{1}H-NMR (400 MHz, $CDCl_3$) 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



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-(cvclohexylidenemethyl)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. NH_4Cl 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 Na_2S0_4, 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-(cvclohexylidenemethyl)-4-(3,5-di -te A/-butylphenyl)pyrimidine **(206c)**

A mixture of compound **206b** (2.0 g, 8.26 mmol), 2-(3,5-di-fert-butylphenyl)-4,4,5,5-tetramethyl-1 ,3,2-dioxaborolane (3.13 g, 9.91 mmol), K_2C0_3 (3.19 g, 23.1 mmol), in 1,4-dioxane (20 mL) were purged with Ar for 15 min in a sealed vial. $Pd(PPh_3)_4$ (0.477 g, 413 μηηοΙ) 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.

Step 4: 5-(Cvclohexylidenemethyl)-4-(3,5-di-rerf-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 Na_2S0_4, evaporated and purified by CC (5% EA in PE) to afford compound **206d** (0.50 g, 45 %) as pale yellow solid.

Step 5: 5-(cvclohexylidenemethyl)-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 $CHCl_3$ (3 x 10 mL). The combined organic layer was dried over Na_2S0_4, evaporated and purified by CC (EA/PE = 1/1) to afford compound **206e** (0.3 g, 36%) as pale yellow solid.

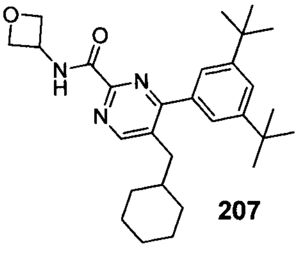
Step 6: 5-(Cvclohexylidenemethyl)-4-(3,5-di-re/t-butylphenyl)pyrimidine-2-carboxamide **(206f)**

A mixture of compound **206e** (150 mg, 369 μιηοΙ) and thionylchloride (133 μL, 1.85 mmol) was refluxed for 2 h. The thionylchloride was evaporated and NH_3 (7N in THF, 1 mL) was added at 0°C. The mixture was stirred at rt for 3 h, evaporated and dissolved in $CHCl_3$ (2 mL) and washed with water (2 x 2 mL). The organic layer was dried over Na_2S0_4, evaporated and purified by CC (30% EtOAc in PE) to afford compound **206f** (0.15 g, quant.) as brown syrup.

Step 7: 5-(Cvclohexylmethyl)-4-(3,5-di-fe/t-butylphenyl)pyrimidine-2-carboxamide **(206)**

Compound **206f** (0.15 g, 370 μηιοΙ) 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, filterd through celite and was washed with MeOH (2 mL). The solvent was evaporated and the obtained crude product was dissolved in $CHCl_3$ (5 mL) and washed with water (5 mL). The organic layer was dried over Na_2S0_4, evaporated and purified by CC (PE/EA = 1/1) to afford compound **206** (70 mg, 50%) as white solid. ^{1}H-NMR (CDCI$_3$, 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 (M+1)$^+$.

Example 207



207

Step 1: 5-(Cvclohexylidenemethyl)-4-(3,5-di-te/t-butylphenyl)-A/-(oxetan-3-yl)pyrimidine-2-carboxamide **(207a)**

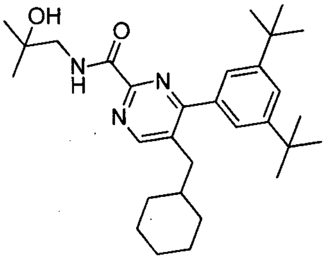
Compound **206e** (0.15 g, 369 μιτιοl) was dissolved in DCM (5 mL) and TEA (74 mg, 770 μηπιοl) was added followed by an excess of propylphosphonic acid anhydride and oxetan-3-amine (32 mg, 443 μηηοl). The mixture was stirred for 16 h at rt and diluted with water. The organic layer was separated, dried over Na$_2$S0$_4$ and evaporated to afford crude compound **207a** (0.15 g, 88%).

Step 2: 5-(Cvclohexylmethyl)-4-(3,5-di-tert-butylphenyl)-/V-(oxetan-3-yl)pyrimidine-2-carboxamide **(207)**

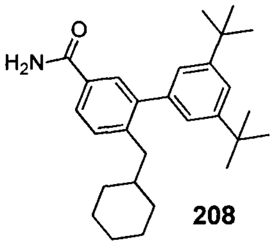
Compound **207a** (0.15 g, 325 μmoI) was dissolved in MeOH (5 mL) and 2N NaOH (0.1 mL) was added. Then Pd/C (20 mg) was added and the mixture was kept under hydrogen atmosphere (ballon pressure). After completion the mixture was filtered through celite and the celite was washed with MeOH (2 mL). The solvent was evaporated and the obtained crude product was dissolved inCHCI$_3$ (5 mL). The organic layer was washed with water (5 mL), dried over Na$_2$S0$_4$, evaporated and purified by CC (PE/EA = 1/1) to afford compound **207** (65 mg, 50%) as colorless solid. ^{1}H-NMR (CDCI$_3$, 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 (M+1)$^+$.

Example 207/1

The following Example was prepared similar as described in Example **207.**

#	Structure	Analytical data
207/1		^{1}H-NMR (CDCI$_3$, 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 (M+1)$^+$

Example 208



208

Step 1: Methyl 3-bromo-4-(bromomethyl)benzoate **(208a)**

AIBN (71 mg, 440 μηηοl) 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-(cvclohexylidenemethyl)benzoic acid **(208b)**

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 at 0°C and extracted with DCM (3 x 10 ml_). The combined organic layer was dried over Na_2S0_4 and evaporated to obtain crude product **208b.**

Step 3: 3',5'-Di-te/t-butyl-6-(cvclohexylidenemethyl **)-[1**,1'-biphenvn-3-carboxylic acid **(208c)**

A mixture of compound **208b** (0.5 g, 1.69 mmol), 2-(3,5-di-terf-butylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.64 g, 2.03 mmol), Na_2C0_3 (0.50 g, 4.74 mmol) in 1,4-dioxane and water was purged with Ar for 15 min. Then $Pd(PPh_3)_4$ (97 mg, 85 mmol) was 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-te/t-butyl-6-(cvclohexylmethyl **)-[1**.1'-biphenvn-3-carboxylic acid **(208d)**

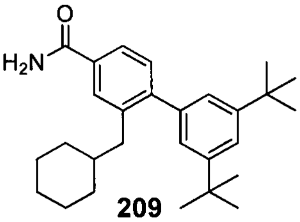
Pd/C (10 mg) was added to a solution of compound **208c** (100 mg, 247 mmol) in MeOH and the reaction was performed under 60 psi hydrogen pressure at rt for 16 h. The mixture was filtered through celite and the filtrate was evaporated. The obtained crude product was partitioned between water and 10% MeOH/DCM. The organic layer was separated and dried over Na_2S0_4 and evaporated. The obtained crude product was triturated with Et_20 and the solid was filtered off and dried under vacuum to afford compound **208d** (45 mg, 45%) as pale yellow solid.

Step 5: 3'.5'-Di-t *rt*-butyl-6-(cvclohexylmethyl **)-ri** .1'-biphenyll-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 NH_3 (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 Na_2S0_4 and evaporated. The obtained crude product was triturated with ACN and dried under vacuum to afford compound **208** (60 mg, 60%). ^{1}H-NMR (DMSO-d_6, 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 $(M+1)^+$.

Example 209

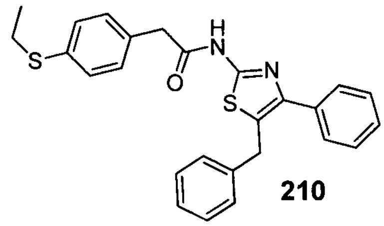
The following Example was prepared using similar procedures as that decribed in Example **208.**



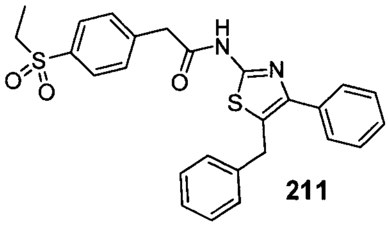
209

^{1}H-NMR (DMSO-de, 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



210



211

Step 1: 5-Benzyl-4-phenylthiazol-2-amine **(210a)**

(2-Amino-4-phenylthiazol-5-yl)(phenyl)methanone (prepared similar as described in WO201 2/0281 00) was reduced with $NaBH_4$ and the obtained alcohol was treated with Et_3SiH and TFA to afford compound **210a.**

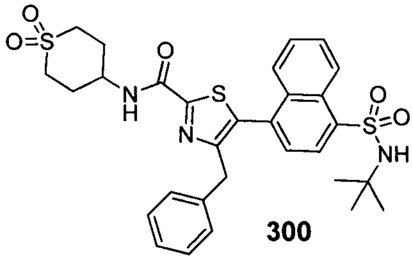
Step 2: /V-(5-Benzyl-4-phenylthiazol-2-yl)-2-(4-(ethylthio)phenyl)acetamide **(210)**

Compound **210a** was coupled with 2-(4-(ethylthio)phenyl)acetic acid similar as described in WO201 2/0281 00 to afford compound **210.**

Step 3: /N/-(5-Benzyl-4-phenylthiazol-2-yl)-2-(4-(ethylsulfonyl)phenyl)acetamide **(211)**

Compound **210** was oxidized with mefa-chloroperoxybenzoic acid to afford compound **211** as a colorless solid. ^{1}H-NMR ($CDCl_3$, 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 $(M+1)^+$.

Example 300



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 Br_2 (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 Na_2S0_4, 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 NH_4OH. and extracted with EA (3x). The combined organic layers were dried over Na_2S0_4, 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/-(fert-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 PPh_3 (118 mg, 0.45 mmol) in DMF (10 mL) was bubbled with N_2 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-(A/-(t *rt*-butyl)sulfamoyl)naphthalen-1-yl)thiazole-2-carboxylate **(300d)**

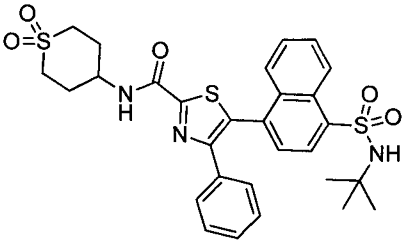
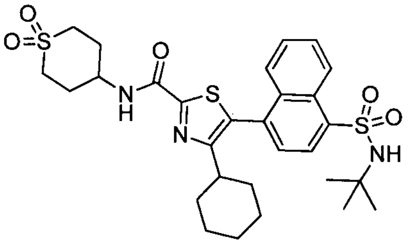
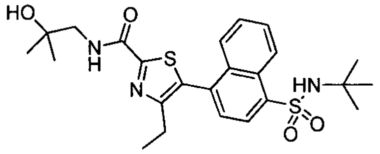
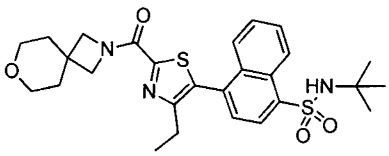
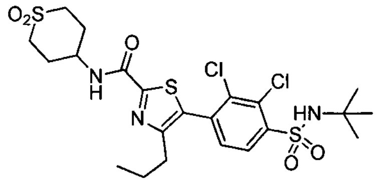
A solution of compound **300c** (200 mg, 0.39 mmol) and KOH (28 mg, 0.5 mmol) in MeOH (5 mL) was stirred at rt for 4 h, concentrated and washed with Et_20 to give crude compound **300d** (210 mg) as an off-white solid.

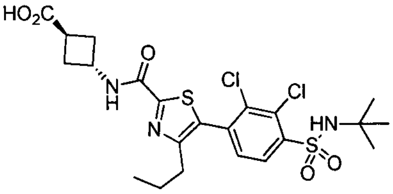
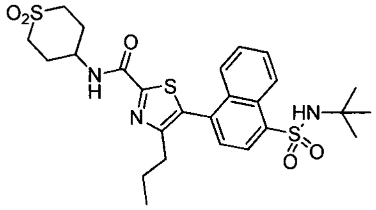
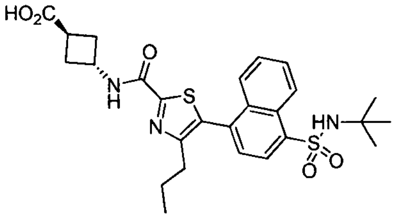
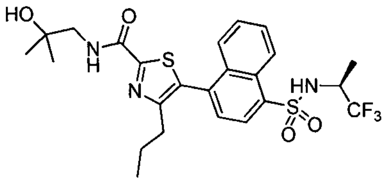
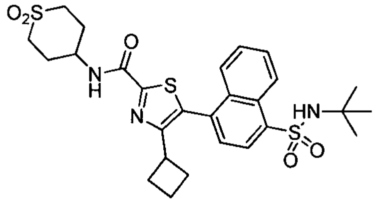
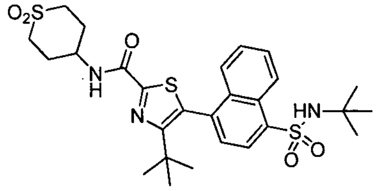
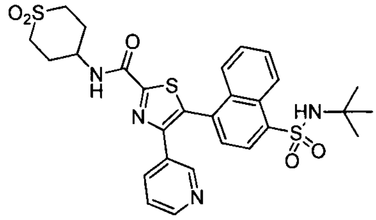
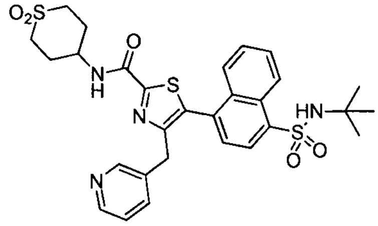
Step 5: 4-Benzyl-5-(4-(A/-(tert-butyl)sulfamoyl)naphthalen-1-yl)-A/-(1 ,1-dioxidotetrahvdro-2H-thiopyran-4-yl)thiazole-2-carboxamide **(300)**

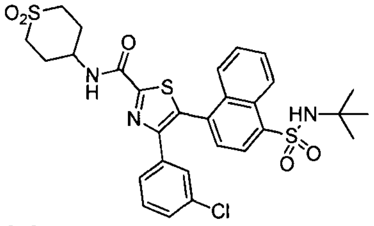
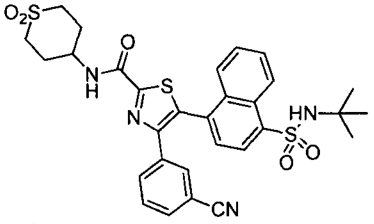
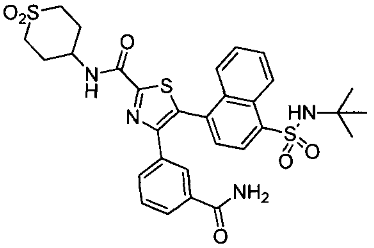
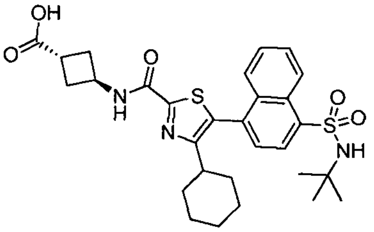
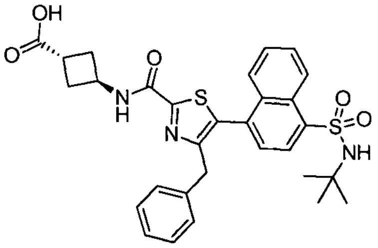
A solution of crude compound **300d** (200 mg, 0.39 mmol), 1,1-dioxo-hexahydro-1-thiopyran-4-ylamine (148 mg, 0.80 mmol), DIEA (206 mg, 1.6 mmol) and HATU (304 mg, 0.80 mmol) in DMF (5 ml_) was stirred overnight at rt, diluted with water and extracted with EA (3x). The combined organic layers were washed with water (3x) and brine consecutively, dried over Na_2S0_4, filtered, concentrated and purified by prep-HPLC to give compound **300** (57 mg, 24% over two steps) as a white solid. ^{1}H-NMR (300 MHz, $CDCl_3$) 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

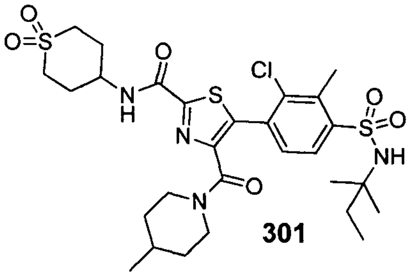
The following Example was prepared similar as described in Example **300.**

#	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, J = 7.5 Hz, 1H), 7.65-7.7.70 (m, 1H), 7.78-7.81 (m, 1H), 8.32 (d, J = 7.5 Hz, 1H), 8.68 (d, J = 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, J = 8.1 Hz, 1H), 7.49 (d, J = 7.5 Hz, 1H), 7.54-7.59 (m, 1H), 7.69-7.74 (m, 2H), 8.35 (d, J = 7.5 Hz, 1H), 8.69 (d, J = 9.3 Hz, 1H). MS 604.3 [M+1]$^+$
300/3		^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.80 (d, 1H, J = 8.4 Hz), 8.35 (m, 1H), 8.25 (m, 1H), 7.95 (s, 1H), 7.75 (m, 4H), 3.32 (d, 2H, J = 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, J = 8.8 Hz), 8.35 (d, 1H, J = 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, J = 8.0 Hz), 7.39 (d, 1H, J = 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, J = 7.2 Hz). MS 582.2 (M+H)$^+$

#	Structure	Analytical data
300/6		^{1}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}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}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 5MS78.2 $(M+H)^+$

Example 301



301

Step 1: 2-(Ethoxycarbonyl)thiazole-4-carboxylic acid **(301a)**

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 H_20 and extracted with EA. The organic layer was washed with brine, dried over Na_2S0_4, 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-(A/-(te/t-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-/V-(terf-pentyl)benzenesulfonamide (301 mg, 0.85 mmol), KOAc (139 mg, 1.42 mmol), PPh_3 (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 Na_2S0_4, 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-(A/-(teft-pentyl)sulfamoyl)phenvn-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 H_20 (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 Na_2S0_4, filtered and concentrated to give compound **301d** (0.9 g, 90%) as a pale yellow solid.

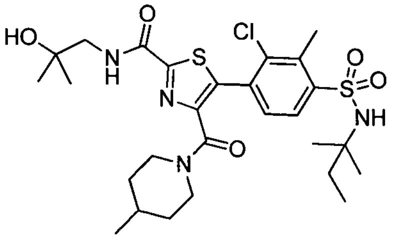
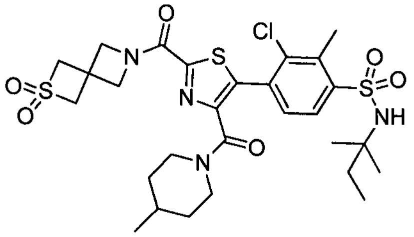
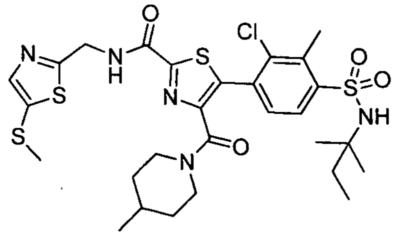
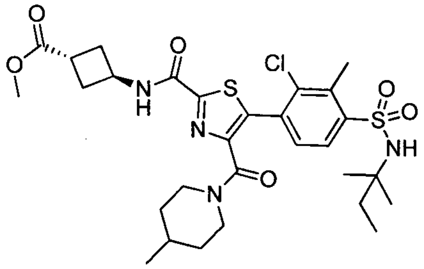
Step 5: 5-(2-Chloro-3-methyl-4-(A/-(terf-pentyl)sulfamovnphenyl)-A/-f 1,1-dioxidotetrahvdro-2H-thiopyran-4-yl)-4-(4-methylpiperidine-1-carbonyl)thiazole-2-carboxamide **(301)**

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 H_20 and diluted with DCM. The organic layer was washed with brine, dried over Na_2S0_4, filtered, concentrated and purified by prep-HPLC to give compound **301** (40 mg, 27%) as white solid. ^{1}H-NMR (300 MHz, $CDCl_3$) 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 $[M+1]^+$.

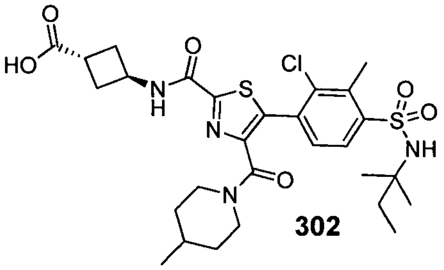
Example 301/1 to 301/4

The following Example was prepared similar as described in Example **301.**

#	Structure	Analytical data

#	Structure	Analytical data
301/1		^{1}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 [M+1]$^+$
301/2		^{1}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 [M+1]$^+$
301/3		n.t.
301/4		n.t.

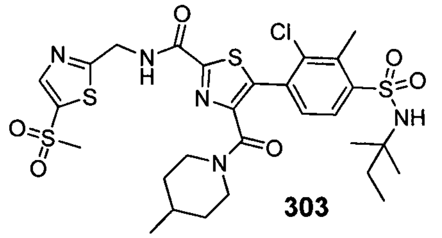
Example 302


302

frans-3-(5-(2-Chloro-3-methyl-4-(N-(fert-^ entyl)sulfamoyl)phenyl)-4-(4-methylpiperidine-1-carbonyl)thiazole-2-carboxamido)cvclobutanecarboxylic acid **(302)**

To a solution of compound **301/4** (60 mg, 94 μmol) in a mixture of THF (5 mL) and H_20 (1 mL) was added LiOH·H_20 (39 mg, 940 pmol), 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_2S0_4, filtered, concentrated and purified by prep-TLC (DCM/MeOH = 15/1) to give compound **302** (40 mg, 68%) as a white solid. ^{1}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), 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

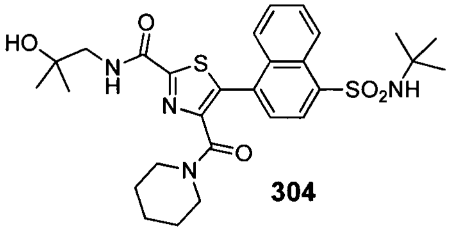


303

5-(2-Chloro-3-methyl-4-(A/-(fertpentyl)sulfamoyl)phenyl)-4-(4-methylpiperidine-1-carbonyl)-*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 H_20 and diluted with DCM. The organic layer was washed with brine, dried over Na_2S0_4, filtered, concentrated and purified by prep-HPLC to give compound **303** (70 mg, 53%) as a white solid. ^{1}H-NMR (300 MHz, $CDCl_3$) 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 $[M+1]^+$.

Example 304



304

Step 1: Ethyl 4-(hvdroxymethyl)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 Na_2C0_3 (15 mL) and water (15 mL), and extracted with EA (6 x 20 mL). The aq. layer was then acidified to pH = 2 with cone. HCl, resulting in the formation of a precipitate. This suspension was extracted with EA. The extracts were pooled, dried with Na_2S0_4, filtered and concentrated to give compound **304a** as a red-brown solid (115 mg, 73%).

Step 2: /V-(2-hvdroxy-2-methylpropyl)-4-(hvdroxymethyl)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, 0.74mmol). 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 Na_2S0_4, 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-(A/-(terf-butyl)sulfamoyl)naphthalen-1 -yl)-/V-(2-hvdroxy-2-methylpropyl)-4-(hydroxymethyl)thiazole-2-carboxamide **(304c)**

A solution of **304b** (103 mg, 0.45 mmol), 4-bromo-/V-tert-butylnaphthalene-1 -sulfonamide (153 mg, 0.45 mmol), K_2C0_3 (124 mg, 0.9 mmol), $Pd(OAc)_2$ (5 mg, 0.01 mmol), PCy_3•HBF_4 (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 Na_2S0_4, 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-(A/-(tert-butyl)sulfamoyl)naphthalen-1-yl)-2-((2-hvdroxy-2-methylpropyl)carbamoyl)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 $NaHC0_3$ and brine, dried with Na_2S0_4, evaporated and purified by CC (PE/EA = 20/1 to 10/1) to give compound **304d** (95 mg, 73%) as a white solid.

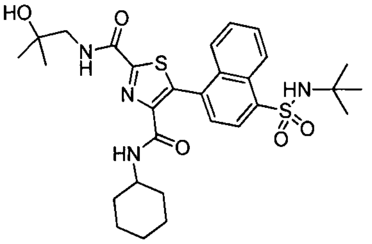
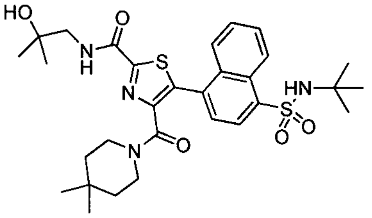
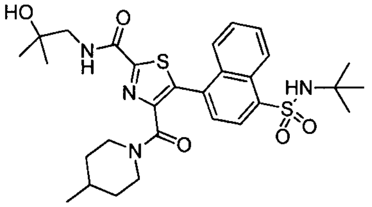
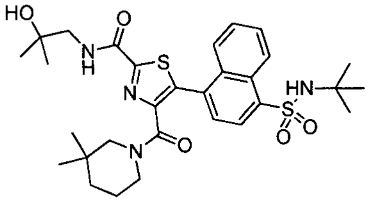
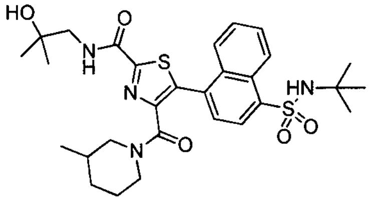
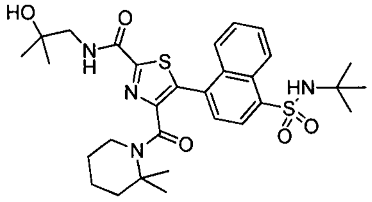
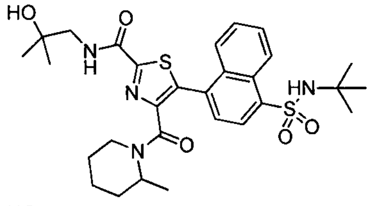
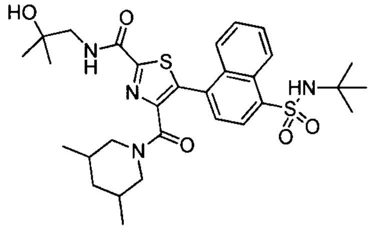
Step 5: 5-(4-(A/-(terf-butyl)sulfamoyl)naphthalen-1 -yl)-A/-(2-hvdroxy-2-methylpropyl)-4-(piperidine-1 -carbonyl)thiazole-2-carboxamide **(304)**

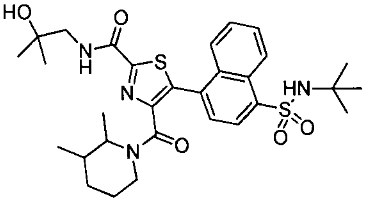
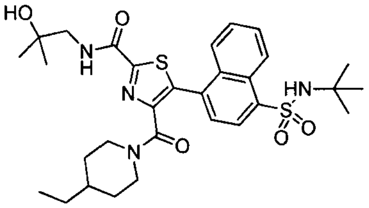
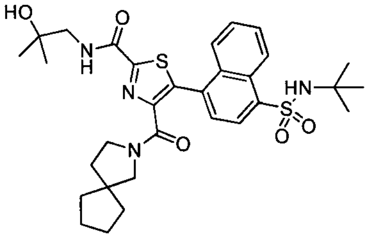
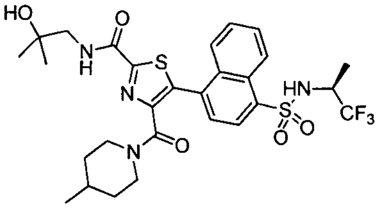
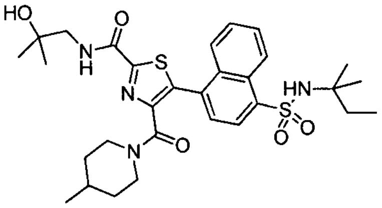
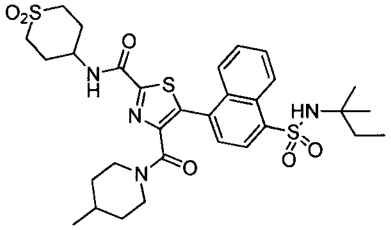
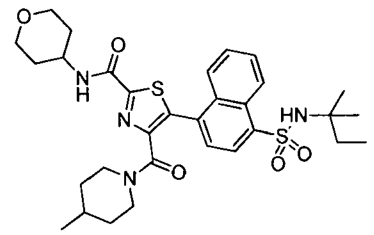
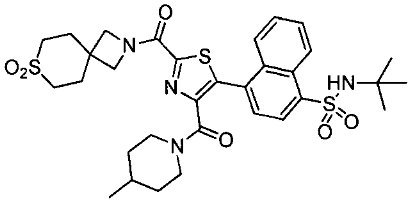
To a solution of **304d** (47 mg, 0.09 mmol) in 3.0 mL DMF was added HATU (13 mg, 0.13 mmol) and DIPEA (35 mg, 0.27 mmol). The mixture was stirred for 60 min and then piperidine (10 mg, 0.1 1 mmol) was added, stirred overnight, quenched with water and extracted with EA. The organic layer was separated, washed with brine and dried over Na_2S0_4. After filtration, the filtrate was evaporated and purified by prep-HPLC to give compound **304** (34 mg, 64%) as a white solid. ^{1}H-NMR (400 MHz, d_6-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 $(M+1)^+$.

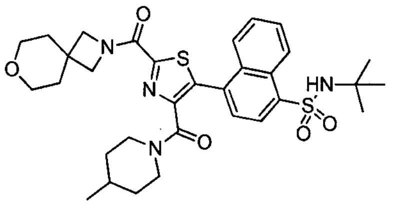
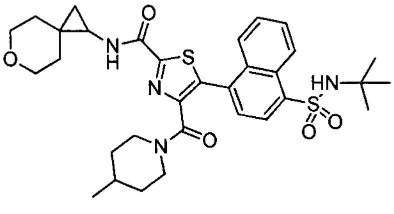
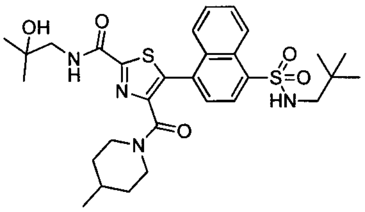
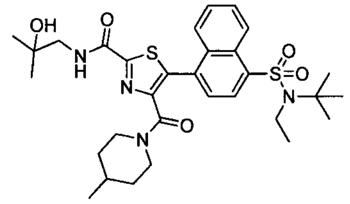
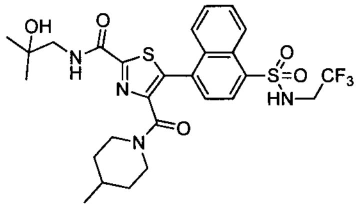
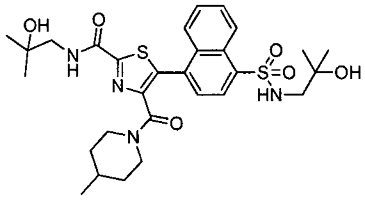
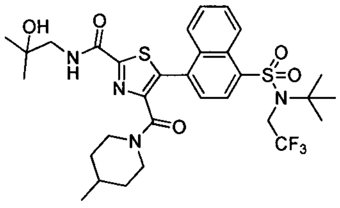
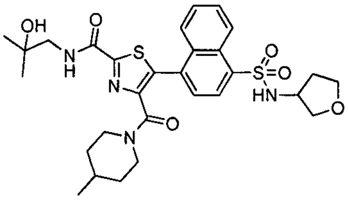
Example 304/1 to 304/27

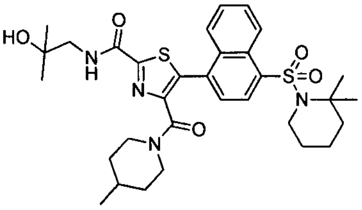
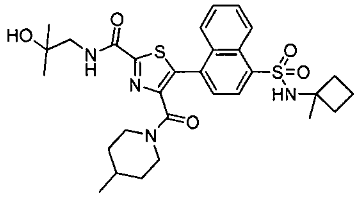
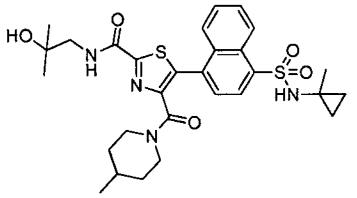
The following examples were prepared similar to Example 304.

#	Structure	Analytical data

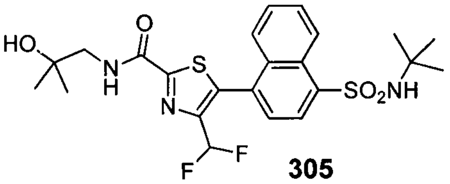
#	Structure	Analytical data
304/1		^{1}H-NMR (400 MHz, d$_6$-DMSO) δ: 8.79-8.74 (m, 2H), 8.33 (d, 1H, J = 8.4 Hz), 8.19 (d, 1H, J = 7.2 Hz), 7.92 (s, 1H), 7.73-7.66 (m, 3H), 7.59 (t, 1H, J = 8.0 Hz), 3.46 (s, 1H), 1.66-1.53 (m, 5H), 1.27-1.06 (m, 20H). MS 587.3 (M+1)$^+$
304/2		^{1}H-NMR (400 MHz, CDCl$_3$) 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}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}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}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}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}H-NMR (400 MHz, 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}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}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 (M+1)$^+$
304/10		^{1}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 (M+1)$^+$
304/11		^{1}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), 3.1 1 (m, 3H), 1.60 (m, 4H), 1.24 (m, 19H). MS 613.3 (M+1)$^+$
304/12		^{1}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 (M+1)$^+$
304/13		^{1}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 (M+1)$^+$
304/14		^{1}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 (M+1)$^+$
304/15		^{1}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 (M+1)$^+$
304/16		MS 673.2 (M+1)$^+$

#	Structure	Analytical data
304/17		^{1}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 (M+1)$^+$
304/18		^{1}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 (M+1)$^+$
304/19		^{1}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 (M+1)$^+$
304/20		^{1}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 (M+1)$^+$
304/21		^{1}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 (M+1)$^+$
304/22		^{1}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 (M+1)$^+$
304/23		^{1}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 (M+1)$^+$
304/24		^{1}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 (M+1)$^+$

#	Structure	Analytical data
304/25		^{1}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}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}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



305

Step 1: Ethyl 5-(4-(A/-(fert-butyl)sulfamoyl)naphthalen-1-yl)-4-formylthiazole-2-carboxylate **(305a)**

A solution of ethyl 5-(4-(/V-(iert-butyl)sulfamoyl)naphthalen-1-yl)-4-(hydroxymethyl)thiazole-2-carboxylate (1.2 g, 2.7 mmol) in DCM (50 mL) was added $Mn0_2$ (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_2S0_4, 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)**

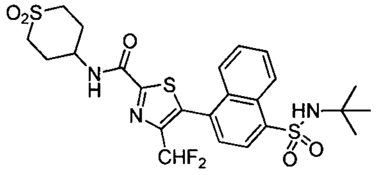
To a solution of compound **305a** (1.1 g, 2.5 mmol) in dry DCM (50 mL) at 0°C was added DAST (0.81 g, 5 mmol) dropwise over 30 min. The mixture was stirred at 0°C for 0.5 h and at rt for 3 h, poured into ice-water and extracted with EA (40 mL x 3). The combined organic layers were washed with brine, dried over Na_2S0_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-(A/-(ferf-butyl)sulfamoyl)naphthalen-1-yl)-4-(difluoromethyl)-/V-(2-hvdroxy-2-methylpropyl)thiazole-2-carboxamide **(305)**

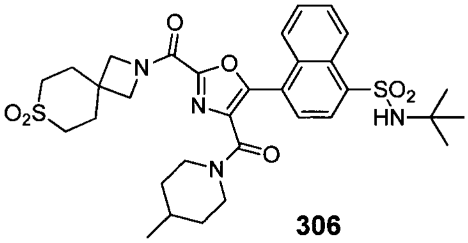
To a solution of compound **305b** (0.66 g, 1.2 mmol) and 1-amino-2-methylpropan-2-ol (0.21 g, 2.4 mmol) in toluene (20 mL) was heated to 95°C overnight, poured into water (40 mL) and extracted with EA (30 mL x 3). The combined organic layers were washed with brine, dried over Na_2S0_4, concentrated and purified by prep-TLC to afford compound **305** (0.5 g, 82%) as a white solid. ^1H-NMR (400 MHz, $CDCl_3$) 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		^1H-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



306

Step 1: Methyl 4-(A/-(tert-butyl)sulfamoyl)-1-naphthoate **(306a)**

A solution of 4-bromo-A/-(terf-butyl)naphthalene-1 -sulfonamide (300 mg, 0.88 mmol), $Pd(AcO)_2$ (19.7 mg, 88 pmol), DPPP (54.4 mg, 0.132 mmol) and NEt_3 (266.6 mg, 2.64 mmol) in CH_3OH (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-(/V-(tert-Butyl)sulfamoyl)-1 -naphthoic acid **(306b)**

A solution of compound **306a** (2.4 g, 7.4 mmol) in CH_3OH/H_20 (10:1, 50 mL) was added ü $OH·H_20$ (0.94 g, 22.4 mmol) and the solution was stirred at rt overnight, concentrated and dissolved in H_20. 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 Na_2S0_4, filtered and concentrated to give compound **306b** (2.2 g, 95%) as a pale white solid.

Step 3: 4-(A/-(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-(A/-(terf-butyl)sulfamoyl)naphthalen-1-vnoxazole-4-carboxylate **(306d)**

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 NEt_3 (400 mg, 4.0 mmol) slowly and the solution was stirred at rt overnight, diluted with EA, washed with sat. NH_4Cl and brine, dried over Na_2SO_4, filtered, concentrated and purified by CC (PE/EA = 3/1) to give compound **306d** (190 mg, 47%) as a yellow solid.

Step 5: 5-(4-(/V-(terf-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 H_2O . 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 Na_2SO_4, filtered and concentrated to give compound **306e** (130 mg, 65%) as a pale white solid.

Step 6: A/-(te^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), 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 Na_2SO_4, 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.

Step 7: Methyl 5-(4-(/V-(tert-butyl)sulfamoyl)naphthalen-1-yl)-4-(4-methylpiperidine-1-carbonvDoxazole-2-carboxylate **(306q)**

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. NH_4Cl, extracted with EA, washed with brine, dried over Na_2SO_4, filtered, concentrated and purified by CC (DCM/MeOH = 100/1) to give compound **306g** (65 mg, 29%) as a white solid.

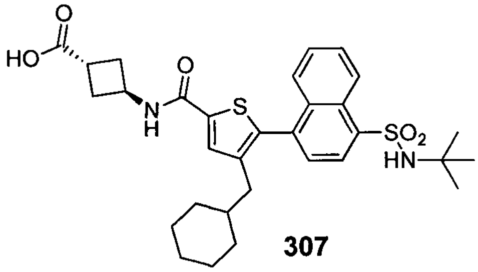
Step 8: 5-(4-(A/-(te/t-Butyl)sulfamoyl)naphthalen-1-yl)-4-(4-methylpiperidine-1-carbonyl)oxazole-2-carboxylic acid **(306h)**

To a solution of compound **306g** (65 mg, 0.13 mmol) in THF/H_2O (3/1, 5 mL) was added LiOH»H_2O (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 Na_2S0_4, filtered and this DCM solution was used for the next reaction without further purification.

Step 9: *N-(*fe/t-Butyl)-4-(2-(7.7-dioxido-7-thia-2-azaspiror3.51nonane-2-carbonvn-4-(4-methyl-piperidine-1 -carbonyl)oxazol-5-yl)naphthalene-1 -sulfonamide **(306)**

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 Na_2S0_4, filtered, concentrated and purified by prep-HPLC to give compound **306** (24 mg, 28% over two steps) as a white solid. ^{1}H-NMR (400 MHz, CD_3OD) 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), 3.1 1-3.20 (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 $(M+1)^+$.

Example 307



307

Step 1: Cvclohexyl(thiophen-3-yl)methanol **(307a)**

To a solution of thiophene-3-carbaldehyde (15.0 g, 134 mmol) in Et_20 (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. NH_4Cl at 0°C and extracted with EA. The organic layer was washed with water and brine, dried over Na_2S0_4, 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: Cvclohexyl(thiophen-3-yl)methyl methanesulfonate **(307b)**

To a solution of compound **307a** (18.8 g, 95.9 mmol) and Et_3N (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.

Step 3: 3-(Cvclohexylmethyl)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 H_2 (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-(cvclohexylmethyl)thiophene **(307d)**

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 Na_2S0_4, 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-(cvclohexylmethyl)thiophene-2-carboxylate **(307e)**

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 N_2 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. NH_4Cl at -78°C and then warmed to rt. After extraction with EA (3x), the combined organic layers were washed with water and brine consecutively, dried over Na_2S0_4, 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-(A/-(te/t-butyl)sulfamoyl)naphthalen-1-yl)-4-(cvclohexylmethyl)thiophene-2-carboxylate **(307f)**

A mixture of compound **307e** (800 mg, 2.42 mmol), compound **P1/2** (1.04 g, 2.67 mmol) $Pd(dppf)Cl_2$ (297 mg, 0.36 mmol) and Na_2C0_3 (771 mg, 7.27 mmol) in dry DME (40 mL) was bubbled with N_2 for 10 min and then refluxed overnight under N_2. 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.

Step 7: 5-(4-(/V-(fe/t-Butyl)sulfamoyl)naphthalen-1-yl)-4-(cvclohexylmethyl)thiophene-2-carboxylic acid **(307q)**

To a solution of compound **307f** (220 mg, 0.428 mmol) in a mixture of MeOH and H_20 (10 mL/1 mL) was added $LiOH·H_20$ (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 was dried with Na_2S0_4, filtered and concentrated to give crude compound **307g** (224 mg) as a pale yellow solid.

Step 8: ^ans-3-(5-(4-(A/-(terf-Butyl)sulfamoyl)naphthalen-1-yl)-4-(cvclohexylmethyl)thiophene-2-carboxamido)cvclobutanecarboxylic acid **(307)**

A mixture of compound **307g** (114 mg, 0.24 mmol), *trans* 3-aminocyclobutanecarboxylic acid 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. ^{1}H-NMR (400 MHz, $CDOD_3$) 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.**

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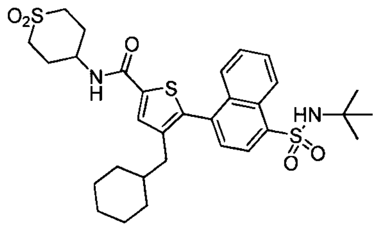
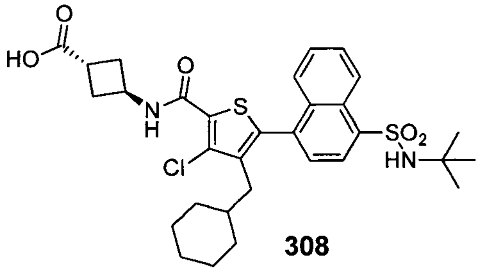
307/1		^{1}H-NMR (400 MHz, DMSO-d_6) δ: 0.53-0.56 (m, 2H), 0.92-1.03 (m, 3H), 1.06 (s, 9H), 1.32-1.46 (m, 7H), 2.06-2.17 (m, 5H), 3.1 1-3.15 (m, 2H), 3.30-3.38 (m, 2H), 4.17-4.24 (m, 1H), 7.61-7.67 (m, 2H), 7.70-7.76 (m, 2H), 7.84 (s, 1H), 7.90 (s, 1H), 8.24 (d, J = 7.6 Hz, 1H), 8.50 (d, J = 7.6 Hz, 1H), 8.78 (d, J = 9.2 Hz, 1H). MS 617.3 $[M+1]^+$

Example 308



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 Br_2 (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. $Na_2S_2O_3$, basified to pH = 8 with sat. $NaHCO_3$ and extracted with Et_2O. The organic layer was washed with water and brine, dried over Na_2SO_4, 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 Na_2SO_4, 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-(cvclohexylmethyl)thiophene-2-carboxylate **(308c)**

To a suspension of compound **308b** (500 mg, 2.0 mmol) and Pd(dppf)Cl_2 (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 N_2 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 Na_2S0_4, filtered, concentrated and purified by CC (PE/EA = 100/1) to give compound **308c** (500 mg, 92%) as a colorless oil.

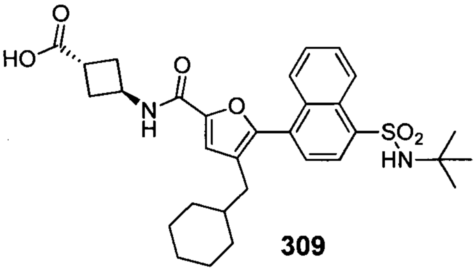
Step 4: Methyl 5-bromo-3-chloro-4-(cvclohexylmethyl)thiophene-2-carboxylate **(308d)**

To a solution of compound **308c** (200 mg, 0.7 mmol) and AcONa (451 mg, 5.5 mmol) in AcOH (10 ml_) was added Br_2 (0.2 mL, 3.7 mmol) dropwise at rt and the solution was stirred at 75°C overnight, cooled to rt, quenched with sat. $Na_2S_20_3$, adjusted pH = 8 with sat. $NaHC0_3$ and extracted with EA. The organic layer was washed with water and brine, dried over Na_2S0_4, filtered, concentrated and purified by prep-HPLC to give compound **308d** (40 mg, 16%) as a pale brown solid.

Step 5: frans-3-(5-(4-(A/-(ferf-Butvnsulfamovnnaphthalen-1 -yl)-3-chloro-4-(cvclohexylmethyl)thiophene-2-carboxamido)cvclobutanecarboxylic 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



309

Step 1: Methyl 4,5-dibromo-3-methylfuran-2-carboxylate **(309a)**

To a suspension of $AlCl_3$ (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, Br_2 (4.1 1 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. Na_2S0_3 twice and brine consecutively, dried over Na_2S0_4, 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 N_2 and the solution was stirred at this temperature for 10 min, quenched with sat. NH_4Cl and extracted with EA (3x). The combined organic layers were washed with water and brine, dried over Na_2S0_4, filtered, concentrated and purified by prep-HPLC to give compound **309b** (50 mg, 19%) as a white solid.

Step 3: Methyl 4-(cvclohexylmethyl)-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 $Pd(dppf)CI_2$ (50 mg, 0.069 mmol) in THF (5.0 mL) was refluxed under N_2 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-(cvclohexylmethyl)-3-methylfuran-2-carboxylate **(309d)**

To the solution of compound **309c** (100 mg, 0.42 mol) in DCM (10.0 mL) was added Br_2 (200 mg, 1.26 mmol) slowly at 0°C and the solution was stirred at rt overnight, diluted with EA and quenched with sat. Na_2S0_3. The aqueous layer was extracted with EA twice. The combined organic layers were washed with water and brine, dried over Na_2S0_4, 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-(A/-(te/i-butyl)sulfamoyl)naphthalen-1-yl)-4-(cvclohexylmethyl)-3-methylfuran-2-carboxylate **(309e)**

The suspension of compound **309d** (105 mg, 0.333 mmol), K_2C0_3 (138 mg, 1.0 mmol), compound **P1/2** (130 mg, 0.333 mmol) and $Pd(dppf)CI_2$ (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-(/V-(fe/†-Butyl)sulfamoyl)naphthalen-1-yl)-4-(cvclohexylmethyl)-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 HCI and extracted with EA. The organic layer was washed with water and brine, dried over Na_2S0_4, filtered and concentrated to give compound **309f** (69 mg, 89%) as a yellow solid.

Step 7: ^ans-3-(5-(4-(A/-(te/t-Butyl)sulfamoyl)naphthalen-1-yl)-4-(cvcloriexylmethyl)furan-2-carboxamido)cvclobutanecarboxylic 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:

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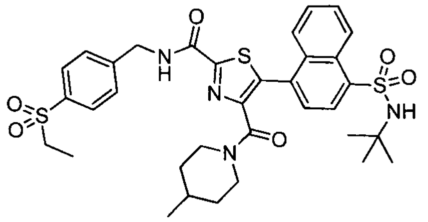
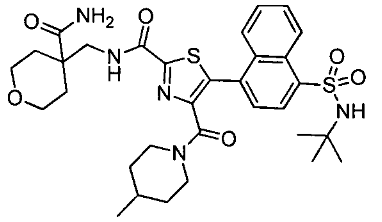
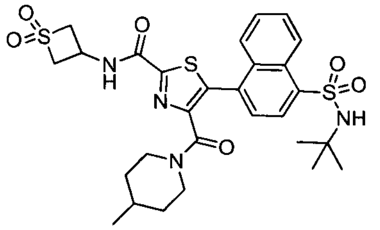
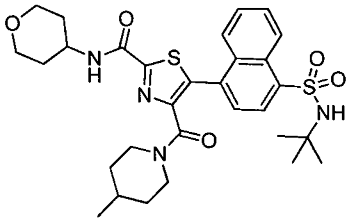
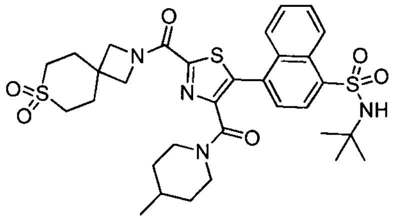
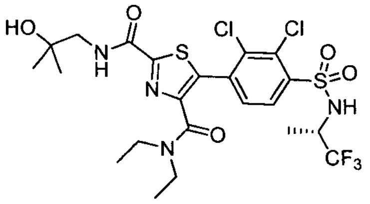
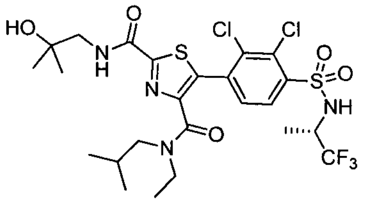
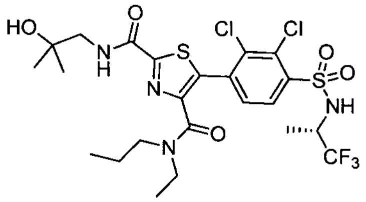
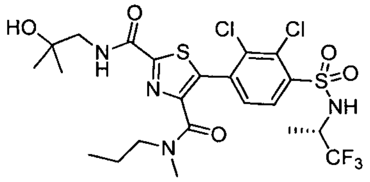
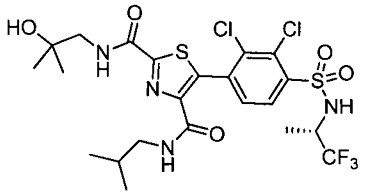
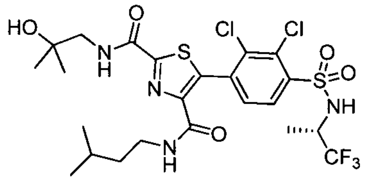
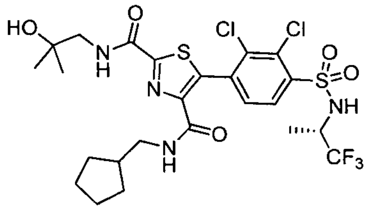
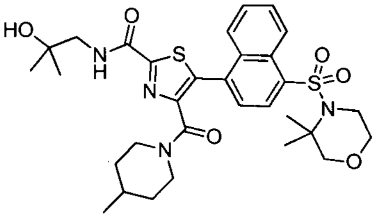
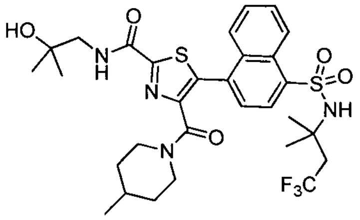
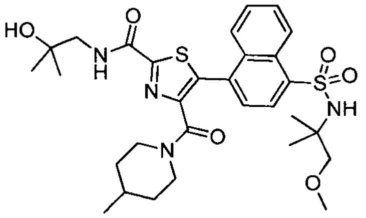
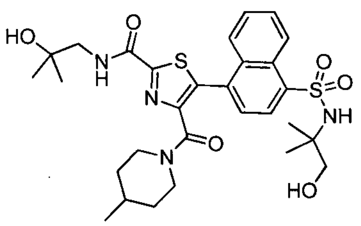
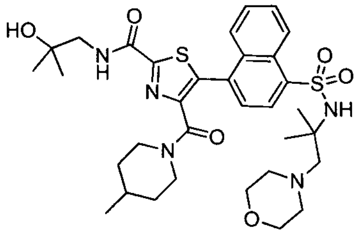
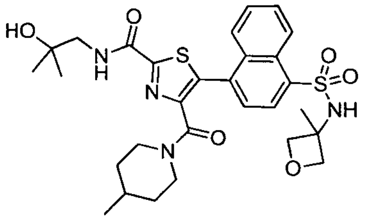
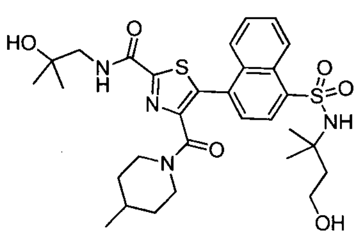
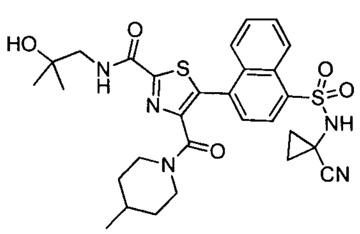
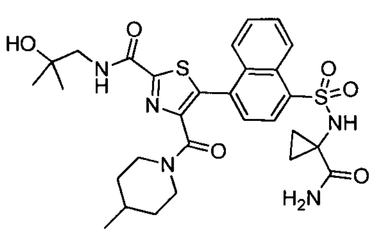
Structure	Structure	Structure
		
		
		
		
		
		
		

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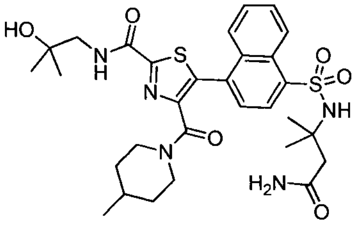
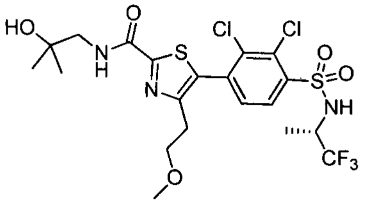
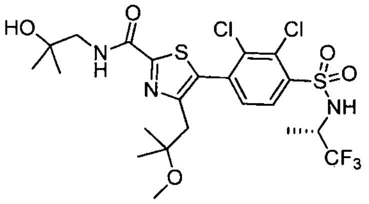
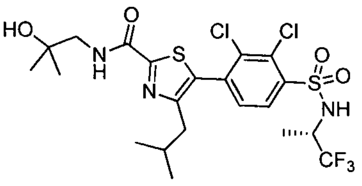
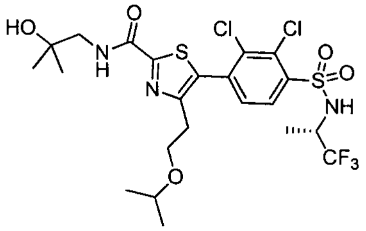
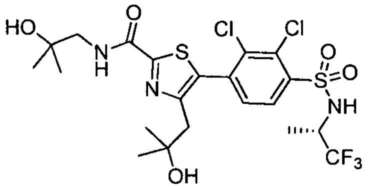
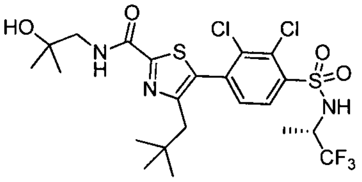
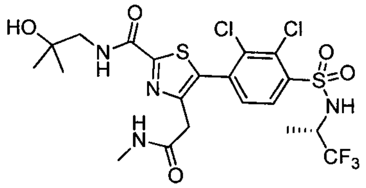
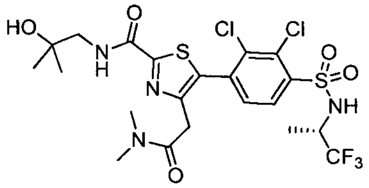
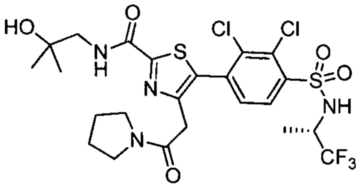
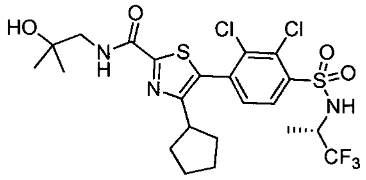
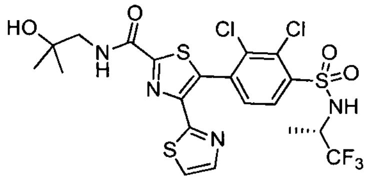
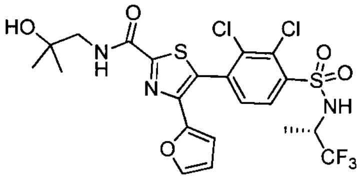
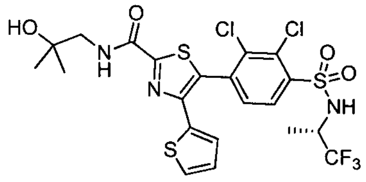
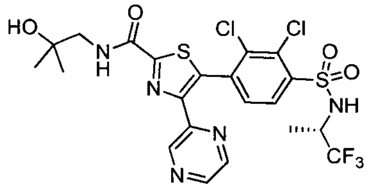
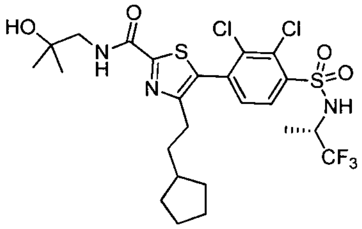
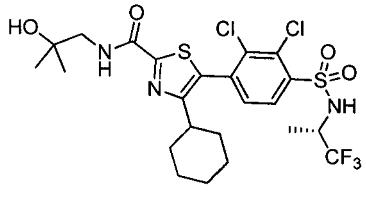
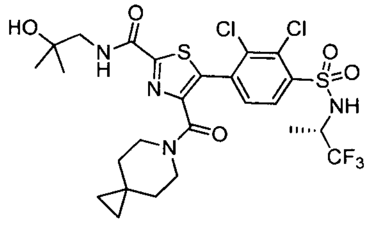
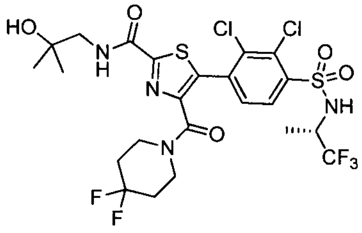
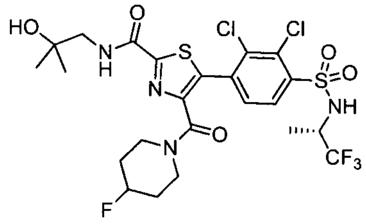
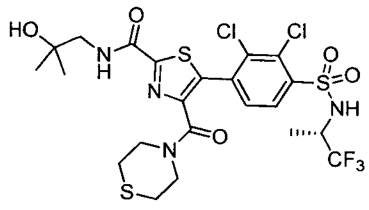
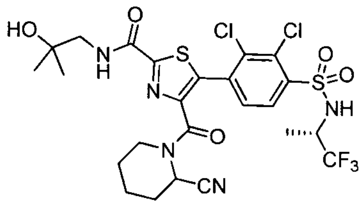
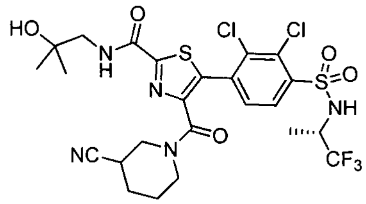
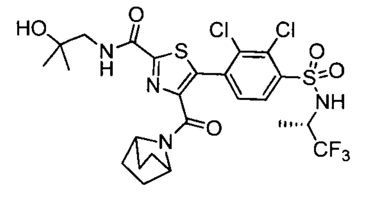
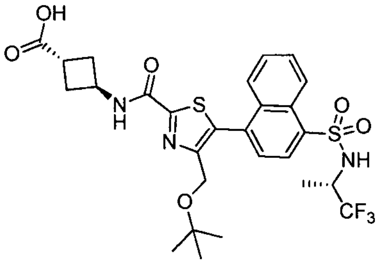
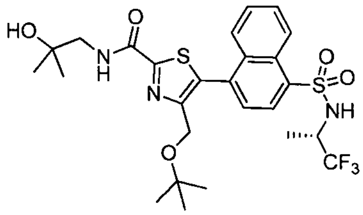
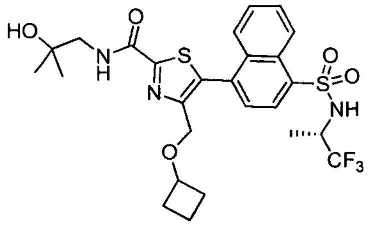
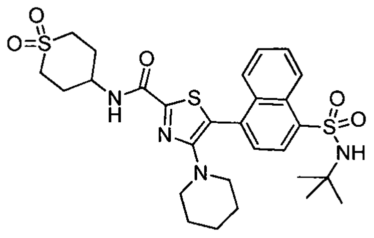
		
		
		
		
		
		
		
		

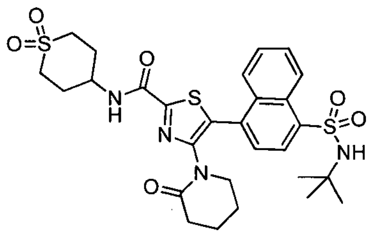
Structure	Structure	Structure

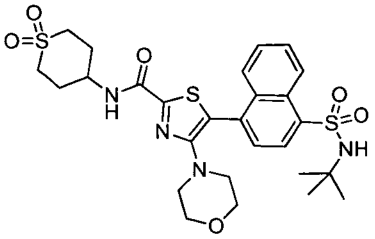












Protein Expression and Purification

Protein expression and purification was done as described in WO2010/049144.

TR-FRET Activity Assay

This method measures the ability of putative ligands to modulate the interaction between the purified bacterial expressed RORy ligand binding domain (LBD) and synthetic /V-terminally biotinylated peptides which are derived from nuclear receptor coactivator proteins such as but not limited to SRC1 (NcoA1), SRC2 (NcoA2,TIF2), SRC3 (NcoA3), PGC1a, PΘOIβ, CBP, GRIP1, TRAP220, RIP140. The peptides used are listed in Table 1 below:

Table 1

Peptide Name (aa range)	DB entry Protein	DB entry DNA	Sequence
SRC1(676-700)	NP_003734	NM_003743.4	NH_2-CPSSHSSLTERHKILHRLLQEGSPS-COOH
TRAP220(631-655)	NP_004765	NM_004774.3	NH_2-PVSSMAGNTKNHPMLMNLLKDNPAQ-COOH
TIF2(628-651)	NP_006531	NM_006540.2	NH_2-GQSRLHDSKGQTKLLQLLTTKSDQ-COOH

The ligand-binding domain (LBD) of RORy 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 RORy-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 µL 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 $MgCl_2$; 35 ng/µL BSA), containing 20-60 ng/well recombinantly expressed RORy-LBD fused to GST, 200-600 nM N-terminally biotinylated peptide, 200 ng/well Streptavidin-xlAPC 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 RORy modulating ligands were diluted. After his 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 RORy-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 RORy and to the RORy-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, IC_{50} 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 nm measurement value/615 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 = Bottom + (Top-Bottom)/(1+10^((LogEC50-X)*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 IC_{50} 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 (IC_{50} FRET) ranging from below 100 nM to about 20 μM. The RORy modulating compounds of the invention desirably have an inhibition in the TR-FRET Activity Assay ranging from below 100 nM to about 1 μM. Table 3 lists the pIC_{50}-value of compounds of the invention. Is 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.

RORvGal4 Reporter Gene Assay

Determination of a ligand mediated Gal4 promoter driven transactivation to quantify ligand binding to RORy was performed as follows: DNA encoding three different RORy 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% CO_2.

For the assay, $5x10^5$ cells were plated per well in 96well plates in 100 µL per well, incubated over night at 37°C in 5% CO_2. The following day, medium was discarded and the cells were transiently transfected using 20 µL 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 (IC_{50} FF resp. IC_{50} RENnorm) ranging from below 10 nM to about 20 µM, and typically, from about 10 nM to about 1 µM. The RORγ modulating compounds of the invention desirably have an inhibition in the Gal4 reporter gene assay ranging from below 10 nM to about 1 μM. Table 3 list the pIC$_{50}$-value of typical examples of compounds of the invention that have an RORy 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 RORyt inhibitor T0901317 (equals 100%) and the pIC$_{50}$-value is underlined, when the efficacy of the compound is below 50% of the reference.

Table 3

Table 3

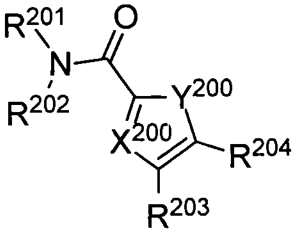
Ex. #	pIC$_{50}$ (FRET/FF/REN)	Ex. #	pICso (FRET/FF/REN)	Ex. #	pICso (FRET/FF/REN)
1	6.5/5.8/5.8	**2**	5.9/6.1/6.0	**3**	5.1/<4.7/<4.7
4	6.8/6.4/6.4	**5**	6.7/6.3/6.1	**6**	6.7/6.2/6.3
6/1	6.5/7.5/7.7	**6/2**	7.0/7.5/7.7	**6/3**	6.5/8.5/8.7
6/4	6.7/8.7/8.7	**6/5**	6.6/8.5/8.7	**6/6**	6.7/9.0/9.0
6/7	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	5.9/7.2/7J3	**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	6.2/6.6/6.5	**7/26**	6.8/7.7/7.9	**7/27**	6.5/6.9/6.9

Ex. #	pICso (FRET/FF/REN)	Ex. #	pICso (FRET/FF/REN)	Ex. #	pICso (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	5^4/6.9/7.0
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	6,2/6.4/6.3	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	5.6/6.1/6.5
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/6.1/6.1
25/1	nt/8.9/8.8	25/2	nt/9.0/9.0		
100	6.6/5^8/5^8	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. #	pICso (FRET/FF/REN)	Ex. #	pICso (FRET/FF/REN)	Ex. #	pICso (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**	7J./7.4/7.8	**201**	6.0/&5/&6
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**	5.4/6.4/6.5
207/1	6.0/6.2/6.1	**208**	6.5/6.3/6.3	**209**	6.4/6.2/6.2
211	5,8/6,3/6.4				
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/7.3/7^5	**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/7.4/7^7	**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/8.0/7.6	**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')



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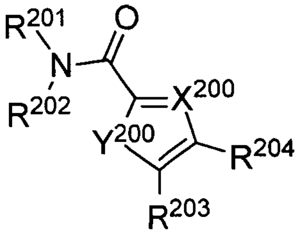


(200")

an enantiomer, diastereomer, tautomer, A/-oxide, solvate, formulation and pharmaceutically acceptable salt thereof,

wherein

R^{201} and R^{202} are independently selected from H, $C_{1\text{-}10}$-alkyl, $C_{2\text{-}10}$-alkenyl, C_2.io-alkynyl, $C_{3\text{-}}i_0$-cycloalkyl, $C_{3\text{-}1_0}$-heterocycloalkyl, $C_{1\text{-}1}$o-alkylene-Cs-io-cycloalkyl, $C_{1\cdot 1_0}$-alkylene-$C_{3\text{-}1_0}$-heterocycloalkyl, $C_{1}\text{-}_{10}$-alkylene-(5-membered heteroaryl), $C_{1\cdot 1_0}$-alkylene-(6-membered aryl), Ci.io-alkylene-(6-membered heteroaryl), SO_2-$C_{1\text{-}10}$-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}, 0-$C_{2\text{-}6}$-alkylene-OR^{211}, C^-alkyl, halo-C^-alkyl, halogen, $C0_2R^{211}$, $CONR^{211}R^{212}$, $CONR^{211}S0_2R^{211}$, COR^{211}, SO_xR^{211}, $S0_3H$, $S0_2NR^{211}R^{212}$, $NR^{211}COR^{211}$, $NR^{211}S0_2R^{211}$, NR^{211}-CO-$NR^{211}R^{212}$, NR^{211}-$S0_2$-$NR^{211}R^{212}$, $C_{3\text{-}i_0}$-cycloalkyl, O-$C_{3\cdot 1_0}$-cycloalkyl, $C_{3\cdot 10}$-heterocycloalkyl, O-$C_{3\cdot 1_0}$-heterocycloalkyl and $NR^{211}R^{212}$;

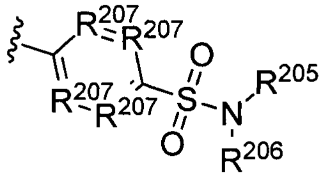
or R^{201} and R^{202} when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing 1 or 2 heteroatoms selected from O, S or N, wherein the ring is unsubstituted or substituted with 1 to 4 substitutents independently selected from the group consisting of halogen, oxo, CN, OR^{211}, SO_xR^{211}, $S0_3H$, $NR^{211}S0_2R^{211}$, $S0_2NR^{211}R^{212}$, $C_{0\text{-}6}$-alkylene-CO_2R^{211}, $CONR^{211}R^{212}$, $CONR^{211}S0_2R^{211}$, COR^{211}, NR^{211}-CO-R^{211}, NR^{211}-CO-$NR^{211}R^{212}$, NR^{211}-$S0_2$-$NR^{211}R^{212}$, $NR^{211}R^{212}$, d-e-alkyl, halo-d-e-alkyl, hydroxy-d-e-alkyl, $C_{3\text{-}8}$-cycloalkyl, 0-$C_{3\text{-}8}$-cycloalkyl, $C_{3\cdot 8}$-heterocycloalkyl and 0-$C_{3\cdot 8}$-heterocycloalkyl,

> wherein cycloalkyl and heterocycloalkyl are unsubstituted or substituted with 1 to 4 substitutents independently selected from the group consisting of halogen, $Ci_{\text{-}3}$-alkyl, halo-d-s-alkyl, OH, O-$G_{1\text{-}3}$-alkyl, 0-halo-Ci. $_3$-alkyl, SOrC^-alkyl, COOH and oxo;

R^{203} is selected from Ci-10-alkyl, fluoro-Ci-i $_0$-alkyl, $C_{0.6}$-alkylene-$C_{3\text{-}1_0}$-cycloalkyl, $C_{0\text{-}6}$-alkylene-$C_{3\text{-}1_0}$-heterocycloalkyl, $C_{0\text{-}6}$-alkylene-(6- to 10-membered aryl), and $C_{0\text{-}6}$-alkylene-(5- to 10-membered heteroaryl), wherein alkyl, alkylene, cycloalkyi, heterocycloalkyi, aryl and heteroaryl is unsubstituted or substituted with 1 to 6 substituents independently selected from the group consisting of oxo, halogen, CN, C_{1-6}-alkyl, halo-d $_{-e}$-alkyl, $C_{3\cdot6}$-cycloalkyl, C_{3-6}-heterocycloalkyl, OR^{212}, $C0_2R^{212}$, $CONR^{212}R^{212}$ and COR^{212}; and

wherein optionally one CH_2 unit in alkyl or alkylene can be replaced by O, SO_x, NH or N(C^-alkyl);

R^{204} is



, wherein

R^{205} and R^{206} is independently selected from H, C_{1-6}-alkyl, halo-$Ci._6$-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, cyclolalkyl, heterocycloalkyi, aryl and heteroaryl are unsubstituted or substituted with 1 to 6 substituents independently selected from the group consisting of halogen, CN, OH, oxo, $Ci._3$-alkyl, halo-$Ci-_3$-alkyl, 0-C $_{1-3}$-alkyl, O-halo-d $_{-3}$-alkyl and $S0_2$-d $_{-3}$-alkyl, $NR^{211}R^{212}$, $C0_2R^{212}$ 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 substitutents independently selected from the group consisting of fluoro, OH, oxo, C^-alkyl and halo-d $_{-4}$-alkyl;

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

two adjacent R^{207} 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 substitutents independently selected from the group consisting of halogen, OH, oxo, d $_{-4}$-alkyl and fluoro-Ci_{4}-alkyl;

R^{208} is independently selected from H, halogen, CN, C_{1-6}-alkyl, fluoro-d. $_6$-alkyl, C_{1-4}-alkylene-OH, d^-alkylene-O-d $_{-3}$-alkyl, d $_{-4}$-alkylene-0-fluoro-d- $_3$-alkyl, OH, 0-Ci. $_6$-alkyl, O-fluoro-d $_{-6}$-alkyl and $C_{3\cdot10}$-cycloalkyl,

wherein alkylene is unsubstituted or substituted with 1 to 3 substituents selected from F and cycloalkyi is unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of F, d $_{-3}$-alkyl and fluoro-Ci- $_3$-alkyl;

R^{209} is selected from H, halogen, CN, $C_{1\cdot3}$-alkyl and fluoro-d. $_3$-alkyl;

Ft^{211} is independently selected from H, d -e-alkyl, Co-6-alkylene-C$_{3\cdot 1_0}$-cycloalkyl and C$_{0-6}$-alkylene-C$_{3}$.io-heterocycloalkyl,

wherein alkyl, alkylene, cycloalkyi and heterocycloalkyi is unsubstituted or substituted with 1 to 6 substituents independently selected from the group consisting of halogen, CN, OH, oxo, C$_{1\text{-}3}$-alkyl, halo-d. $_{3}$-alkyl, 0 -C$_{1\cdot 3}$-alkyl, O-halo-d -$_{3}$-alkyl, NH$_{2}$, NH(d. $_{3}$-alkyl), N(Ci .$_{3}$-alkyl)$_{2}$, C$_{3\cdot 6}$-heterocycloalkyl, C$_{3\text{-}6}$-cycloalkyl and S0 $_{2}$-Ci -$_{3}$-alkyl,

wherein cycloalkyi and heterocycloalkyi 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, d .$_{6}$-alkyl, halo-C$_{1\cdot 6}$-alkyl and C$_{3\cdot 6}$-cycloalkyl;

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

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

x is independently selected from 0, 1 and 2;

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

2. The compound according to claim 1 wherein

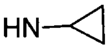
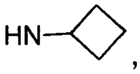
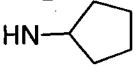
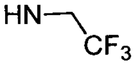
R$^{20^1}$ is selected from H, C$_{1\text{-}1}$o-alkyl, C$_{3\cdot 1_0}$-cycloalkyl, C$_{3\cdot 1_0}$-heterocycloalkyl, C$_{1}$-$_{1}$o-alkylene-C$_{3}$.io-cycloalkyl, d -$_{1}$o-alkylene-C$_{3\text{-}_{10}}$-heterocycloalkyl, d -$_{1_0}$-alkylene-(5-membered heteroaryl), C$_{1\text{-}10}$-alkylene-(6-membered aryl), d .$_{10}$-alkylene-(6-membered heteroaryl) and SO$_{2}$-C$_{1}$-$_{1_0}$-alkyl, wherein alkyl, alkenyl, alkynyl, alkylene, cycloalkyi, heterocycloalkyi, aryl and heteroaryl is unsubstituted or substituted with 1 to 7 substituents independently selected from the group consisting of oxo, CN, OR^{211}, 0 -C$_{2\text{-}6}$-alkylene-OR $^{21^1}$, d -e-alkyl, halo-d. $_{6}$-alkyl, halogen, C0 $_{2}$R$^{21^1}$, CONR $^{21^1}$R^{212}, CONR $^{21^1}$S0 $_{2}$R$^{21^1}$, COR ^{211}, SO$_{x}$R^{211}, S0 $_{3}$H, S0 $_{2}$NR^{211}R^{212}, NR$^{2^{11}}$COR ^{211}, NR$^{2^{11}}$S0 $_{2}$R^{211}, NR$^{2^1}$1-CO-NR $^{21^1}$R^{212}, NR$^{2^{11}}$-S0 $_{2}$-NR $^{2^{11}}$R^{212}, C$_{3\cdot 10}$-cycloalkyl, O-C$_{3\text{-}1_0}$-cycloalkyl, C$_{3\text{-}1_0}$-heterocycloalkyl, O-C $_{3\cdot 10}$-heterocycloalkyl and NR^{211}R^{212};

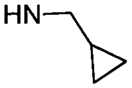
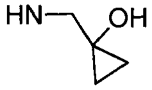
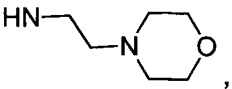
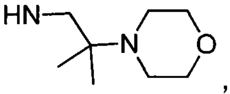
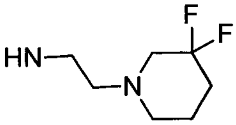
R^{202} is selected from H, d .$_{6}$-alkyl, halo-d. $_{6}$-alkyl and hydroxy-d. $_{6}$-alkyl;

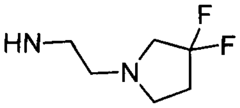
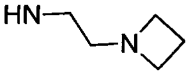
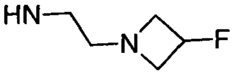
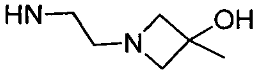
or R^{201} and R^{202} when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing 1 or 2 heteroatoms selected from O, S or N, wherein the ring is unsubstituted or substituted with 1 to 4 substitutents independently selected from the group consisting of halogen, oxo, CN, OR^{211}, SO$_{x}$R$^{21^1}$, S0 $_{3}$H, NR^{211}S0 $_{2}$R^{211}, S0 $_{2}$NR^{21}1R^{212}, Co$_{6}$-alkylene-C0 $_{2}$R^{211}, CONR ^{211}R^{212}, CONR ^{211}S0 $_{2}$R^{211}, COR ^{211}, NR$^{2^{11}}$-CO-R ^{211}, NR^{21}1-CO-NR ^{21}1R^{212}, NR^{211}-S0 $_{2}$-NR $^{21^1}$R^{212}, NR$^{2^{11}}$R^{212}, d -e-alkyl, halo-d. $_{6}$-alkyl, hydroxy-d. $_{6}$-alkyl, C$_{3\text{-}8}$-cycloalkyl, 0 -C$_{3\cdot 8}$-cycloalkyl, C$_{3\cdot 8}$-heterocycloalkyl and 0 -C$_{3\cdot 8}$-heterocycloalkyl, wherein cycloalkyi and heterocycloalkyi are unsubstituted or substituted with 1 to 4 substitutents independently selected from the group consisting of halogen, $C_{1\text{-}3}$-alkyl, halo-d $_{\text{-}3}$-alkyl, OH, O-$C_{1\text{-}3}$-alkyl, 0-halo-d. $_{3}$-alkyl, S0 $_{2}$-$C_{1\text{-}3}$-alkyl, COOH and oxo.

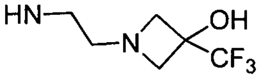
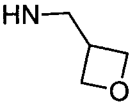
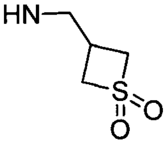
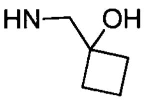
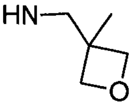
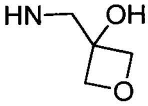
3. The compound according to any of claims 1 to 2 wherein $NR^{201}R^{202}$ is selected from

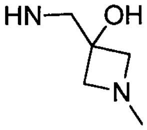
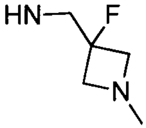
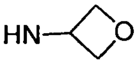
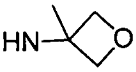
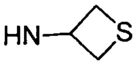
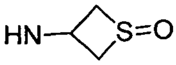
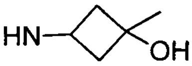
NHMe, NHEt, NH'Pr, NH'Bu, $NHCH_2CONH_2$, $NHCH_2CONMe_{2>}$ $NHCH_2CH_2OH$, $NHCH_2CH_2OMe$, $NHCH_2CH_2S0\ _2Me$, $NHCH_2CH_2S0\ _2NH_2$, $NH(CH_2)_3OH$, $NH(CH_2)_3OMe$, $NH(CH_2)_4OH$, $NH(CH_2)_4OMe$, $NH(CH_2)_5OH$, $NH(CH_2)_2C0\ _2H$, $NH(CH_2)_3C0\ _2H$, $NH(CH_2)_4C0\ _2H$, $NH(CH_2)_5C0\ _2H$, $NHCH_2CH(CF_3)OH$, $NHCH_2C(Me)(CF_3)OH$, $NHCH_2CMe_2OH$, $NHCH_2CH_2CMe_2OH$, $NHCH_2CMe_2NHCH_2CF_3$, $NHCH(Me)CMe_2OH$, $NHCH_2CMe_2OMe$, $NHCH_2CMe_2C0\ _2H$, $NHCH_2CMe_2CONHMe$, $NHCH_2CMe_2CONMe_{2>}$ $NHCH_2CMe_2NHS0\ _2Me$, $NH(CH_2)_3S0Me$, $NH(CH_2)_5S0\ _2Me$, $NH(CH_2)_5S0\ _2NH_2$, $NH(CH_2)_3NHS0\ _2Me$, $NH(CH_2)_20(CH\ _2)_2OH$, $NHCH_2CHMeOH$, $NH(CH_2)_5SOMe$, $NH(CH_2)_3S0\ _2Me$, $NHC(CH\ _2OH)_3$, $NHCH_2CH(OH)CH_2OH$, $N(CH_2CH_2OH)_2$,

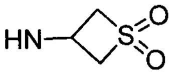
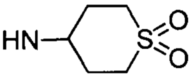
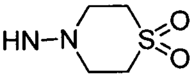
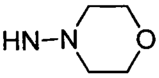
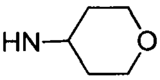
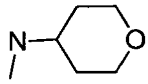
,
,
,
,

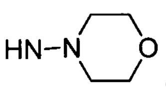
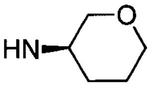
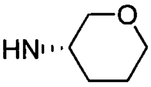
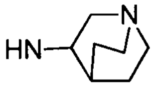
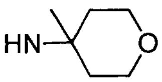
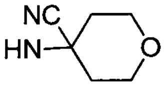
,
,
,
,
,

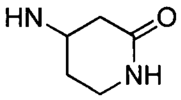
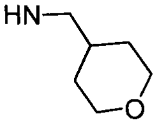
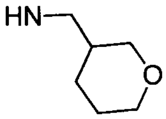
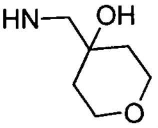
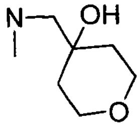
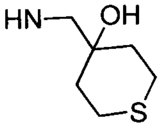
,
,
,
,

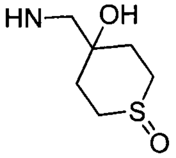
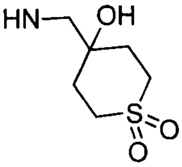
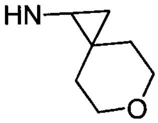
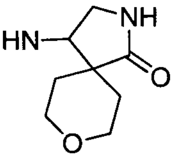
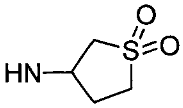
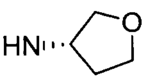
,
,
,
,
,
,

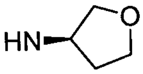
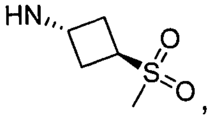
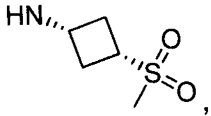
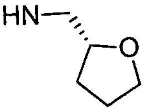
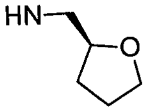
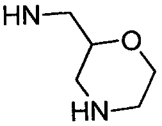
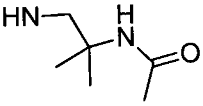
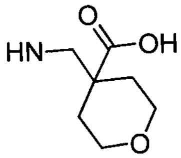
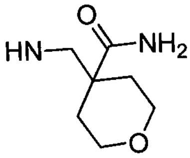
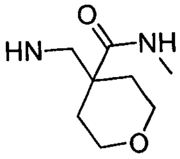
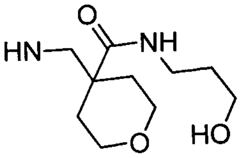
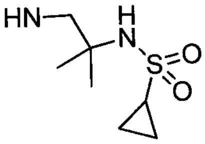
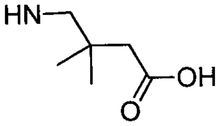
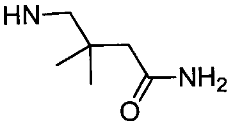
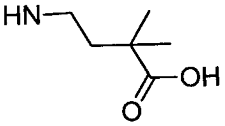
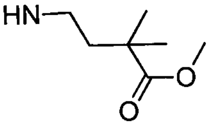
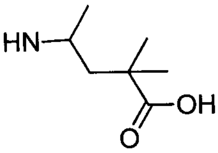
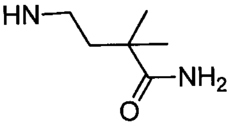
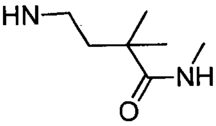
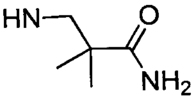
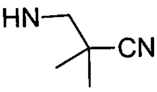
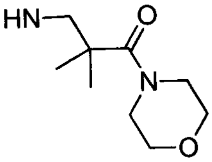
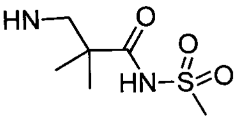
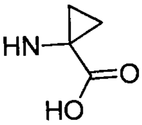
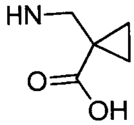
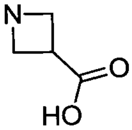
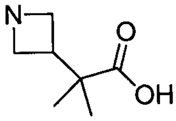
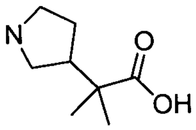
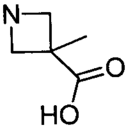
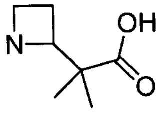
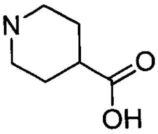
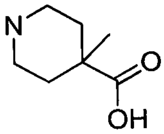
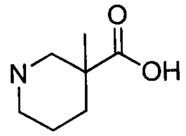
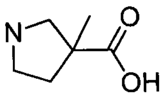
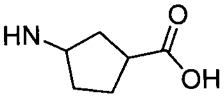
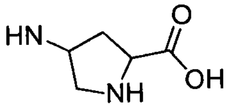
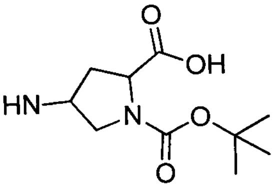
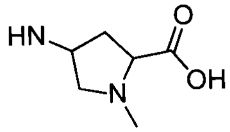
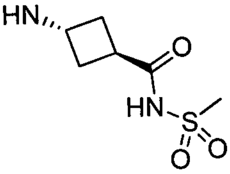
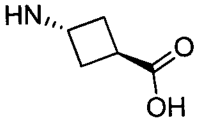
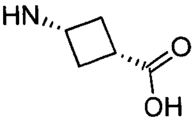
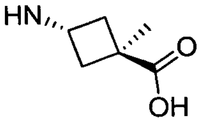
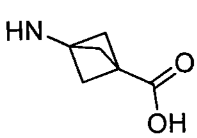
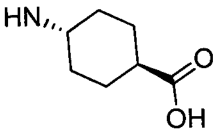
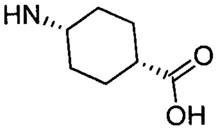
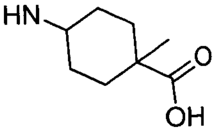
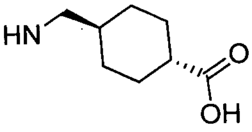
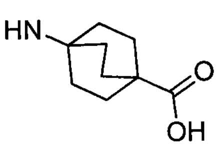
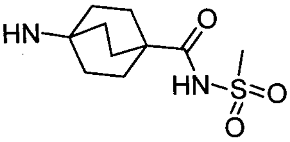
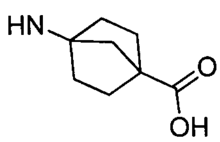
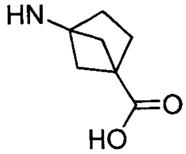
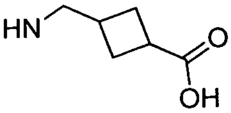
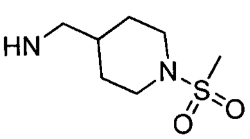
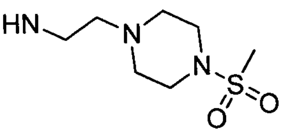
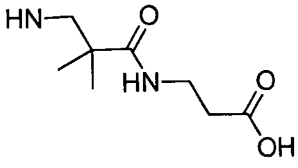
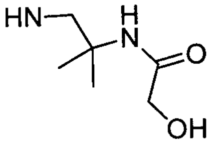
,
,
,
,
,
,
,

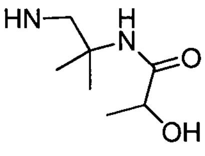
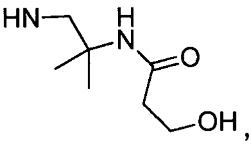
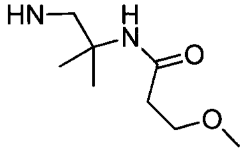
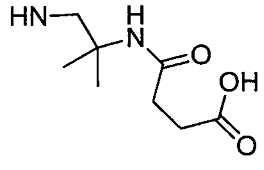
,
,
,
,
,
,

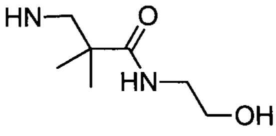
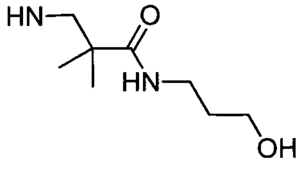
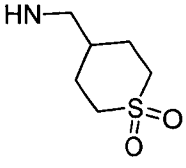
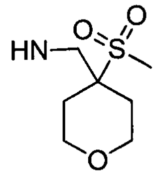
,
,
,
,
,
,

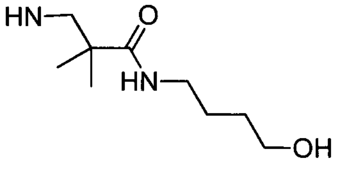
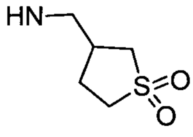
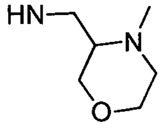
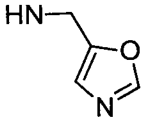
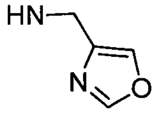
,
,
,
,
,
,

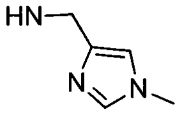
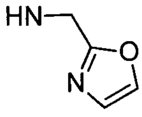
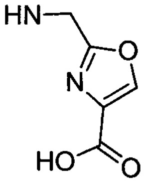
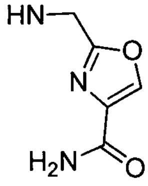
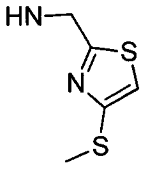
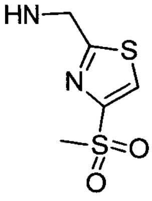
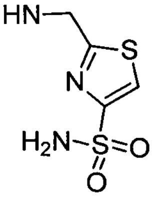
,
,
,
,
,
,

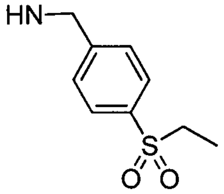
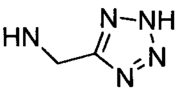
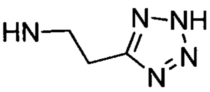
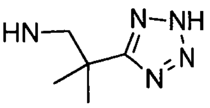
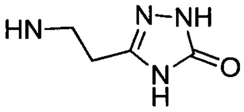
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,

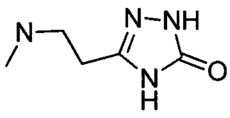
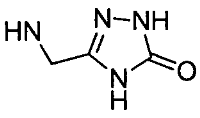
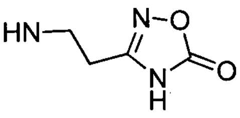
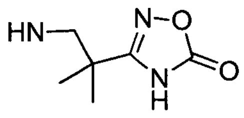
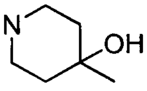
,
,
,
,

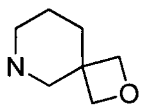
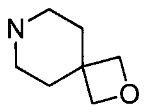
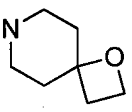
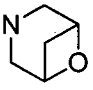
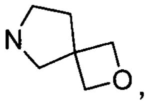
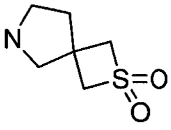
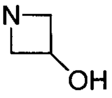
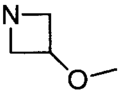
,
,
,
,

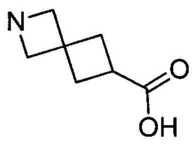
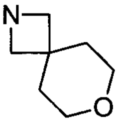
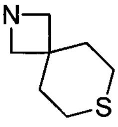
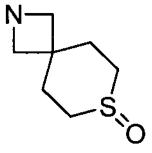
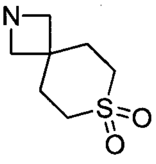
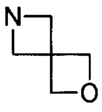
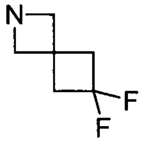
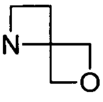
,
,
,
,
,

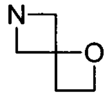
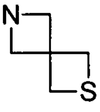
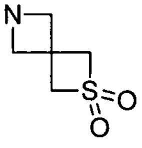
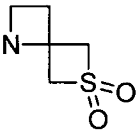
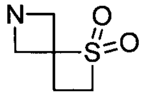
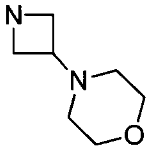
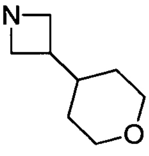
,
,
,
,
,
,
,

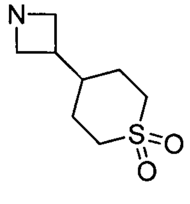
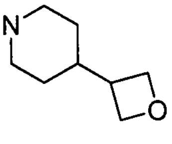
,
,
,
,
,

,
,
,
,
,

,
,
,
,
,
,
,
,

,
,
,
,
,
,
,
,

,
,
,
,
,
,
,

,
,
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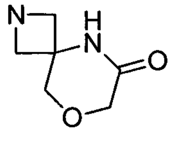
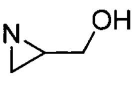
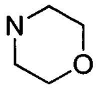
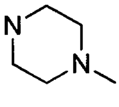
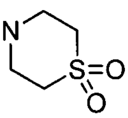
,
,
,
,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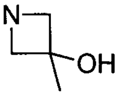
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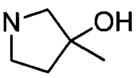
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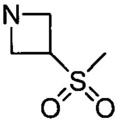
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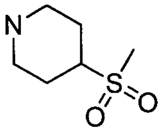
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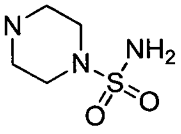
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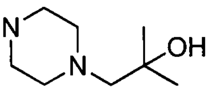
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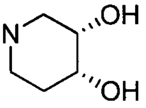
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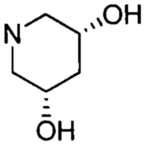
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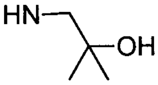
4. The compound according to any of claims 1 to 3 wherein $NR^{201}R^{202}$ is selected from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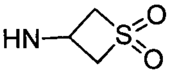
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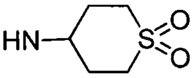
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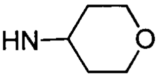
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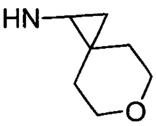
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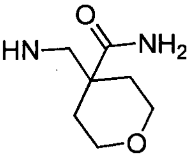
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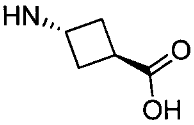
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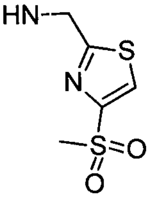
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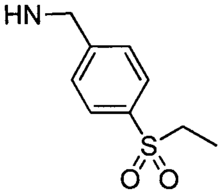
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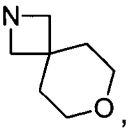
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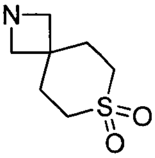
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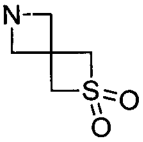
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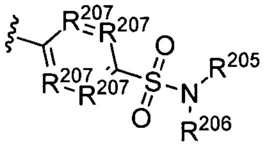
5. The compound according to any of claims 1 to 4 wherein R^{204} is selected from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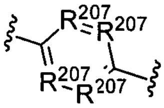
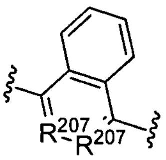
wherein all R^{207} are CR^{208} or one R^{207} is N and the three other R^{207} are CR^{208}; or

wherein  is selected from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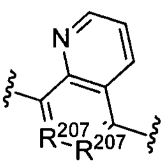
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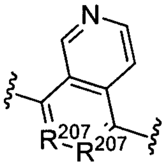
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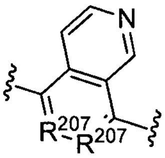
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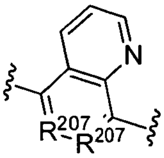
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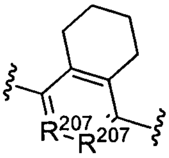
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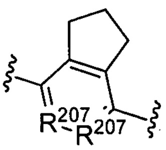
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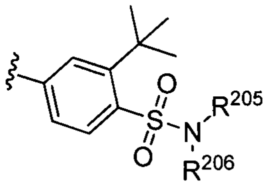
wherein the additional ring is unsubstituted or substituted with 1 to 4 substitutents independently selected from the group consisting of halogen, OH, oxo, $C_{1\text{-}4}$-alkyl and fluoro-Ci$_{-4}$-alkyl.

6. The compound according to any of claims 1 to 5 wherein R^{204} is selected from



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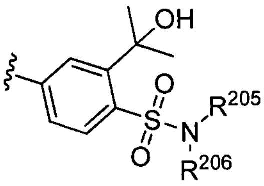

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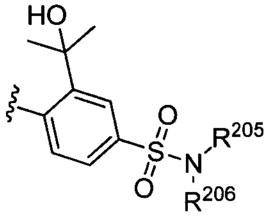

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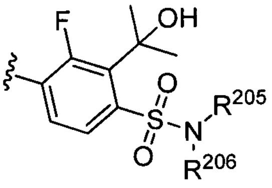

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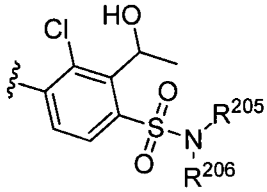

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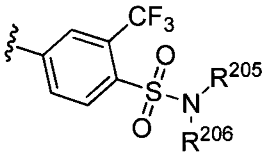

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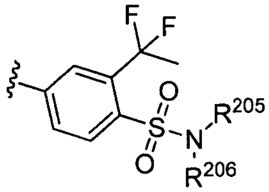

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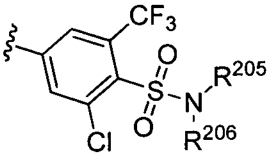

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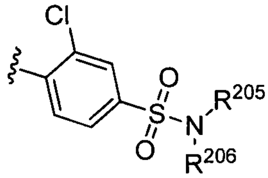

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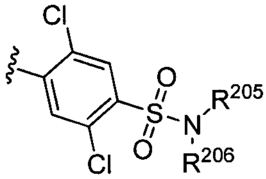

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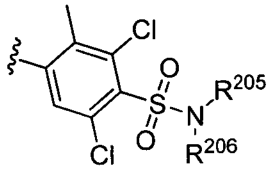

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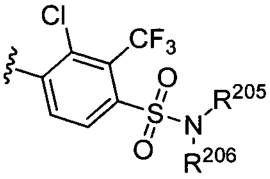

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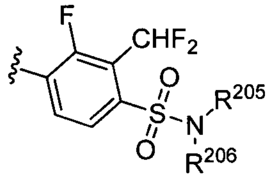

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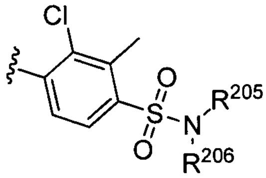

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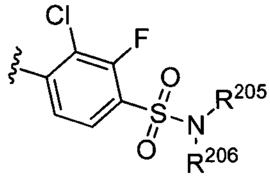

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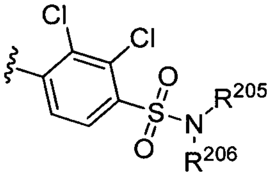

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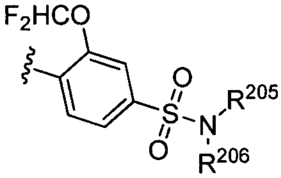

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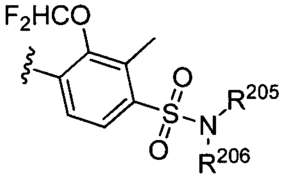

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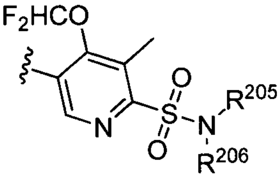

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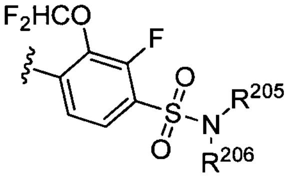

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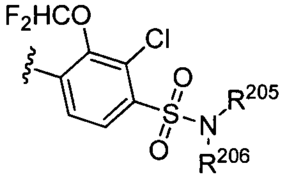

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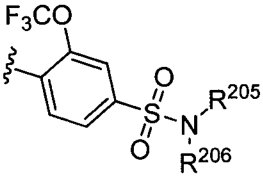

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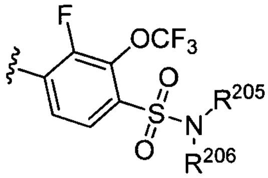

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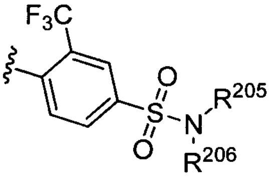

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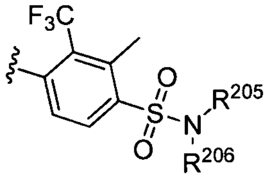

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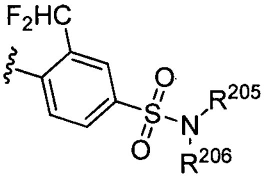

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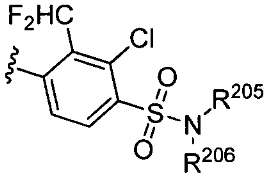

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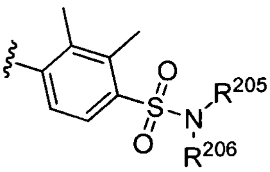

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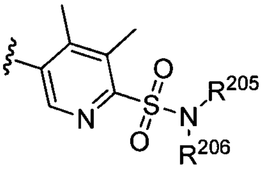

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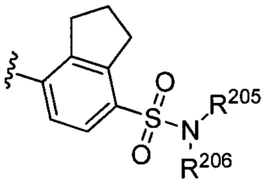

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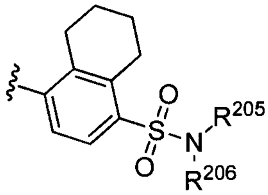

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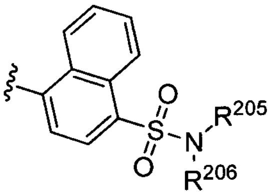

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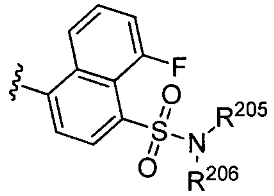

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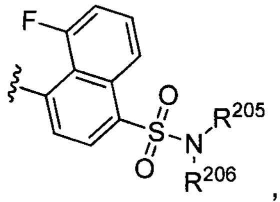

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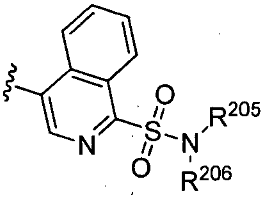

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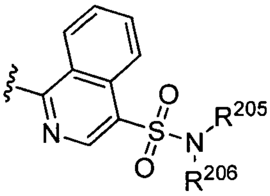

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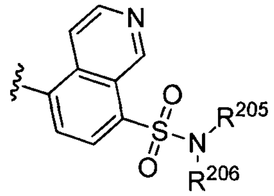

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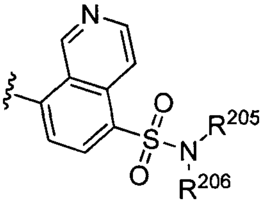

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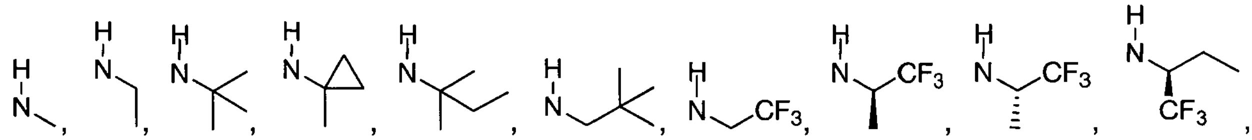
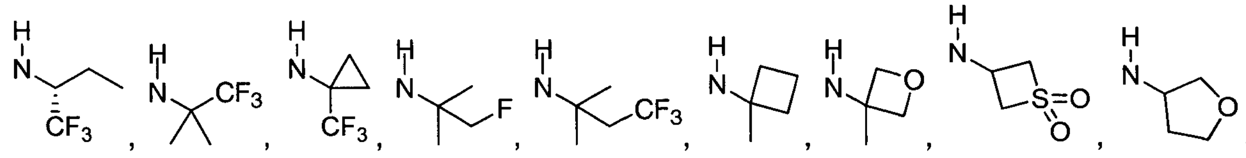
wherein

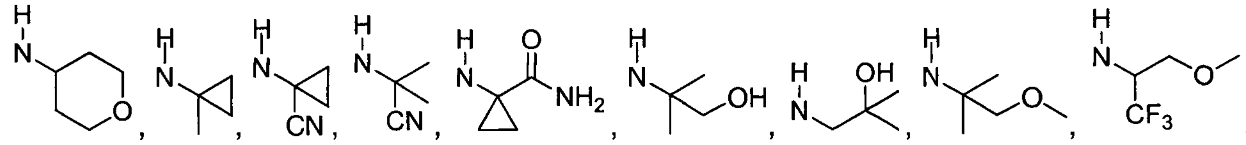
R^{205} and R^{206} is independently selected from H, $C_{1\text{-}6}$-alkyl, halo-Ci.₆-alkyl, C_0-₆-alkylene-$C_{3\text{-}8}$-cycloalkyl, $C_{0\text{-}6}$-alkylene-$C_{3\text{-}8}$-heterocycloalkyl, 5- or 6-membered heteroaryl and 6-membered aryl, wherein alkyl, alkylene, cyclolalkyi, heterocycloalkyi, aryl and heteroaryl are unsubstituted or substituted with 1 to 6 substituents independently selected from the group consisting of halogen, CN, OH, oxo, $C_{1\text{-}3}$-alkyl, halo-Ci.$_3$-alkyl, O-d -₃-alkyl, 0-halo-Ci. $_3$-alkyl, S0 $_2$-$C_{1\text{-}3}$-alkyl, $NR^{211}R^{212}$, C0 $_2R^{212}$ and $CONR^{211}R^{212}$;

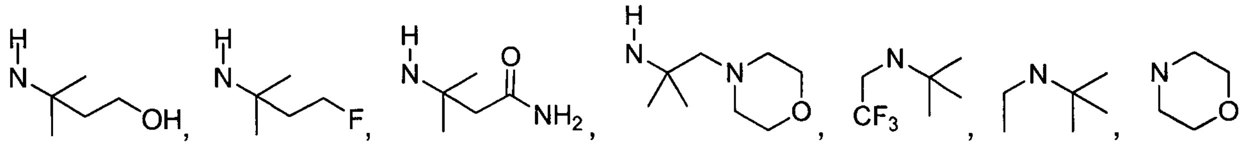
and optionally wherein R^{205} and R^{206} when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing 1 or 2 heteroatoms selected from O, S or N, wherein the ring is unsubstituted or substituted with 1 to 4 substitutents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

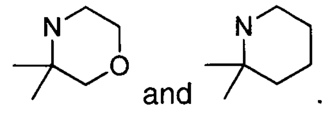
7. The compound according to any of claims 1 to 6 wherein $NR^{205}R^{206}$ is selected from











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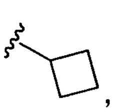
8. The compound according to any of claims 1 to 7 wherein

R^{203} is selected from C_{1-8}-alkyl, fluoro-C_{1-8}-alkyl, C_{0-2}-alkylene-C_{3-8}-cycloalkyl, C_{0-2}-alkylene-C_{3-8}-heterocycloalkyl, C_{0-2}-alkylene-(6- to 10-membered aryl) and C_{0-2}-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, $CH_2CH_2CH_3$, $C(CH_3)_3$, $CH_2OC(CH_3)_3$,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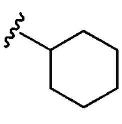
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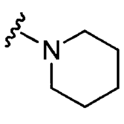
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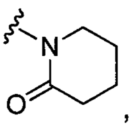
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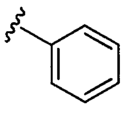
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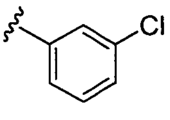
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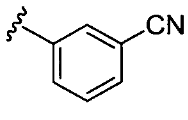
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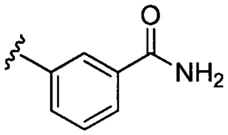

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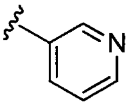

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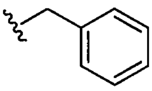
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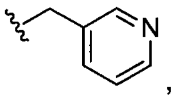

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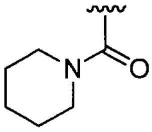

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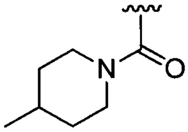

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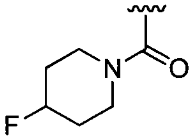

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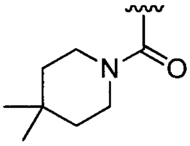

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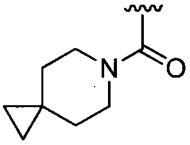

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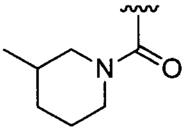

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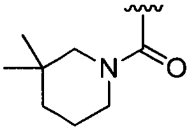

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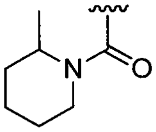

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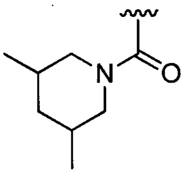

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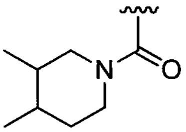

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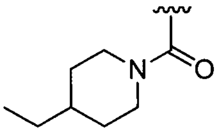

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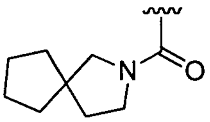

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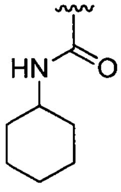

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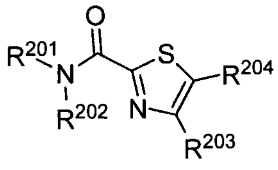
10. The compound according to any of claims 1 to 9 wherein the compound is represented by a Formula selected from



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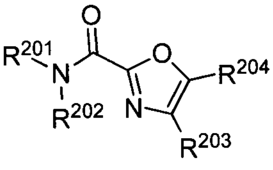

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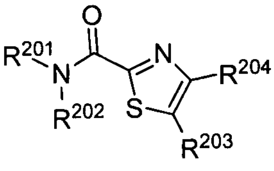

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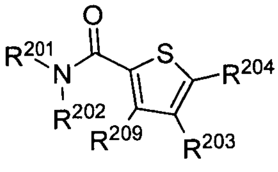

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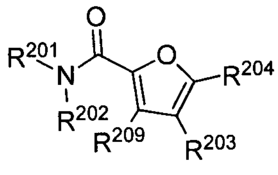
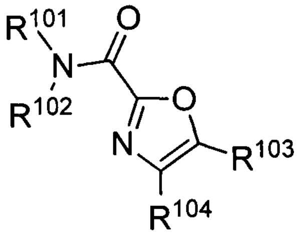


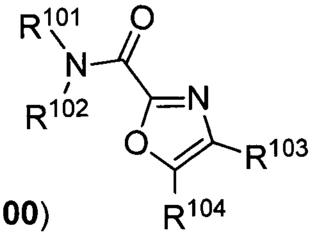
, wherein

R^{209} is selected from H, fluoro, chloro and methyl.

11. A compound represented by Formula **(100)** and Formula **(100')**



(100)



(100')

an enantiomer, diastereomer, tautomer, /V-oxide, solvate, formulation and pharmaceutically acceptable salt thereof,

wherein

R^{1o1} and **R^{102}** 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-**$C_{3\text{-io}}$**-cycloalkyl, d -io-alkylene-QMo-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^{111}**, **0-C $_{2-6}$-alkylene-OR^{111}**, d-e-alkyl, halo-d-e-alkyl, halogen, **$C0_2R^{111}$**, **$CONR^{111}R^{112}$**, **$CONR^{111}S0_2R^{111}$**, **COR^{111}**, **SO_xR^{111}**, **$S0_3H$**, **$S0_2NR^{111}R^{112}$**, **$NR^{111}COR^{111}$**, **$NR^{111}S0_2R^{111}$**, **NR^{111}-CO-$NR^{111}R^{112}$**, **NR^{111}-$S0_2$-$NR^{111}R^{112}$**, **C_{3-10}**-cycloalkyl, **O-C_{3-10}**-cycloalkyl, **C_{3-10}**-heterocycloalkyl, **O-C_{3-10}**-heterocycloalkyl and **$NR^{111}R^{112}$**;

or **R^{101}** and **R^{102}** 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 substitutents independently selected from the group consisting of halogen, oxo, **CN**, **OR^{111}**, **SO_xR^{111}**, **$S0_3H$**, **$NR^{111}S0_2R^{111}$**, **$S0_2NR^{111}R^{112}$**, C_{0-6}-alkylene-**CO_2R^{111}**, **$CONR^{111}R^{112}$**, **$CONR^{111}S0_2R^{111}$**, **COR^{111}**, **NR^{111}-CO-R^{111}**, **NR^{111}-CO-$NR^{111}R^{112}$**, **NR^{111}-$S0_2$-$NR^{111}R^{112}$**, **$NR^{111}R^{112}$**, C_{1-6}-alkyl, halo-**Ci** $_{-6}$-alkyl, hydroxy-d. $_6$-alkyl, C_{3-8}-cycloalkyl, 0 -**C_{3-8}**-cycloalkyl, **C_{3-8}**-heterocycloalkyl and 0 -**C_{3-8}**-heterocycloalkyl,

wherein cycloalkyl and heterocycloalkyl are unsubstituted or substituted with 1 to 4 substitutents independently selected from the group consistinf of halogen, **C_{1-3}**-alkyl, halo-d-3-alkyl, **OH**, 0-d. $_3$-alkyl, 0-halo-d. $_3$-alkyl, $S0_2$-d. $_3$-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 **N**, **O** and S,

wherein aryl and heteroaryl is optionally substituted with 1 to 5 substituents independently selected from the group consisting of halogen, d $_{-6}$-alkyl, d $_{-6}$-alkenyl, d -

$_6$-alkynyl, halo-Ci-e-alkyl, OH, 0-C$_{1\text{-}e}$-alkyl, O-halo-Cve-alkyl, C$_{0\text{-}6}$-alkylene-C$_3$-io-cycloalkyl, Co.6-alkylene-C3$_{\cdot 10}$-heterocycloalkyl, C$_{0\text{-}6}$-alkylene-(5- or 6-membered heteroaryl), C$_{1\cdot 6}$-alkylene-0-R^{131}, C$_{0\text{-}6}$-alkylene-CN, Co.$_6$-alkylene-N(R^{131})$_2$, O-C$_{3\cdot 10}$-cycloalkyl, 0-C$_{1\text{-}6}$-alkylene-0-R^{131}, O-C$_{3\text{-}10}$-heterocycloalkyl, C$_{0\text{-}6}$-alkylene-COOR^{131}, C$_{0\text{-}6}$-alkylene-C(0)R^{131}, C$_{0\text{-}6}$-alkylene-C(O)N(R^{131})$_2$, C$_{0\text{-}6}$-alkylene-N(R^{131})C(O)R^{131}, C$_{0\cdot 6}$-alkylene-SO-R^{131}, C$_{0\text{-}6}$-alkylene-SO$_2$-R^{131}, C$_{0\text{-}6}$-alkylene-SO$_2$-N(R^{131})$_2$, C$_{0\text{-}6}$-alkylene-N(R^{131})S0$_2$-R^{131}, C$_{0\text{-}6}$-alkylene-S0$_2$-C$_3$.io-heterocycloalkyl and C$_{0\text{-}6}$-alkylene-SO$_2$-C$_{3\cdot 10}$-heterocycloalkyl,

wherein alkylene, cycloalkyi, heterocycloalkyi 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$_{1\text{-}3}$-alkyl, halo-C$_{1\text{-}3}$-alkyl, OH, oxo, =N-OR^{132}, 0-C$_{1\text{-}3}$-alkyl and 0-halo-Ci_$_3$-alkyl,

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 or N, wherein the ring is unsubstituted or substituted with 1 to 7 substituents independently selected from the group consisting of halogen, C$_{1\text{-}6}$-alkyl, halo-d.$_6$-alkyl, C$_{3\text{-}6}$-cycloalkyl, C$_{3\cdot 6}$-heterocycloalkyl, oxo, =N-OR^{132}, OH, O-d-e-alkyl and 0-halo-Ci.$_6$-alkyl;

R^{104} is selected from (CR^{108}R^{109})R^{140}, (C=0)R^{140}, OR^{140}, SO$_y$-R^{107} and C$_{3\cdot 6}$-cycloalkyl, which is spirocyclic fused with R^{140},

wherein cycloalkyi is unsubstituted or substituted with 1 to 4 substituents independently selected from the group consisting of F, CH$_3$ and CF$_3$;

R^{107} is selected from C$_{3\cdot 10}$-cycloalkyl and C$_{3\cdot 10}$-heterocycloalkyl,

wherein cycloalkyi and heterocycloalkyi are unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of halogen, OH, oxo, O-d-e-alkyl, 0-halo-Ci.$_6$-alkyl, Ci_$_6$-alkyl, halo-Ci.$_6$-alkyl, cycloalkyi and heterocycloalkyi;

R^{108} is selected from H, F, d$_{\text{-}3}$-alkyl, halo-d.$_3$-alkyl, OH, 0-d.$_3$-alkyl and 0-halo-d.$_3$-alkyl;

R^{109} is selected from H, F, d$_{\cdot 3}$-alkyl and halo-C$_{1\text{-}3}$-alkyl;

R^{111} is independently selected from H, Ci_$_6$-alkyl, C$_{0.6}$-alkylene-C$_3$.io-cycloalkyl and C$_{0\text{-}6}$-alkylene-C$_{3\cdot 10}$-heterocycloalkyl,

wherein alkyl, alkylene, cycloalkyi and heterocycloalkyi is unsubstituted or substituted with 1 to 6 substituents selected from the group consisting of halogen, CN, OH, oxo, d-$_3$-alkyl, halo-d$_{\text{-}3}$-alkyl, O-d$_{\text{-}3}$-alkyl, 0-halo-d.$_3$-alkyl, NH$_2$, NH(C$_{1\text{-}3}$-alkyl), N(Ci.$_3$-alkyl)$_2$, C$_{3\cdot 6}$-heterocycloalkyl, C$_{3\cdot 6}$-cycloalkyl and S0$_2$-d$_{\text{-}3}$-alkyl, wherein cycloalkyi and heterocycloalkyi 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^{112} is independently selected from H, d $_{-6}$-alkyl, halo-d. $_6$-alkyl and $C_{3\cdot6}$-cycloalkyl;

R^{131} is independently selected from H, d-e-alkyl, halo-Ci. $_6$-alkyl, Co.$_6$-alkylene-C $_{3\text{-}8}$-cycloalkyl, Co-6-alkylene-$C_{3\cdot8}$-heterocycloalkyl, 5- or 6-membered heteroaryl and 6-membered aryl, wherein alkyl, alkylene, cyclolalkyi, heterocycloalkyi, aryl and heteroaryl are unsubstituted or substituted with 1 to 6 substituents independently selected from the group consisting of halogen, CN, OH, oxo, =N-OR ^{132}, $C_{1\text{-}3}$-alkyl, halo-d. $_3$-alkyl, 0-d. $_3$-alkyl, 0-halo-d- $_3$-alkyl and S0 $_2$-d. $_3$-alkyl;

and optionally wherein two R^{131} 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 substitutents independently selected from the group consisting of fluoro, OH, oxo, d-4-alkyl and halo-d_ $_4$-alkyl;

R^{132} is independently selected from H, d-e-alkyl, halo-d. $_6$-alkyl and $C_{3\cdot6}$-cycloalkyl;

R^{140} is $C_{3\text{-}10}$-cycloalkyl, which is unsubstituted or substituted with 1 to 5 substituents independently selected from the group consisting of halogen, OH, oxo, 0-d. $_6$-alkyl, 0-halo-Ci. $_6$-alkyl, d-e-alkyl, halo-d. $_6$-alkyl, $C_{3\text{-}8}$-cycloalkyl and $C_{3\text{-}8}$-heterocycloalkyl;

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

12. The compound according to claim 11 wherein

R^{101} is selected from H, Ci-10-alkyl, $C_{3\text{-}10}$-cycloalkyl, $C_{3\cdot10}$-heterocycloalkyl, d-io-alkylene-C $_{3\cdot10}$-cycloalkyl, $C_{1\cdot10}$-alkylene-C $_{3\cdot10}$-heterocycloalkyl, Ci-io-alkylene-(5-membered heteroaryl), d $_{\text{-}10}$-alkylene-(6-membered aryl) and $C_{1\text{-}1}$o-alkylene-(6-membered heteroaryl), wherein alkyl, alkenyl, alkynyl, alkylene, cycloalkyi, heterocycloalkyi, aryl and heteroaryl is unsubstituted or substituted with 1 to 7 substituents independently selected from the group consisting of oxo, CN, OR^{111}, 0-C $_{2\cdot6}$-alkylene-OR ^{111}, d-e-alkyl, halo-d-e-alkyl, halogen, C0 $_2R^{111}$, CONR $^{111}R^{112}$, $CONR^{111}S0_2R^{111}$, COR^{111}, SO_xR^{111}, S0 $_3$H, S0 $_2NR^{111}R^{112}$, $NR^{111}COR^{111}$, $NR^{111}S0_2R^{111}$, NR^{111}-CO-NR $^{111}R^{112}$, NR^{111}-S0 $_2$-$NR^{111}R^{112}$, $C_{3\cdot8}$-cycloalkyl, 0-C $_{3\text{-}8}$-cycloalkyl, $C_{3\cdot8}$-heterocycloalkyl, 0-C $_{3\cdot8}$-heterocycloalkyl and $NR^{111}R^{112}$;

R^{102} is selected from H, $C_{1\text{-}3}$-alkyl, fluoro-Ci. $_3$-alkyl and hydroxy-Ci. $_3$-alkyl;

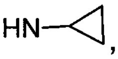
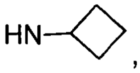
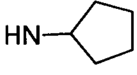
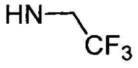
or R^{101} and R^{102} when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing 1 or 2 heteroatoms selected from O, S or N, wherein the ring is unsubstituted or substituted with 1 to 4 substitutents independently selected from the group consisting of halogen, oxo, CN, OR^{111},

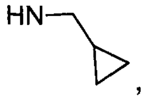
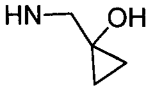
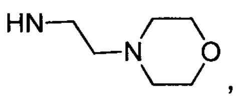
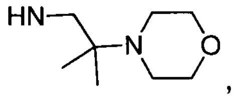
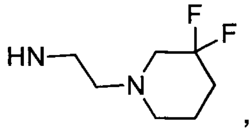
SO_xR^{111}, $S0_3H$, $NR^{1 1 1}S0_2R^{111}$, $S0_2NR^{1 1 1}R^{112}$, $C_{0\cdot 6}$-alkylene-**$CO_2R^{1 11}$, $CONR^{1 11}R^{112}$, $CONR^{111}S0_2R^{111}$, COR^{111}, $NR^{1 11}$-CO-R^{111}, $NR^{11 1}$-CO-$NR^{111}R^{112}$, NR^{111}-$S0_2$-$NR^{111}R^{1 12}$, $NR^{11}{}_1R^{112}$,** $C_{1\text{-}e}$-alkyl, halo-**$C_{1\text{-}e}$**-alkyl, hydroxy-**$C_{1\cdot 6}$**-alkyl, **$C_{3\text{-}8}$**-cycloalkyl, 0 -**$C_{3\cdot 8}$**-cycloalkyl, **$C_{3\text{-}8}$**-heterocycloalkyl and 0 -**$C_{3\cdot 8}$**-heterocycloalkyl,

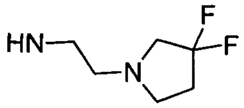
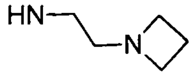
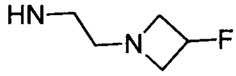
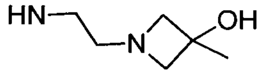
wherein cycloalkyi and heterocycloalkyi are unsubstituted or substituted with 1 to 4 substitutents independently selected from the group consisting of halogen, $C_{1\text{-}3}$-alkyl, halo-**$C_{1\cdot 3}$**-alkyl, **OH,** O-C^-alkyl, 0-halo -**$C_{1\text{-}3}$**-alkyl, $S0_2$-**Ci**$_{\cdot 3}$-alkyl, **COOH** and oxo.

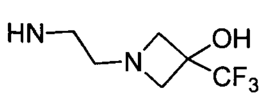
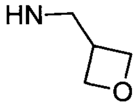
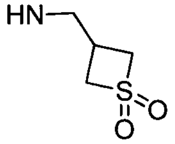
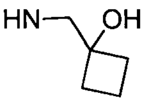
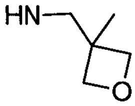
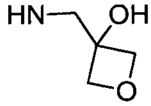
13. The compound according to any of claims 1 1 to 12 wherein $NR^{1 0 1}R^{102}$ is selected from

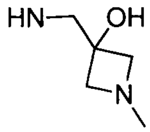
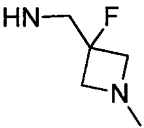
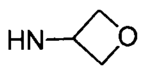
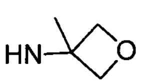
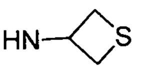
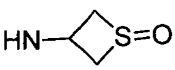
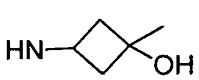
NHMe, NHEt, NH'Pr, NH'Bu, $NHCH_2CONH_2$, $NHCH_2CONMe_2$, $NHCH_2CH_2OH$, $NHCH_2CH_2OMe$, $NHCH_2CH_2S0_2Me$, $NHCH_2CH_2S0_2NH_2$, $NH(CH_2)_3OH$, $NH(CH_2)_3OMe$, $NH(CH_2)_4OH$, $NH(CH_2)_4OMe$, $NH(CH_2)_5OH$, $NH(CH_2)_2C0_2H$, $NH(CH_2)_3C0_2H$, $NH(CH_2)_4C0_2H$, $NH(CH_2)_5C0_2H$, $NHCH_2CH(CF_3)OH$, $NHCH_2C(Me)(CF_3)OH$, $NHCH_2CMe_2OH$, $NHCH_2CH_2CMe_2OH$, $NHCH_2CMe_2NHCH_2CF_3$, $NHCH(Me)CMe_2OH$, $NHCH_2CMe_2OMe$, $NHCH_2CMe_2C0_2H$, $NHCH_2CMe_2CONHMe$, $NHCH_2CMe_2CONMe_2$, $NHCH_2CMe_2NHS0_2Me$, $NH(CH_2)_3SOMe$, $NH(CH_2)_5S0_2Me$, $NH(CH_2)_5S0_2NH_2$, $NH(CH_2)_3NHS0_2Me$, $NH(CH_2)_20(CH_2)_2OH$, $NHCH_2CHMeOH$, $NH(CH_2)_5SOMe$, $NH(CH_2)_3S0_2Me$, $NHC(CH_2OH)_3$, $NHCH_2CH(OH)CH_2OH$, $N(CH_2CH_2OH)_2$,

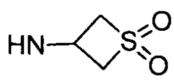
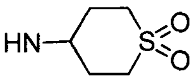
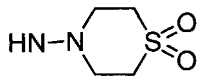
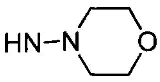
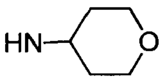
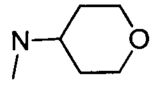
,
,
,
,

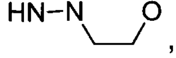
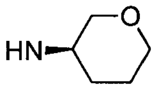
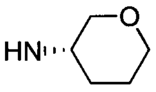
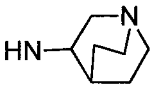
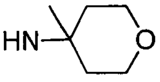
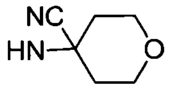
,
,
,
,
,

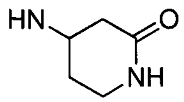
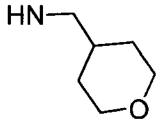
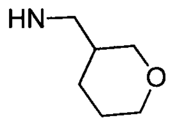
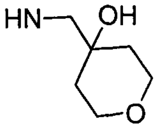
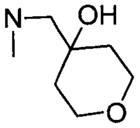
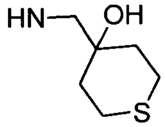
,
,
,
,

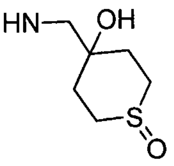
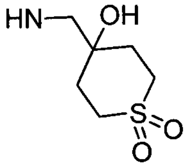
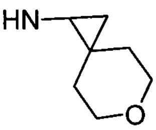
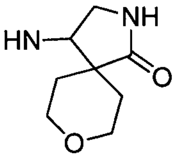
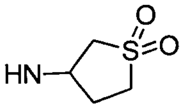
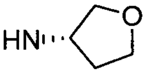
,
,
,
,
,
,

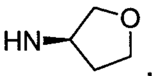
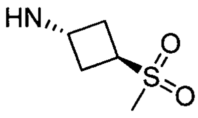
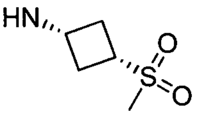
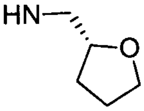
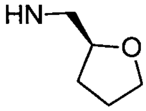
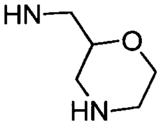
,
,
,
,
,
,
,

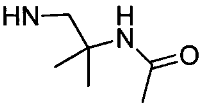
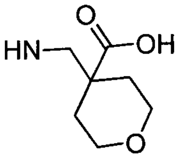
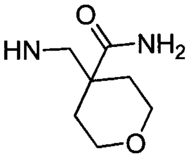
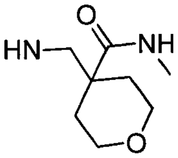
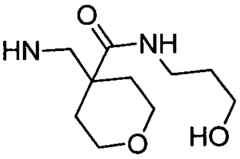
,
,
,
,
,
,

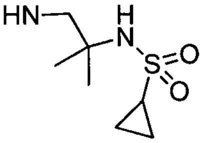
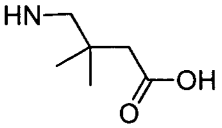
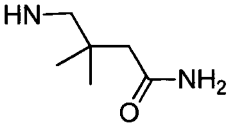
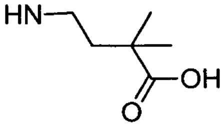
,
,
,
,
,
,

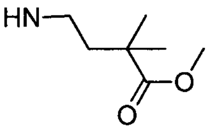
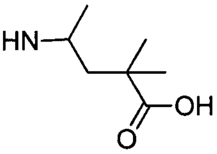
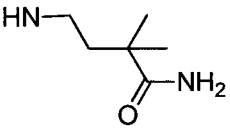
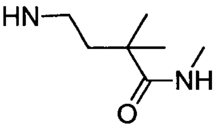
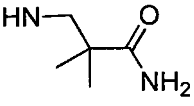
,
,
,
,
,
,

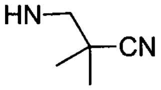
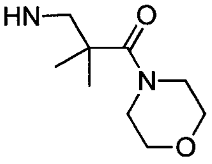
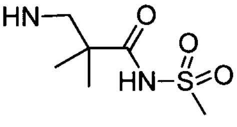
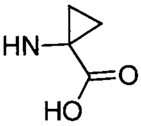
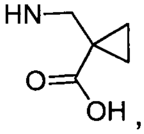
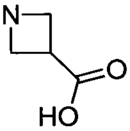
 ,
 ,
 ,
 ,
 ,
 ,

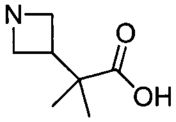
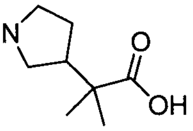
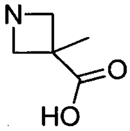
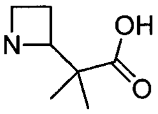
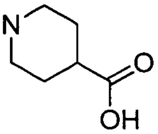
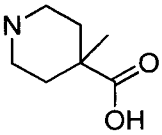
 ,
 ,
 ,
 ,
 ,
 ,

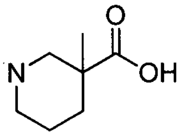
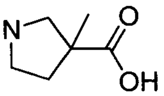
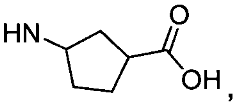
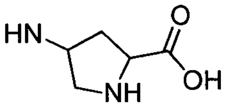
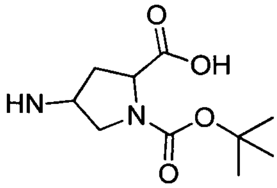
 ,
 ,
 ,
 ,
 ,

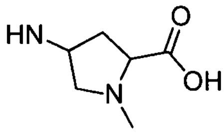
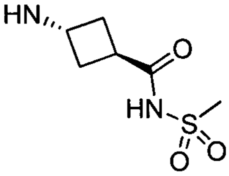
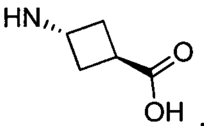
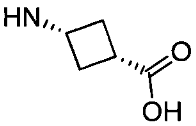
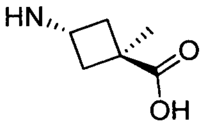
 ,
 ,
 ,
 ,

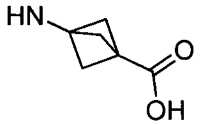
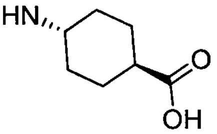
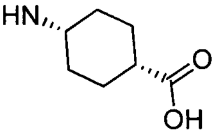
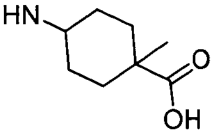
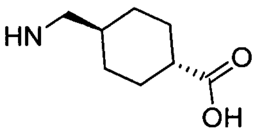
 ,
 ,
 ,
 ,
 ,

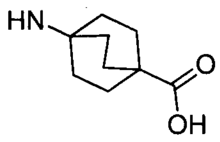
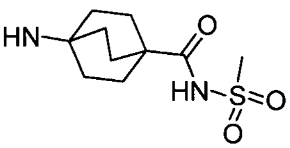
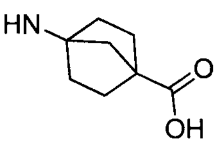
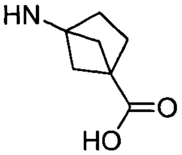
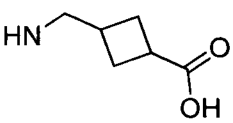
 ,
 ,
 ,
 ,
 ,
 ,

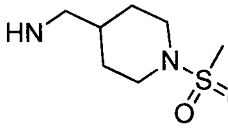
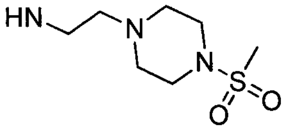
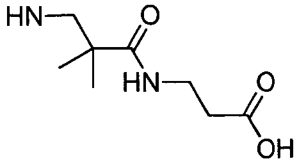
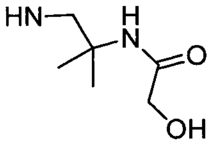
 ,
 ,
 ,
 ,
 ,
 ,

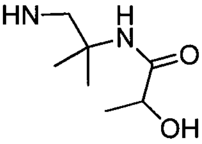
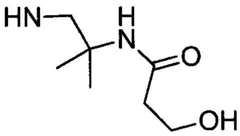
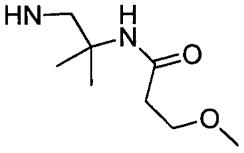
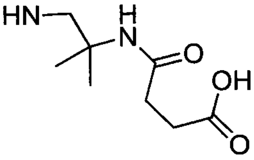
 ,
 ,
 ,
 ,
 ,

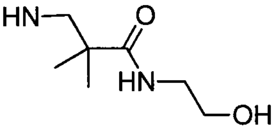
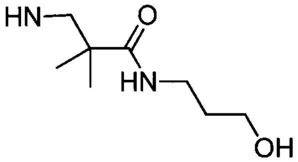
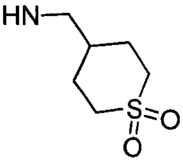
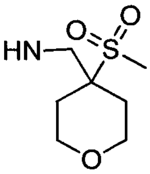
 ,
 ,
 ,
 ,
 ,

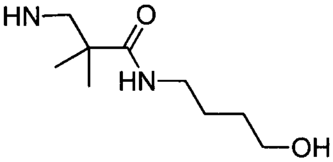
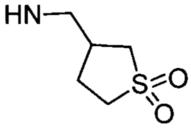
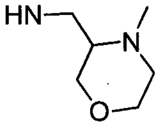
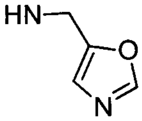
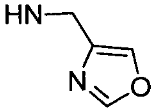
 ,
 ,
 ,
 ,
 ,

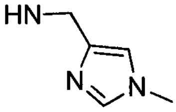
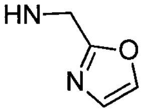
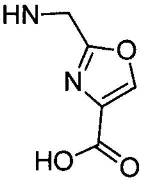
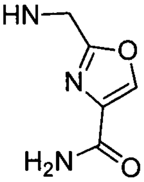
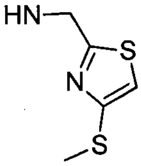
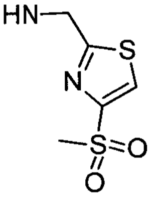
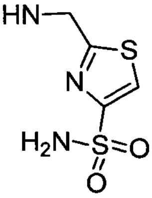
 ,
 ,
 ,
 ,
 ,

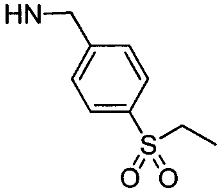
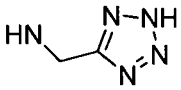
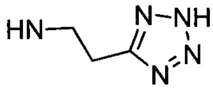
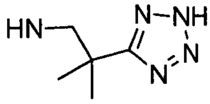
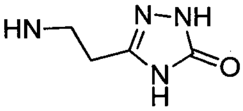
,
,
,
,

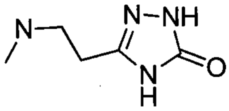
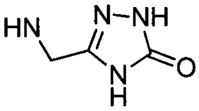
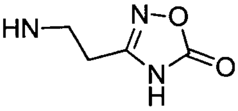
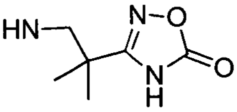
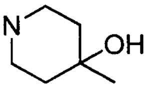
,
,
,
,

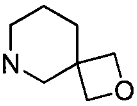
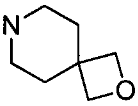
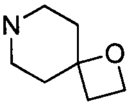
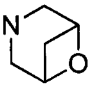
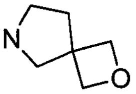
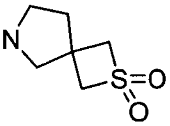
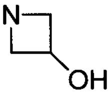
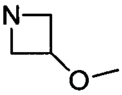
,
,
,
,

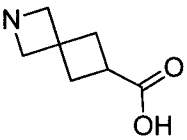
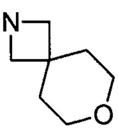
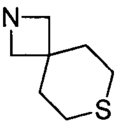
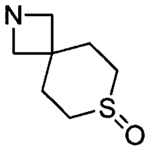
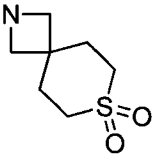
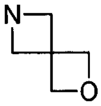
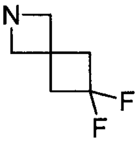
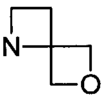
,
,
,
,
,

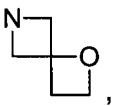
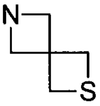
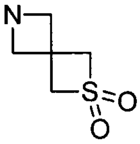
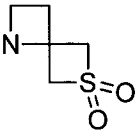
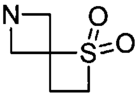
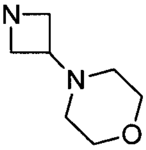
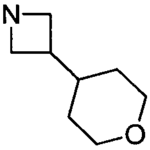
,
,
,
,
,
,
,

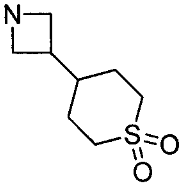
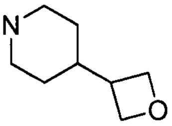
,
,
,
,
,

,
,
,
,
,

,
,
,
,
,
,
,
,

,
,
,
,
,
,
,
,

,
,
,
,
,
,
,

,
,
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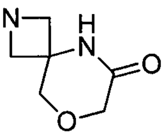
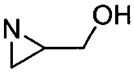
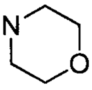
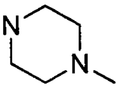
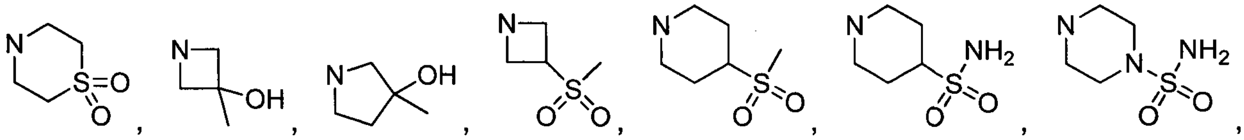
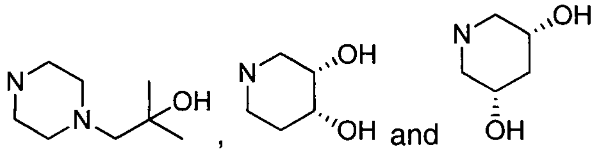
,
,
,
,





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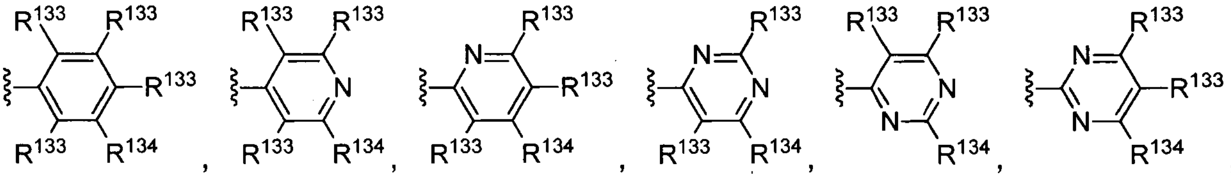
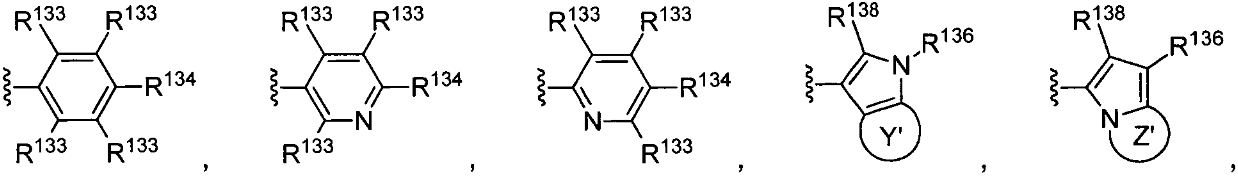
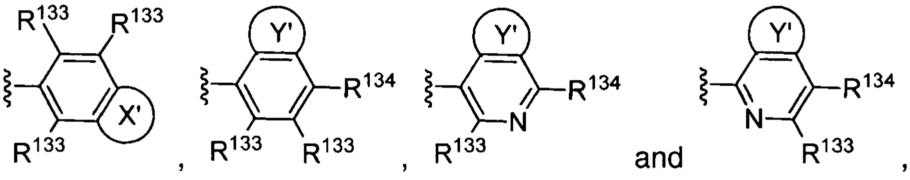
14. The compound according to any of claims 11 to 13 wherein

R^{103} is selected from







wherein

R^{133} is independently selected from H, halogen, CN, C_{1-6}-alkyl, fluoro -Ci.$_{6}$-alkyl, Ci-$_{4}$-alkylene-OH, C_{1-4}-alkylene-O-C_{1-3}-alkyl, d .$_{4}$-alkylene -0-fluoro-Ci.$_{3}$-alkyl, OH, 0-d. $_{6}$-alkyl, O-fluoro-d.$_{6}$-alkyl, NH-C $_{1-6}$-alkyl, NH-fluoro-Ci.$_{6}$-alkyl and $C_{3\cdot10}$-cycloalkyl,

wherein alkylene is unsubstituted or substituted with 1 to 3 substituents selected from F and cycloalkyi is unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of F, C_{1-3}-alkyl and fluoro -Ci.$_{3}$-alkyl;

R^{134} is independently selected from H, halogen, CN, C_{1-6}-alkyl, fluoro -Ci-$_{6}$-alkyl, d .$_{4}$-alkylene-OH, $C_{1\cdot4}$-alkylene -0-Ci.$_{3}$-alkyl, $C_{1\cdot4}$-alkylene -0-fluoro-d-$_{3}$-alkyl, OH, O-C^-alkyl, 0-fluoro-Ci.$_{6}$-alkyl, NH-d-e-alkyl, NH-fluoro-Ci.$_{6}$-alkyl, $C_{3\cdot10}$-cycloalkyl, C_{0}-$_{6}$-alkylene-C3 -io-heterocycloalkyl, 5-membered heteroaryl, 6-membered heteroaryl, $C(0)N(R^{137})_2$ and $S0_2N(R^{137})_2$,

wherein alkylene is unsubstituted or substituted with 1 to 3 substituents selected from F and cycloalkyi, heterocycloalkyl and heteroaryl is unsubstituted or substituted with 1 to 3 substituents independently selected from F, d -$_{3}$-alkyl, fluoro-d -$_{3}$-alkyl, OH, 0-C_{1-3}-alkyl and fluoro -0-Ci.$_{3}$-alkyl;

R^{135} is selected from halogen, C_{1-e}-alkyl, halo-d $_{-e}$-alkyl, C_{3-6}-cycloalkyl, C_{3-6}-heterocycloalkyl, oxo, =N-OR ^{132}, OH, 0 -Ci.6 -alkyl and O -halo-d $_{-6}$-alkyl;

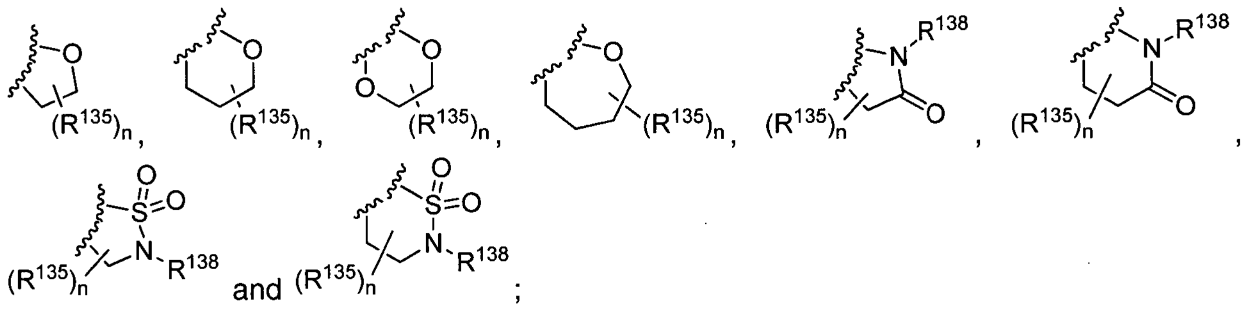
R^{136} is selected from C_{1-6}-alkyl, fluoro-CWalkyl, C(0)N(R ^{137})$_2$ and S0 $_2$N(R ^{137})$_2$;

R^{137} is independently selected from H, C_{1-6}-alkyl, halo-Ci $_{-6}$-alkyl, Co-4-alkylene-C_{3-6}-cycloalkyl and C_{0-4}-alkylene-C_{3-6}-heterocycloalkyl, wherein alkyl and alkylene is unsubtituted or substituted with 1 to 4 substituents selected from the group consisting of halogen, OH, 0-C $_{1-3}$-alkyl and CN; and cycloalkyl or heterocycloalkyi is unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of F, CN, OH, oxo, C_{1-3}-alkyl and fluoro-Ci-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 heteroatoms selected from O, S or N, wherein the ring is unsubstituted or substituted with 1 to 4 substitutents independently selected from the group consisting of 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-Ci $_{-3}$-alkyl;

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

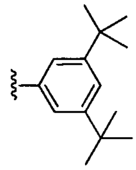
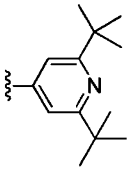
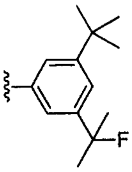
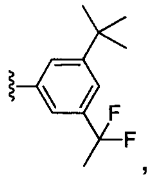
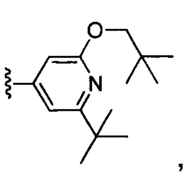
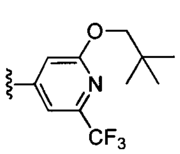
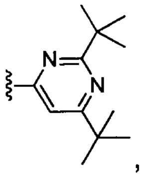
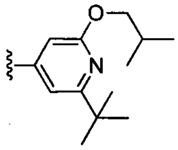
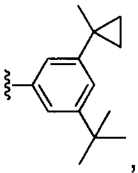
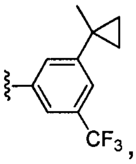
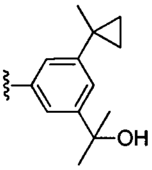
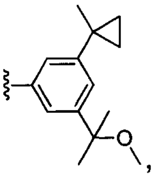
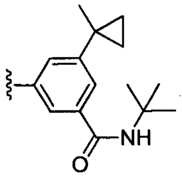
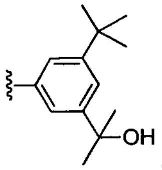
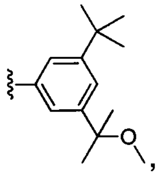
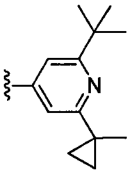
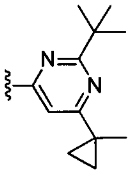
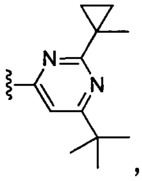
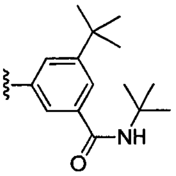
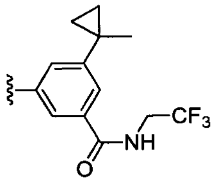
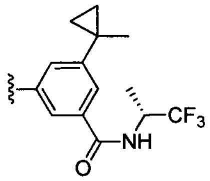
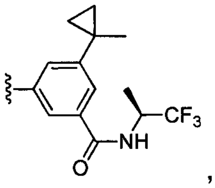
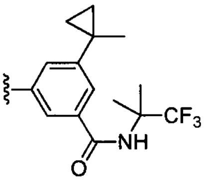
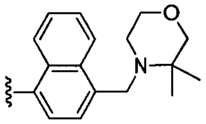
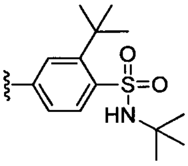
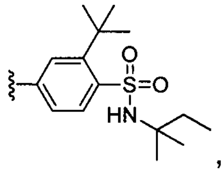
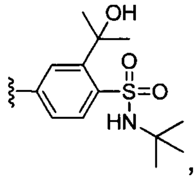
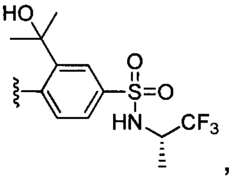
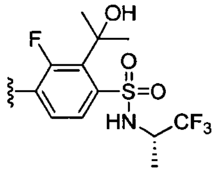
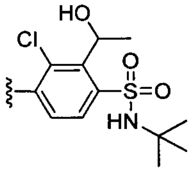
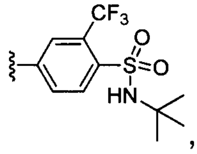
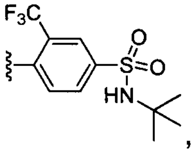
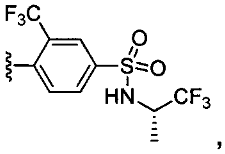
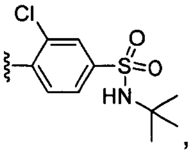
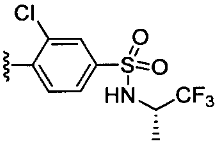
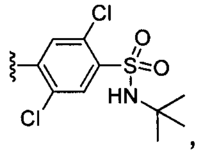
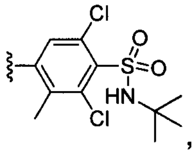
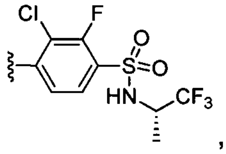
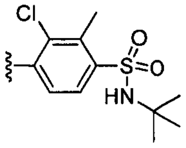
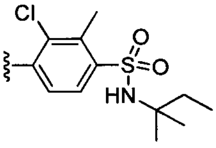
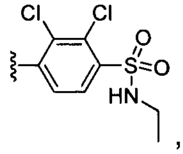
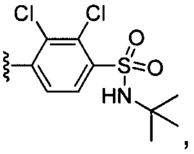
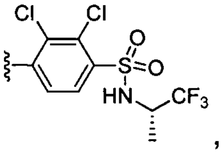
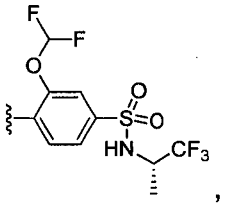
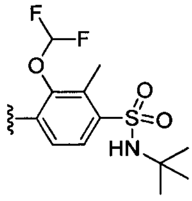
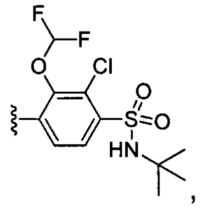
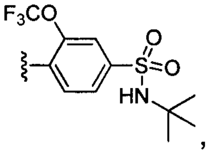
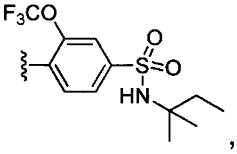
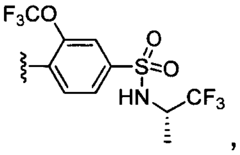
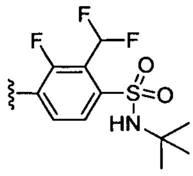
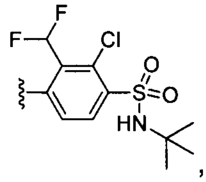
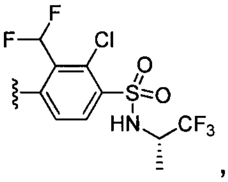
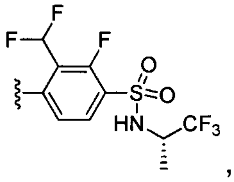
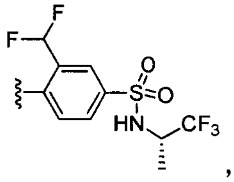
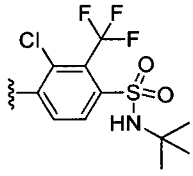


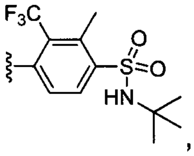
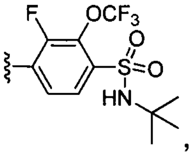
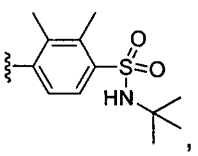
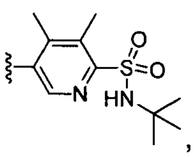
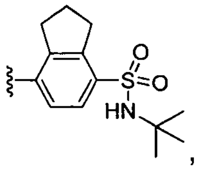
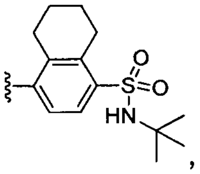
Y' is an annelated 5- or 6-membered carbocycle, an annelated 6-membered aryl or an annelated 6-membered heteroaryl containing 1 to 2 nitrogen atoms, wherein the carbocycle, aryl or heteroaryl is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of fluoro, C_{1-3}-alkyl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

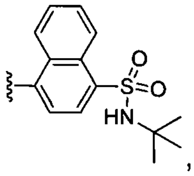
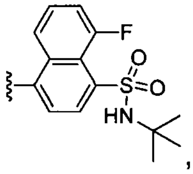
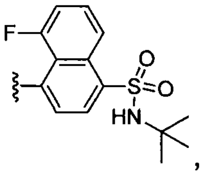
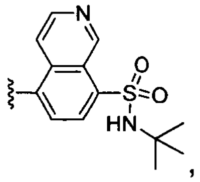
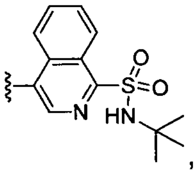
Z' is an annelated 6-membered cycle forming a heteroaryl containing 1 to 2 nitrogen atoms, wherein the heteroaryl is unsubstituted or substituted with 1 to 3 substituents selected from fluoro, C_{1-3}-alkyl and fluoro-C^-alkyl;

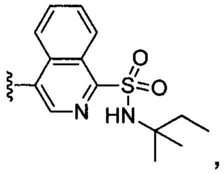
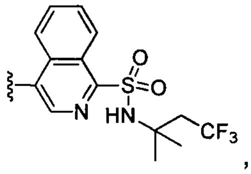
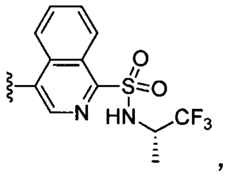
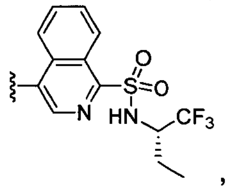
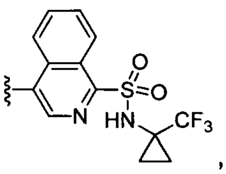
n is selected from 1 to 4.

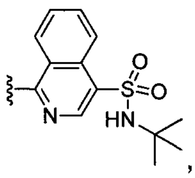
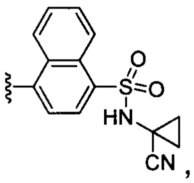
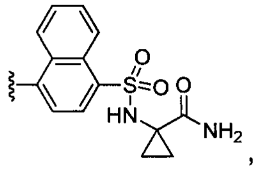
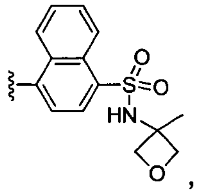
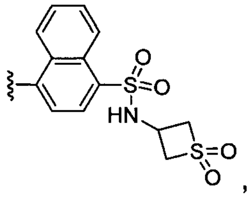
15. The compound according to any of claims 11 to 14 wherein R^{103} is selected from

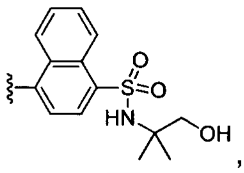
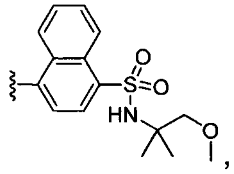
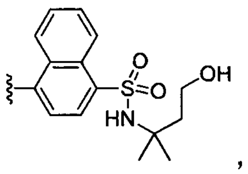
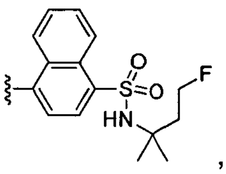
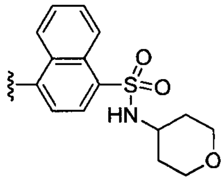
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,

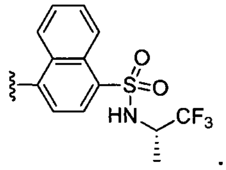
,
,
,
,
,
,

,
,
,
,
,

,
,
,
,
,

,
,
,
,
,

,
,
,
,
,

and .

16. The compound according to any of claims 11 to 15 wherein

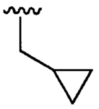
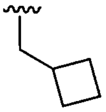
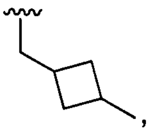
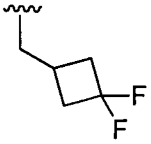
R^{104} is selected from $(CR^{108}R^{109})R^{140}$ and $(C{=}O)R^{140}$;

R^{108} is 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^{109} is selected from H, F and CH_3;

R^{140} 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, halo-C_{1-6}-alkyl, cycloalkyl and heterocycloalkyl.

17. The compound according to any of claims 11 to 16 wherein R^{104} is selected from

,
,
,

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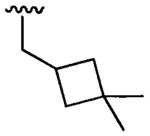
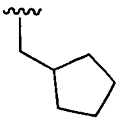
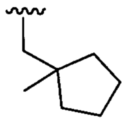
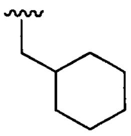
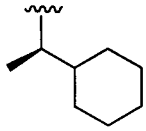
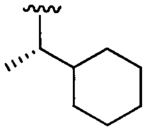
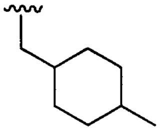
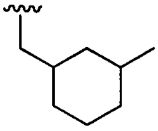
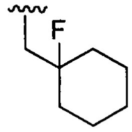
,
,
,
,

,
,
,
,

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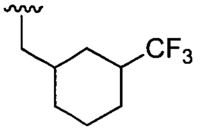
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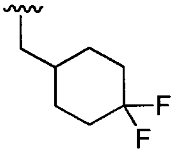
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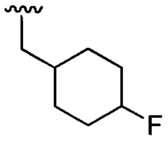
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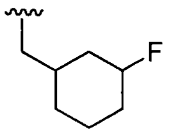
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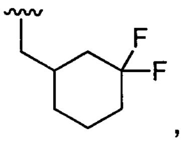
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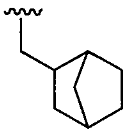
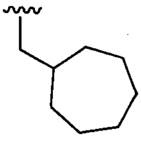
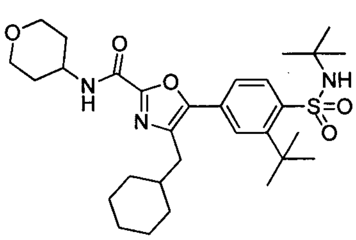
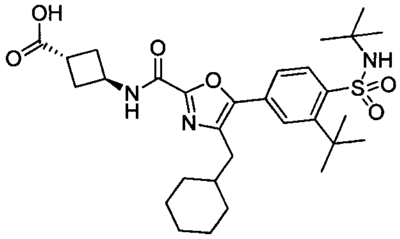
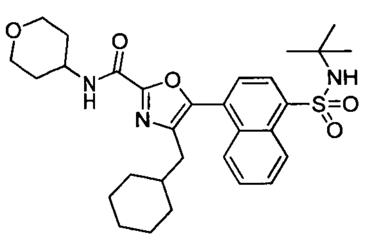
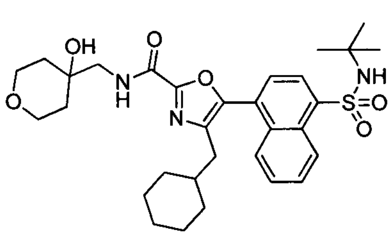
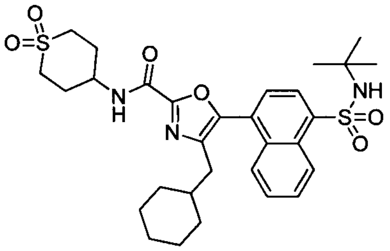
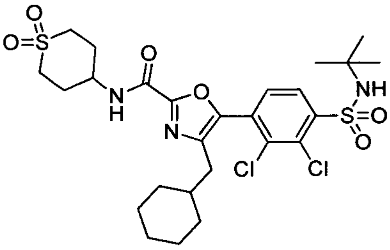
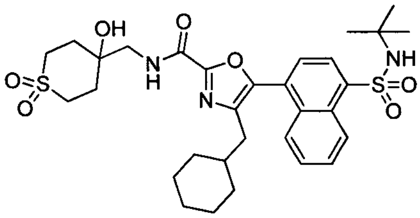
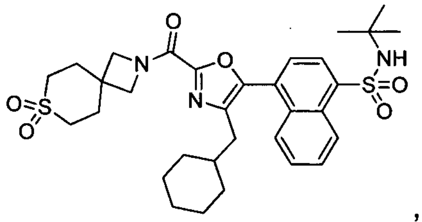
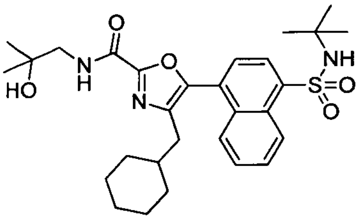
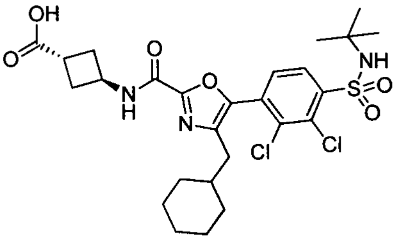
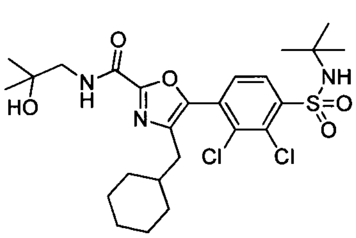
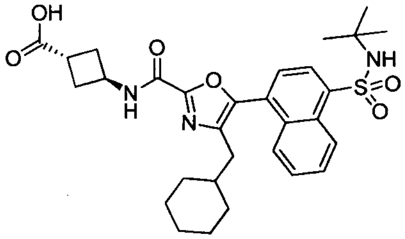
 and .

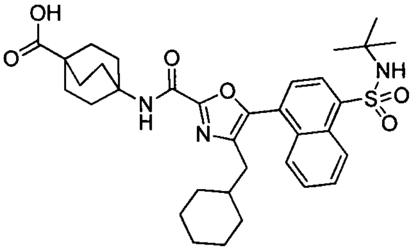
18. The compound of any of claims 11 to 17 selected from the group consisting of

,
,
,

,
,
,

,
,
,

,
,
,



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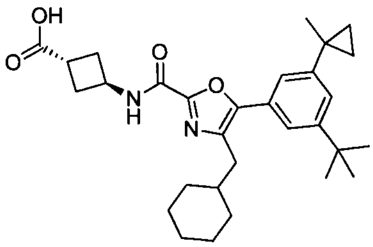

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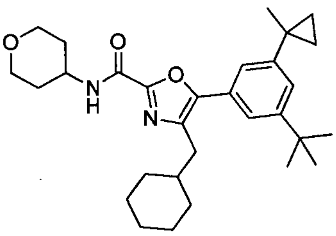

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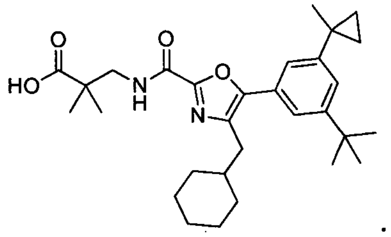

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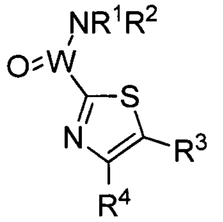
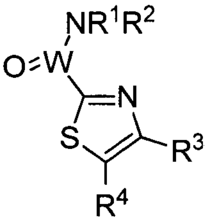
and an enantiomer, diastereomer, tautomer, A/-oxide, solvate and pharmaceutically acceptable salt thereof.

19. A compound represented by Formula **(1)** or Formula **(1')**



(1)



(1')

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

R^1 and **R^2** are independently selected from **H**, $C_{1\text{-}10}$-alkyl, $C_{2\text{-}10}$-alkenyl, $C_{2\text{-}10}$-alkynyl, **C_3-io-**cycloalkyl, $C_{3\text{-}10}$-heterocycloalkyl, $C_{1\text{-}1}$o-alkylene-**$C_{3\text{-}1}$o-**cycloalkyl, $C_{1\text{-}10}$-alkylene-**$C_{3\text{-}10}$-**heterocycloalkyl, C_1-io-alkylene-iS-membered heteroaryl) and **SO_2-$C_{1\text{-}10}$-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**, **OR^{11}**, 0-$C_{2\text{-}6}$-alkylene-**OR^{11}**, C^-alkyl, halo-C^-alkyl, halogen, **$C0_2R^{11}$**, **$CONR^{11}R^{12}$**, **$CONR^{11}S0_2R^{11}$**, **COR^{11}**, **SO_xR^{11}**, **$S0_3H$**, **$S0_2NR^{11}R^{12}$**, **$NR^{11}COR^{11}$**, **$NR^{11}S0_2R^{11}$**, **NR^{11}-CO-$NR^{11}R^{12}$**, **NR^{11}-$S0_2$-$NR^{11}R^{12}$**, $C_{3\text{-}10}$-cycloalkyl, **O-$C_{3\text{-}10}$**-cycloalkyl, $C_{3\text{-}10}$-heterocycloalkyl, **0-$C_{3\text{-}10}$**-heterocycloalkyl and **$NR^{11}R^{12}$**;

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 substitutents independently selected from the group consisting of halogen, oxo, **CN**, **OR^{11}**, **SO_xR^{11}**, **$S0_3H$**, **$NR^{11}S0_2R^{11}$**, **$S0_2NR^{11}R^{12}$**, $C_{0\text{-}6}$-alkylene-**CO_2R^{11}**, **$CONR^{11}R^{12}$**, **$CONR^{11}S0_2R^{11}$**, **COR^{11}**, **NR^{11}-CO-R^{11}**, **NR^{11}-CO-$NR^{11}R^{12}$**, **NR^{11}-$S0_2$-$NR^{11}R^{12}$**, **$NR^{11}R^{12}$**, C^-alkyl, halo-**$C_{1\text{-}6}$-**

alkyl, hydroxy-^. $_6$-alkyl, **C**$_{3\cdot8}$-cycloalkyl, 0 **-C**$_{3\cdot8}$-cycloalkyl, **C**$_{3\text{-}8}$-heterocycloalkyl and **0-C** $_{3\cdot8}$-heterocycloalkyl,

wherein cycloalkyi and heterocycloalkyi are unsubstituted or substituted with 1 to 4 substitutents independently selected from the group consisting of halogen, **C**$_{1\text{-}3}$-alkyl, halo-d $_{\text{-}3}$-alkyl, **OH,** 0-d. $_3$-alkyl, 0-halo-d. $_3$-alkyl, S0 $_2$-d. $_3$-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**$_{1\text{-}6}$-alkyl, d $_{\text{-}6}$-alkenyl, **Ci.** $_6$-alkynyl, halo-d $_{\text{-}e}$-alkyl, **OH,** 0 **-Ci** $_{\text{-}6}$-alkyl, **O**-halo-**C**^-alkyl, **C$_{0\text{-}6}$-alkylene-C** $_{3\text{-}10}$-cycloalkyl, **C**$_{0.6}$-alkylene**-C**$_{3\text{-}10}$-heterocycloalkyl, **C**$_{0\text{-}6}$-alkylene-(5- or 6-membered heteroaryl), d $_{\cdot6}$-alkylene-0 **-R^{31}, C**$_{0\cdot6}$-alkylene**-CN, C**$_{0\cdot6}$-alkylene**-N(R ^{31})$_2$, C**$_{0\cdot6}$-alkylene-**O-C** $_{3\cdot10}$-cycloalkyl, 0 **-C**$_{1\cdot6}$-alkylene-0 **-R^{31}, C**$_{0\text{-}6}$-alkylene**-O-C** $_{3\text{-}10}$-heterocycloalkyl, **C**$_{0\text{-}6\text{-}}$ **alkylene-COOR** ^{31}, **C**$_{0\text{-}6}$-alkylene**-C(O)R** ^{31}, **C**$_{0.6}$**-alkylene-C(O)N(R** ^{31}**)$_2$, C**$_{0\text{-}6}$-alkylene-**N(R^{31})C(0)R** ^{31}, **Co-6-alkylene-SO-R** ^{31}, **C** o$_{\text{-}6}$-alkylene-S0 $_2$**-R^{31}, C$_{0\text{-}6}$-alkylene-SO** $_2$**-N(R ^{31})$_2$, C$_{0\text{-}6}$-alkylene-N(R** ^{31})**SO$_2$-R^{31}, C**$_{0\text{-}6}$-alkylene-SO $_2$**-C**$_{3\text{-}10}$-heterocycloalkyl and **C**$_{0\text{-}6}$-alkylene-S0 $_2$**-C$_3$.io**-heterocycloalkyl,

wherein alkyl, alkenyl, alkynyl, alkylene, cycloalkyi, heterocycloalkyi 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**$_{1\text{-}3}$-alkyl, halo-d $_3$-alkyl, **OH,** oxo, **=N-OR** ^{32}, O-C^-alkyl, **O**-halo-d $_{\text{-}3}$-alkyl, **N(R^{31})$_2$, COOH, CON(R** ^{31}**)$_2$, NR^{31}-COR** ^{31}, **C**$_{3\cdot10}$-cycloalkyl, **C**$_{3\text{-}10}$-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, S0 $_2$ or **NR^{31},** 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-**Ci-e**-alkyl, **C**$_{3\cdot6}$-cycloalkyl, **C**$_{3\cdot6}$-heterocycloalkyl, oxo, **=N-OR** ^{32}, **OH, 0-Ci_** $_6$-alkyl and 0-halo-d- $_6$-alkyl;

R^4 is selected from **(CR^{8}R^9)R^{40}, (C=0)R** ^{40}, **O R^{40}, NR^{41}R^{40}, SO$_y$-R^7** and **C**$_{3\text{-}6}$-cycloalkyl, which is spirocyclic fused with **R^{40},**

wherein cycloalkyi is unsubstituted or substituted with 1 to 4 substituents independently selected from the group consisting of **F, CH$_3$** and **CF$_3$;**

R^7 is selected from **C**$_{3\cdot10}$-cycloalkyl and **C**$_{3\cdot10}$-heterocycloalkyl, wherein cycloalkyl and heterocycloalkyi are unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of halogen, OH, oxo, O-C_{1-6}-alkyl, 0-halo-Ci. $_{6}$-alkyl, Ci $_{-6}$-alkyl, halo-d. $_{6}$-alkyl, cycloalkyl and heterocycloalkyi;

R^8 and R^9 are independently selected from H, F, $C_{1.3}$-alkyl, halo-d $_{-3}$-alkyl, OH, 0-d. $_{3}$-alkyl and 0-halo-d. $_{3}$-alkyl;

R^{11} is independently selected from H, $C_{1.6}$-alkyl, $C_{0.6}$-alkylene-C_{3}.io-cycloalkyl and **C_{0}-6-** alkylene-$C_{3\text{-}10}$-heterocycloalkyl,

wherein alkyl, alkylene, cycloalkyl and heterocycloalkyi is unsubstituted or substituted with 1 to 6 substituents selected from the group consisting of halogen, CN, OH, oxo, d . $_{3}$-alkyl, halo-Ci. $_{3}$-alkyl, 0-Ci. $_{3}$-alkyl, 0-halo-d. $_{3}$-alkyl, NH_2, NH(C_{1-3}-alkyl), N(C_{1-3}-alkyl)$_2$, $C_{3.6}$-heterocycloalkyl, $C_{3\text{-}6}$-cycloalkyl and S0 $_{2}$-$C_{1\text{-}3}$-alkyl,

wherein cycloalkyl and heterocycloalkyi 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^{12} is independently selected from H, Ci $_{-6}$-alkyl, halo-Ci $_{-6}$-alkyl and $C_{3.6}$-cycloalkyl;

R^{31} is independently selected from H, d $_{-6}$-alkyl, halo-C_{1-6}-alkyl, $C_{0\text{-}6}$-alkylene-$C_{3\text{-}8}$-cycloalkyl, $C_{0\text{-}6}$-alkylene-$C_{3\text{-}8}$-heterocycloalkyl, 5- or 6-membered heteroaryl and 6-membered aryl, wherein alkyl, alkylene, cyclolalkyi, heterocycloalkyi, aryl and heteroaryl are unsubstituted or substituted with 1 to 6 substituents independently selected from the group consisting of halogen, CN, OH, oxo, =N-OR^{32}, $C_{1\text{-}3}$-alkyl, halo-d $_{-3}$-alkyl, O-d $_{-3}$-alkyl, 0-halo-C $_{1-3}$-alkyl and SO2-C1. $_{3}$-alkyl;

and optionally wherein two R^{31} 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 substitutents independently selected from the group consisting of fluoro, OH, oxo, d $_{-4}$-alkyl and halo-d $_{-4}$-alkyl;

R^{32} is independently selected from H, d-e-alkyl, halo-d. $_{6}$-alkyl and $C_{3.6}$-cycloalkyl;

R^{40} is $C_{3\text{-}10}$-cycloalkyl, which is unsubstituted or substituted with 1 to 5 substituents independently selected from the group consisting of halogen, OH, oxo, 0-d $_{-6}$-alkyl, O-halo-d. $_{6}$-alkyl, d $_{6}$-alkyl, halo-d-e-alkyl, $C_{3\text{-}8}$-cycloalkyl and $C_{3\text{-}8}$-heterocycloalkyl;

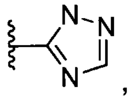
R^{41} is selected from H, d-e-alkyl $_{>}C_{3.6}$-cycloalkyl and $C_{3\text{-}6}$-heterocycloalkyl,

wherein alkyl, cycloalkyl and heterocycloalkyi is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of OH, oxo, CN, halogen, 0-d. $_{6}$-alkyl, O-halo-d-e-alkyl, $C_{3.6}$-heterocycloalkyl and $C_{3\text{-}6}$-cycloalkyl;

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

W is selected from C or S=0;

with the proviso that for R^3 the 5-14 membered mono-, bi- or tricyclic heteroaryl containing ring is not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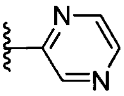
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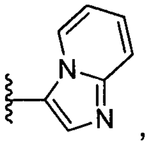
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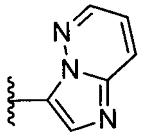
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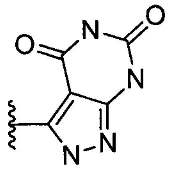
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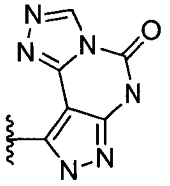
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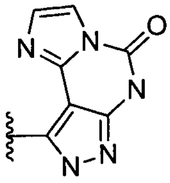

or a 5-membered aromatic heterocyclic group containing at least one oxygen atom.

20. The compound according to claim 19 wherein W is C.

21. The compound according to any of claims 19 to 20 wherein

R^4 is selected from $(CR^8R^9)R^{40}$, $(C=0)R^{40}$ and OR^{40};

R^8 is selected from H, F, CH_3, CF_3 and O- CH_3;

R^9 is selected from H, F and CH_3;

R^{40} is $C_{3\cdot 8}$-cycloalkyl, which is unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of fluoro, CH_3 and CF_3.

22. The compound according to any of claims 19 to 21 wherein

R^1 is selected from H, $C_{1\text{¬}10}$-alkyl, $C_{3\text{-}10}$-cycloalkyl, $C_{3\text{-}i0}$-heterocycloalkyl, $C_{1\text{-}1}$o-alkylene-QMo-cycloalkyl, $C_{1\text{-}1}$o-alkylene-$C_{3\text{-}10}$-heterocycloalkyl and C^o-alkylene-^-membered heteroaryl), wherein alkyl, alkenyl, alkynyl, alkylene, cycloalkyi and heterocycloalkyi is unsubstituted or substituted with 1 to 7 substituents independently selected from the group consisting of oxo, CN, OR^{11}, 0-$C_{2\cdot 6}$-alkylene-OR^{11}, C^-alkyl, halo-Ci.$_6$-alkyl, halogen, $C0_2R^{11}$, $CONR^{11}R^{12}$, $CONR^{11}S0_2R^{11}$, COR^{11}, SO_xR^{11}, $S0_3H$, $S0_2NR^{11}R^{12}$, $NR^{11}COR^{11}$, $NR^{11}S0_2R^{11}$, NR^{11}-CO-$NR^{11}R^{12}$, NR^{11}-$S0_2$-$NR^{11}R^{12}$, $C_{3\cdot 10}$-cycloalkyl, O-$C_{3\cdot 10}$-cycloalkyl, $C_{3\text{-}10}$-heterocycloalkyl, 0-$C_{3\text{-}10}$-heterocycloalkyl and $NR^{11}R^{12}$;

R^2 is selected from H, $C_{1\text{-}6}$-alkyl, halo-Ci-$_6$-alkyl and hydroxy-Ci-e-alkyl;

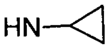
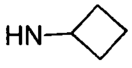
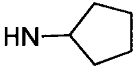
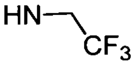
or R^1 and R^2 when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing 1 or 2 heteroatoms selected from O, S or N, wherein the ring is unsubstituted or substituted with 1 to 4 substitutents independently selected from the group consisting of halogen, oxo, CN, OR^{11}, SO_xR^{11}, $S0_3H$, $NR^{11}S0_2R^{11}$, $S0_2NR^{11}R^{12}$, $C_{0\text{-}6}$-alkylene-CO_2R^{11}, $CONR^{11}R^{12}$, $CONR^{11}S0_2R^{11}$, COR^{11}, NR^{11}-CO-R^{11}, NR^{11}-CO-$NR^{11}R^{12}$, NR^{11}-$S0_2$-$NR^{11}R^{12}$, $NR^{11}R^{12}$, $C_{1\cdot e}$-alkyl, halo-$C_{1\text{-}6}$-

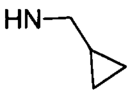
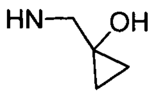
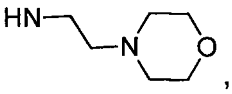
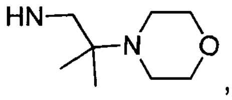
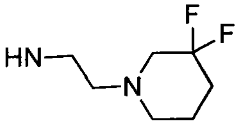
alkyl, hydroxy-Ci $_{\cdot6}$-alkyl, $C_{3\text{-}8}$-cycloalkyl, 0-C $_{3\cdot8}$-cycloalkyl, $C_{3\cdot8}$-heterocycloalkyl and 0-C $_{3\cdot8}$-heterocycloalkyl,

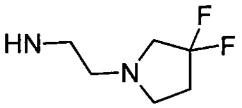
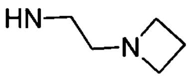
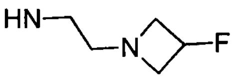
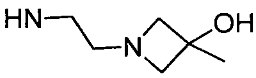
wherein cycloalkyi and heterocycloalkyi are unsubstituted or substituted with 1 to 4 substitutents independently selected from the group consisting of halogen, C $_{1\text{-}3}$-alkyl, halo-Ci. $_3$-alkyl, OH, O-C^-alkyl, 0-halo-C $_{1\text{-}3}$-alkyl, SO_2-$C_{1\text{-}3}$-alkyl, COOH and oxo.

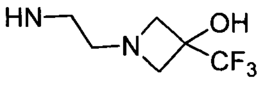
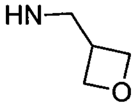
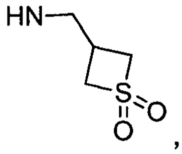
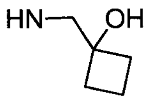
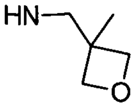
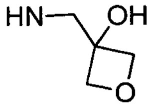
23. The compound according to any of claims 19 to 22 wherein NR^1R^2 is selected from

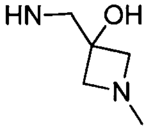
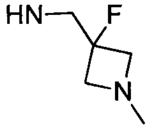
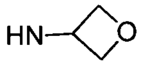
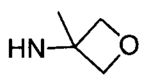
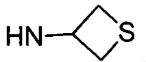
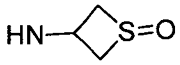
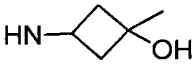
NHMe, NHEt, NH^{i}Pr, NH'Bu, $NHCH_2CONH_2$, $NHCH_2CONMe_2$, $NHCH_2CH_2OH$, $NHCH_2CH_2OMe$, $NHCH_2CH_2S0\ _2Me$, $NHCH_2CH_2S0\ _2NH_2$, $NH(CH_2)_3OH$, $NH(CH_2)_3OMe$, $NH(CH_2)_4OH$, $NH(CH_2)_4OMe$, $NH(CH_2)_5OH$, $NH(CH_2)_2C0\ _2H$, $NH(CH_2)_3C0\ _2H$, $NH(CH_2)_4C0\ _2H$, $NH(CH_2)_5C0\ _2H$, $NHCH_2CH(CF_3)OH$, $NHCH_2C(Me)(CF_3)OH$, $NHCH_2CMe_2OH$, $NHCH_2CH_2CMe_2OH$, $NHCH_2CMe_2NHCH_2CF_3$, $NHCH(Me)CMe_2OH$, $NHCH_2CMe_2OMe$, $NHCH_2CMe_2C0\ _2H$, $NHCH_2CMe_2CONHMe$, $NHCH_2CMe_2CONMe_2$, $NHCH_2CMe_2NHS0\ _2Me$, $NH(CH_2)_3SOMe$, $NH(CH_2)_5S0\ _2Me$, $NH(CH_2)_5S0\ _2NH_2$, $NH(CH_2)_3NHS0\ _2Me$, $NH(CH_2)_20(CH\ _2)_2OH$, $NHCH_2CHMeOH$, $NH(CH_2)_5SOMe$, $NH(CH_2)_3SO_2Me$, $NHC(CH_2OH)_3$, $NHCH_2CH(OH)CH_2OH$, $N(CH_2CH_2OH)_2$,

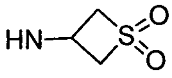
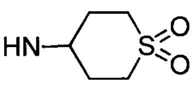
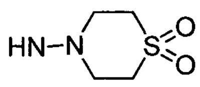
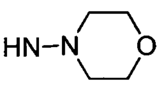
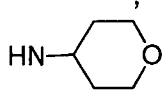
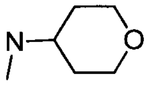
,
,
,
,

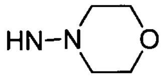
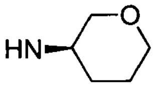
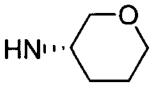
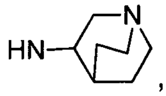
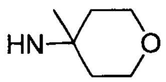
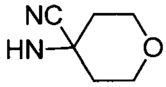
,
,
,
,
,

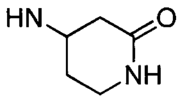
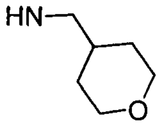
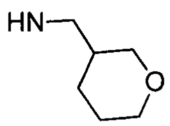
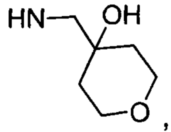
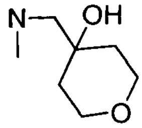
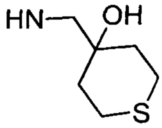
,
,
,
,

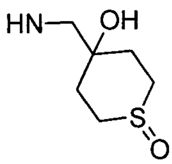
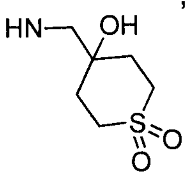
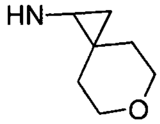
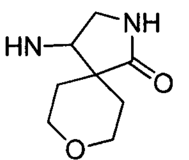
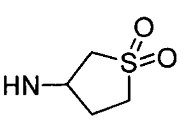
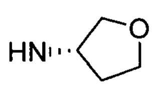
,
,
,
,
,
,

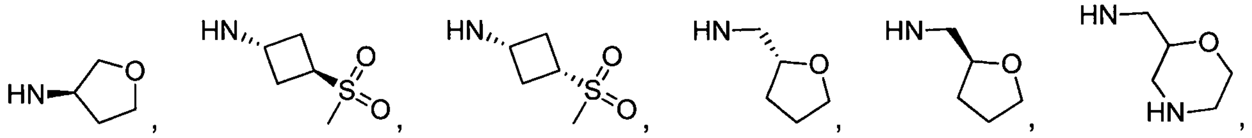
,
,
,
,
,
,
,

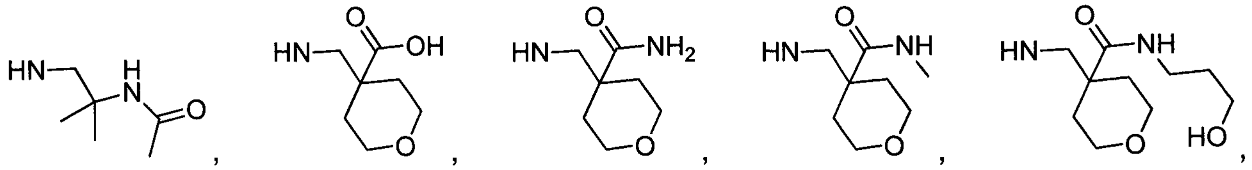
,
,
,
,
,
,

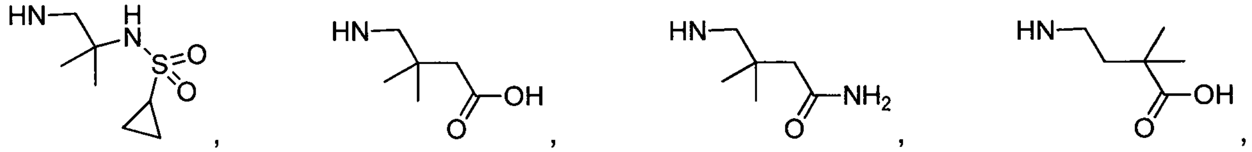
,
,
,
,
,
,

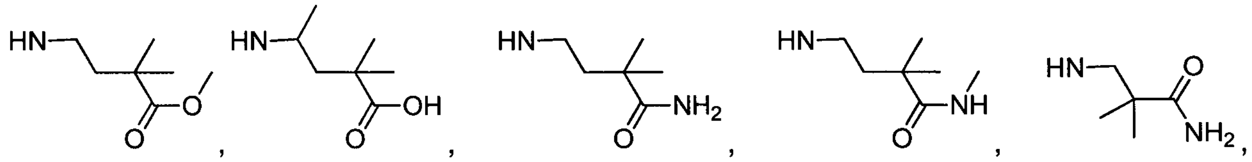
,
,
,
,
,
,

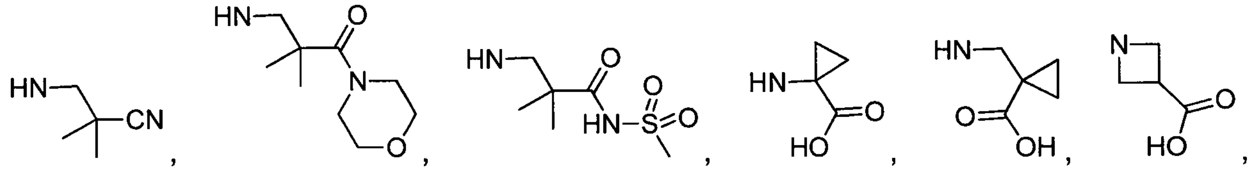
,
,
,
,
,
,

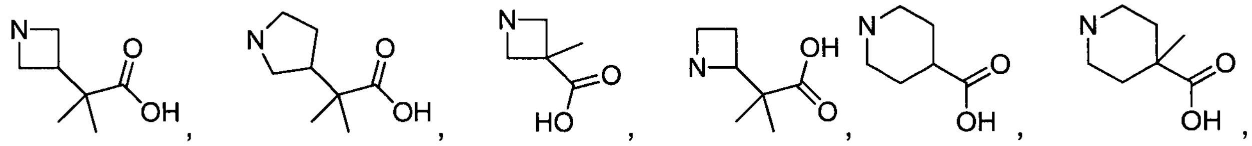


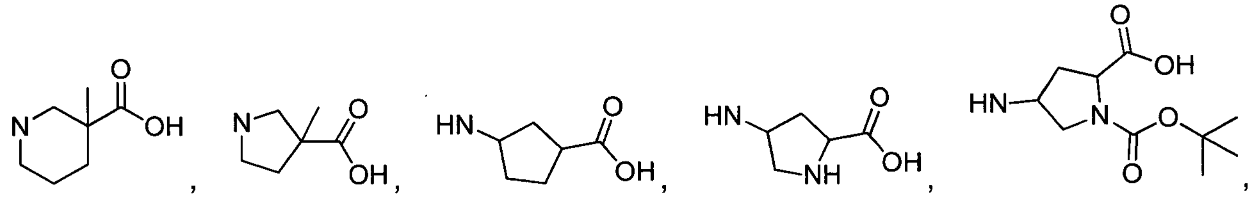


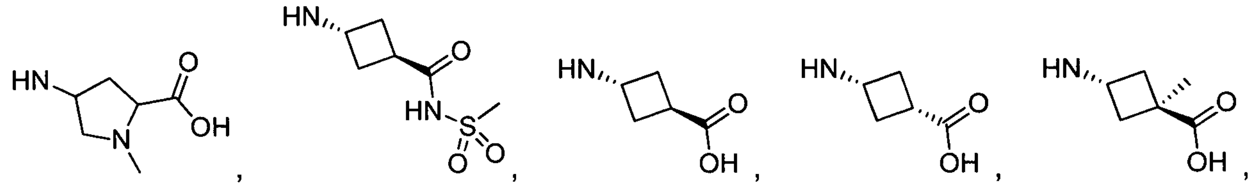


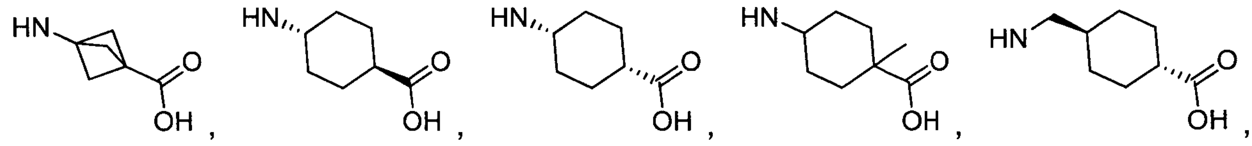


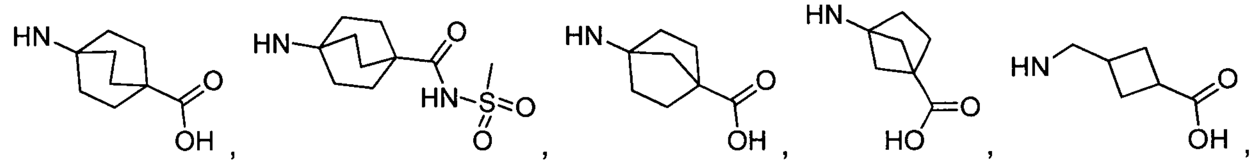


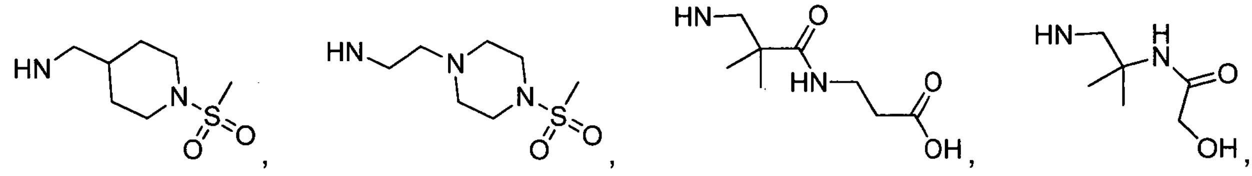


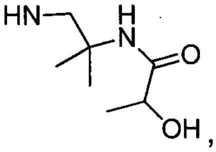
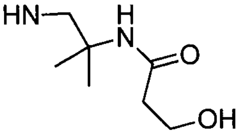
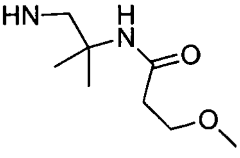
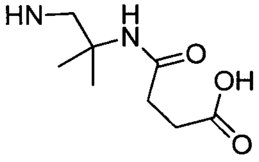
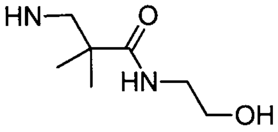
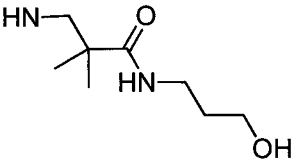
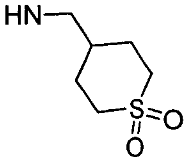
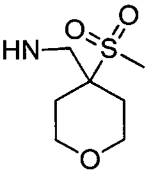
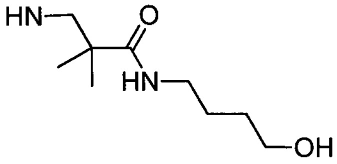
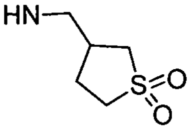
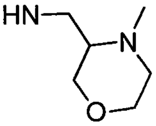
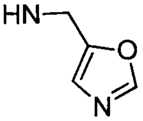
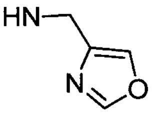
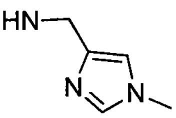
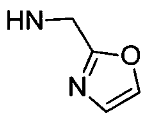
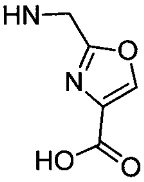
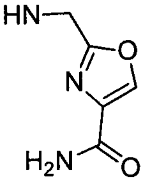
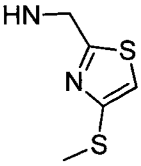
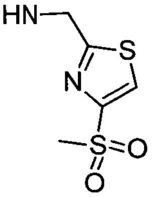
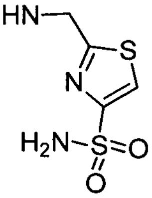
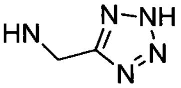
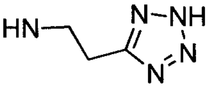
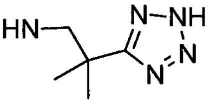
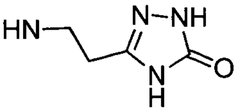
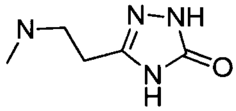
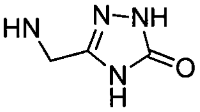
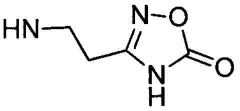
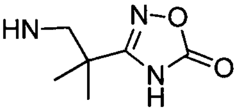
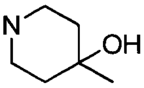
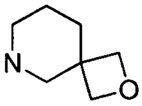
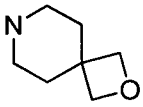
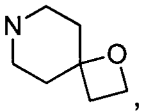
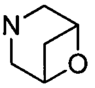
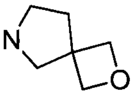
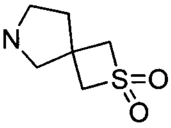
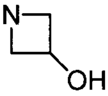
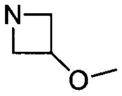
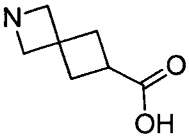
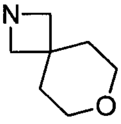
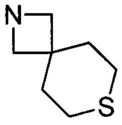
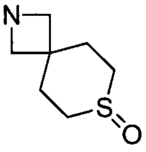
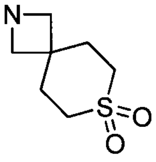
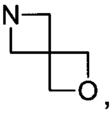
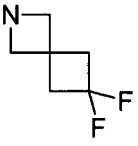
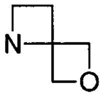
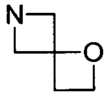
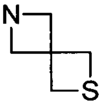
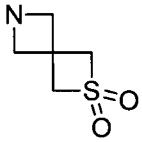
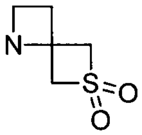
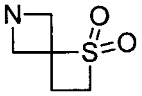
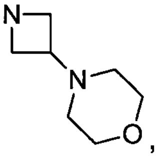
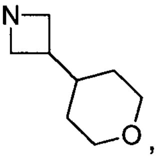
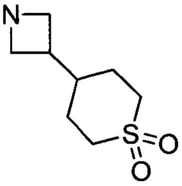
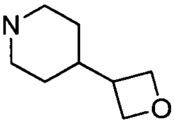
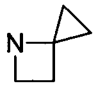
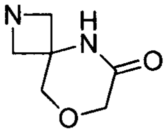
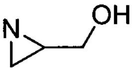
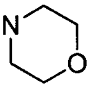
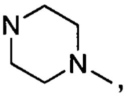
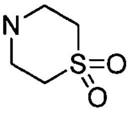
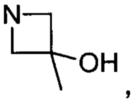
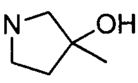


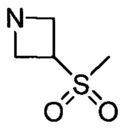
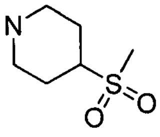
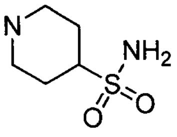
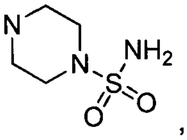
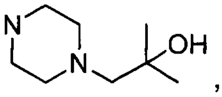
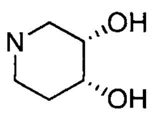
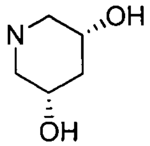








,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,

,
,
,
,
,
 and
.

24. The compound according to any of claims 19 to 23 wherein

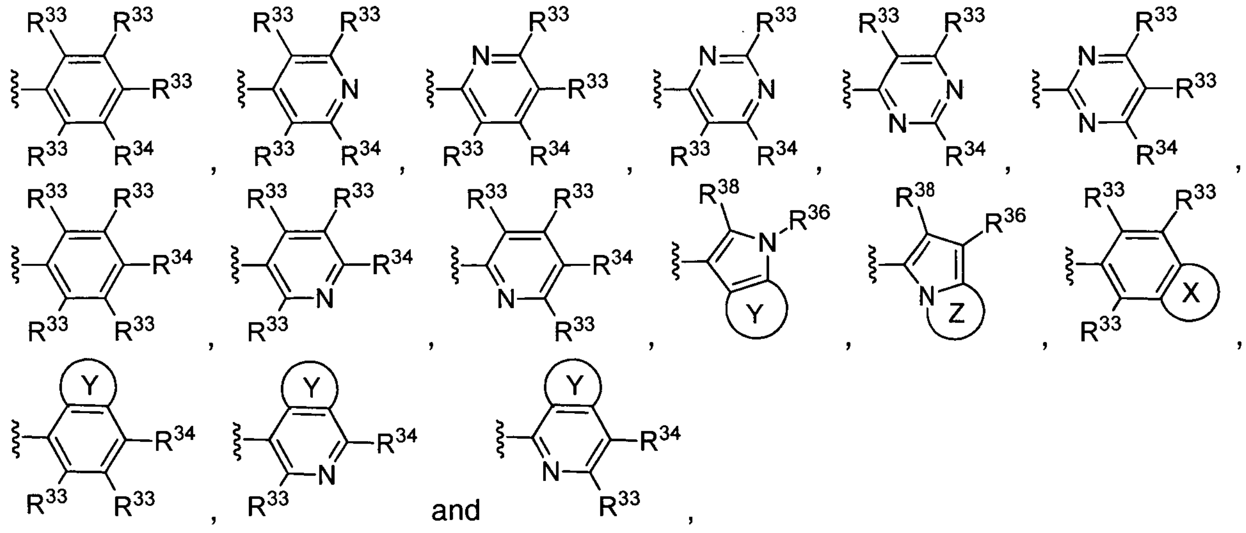
R^3 is a 6-10 membered mono- or bicyclic aryl or a 5-10 membered mono- or bicyclic heteroaryl containing 1 to 4 heteroatoms independently selected from the group consisting of N, O and S

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-d -e-alkyl, **OH,** 0 -Ci $_{-6}$-alkyl, 0-halo -Ci $_{.6}$-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(0)R^{31}, C_{0-6}-alkylene-C(0)N(R^{31})$_2$, C_{0-6}-alkylene-SO_2-N(R^{31})$_2$, C_{0-6}-alkylene-S0$_2$-R^{31}, 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-OR ^{32}, N(R^{31})$_2$, O-C_{1-6}-alkyl; **COOH,** CON(R^{31})$_2$, **CN,** NR^{31}-COR ^{31}, 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,** S0$_2$ or NR^{31}, wherein the ring is unsubstituted or substituted with 1 to 4 substituents independently selected from halogen, oxo, =N-OR ^{32}, **OH,** 0 -C_{1-6}-alkyl, O-halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{3-6}-cycloalkyl and halo-Ci $_{-6}$-alkyl.

25. The compound according to any claim 19 to 24 wherein R^3 is selected from



wherein

R^{33} is independently selected from **H**, halogen, **CN**, **C**$_{1\_6}$-alkyl, fluoro**-C**$_{1-6}$-alkyl, d $_{-4}$-alkylene-**OH**, **C**$_{1.4}$-alkylene-0-d. $_{3}$-alkyl, **C**$_{1.4}$-alkylene-0-fluoro-d. $_{3}$-alkyl, **OH**, 0**-Ci**$_{.6}$-alkyl, **O**-fluoro-d. $_{6}$-alkyl, **NH-Ci**$_{-6}$-alkyl, **N**H-fluoro-d. $_{6}$-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-d. $_{3}$-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-0 **-Ci**$_{.3}$-alkyl, d^-alkylene **-O**-fluoro-**C**$_{1-3}$-alkyl, **OH**, 0-d. $_{6}$-alkyl, **O**-fluoro-d. $_{6}$-alkyl, **NH-C**$_{1-6}$-alkyl, **N**H-fluoro-d $_{-e}$-alkyl, **C**$_{3-10}$-cycloalkyl, **C**$_{0-6}$-alkylene-**C**$_{3-10}$-heterocycloalkyl, 5-membered heteroaryl, 6-membered heteroaryl, **C(0)N(R** ^{37}**)**$_{2}$ and **S0** $_{2}$**N(R**^{37}**)**$_{2}$,

wherein alkylene is unsubstituted or substituted with 1 to 3 substituents selected from **F** and cycloalkyl, heterocycloalkyi and heteroaryl is unsubstituted or substituted with 1 to 3 substituents independently selected from **F**, C$_{1-3}$-alkyl, fluoro-d. $_{3}$-alkyl, **OH**, 0 **-Ci** $_{-3}$-alkyl, fluoro-0 **-Ci** $_{-3}$-alkyl;

R^{35} is selected from halogen, C$_{1\_6}$-alkyl, halo-d. $_{6}$-alkyl, C$_{3-6}$-cycloalkyl, C$_{3-6}$-heterocycloalkyl, oxo, **OH**, 0-d. $_{6}$-alkyl and **O**-halo-**Ci-e**-alkyl;

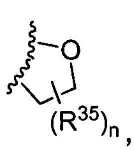
R^{36} is selected from d $_{-6}$-alkyl, fluoro**-C**$_{1-6}$-alkyl, **C(0)N(R** ^{37}**)**$_{2}$, **S0** $_{2}$**N(R**^{37}**)**$_{2}$;

R^{37} is independently selected from **H**, **C**$_{1-6}$-alkyl, halo-d. $_{6}$-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**, 0 **-C**$_{1-3}$-alkyl, **CN**, **CONH** $_{2}$; and cycloalkyl or heterocycloalkyi 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;

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 substitutents independently selected from fluoro, OH, oxo, C_{1-4}-alkyl and halo-C_{1-4}-alkyl;

R^{38} 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



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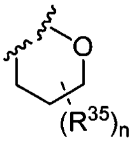

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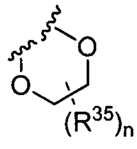

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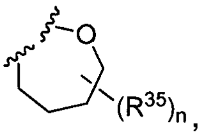

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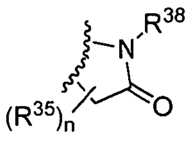

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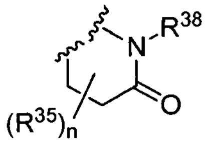

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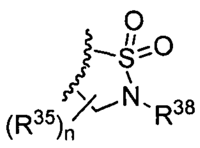

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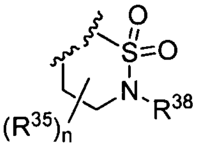


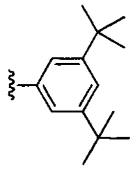
;

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 halogen, $C_{1\text{-}3}$-alkyl and fluoro-C!-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^-alkyl and fluoro-Ci.$_3$-alkyl;

n is selected from 1 to 4.

26. The compound according to any of claims 19 to 25 wherein R^3 is selected from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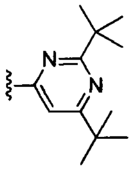

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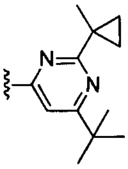

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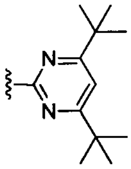

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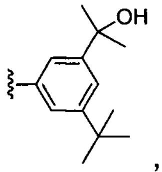

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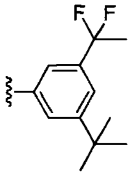

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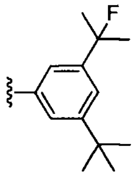

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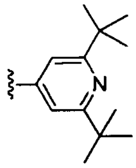

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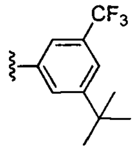

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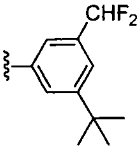

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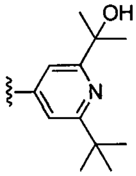

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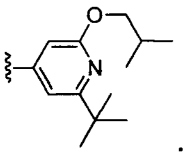

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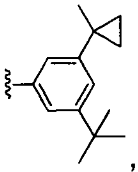
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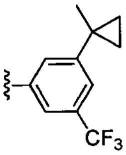

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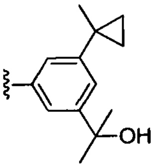

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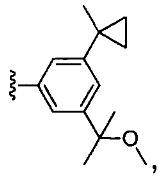

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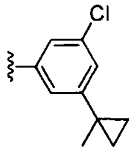

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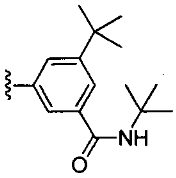

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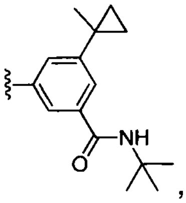

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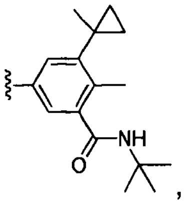

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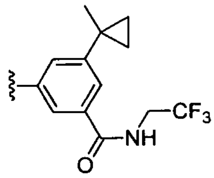

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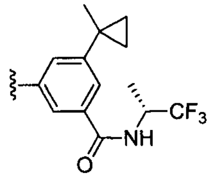

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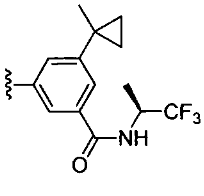

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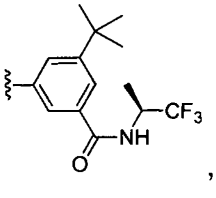

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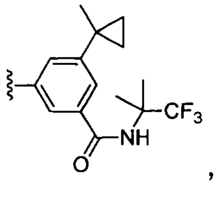

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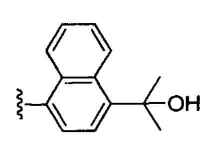

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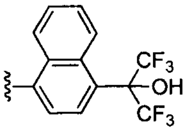
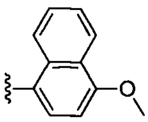
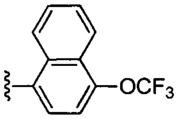
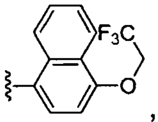
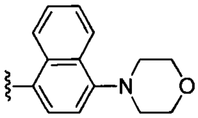
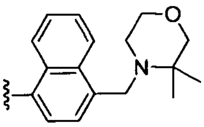
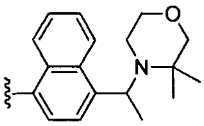
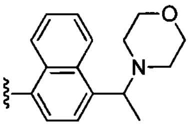
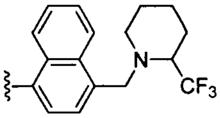
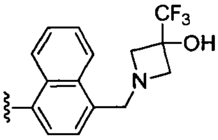
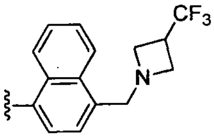
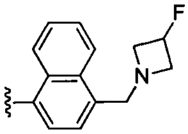
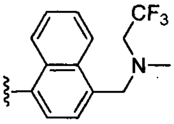
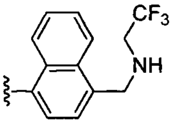
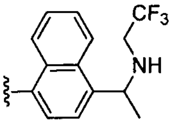
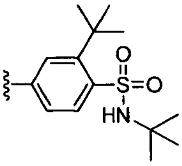
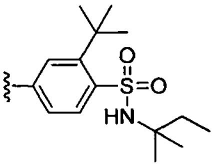
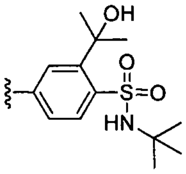
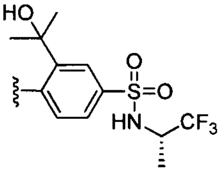
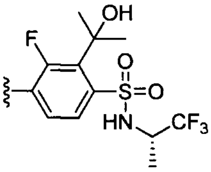
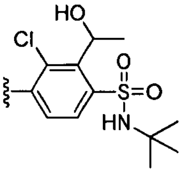
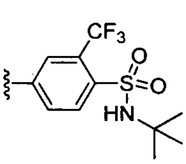
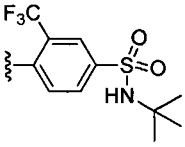
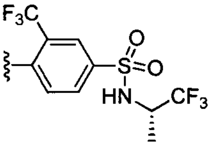
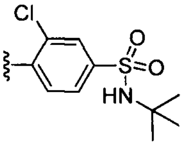
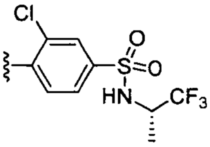
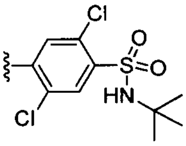
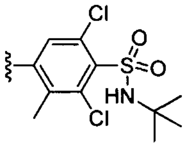
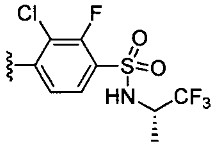
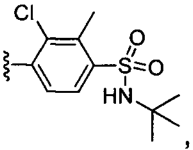
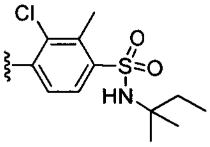
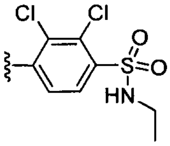
,
,
,
,
,
,

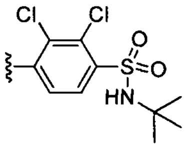
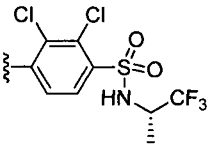
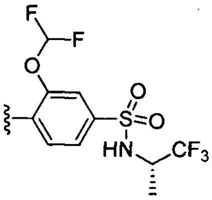
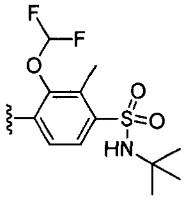
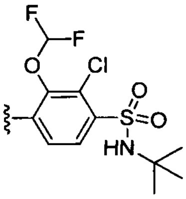
,
,
,
,
,

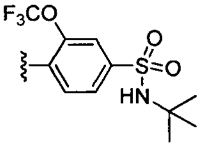
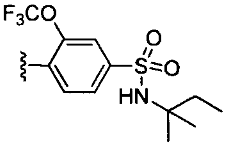
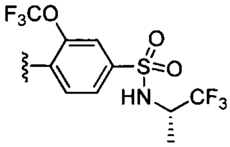
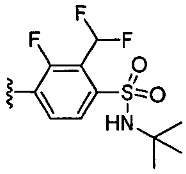
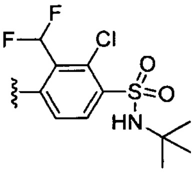
,
,
,
,
,
,

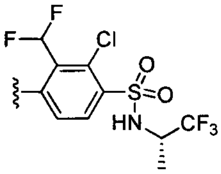
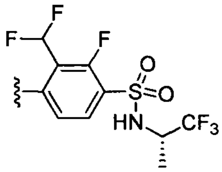
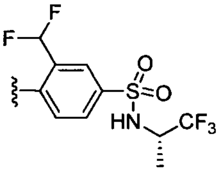
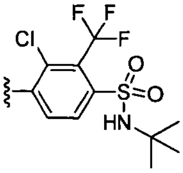
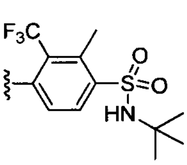
,
,
,
,
,

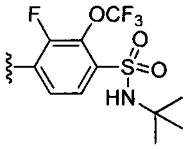
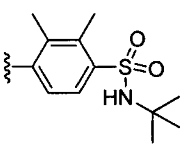
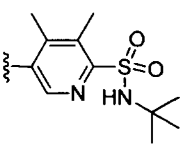
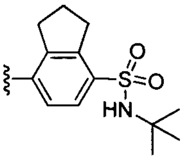
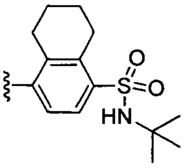
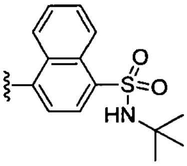
,
,
,
,
,

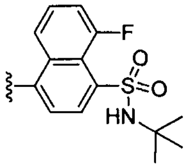
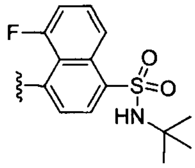
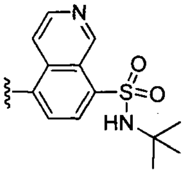
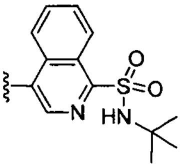
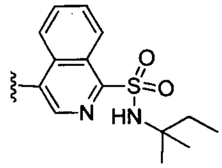
,
,
,
,
,

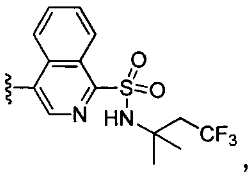
,
,
,
,
,

,
,
,
,
,

,
,
,
,
,

,
,
,
,
,
,

,
,
,
,
,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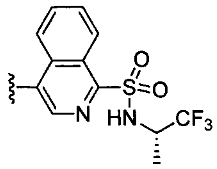
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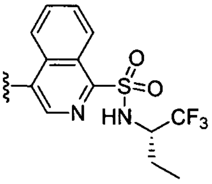
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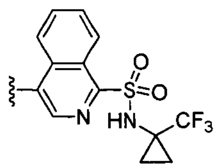
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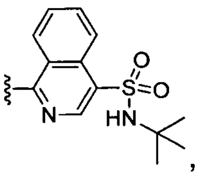
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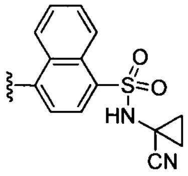
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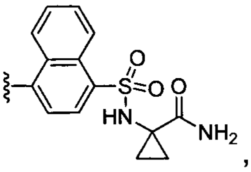
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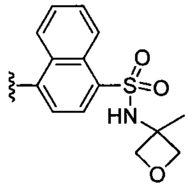
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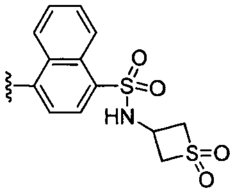
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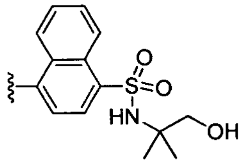
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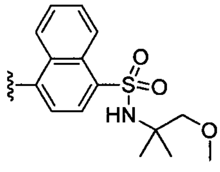
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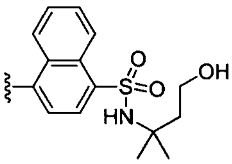
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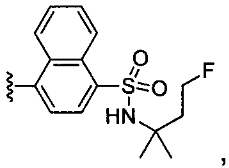
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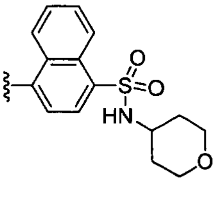
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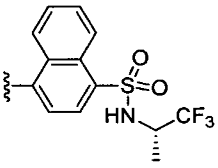
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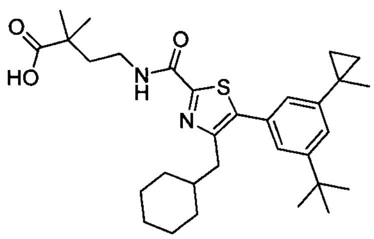
27. The compound according to any of claims 19 to 26 represented by Formula **(1).**

28. The compound according to any of claims 19 to 27, wherein the compound is selected from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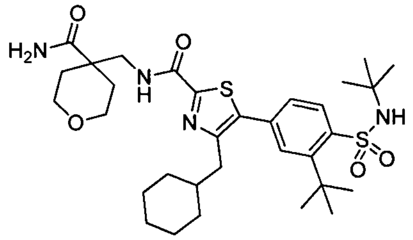
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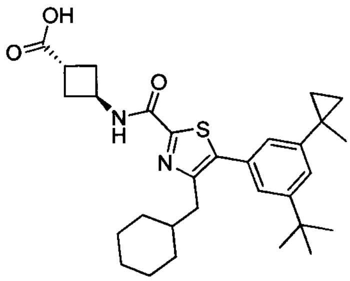
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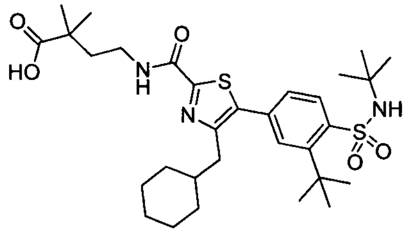
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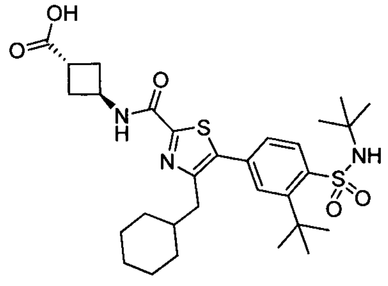
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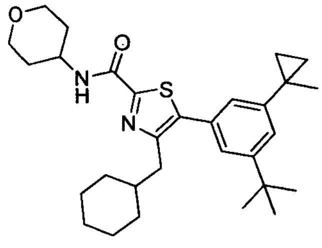
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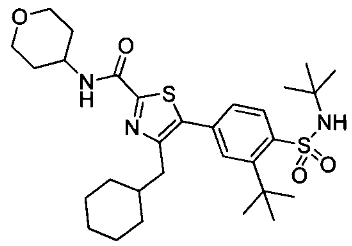
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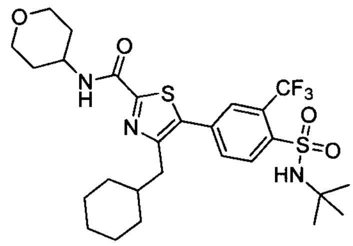
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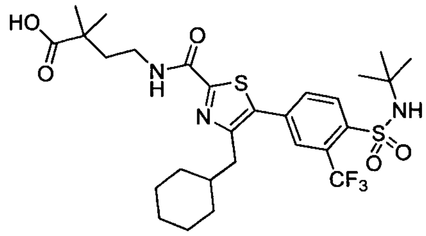
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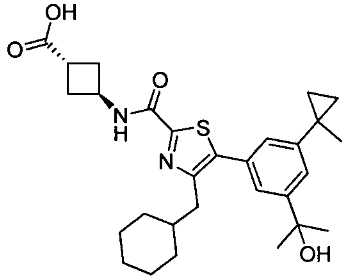
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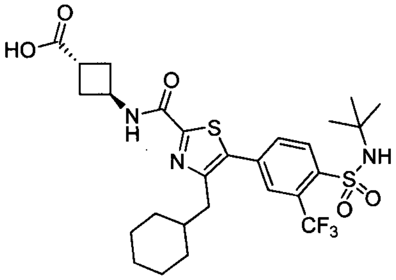
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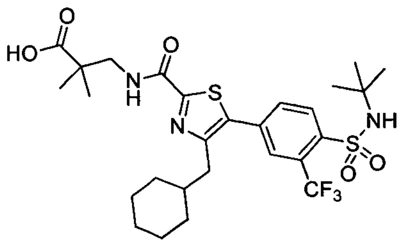
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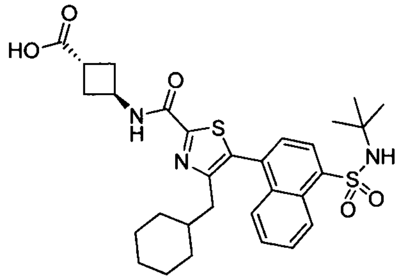
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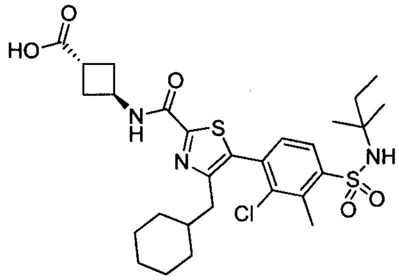
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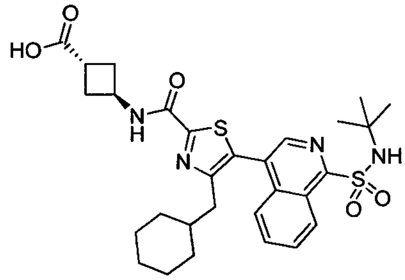
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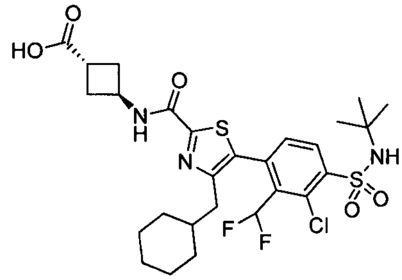
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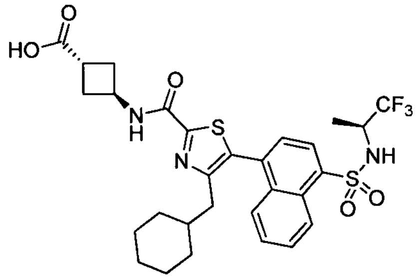
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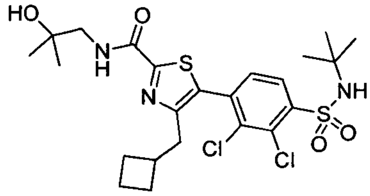
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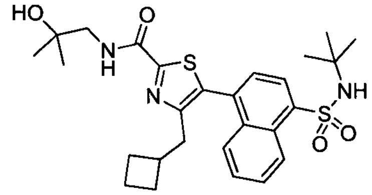
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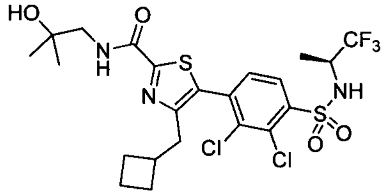
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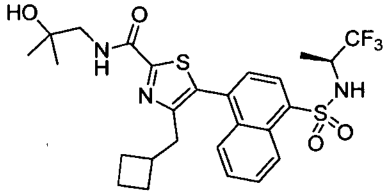
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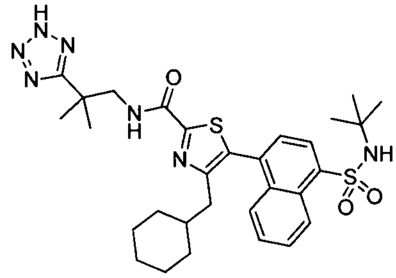
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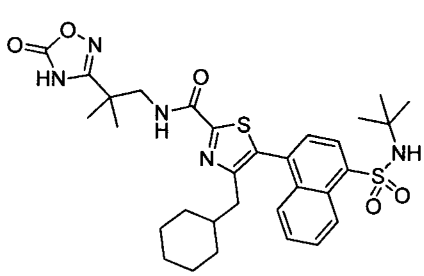
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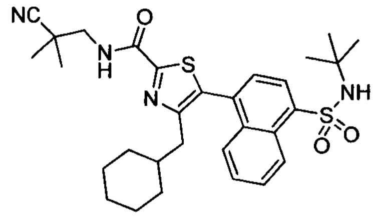
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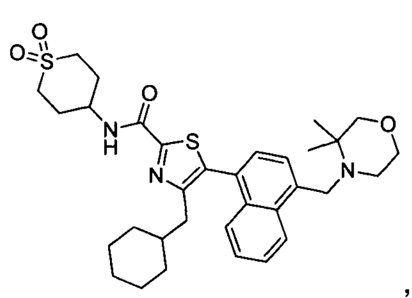

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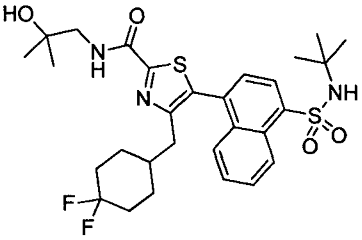

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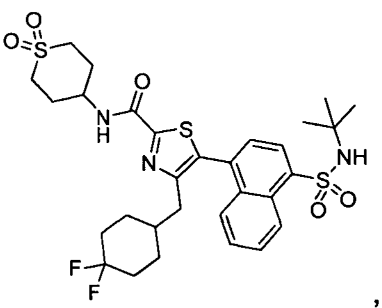

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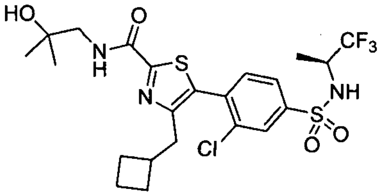

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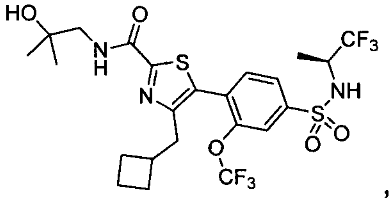

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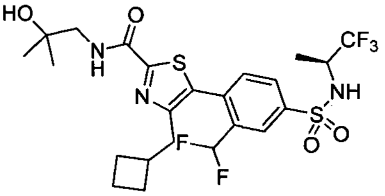

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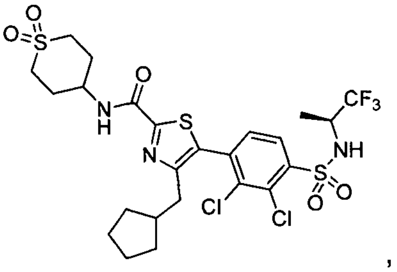

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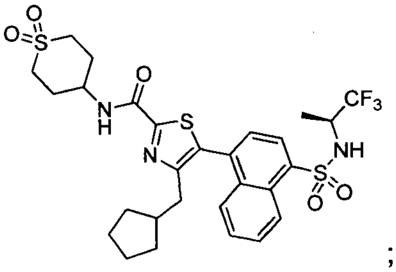
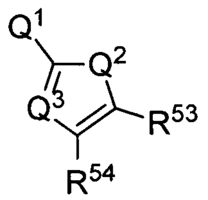


;

and an enantiomer, diastereomer, tautomer, /V-oxide, solvate and pharmaceutically acceptable salt thereof.

29. A compound according to Formula **(2)** or Formula **(2')**



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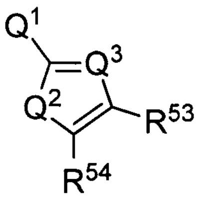


(2')

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

wherein

Q^1 is selected from **CO-NR** ^{51}**R**^{52}, **CO-R** ^{52}, **C0** $_2$**R**^{51}, **S0** $_2$**-NR** ^{51}**R**^{52}, **S0** $_2$**-R**^{52}, **N R**^{52}**CO-R** ^{51} and **N R**^{52}**S0** $_2$**-R**^{51};

Q^2 is selected from -0-, **-S-**, **-CR** ^{55}**=CR** ^{56}**-**, **-N=CR** ^{56}**-**, **-CR** ^{55}**=N-** and **-N=N-;**

Q^3 is selected from N and **C R**^{55};

R^{51} and **R**^{52} are independently selected from H, $C_{1\text{-}10}$-alkyl, **C**$_{2\text{-}10}$-alkenyl, **C**$_{2\text{-}10}$-alkynyl, **C**$_{0\text{-}10}$-alkylene-**C**$_{3\text{-}10}$-cycloalkyl, **C**$_{0\text{-}10}$-alkylene-**C**$_{3\text{-}10}$-heterocycloalkyl, **C**$_{0\text{-}10}$-alkylene-heteroaryl and **C**$_{0\text{-}10}$-alkylene-aryl, wherein alkyl, alkenyl, alkynyl, alkylene, cycloalkyi, heterocycloalkyi, aryl and heteroaryl is unsubstituted or substituted with 1 to 7 substituents independently selected from the group consisting of oxo, **CN**, **O R**^{61}, 0 -**C**$_{2\text{-}6}$-alkylene-**OR** ^{61}, $C_{1\text{-}6}$-alkyl, halo-**C**$_{1\text{-}6}$-alkyl, halogen, **C0** $_2$**R**^{61}, **CONR** ^{61}**R**^{62}, **CONR** ^{61}**S0** $_2$**R**^{62}, **COR** ^{61}, **SO**$_x$**R**^{61}, S0 $_3$H, **S0** $_2$**N R**^{61}**R**^{62},

$NR^{61}COR^{61}$, $NR^{61}S0_2R^{61}$, NR^{61}-CO-$NR^{61}R^{62}$, NR^{61}-$S0_2$-$NR^{61}R^{62}$, $C_{3\cdot6}$-cycloalkyl, 0-$C_{3\cdot6}$-cycloalkyl, $C_{3\cdot6}$-heterocycloalkyl, 0 -$C_{3\cdot6}$-heterocycloalkyl and $NR^{61}R^{62}$;

or R^{51} and R^{52} 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^{61}, SO_xR^{61}, $S0_3H$, $NR^{61}S0_2R^{61}$, $S0_2NR^{61}R^{62}$, $C0_2R^{61}$, $CONR^{61}R^{62}$, $CONR^{61}S0_2R^{62}$, COR^{61}, NR^{61}-CO-R^{61}, NR^{61}-CO-$NR^{61}R^{62}$, NR^{61}-$S0_2$-$NR^{61}R^{62}$, $NR^{61}R^{62}$, C^-alkyl, halo-C^-alkyl, hydroxy-d.$_6$-alkyl, $C_{3\cdot6}$-cycloalkyl, 0 -$C_{3\text{-}6}$-cycloalkyl, $C_{3\cdot6}$-heterocycloalkyl and 0 -$C_{3\text{-}6}$-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 independently selected from the group consisting of halogen, CN, $C_{1\text{-}6}$-alkyl, $C_{1\text{-}6}$-alkenyl, $C_{1\text{-}6}$-alkynyl, halo-$Ci_{\text{-}6}$-alkyl, OH, O-d -e-alkyl, 0-halo -$Ci_{\cdot6}$-alkyl, $Co_{\text{-}6}$-alkylene -$C_{3\text{-io}}$-cycloalkyl, C_0-6-alkylene-O-$C_{3\cdot10}$-cycloalkyl, C_0-6-alkylene-$C_{3\cdot1o}$-heterocycloalkyl, $C_{0\cdot6}$-alkylene-$COOR^{81}$, $C_{0\text{-}6}$-alkylene-C(O)R^{81}, $C_{0\text{-}6}$-alkylene-C(O)N$(R^{81})_2$, $C_{0\text{-}6}$-alkylene -SO_2-N$(R^{81})_2$, C_0-6-alkylene-SO_2-R^{81}, $C_{0\text{-}6}$-alkylene-(6-10-membered mono- or bicyclic aryl) and C_0-6-alkylene-(6-10-membered mono- or bicyclic 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 $C_{1\text{-}6}$-alkyl, halo-$Ci_{\cdot6}$-alkyl, halogen, OH, oxo, =N-OR^{82}, N$(R^{81})_2$, 0 -C_1.e-alkyl, 0-halo -$C_{1\text{-}6}$-alkyl, COOH, CON$(R^{81})_2$, CN, NR^{81}-COR^{81}, $C_{3\cdot10}$-cycloalkyl, $C_{3\cdot10}$-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, $S0_2$ or NR^{81}, wherein the ring is unsubstituted or substituted with one to four substituents independently selected from the group consisting of halogen, oxo, =N-OR^{82}, OH, 0 -$C_{1\text{-}6}$-alkyl, 0-halo -$C_{1\cdot6}$-alkyl, $C_{1\text{-}6}$-alkyl, $C_{3\cdot6}$-cycloalkyl and halo-$C_{1\text{-}e}$-alkyl;

R^{54} is selected from $C_{0\text{-}6}$-alkylene-R^{57}, C_3-cycloalkyl-R^{57}, O-$C_{0\text{-}5}$-alkylene-R^{57}, NR^{91}-$C_{0\text{-}5}$-alkylene-R^{57} and SO_x-$C_{0\text{-}5}$-alkylene-R^{57},

wherein alkylene is unsubstituted or substituted with 1 to 5 substituents independently selected from the group consisting of halogen, OH, oxo, =N-OR^{82}, N$(R^{81})_2$, 0-$C_{1\text{-}6}$-alkyl, COOH, CON$(R^{81})_2$, CN, NR^{81}-COR^{81}, $C_{3\cdot6}$-cycloalkyl and $C_{3\cdot6}$-heterocycloalkyl;

R^{55} and R^{56} are independently selected from H, halogen, CN, d $_{\cdot6}$-alkyl and 0 -$C_{1\text{-}6\text{-}}$alkyl, wherein alkyl is unsubstituted or substituted with 1 to 5 substituents independently selected from the group consisting of halogen, OH, oxo, O-**Ci-3**-alkyl; 0-halo **-Ci** $_{-3}$-alkyl and $C_{3\cdot 6}$-cycloalkyl;

R^{57} is selected from $C_{1\cdot 10}$-alkyl, $C_{3\cdot 10}$-cycloalkyl, $C_{3\cdot 10}$-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, 0 **-Ci** $_{\cdot 6}$-alkyl, O-halo-d -e-alkyl, d -e-alkyl, halo-**Ci** $_{\cdot 6}$-alkyl, cycloalkyl and heterocycloalkyl;

R^{61} and R^{81} independently selected from H, C_{1-6}-alkyl, $C_{3\cdot 10}$-cycloalkyl, C_{3-10}-heterocycloalkyl, phenyl, and 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 3 substituents selected from the group consisting of C_{1-6}-alkyl, halo-C_{1}-e-alkyl, OH, **O-Ci-e-**alkyl, 0-halo-d. $_{6}$-alkyl, phenyl, heteroaryl, halogen, NH_2, NH(d -e-alkyl), **N(Ci** -6-alkyl)$_2$, $C_{3\cdot 10}$-heterocycloalkyl, $C_{3\cdot 10}$-cycloalkyl, S0 $_2$-d -3-alkyl, oxo and **CN,**

wherein cycloalkyl and heterocycloalkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of C_{1-6}-alkyl, halo-C_{1-6}-alkyl, OH, 0-C $_{1-6}$-alkyl, 0-halo **-Ci** $_{\cdot 6}$-alkyl, phenyl, heteroaryl, halogen, NH_2, NH(d- $_6$-alkyl), **N(Ci.** $_6$- alkyl)$_2$ and $C_{3\cdot 10}$-cycloalkyl,

wherein phenyl and heteroaryl are unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of OH, 0 -C_{1-6}-alkyl, O-halo **-Ci-e-**alkyl, halogen, C_{1-6}-alkyl, halo-**Ci** $_{\cdot 6}$-alkyl, NH_2, **NH(C** $_{1-6}$-alkyl), N(C_{1-6}-alkyl)$_2$ and C_{3}-i$_0$-cycloalkyl;

R^{62} and R^{82} are independently selected from H, d -e-alkyl, halo-**Ci** $_{\cdot 6}$-alkyl and $C_{3\cdot 10}$-cycloalkyl;

R^{91} is selected from H, d -e-alkyl, C_{3-6}-cycloalkyl and $C_{3\cdot 6}$-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, 0-C $_{1-6}$-alkyl, O-halo-C$_{1}$-e-alkyl, $C_{3\text{-}6}$-heterocycloalkyl and $C_{3\cdot 6}$-cycloalkyl;

x is independently selected from 0, 1 and 2;

for use in the treatment or prophylaxis of a disease or disorder associated with the inhibition or activation of the RORy receptor;

with the proviso that compounds of Formula **(2')** with Q^1 is NHCO-R^{51}, Q^2 is sulfur, Q^3 is nitrogen, R^{53} and R^{57} are optionally substituted aryl and R^{54} is COR^{57} are excluded.

30. The compound for use according to claim 29 wherein

Q^1 is selected from CO-NR^{51}R^{52} and NR^{52}CO-R^{51};

Q^2 is selected from -O- and -S-; and

Q^3 is N.

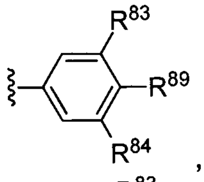
31. The compound for use according to any of claims 29 to 30 wherein

R^{51} is selected from H, C$_{1\text{-}10}$-alkyl, C$_0$.io-alkylene-C3 .$_{10}$-cycloalkyl, and C$_0$-io-**alkylene-C**$_{3\text{-}10}$-heterocycloalkyl, wherein alkyl, alkylene, cycloalkyi and heterocycloalkyi is unsubstituted or substituted with 1 to 7 substituents independently selected from the group consisting of oxo, OR^{61}, C$_1$-e-alkyl, halo-C$_{1\text{-}6}$-alkyl, halogen, C0$_2$R^{61}, CONR^{61}R^{62}, CONR^{61}S0$_2$R^{62}, COR^{61}, NR^{61}COR^{61}, NR^{61}S0$_2$R^{61}, NR^{61}-CO-NR^{61}R^{62}, NR^{61}-S0$_2$-NR^{61}R^{62}, C$_{3\text{-}6}$-cycloalkyl, **0-C**$_{3\text{-}6}$-cycloalkyl, C$_{3\text{-}6}$-heterocycloalkyl and 0-C$_{3\text{-}6}$-heterocycloalkyl;

R^{52} is selected from the group consisting of H, C1.6 alkyl and **halo-Ci**$_{\text{-}6}$ alkyl;

or R^{51} and R^{52} 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^{61}, SO$_x$R^{61}, S0$_3$H, NR^{61}S0$_2$R^{61}, S0$_2$NR^{61}R^{62}, C0$_2$R^{61}, CONR^{61}R^{62}, CONR^{61}S0$_2$R^{62}, COR^{61}, NR^{61}-CO-R^{61}, NR^{61}-CO-NR^{61}R^{62}, NR^{61}-S0$_2$-NR^{61}R^{62}, NR^{61}R^{62}, C^-alkyl, halo-C^-alkyl, hydroxy-C,. 6-alkyl, C$_{3\text{-}6}$-cycloalkyl, 0-C$_{3\text{-}6}$-cycloalkyl, C$_{3\text{-}6}$-heterocycloalkyl and 0-C$_{3\text{-}6}$-heterocycloalkyl.

32. The compound for use according to any of claims 29 to 31 wherein R^{53} is selected from



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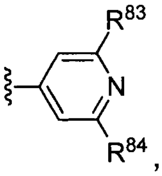

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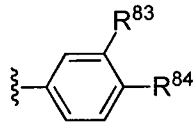

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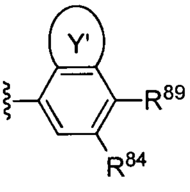

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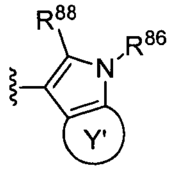

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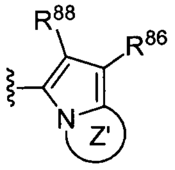
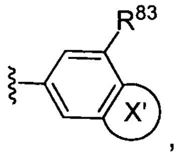


and



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wherein

R^{83} is selected from halogen, C$_{1\text{-}6}$-alkyl, fluoro-Ci-e-alkyl, C^-alkylene-OH, d-4-alkylene-CN, C$_{1\text{-}4}$-alkylene-0-Ci$_{\text{-}3}$-alkyl, C$_1$^-alkylene-O-fluoro-Ci-ralkyl, 0-C$_{1\text{-}6}$-alkyl, 0-fluoro-C$_{1\text{-}6}$-alkyl, C$_3$.$_{10}$-cycloalkyl, C(0)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 the group consisting of F, d $_{-3}$-alkyl and fluoro-d- $_3$-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(0)N(R ^{87})$_2$ and S(0 $_2$)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 the group consisting of F, d $_{.3}$-alkyl and fluoro-d. $_3$-alkyl;

R^{86} is selected from C^-alkyl, fluoro-Cm-alkyl, C(0)N(R ^{87})$_2$ and S(0 $_2$)N(R^{87})$_2$,

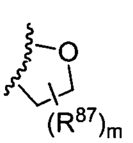
R^{87} is independently selected from H, Ci-e-alkyl, fluoro-d. $_6$-alkyl, Co.3-alkylene-Ci $_{-6}$-cycloalkyl, Ci-e-alkylene-OH, $C_{1 .6}$-alkylene-0-C $_{1-3}$-alkyl and d-e-alkylene-CN, wherein alkylene and cycloalkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of F, C_{1-3}-alkyl and fluoro-d $_{-3}$-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 the group consisting of fluoro, oxo, d $_{.4}$-alkyl and halo-C_{1-4}-alkyl;

R^{88} is selected from H, C_{1-3}-alkyl and fluoro-d. $_3$-alkyl;

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

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



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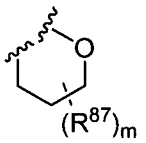

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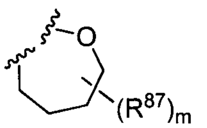

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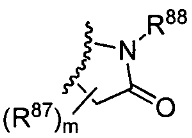

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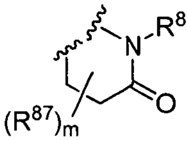

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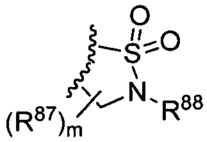
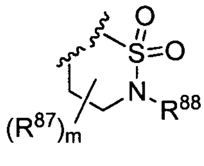


and


;

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 the group consisting of fluoro, d $_{.3}$-alkyl and fluoro-d. $_3$-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 the group consisting of fluoro, C_{1-3}-alkyl and fluoro-d- $_3$-alkyl; and

m is selected from 1 to 4.

33. The compound for use according to any of claims 29 to 32 wherein

R^{54} is selected from $C_{1\text{-}6}$-alkylene-R^{57}, O-R^{57} and S0$_2$-R^{57},

wherein alkylene is unsubstituted or substituted with 1 to 5 substituents independently selected from the group consisting of halogen, OH, oxo, 0-Ci.$_6$-alkyl, CN and $C_{3\text{-}6}$-cycloalkyl;

R^{57} is selected from $C_{1\text{-}10}$-alkyl, $C_{3\text{-}10}$-cycloalkyl, $C_{3\text{-}10}$-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, 0-$C_{1\text{-}3}$-alkyl, 0-halo-Ci$_{\text{-}3}$-alkyl, $C_{1\text{-}3}$-alkyl, halo-Ci.$_3$-alkyl, cycloalkyl and heterocycloalkyl.

34. The compound according to any of claims 1 to 28 as medicament.

35. The compound according to any of claims 1 to 28 for use in the treatment or prophylaxis of a disease or disorder associated with the inhibition or activation of the RORy receptor.

36. The compound for use according to claim 35, 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, 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 thromobotic purpura, myasthenia gravis, Sjorgren's syndrome, scleroderma, ulcerative colitis, epidermal hyperplasia, glomerulonephritis, chronic obstructive pulmonary disease and amyotrophic lateral sclerosis.

37. A pharmaceutical composition comprising a compound according to any of claims 1 to 33 and a pharmaceutically acceptable carrier or excipient.

38. The compound for use according to any of claims 29 to 33, wherein the disease or disorder 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 thromobotic purpura, myasthenia gravis, Sjorgren's syndrome, scleroderma, ulcerative colitis, epidermal hyperplasia, glomerulonephritis, chronic obstructive pulmonary disease and amyotrophic lateral sclerosis.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2013/001593

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

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

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

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

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

see additional sheet

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

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

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

11-28, 30(completely) ; 1-10, 29, 31-38(partially)

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

Remark on Protest

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

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

☒ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2013/001593

A. CLASSIFICATION OF SUBJECT MATTER

INV.	C07D277/56	C07D417/04	C07D417/12	C07D417/14	A61K31/427
	A61P3/10	A61P17/06	A61P19/02	C07D333/38	C07D239/28
	C07D413/12	C07D263/34	C07D493/08	C07D493/10	C07D495/10

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2012/027965 A1 (GLAXO GROUP LTD [GB]; WANG YONGHUI [CN]; CAI WEI [CN]; LIU QIAN [CN];) 8 March 2012 (2012-03-08) cited in the application claim 1 -----	1-20
A	WO 2012/028100 A1 (GLAXO GROUP LTD [GB]; WANG YONGHUI [CN]; YANG TING [CN]; LIU QIAN [CN]) 8 March 2012 (2012-03-08) cited in the application claim 1 -----	1-20
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☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search 22 October 2013	Date of mailing of the international search report 28/10/2013
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Beligny, Samuel

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2008/083070 AI (NEUR0GEN CORP [US]; BAKTHAVATCHALAM RAJAG0PAL [US]; ZHANG LUYAN [US];) 10 July 2008 (2008-07-10) claims 1, 8 page 48; compounds d, j, k, 1, p, x, z, aa	29-33, 37,38
X	W0 2007/087427 A2 (V0 NHA H [US] ET AL V0 NHA HUU [US] ET AL) 2 August 2007 (2007-08-02) page 61 - page 75; table 1; compounds 47, 116-120 claims 1, 129, 132	29-33, 37,38
X	W0 2006/004984 AI (VERTEX PHARMA [US]; PIERARD FRANCOISE [GB]; JIMENEZ JUAN-MIGUEL [GB];) 12 January 2006 (2006-01-12) page 21 - page 22; compounds I-11, 1-13, 1-15, 1-19 claims 1, 21, 60	11-18, 29-33, 37,38
X	US 2006/094723 AI (DUNKERN T0RSTEN [DE] ET AL) 4 May 2006 (2006-05-04) 4-Methyl-5-(4-pyridinyl)thiazole-2-carboxamide; claim 17 page 3, paragraph [0032] - paragraph [0034]	29-33, 37,38
A	W0 2012/064744 A2 (LYCERA CORP [US]; GLICK GARY D [US]; T00G00D PETER L [US]; ROMERO ARTH) 18 May 2012 (2012-05-18) claims 1, 91 page 119; compounds 111-80	1-38
X	US 2011/224202 AI (CUTSHALL NEIL S [US] ET AL) 15 September 2011 (2011-09-15) page 49 - page 52; examples 55, 58 claims 3, 37	29,31, 32,37,38
X	US 2005/032859 AI (CHEN YUHPYNG L [US]) 10 February 2005 (2005-02-10) page 14; example 24 claims 1, 17	29-31, 33,37,38
X	WO 96/36617 AI (SEARLE & CO [US]; TALLEY JOHN J [US]; BERTENSHAW STEPHEN [US]; ROGIER) 21 November 1996 (1996-11-21) cited in the application claim 1 page 163 - page 164; example 72 page 5 - page 6	1-10

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2002/022729 A1 (KAWAI AKIYOSHI [JP] ET AL) 21 February 2002 (2002-02-21) page 30 - page 31; examples 1, 4, 5, 9, 17, 18, 27 claims 1, 11, 13 -----	29,31, 37,38
X	US 2006/199817 A1 (TASKER ANDREW [US] ET AL) 7 September 2006 (2006-09-07) page 38 - page 39; examples 46, 47 claims 1, 32-34 -----	29,31, 37,38
X	US 5 571 810 A (MATSUO MASAAKI [JP] ET AL) 5 November 1996 (1996-11-05) claim 1 column 1, line 25 - line 53 column 27 - column 38; examples 6, 15.1, 18.1, 18.8, 20 -----	1-10,29, 31-33, 37,38
X,P	WO 2012/100732 A1 (GLAXO GROUP LTD [GB]; WANG YONGHUI [CN]; YANG TING [CN]) 2 August 2012 (2012-08-02) claims 1, 14 -----	29, 31-33, 37,38

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Information on patent family members

International application No
PCT/EP2013/001593

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International application No
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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 19-28(completely) ; 1-10, 29-38(partially)

   Compound according to formula (2) and (2') wherein Q2 is S, Q3 is N, and Ql is C0-NR51R52 or S02-NR51R52

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2. claims: 29, 31-38 (al 1 partially)

   Compound according to formula (2) and (2') wherein Q2 is S, Q3 is N, and Ql is C0-R52, C02R51, or S02-R52

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3. claims: 29-38(partially)

   Compound according to formula (2) and (2') wherein Q2 is S, Q3 is N, and Ql is NR52C0-R51 or NR52S02-R51

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4. claims: ll-18(completely) ; 1-10, 29-38(partially)

   Compounds according to formulae (2) and (2') wherein Q2 is 0 and Q3 is N

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5. claims: 1-10, 29, 31-38 (al 1 partially)

   Compound according to formula (2) and (2') wherein the ring containing Q2 and Q3 is other than thiazole or oxazole

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6. claims: 29, 31-38 (al 1 partially)

   Compound according to formula (2) and (2') wherein wherein the ring containing Q2 and Q3 is a 6-membered ring

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