SUBSTITUTED AMINOTHIAZOLES AS DGKZETA INHIBITORS FOR IMMUNE ACTIVATION

The present invention covers substituted aminothiazole compounds of general formula (I) as described and defined herein, methods of preparing said compounds, intermediate compounds useful for preparing said compounds, pharmaceutical compositions and combinations comprising said compounds, and the use of said compounds for manufacturing pharmaceutical compositions for the treatment or prophylaxis of diseases, in particular of diacylglycerol kinase zeta (DGKzeta, DGKζ) regulated disorders, as a sole agent or in combination with other active ingredients.

The compounds of general formula (I) inhibit DGKζ and, by this, enhance T cell mediated immune response. This is a new strategy to use the patient's own immune system to overcome immunoevasive strategies utilized by many neoplastic disorders, respectively cancer and by this enhancing anti-tumor immunity. Furthermore, said compounds are used in particular to treat disorders such as viral infections or conditions with dysregulated immune responses or other disorders associated with aberrant DGKζ signaling.

The present invention further relates to the use of the compounds of general formula (I) for manufacturing pharmaceutical compositions for enhancement of T cell mediated immune response.

The present invention further relates to the use of the compounds of general formula (I) for manufacturing pharmaceutical compositions for the treatment of cancer.

The present invention further relates to the use of the compounds of general formula (I) for manufacturing pharmaceutical compositions for the treatment or prophylaxis of virus infections, lymphoproliferative disorders, asthma, eye diseases, and type 2 diabetes/ insulin resistance.

Background

Diacylglycerol kinases (DGKs) represent a family of enzymes that catalyze phosphorylation of the membrane lipid sn-1,2 diacylglycerol (DAG) to form phosphatidic acid (PA) (T.O. Eichmann and A. Lass, Cell. Mol. Life Sci. 2015, 72, 3931-3952). In T cells, DAG is formed downstream of the T cell receptor (TCR) after activation of the gamma 1 isoform of phospholipase C (PLCγ1) and cleavage of phosphatidylinositol 4,5-biphosphate (PIP2) into DAG and an additional second messenger, inositol 1,4,5-triphosphate (IP3) (S. Krishna and X.-P. Zhong, Front. Immunol. 2013, 4, 178). Whereas, IP3 is important in facilitating release of calcium from the endoplasmic reticulum, DAG interacts with other proteins important in TCR signal transduction, such as Protein kinase Cθ (E. J. Quann et al., Nat. Immunol. 2011, 12 (7), 647-654) and the Ras activating protein RasGRP1 (S. Krishna and X.-P. Zhong, Front. Immunol. 2013, 4, 178). Although, three isoforms of DGK are known to be present within T cells [DGKα (DGKalpha), DGKδ (DGKdelta), and DGKζ (DGKzeta)], only two, DGKα and DGKζ, are thought to play an

important role in facilitating DAG metabolism downstream of the TCR (R. P. Joshi and G. A. Koretzky, Int. J. Mol. Sci. 2013, 14 (4), 6649-6673).

Targeting the activity of DGKζ in T cells, either by germline deletion, or with chemical inhibitors, results in enhanced and sustained signaling downstream of T cells, as assessed by prolonged phosphorylation of downstream molecules, such as extracellular signal-related kinases 1/2 (ERK1/2) and NFκB (X.-P.-Zhong et al., Nat. Immunol. 2003, 4, 882-890; B. A. Olenchock et al., Nat. Immunol. 2006, 7 (11), 1174-1181; M. J. Riese et al., J. Biol. Chem. 2011, 286, 5254-5265; E. M. Wesley et al., ImmunoHorizons 2018, 2 (4), 107-118).

Deletion of DGKζ in T cells leads to enhanced production of effector cytokines, such as IL2, IFNγ and enhanced proliferation (X.-P. Zhong et al., Nat. Immunol. 2003, 4, 882-890; B. A. Olenchock et al., Nat. Immunol. 2006, 7 (11), 1174-1181, E. M. Riese et al., J. Biol. Chem. 2011, 286, 5254-5264).

Adoptive transfer of DGKζ deficient T cell reduced leukaemia burden after inoculation of C1498.SIY leukaemia cells compared to control. Also, DGKζ deficient T cells are at least partially resistant to PD1 mediated inhibitory signals (W. Jing et al., Cancer Res. 2017, 77 (20), 5676-5686). In addition, DGKζ deficient mice have reduced tumor sizes compared to control after orthotopic tumor injection of a pancreatic tumor model (E. M. Wesley et al., ImmunoHorizons, 2018, 2 (4), 107-118). Also, S. Wee et al. inoculated C57BL/6 mice with a variety of syngeneic tumor cell lines - MC38 colon carcinoma, B16F1 melanoma, and C1498 leukemia - and analysed survival and tumor growth between mice deficient in DGKζ in the presence or absence of anti-PD1 treatment. DGKζ-/- mice suppressed growth of subcutaneously implanted tumor cells in the three model systems and the combination of DGKζ-deficiency and anti-PD1 was additive in tumor control (S. Wee et al., Proceedings of the American Association for Cancer Research Annual Meeting 2019; Cancer Res. 2019, 79 (13 Suppl): Abstract nr 936).

These findings suggest that DGKζ might serve as a useful target for enhancing T cell anti-tumor activity.

Additionally, the adoptive transfer of CAR (chimeric antigen receptor)-T cells deficient in DGKζ demonstrated increased efficacy compared to wild type CAR T cells in the treatment of murine mesothelioma (M. J. Riese et al., Cancer Res. 2013, 73 (12), 3566-3577) and a glioblastoma xenograft mouse model in combination with DGKα knockout (I.-Y. Jung et al., Cancer Res. 2018, 78 (16), 4692-4703).

Also, DGKζ-deficient mice mounted a more robust immune response to lymphocytic choriomeningitis virus infection than did wild-type mice (X.-P. Zhong et al., Nat. Immunol. 2003, 4, 882-890).

DGKζ is also relevant in natural killer (NK) cells. Upon stimulation through multiple activating receptors, NK cells from mice lacking DGKζ display increased cytokine production and

degranulation in an ERK-dependent manner. Additionally, they have improved cytotoxic functions against tumor cell lines. (E. Yang et al. J. Immunol. 2016, 197(3), 934-41.)

Apart from immune-cell regulation, DGKζ also plays a role in cancer, mediating numerous aspects of cancer cell progression including proliferation, apoptosis, survival, invasion and tumorigenicity, e.g. in osteosarcoma, colon cancer, breast cancer, prostate cancer, glioma and leukemia models (W. Yu et al., Front. Oncol. 2019, 8:655; K. Cai et al., BMC Cancer 2014 ,14:208; J. Diao et al., Mol. Neurobiol. 2016; 53, 5425-35; H. Li et al. Pharmazie 2019, 74(7): 418-422).

In addition, DGKζ knock-out diminished both airway inflammation and airway hyperresponsiveness in mice and also reduced bronchoconstriction of human airway samples in vitro by blocking T helper 2 (TH2) differentiation (B. A. Singh et al., Sci. Signal. 2019, 12: eaax3332).

Taken together, the findings from these studies argue that restraining DGKζ activity in T cells and tumor cells may prove valuable in generating more vigorous immune responses against pathogens and tumors and in ameliorating Th2 driven (auto-) immune diseases (in re-balancing the immune-system).

Furthermore, inhibition of DGKα has the potential to reverse the life-threatening Epstein-Barr virus (EBV) -associated immunopathology that occurs in X-linked lymphoproliferative disease (XLP-1) patients (E. Ruffo et al., Sci. Transl. Med. 2016, 8: (321):321ra7; S. Velnati et al., Eur. J. Med. Chem. 2019, 164, 378-390). Based on the underlying mode of action, it can be assumed that inhibition of DGKζ would have a similar effect.

The DGKα-inhibitor II (R59949) could suppress retinal neovascularization and protect retinal astrocytes in an Oxygen-Induced Retinopathy Model (L. Yang et al., J. Mol. Neurosci. 2015, 56, 78-88). Also, based on the underlying mode of action, it can be assumed that inhibition of DGKζ would have a similar effect.

In a DGKζ knock-out mouse it was shown that DGKζ deficiency increases protection against insulin resistance (B. Benziane et al., J. Lipid Res. 2017, 58 (12), 2324–2333).

In summary, inhibiting DGKζ activity has a therapeutic potential in targeting tumors directly as well as addressing virus infections, lymphoproliferative disorders, asthma, eye diseases, and type 2 diabetes/ insulin resistance.

Prior Art

WO2020/006016 and WO2020/006018 describe Naphthyridinone compounds as T cell activators, which inhibit the activity of DGKα and/or DGKζ, for treatment of viral infections and proliferative disorders, such as cancer. WO2021/041588 describes pyridopyrimidinonyl compounds as T cell activators, which inhibit the activity of DGKα and/or DGKζ, for treatment of viral infections and proliferative disorders, such as cancer.

2,4,5-trisubstituted triazole derivatives featuring a substituted amino group attached to C-2 of the thiazole core have been disclosed in published patent applications in various technical contexts but not in the context of DGK inhibition.

WO 2014/181287 discloses heterocyclyl compounds as inhibitors of Interleukin 17 and Tumour Necrosis Factor alpha.

WO 2014/173904 discloses compounds having antibacterial activity.

WO 2009/149054 discloses small molecule inhibitors for the treatment or prevention of Dengue fever infection.

WO 2007/130075 discloses aminothiazole derivatives as human stearoyl-CoA desaturase inhibitors.

WO 2012/064715 discloses compositions and methods relating to heat shock transcription factor activating compounds and targets thereof.

WO 2005/103022 discloses substituted thiazole and pyrimidine derivatives as melanocortin receptor modulators.

CN 106109467 discloses the medical application of aromatic compounds, including thiazoles, in treating pyrazinamide-resistant tuberculosis.

WO 2015/199206 discloses compounds derived from a six-membered ring as TRPV4 inhibitors.

WO 2015/046193 discloses aromatic heterocyclic amine derivatives as TRPV4 inhibitors.

CN 103159695 discloses thiazole compounds capable of restraining human immunodeficiency (HIV) virus replication and effective against drug-resistant HIV virus strains.

WO 2013/056684 discloses thiazole derivatives as dihydroorotate dehydrogenase (DHODH) inhibitors.

WO 2013/033037 discloses compounds of various chemotypes, *inter alia* thiazole derivatives, as antiprion compounds.

WO 2012/075393 discloses compounds of various chemotypes, *inter alia* thiazole derivatives, as activators of proteasomal degradation.

JP 2011032254 discloses compounds of various chemotypes, *inter alia* thiazole derivatives, as pest controlling agents.

WO 2009/041790 discloses 2,4,5-trisubstituted thiazole derivatives as inhibitors of the sphingosylphosphorylcholine (SPC) receptor for treatment of inflammatory diseases.

WO 2008/090382 discloses thiazole and oxazole derivatives for use in the treatment of prion diseases, cancer, and conditions of the central nervous system as well as in the regulation of stem cells.

WO 2007/022415 discloses substituted 2-aminothiazoles for treating neurodegenerative diseases.

WO 2006/122011 discloses thiazole compounds and methods of use in treating viral infections, particularly hepatitis C virus infections.

WO 2006/078287 discloses derivatives of various 5-membered heteroarenes, *inter alia* thiazoles, as inhibitors of phosphodiesterase 4B.

WO 2005/102318, WO 2005/102325, WO 2005/102326, WO 2005/102346, WO 2005/102455, WO 2005/112920, WO 2005/115304, WO 2005/115385 all deal with c-Kit inhibitors of various chemotypes, including 2-aminothiazole derivatives, and various uses thereof.

EP 1543824 and US 2005/0137239 disclose thiazole derivatives to counter glycation.

WO 2004/014884 discloses thiazole derivatives as neuropeptide Y receptor ligands.

WO 2019/133445 discloses aminothiazole derivatives as inhibitors of Vanin-1.

WO 2021/043966 discloses substituted five-membered nitrogen containing heteroaryl compounds as inhibitors of the NOD-like receptor (NLR) family, pyrin domain-containing protein 3 (NLRP3).

2,4,5-trisubstituted triazole derivatives structurally related to the compounds of the present invention but yet structurally distinct have also been disclosed in several scientific publications.

D. Kikelj and U. Urleb, Science of Synthesis (2002), 11, 627-833, is a general review on the synthesis of thiazoles. By far most of the specific compounds disclosed are, besides having the thiazole core in common with the compounds of the present invention, structurally distant from these. Several indivdual compounds disclosed therein, namely those disclosed on pp 651, 681-683, and 719, and including {4-methyl-2-[methyl(phenyl)amino]-1,3-thiazol-5-yl}(phenyl)methanone, are somewhat structurally related to the compounds of the present invention but yet structurally distinct.

2,4,5-trisubstituted triazole derivatives structurally related to the compounds of the present invention but yet structurally distinct have also been disclosed in several journal articles.

None of the journal articles listed below, which also disclose some compounds which are somewhat structurally related to the compounds of the present invention but yet structurally distinct, disclose a therapeutic of pharmaceutical application of the compounds disclosed therein.

S. Titus et al., Tetrahedron Lett. 2014, 55, 5465-5467, disclose a four-component synthesis of 4-hydrazinothiazole derivatives.

T. N. Birkinshaw et al., J. Chem. Soc. Perkin Trans. 1, 1988, 2209-2212, disclose spectrometric and chemical studies on 5-acyl and 5-nitroso-2-(N,N-disubstituted amino)thiazoles.

R. A. Funnell et al., J. Chem. Soc. Perkin Trans. 1, 1987, 2311-2315 disclose a study on the formation of isomeric 2-(N,N-disubstituted amino) thiazol-5-yl ketones.

J. C. Brindley et al., J. Chem. Soc. Perkin Trans. 1, 1987, 1153-1158 disclose the conversion of N'-substituted N-acyl and N-imidoyl thioureas into 2-(N,N-disubstituted amino) thiazol-5-yl ketones.

G. D. Meakins et al., J. Chem. Soc. Chem. Comm. 1984, 837-838, disclose a chemical reaction unexpectedly yieding 5-benzoyl-4-methyl-2-(N-methyl-N-phenylamino)thiazole.

K. Akiba et al., Tetrahedron Lett. 1975, 7, 459-462, disclose the synthesis of certain 2-arylaminothiazoles by 1,3-cycloaddition of 4-aryl-3-arylimino-5-imino-1,2-4-thiadiazolidine (also known as Hector's base) and acetylenes.

Finally, three structures which are somewhat structurally related to the compounds of the present invention but yet structurally distinct, are disclosed in the database Chemical Abstracts Registry (CAS Registry®), all without a reference and without a technical application, having the CAS Registry numbers 1349635-19-3, 1349215-57-1, and 1348293-02-6.

However, the state of the art does not describe:

- the specific substituted aminothiazole compounds of general formula (I) of the present invention as described and defined herein, *i.e.* compounds having a 2-aminothiazole core bearing:
    - an optionally substituted benzoyl or 6-membered heteroaroyl group attached to C-5,
    - a $-NH_2$ or methyl group attached to C-4,

- and (i) an optionally substituted phenyl or 5- or 6-membered heteroaryl group and (ii) an alkyl group laterally substituted with a group $-S(=O)_2-NH_2$, or, particularly, $-C(=O)-NH_2$, both (i) and (ii) being attached to the nitrogen atom attached to C-2, said laterally substituted alkyl group being essential for potent inhibition of DGKζ as shown in comparative experiments, *infra*,

or stereoisomers, tautomers, N-oxides, hydrates, solvates, salts thereof, or mixtures of same, as described and defined herein, and as hereinafter referred to as "compounds of general formula (I)" or "compounds of the present invention",

- or their pharmacological activity.

WO 2021/028382, relating to a different chemotype ([1,2,4]triazolo[1.5-c]quinazolin-5-amine compounds) according to formula (I) and abstract, discloses a single compound name N^2-(4-amino-5-benzoyl-1,3-thiazol-2-yl)-N^2-(3-methylphenyl)alaninamide, without providing a synthesis protocol and without biological data relating to said compound name.

It is desirable to provide novel compounds having prophylactic and therapeutic properties.

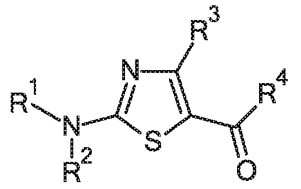
Accordingly, it is an object of the present invention to provide compounds and pharmaceutical compositions comprising these compounds used for prophylactic and therapeutic use in DGKζ regulated disorders in a T cell immune-stimulatory or immune-modifing manner. DGKζ regulated disorders comprise conditions with dysregulated immune responses, particularly in an immunologically supressed tumor microenvironment in cancer, autoimmune diseases, viral infections as well as other disorders associated with aberrant DGKζ signalling. Said compounds can be used as sole agent or in combination with other active ingredients.

It has now been found, and this constitutes the basis of the present invention, that the compounds of the present invention have surprising and advantageous properties.

In particular, the compounds of the present invention have surprisingly been found to effectively inhibit the DGKζ protein and, by this, enhance T-cell mediated immunity. Accordingly, they provide novel structures for the treatment diseases of mammals, including humans, in particular of cancers, and may therefore be used for the treatment or prophylaxis of hyperproliferative disorders, such as cancer, for example.

DESCRIPTION of the INVENTION

In accordance with a first aspect, the present invention covers compounds of general formula (I):



(I)

in which :

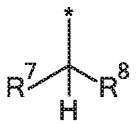
R^1 represents a phenyl or 6-membered heteroaryl group optionally substituted, one, two, or three times, each substituent independently selected from a halogen atom or a group selected from hydroxy, cyano, nitro, C_1-C_6-alkyl, (phenyl)-(C_1-C_3-alkyl)-, C_1-C_6-haloalkyl, C_1-C_6-alkoxy, (phenyl)-(C_1-C_3-alkoxy)-, C_1-C_6-haloalkoxy, -N(R^5)(R^6),

wherein the phenyl groups in said (phenyl)-(C_1-C_3-alkyl)- and (phenyl)-(C_1-C_3-alkoxy)- groups are optionally substituted one or two times, each substituent independently selected from a halogen atom or a group selected from cyano, methyl, ethyl, trifluoromethyl, methoxy, ethoxy, dimethylamino and trifluoromethoxy,

or two substituents attached to adjacent carbon atoms of said phenyl or 6-membered heteroaryl group together form a bivalent group selected from –$(CH_2)_3$-, -$(CH_2)_4$-, -$(CH_2)_2$-O-, -$(CH_2)_3$-O-, -CH_2-O-CH_2-, -$(CH_2)_2$-O-CH_2-, -O-CH_2-O-, -O-CH_2-CH_2-O-, -O-CF_2-O-, -O-CH_2-CF_2-O-, and -O-CF_2-CF_2-O-,

or

R^1 represents a 5-membered heteroaryl group optionally substituted one or two times, each substituent independently selected from a halogen atom or a group selected from cyano, C_1-C_3-alkyl, and C_1-C_3-alkoxy;

R^2 represents a group  ,

wherein "*" indicates the point of attachment to the nitrogen atom to which R^2 is attached;

R^3 represents a group selected from methyl and -NH_2;

R^4 represents a phenyl or 6-membered heteroaryl group optionally substituted, one, two, or three times, each substituent independently selected from a halogen atom or a group selected from cyano, nitro, C_1-C_6-alkyl, (phenyl)-(C_1-C_3-alkyl)-, (5- or 6-membered heteroaryl)-(C_1-C_3-alkyl)-, (C_3-C_7-cycloalkyl)-(C_1-C_3-alkyl)-, ((R^9)O)-(C_1-C_6-alkyl)-, C_1-C_6-haloalkyl, C_3-C_7-cycloalkyl, -OR^9, -N(R^{10})(R^{11}), ((R^{10})(R^{11})N)-(C_1-C_3-alkyl)-, -C(=O)-N(R^{12})(R^{13}), -S(=O)$_n$-R^{14}, -C(=O)R^{14}, -C(=O)-OR^{17}, and a 5- or 6-membered heteroaryl group which itself is optionally substituted with one or two substituents selected from a halogen atom and a methyl group,

or two substituents attached to adjacent carbon atoms of said phenyl or 6-membered heteroaryl group together form a bivalent group selected from –(CH_2)$_3$-, -(CH_2)$_4$-, -(CH_2)$_2$-O-, -(CH_2)$_3$-O-, -CH_2-O-CH_2-, -(CH_2)$_2$-O-CH_2-, -O-CH_2-O-, -O-CH_2-CH_2-O-, -O-CF_2-O-, -O-CH_2-CF_2-O-, and -O-CF_2-CF_2-O-;

R^5 and R^6 represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_4-alkyl, (C_1-C_4-alkyl)-C(=O)-, C_3-C_4-cycloalkyl and (phenyl)-(C_1-C_3-alkyl)-,

or

R^5 and R^6, together with the nitrogen atom to which they are attached, represent a monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group which is optionally substituted one, two or three times, each substituent independently selected from a halogen atom or a group selected from oxo, hydroxy, C_1-C_4-alkyl, (C_1-C_4-alkyl)-C(=O)-, C_3-C_4-cycloalkyl and C_1-C_4-alkoxy;

R^7 represents a hydrogen atom or a C_1-C_2-alkyl group;

R^8 represents a group selected from -C(=O)-NH_2 and -S(=O)$_2$-NH_2;

R^9 represents a hydrogen atom or a group selected from C_1-C_6-alkyl, (5- or 6-membered heteroaryl)-(C_1-C_3-alkyl)-, (phenyl)-(C_1-C_3-alkyl)-, C_1-C_6-haloalkyl, C_2-C_4-hydroxyalkyl, (C_1-C_3-alkoxy)-C_2-C_3-alkyl-, ((C_1-C_3-alkyl)-C(=O)-O)-C_2-C_3-alkyl-, -C(R^{18})(R^{19})-C(=O)-OR^{17}, -C(R^{18})(R^{19})-C(=O)-N(R^{20})(R^{21}), -C(=O)-N(R^{20})(R^{21}), phenyl and 5- or 6-membered heteroaryl group,

wherein the phenyl group within said (phenyl)-(C_1-C_3-alkyl)- group and said phenyl group itself, and the 5- or 6-membered heteroaryl group within said (5- or 6-membered heteroaryl)-(C_1-C_3-alkyl)- group and said 5- or 6-membered heteroaryl group itself are optionally substituted one or two times, each substituent

independently selected from a halogen atom or a group selected from cyano, methyl, ethyl, trifluoromethyl, methoxy, ethoxy, dimethylamino and trifluoromethoxy;

R^{10} and R^{11} represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_2-C_4-hydroxyalkyl, (C_1-C_3-alkoxy)-C_2-C_3-alkyl-, ((R^{22})(R^{23})N)-C_2-C_3-alkyl, (C_3-C_7-cycloalkyl)-(C_1-C_3-alkyl)-, (C_1-C_4-alkyl)-C(=O)-, C_3-C_7-cycloalkyl, (C_3-C_7-cycloalkyl)-C(=O)-, (phenyl)-(C_1-C_3-alkyl)-, (phenyl)-(C_1-C_3-alkyl)-C(=O)-, (phenyl)-(C_1-C_3-alkyl)-O-C(=O)-, phenyl and a 5- or 6-membered heteroaryl group,

wherein C_3-C_7-cycloalkyl, and the C_3-C_7-cycloalkyl within said (C_3-C_7-cycloalkyl)-(C_1-C_3-alkyl)- and (C_3-C_7-cycloalkyl)-C(=O)- groups are optionally substituted one or two times, each substituent independently selected from a fluorine atom or a group selected from cyano, C_1-C_2-alkyl and C_1-C_2-haloalkyl,

and wherein said phenyl and said 5- or 6-membered heteroaryl group, and the phenyl groups within said (phenyl)-(C_1-C_3-alkyl)-, (phenyl)-(C_1-C_3-alkyl)-C(=O)- and (phenyl)-(C_1-C_3-alkyl)-O-C(=O)- groups, are optionally substituted one or two times, each substituent independently selected from a halogen atom or a group selected from cyano, methyl, ethyl, trifluoromethyl, methoxy, ethoxy, dimethylamino and trifluoromethoxy,

or

R^{10} and R^{11}, together with the nitrogen atom to which they are attached, represent a monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group, or a bicyclic nitrogen containing 5- to 11-membered heterocycloalkyl group, which are optionally substituted one, two or three times, each substituent independently selected from a halogen atom or a group selected from cyano, oxo, hydroxy, C_1-C_4-alkyl, C_1-C_4-haloalkyl, (C_1-C_4-alkyl)-C(=O)-, C_3-C_7-cycloalkyl, C_1-C_4-alkoxy, -N(R^{22})(R^{23}), and a monocyclic 4- to 7-membered heterocycloalkyl group;

R^{12} and R^{13} represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-hydroxyalkyl, (C_1-C_4-alkoxy)-C_2-C_3-alkyl-, (C_1-C_4-haloalkoxy)-C_2-C_3-alkyl-, (phenoxy)-C_2-C_3-alkyl-, C_3-C_7-cycloalkyl, monocyclic 4- to 7-membered heterocycloalkyl and (phenyl)-(C_1-C_3-alkyl)-,

wherein C_3-C_7-cycloalkyl and monocyclic 4- to 7-membered heterocycloalkyl are optionally substituted one, two or three times, each substituent independently

selected from a halogen atom or a group selected from cyano, oxo, hydroxy, C_1-C_4-alkyl, (C_1-C_4-alkyl)-C(=O)-, C_3-C_4-cycloalkyl and C_1-C_4-alkoxy,

and wherein the phenyl groups within said (phenoxy)-C_2-C_3-alkyl- group and said (phenyl)-(C_1-C_3-alkyl)- group are optionally substituted one or two times, each substituent independently selected from a halogen atom or a group selected from cyano, methyl, ethyl, trifluoromethyl, methoxy, ethoxy, dimethylamino and trifluoromethoxy,

or

R^{12} and R^{13}, together with the nitrogen atom to which they are attached, represent a monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group which is optionally substituted one, two or three times, each substituent independently selected from a halogen atom or a group selected from cyano, oxo, hydroxy, C_1-C_4-alkyl, (C_1-C_4-alkyl)-C(=O)-, C_3-C_4-cycloalkyl and C_1-C_4-alkoxy;

R^{14} represents a group selected from C_1-C_4-alkyl, C_1-C_4-haloalkyl and phenyl,

wherein the phenyl group is optionally substituted one or two times, each substituent independently selected from a halogen atom or a group selected from cyano, methyl, ethyl, trifluoromethyl, methoxy, ethoxy, dimethylamino and trifluoromethoxy;

R^{17} represents a C_1-C_4-alkyl group;

R^{18} and R^{19} represent, independently from each occurrence, a hydrogen atom or a C_1-C_4-alkyl group;

R^{20} represents a hydrogen atom or a group selected from C_1-C_6-alkyl, C_3-C_4-alkenyl, C_3-C_4-alkynyl, C_1-C_3-alkoxy, C_3-C_7-cycloalkyl, bicyclic C_5-C_{11}-cycloalkyl, adamantyl, monocyclic 4- to 7-membered heterocycloalkyl, bicyclic 5- to 11-membered heterocycloalkyl, phenyl, naphthyl, and 5- to 10-membered heteroaryl,

wherein said C_1-C_6-alkyl group is optionally substituted one, two or three times, each substituent independently selected from a halogen atom or a group selected from hydroxy, cyano, C_1-C_3-alkoxy, -N(R^{22})(R^{23}), C_3-C_7-cycloalkyl, bicyclic C_5-C_{11}-cycloalkyl, adamantyl, monocyclic 4- to 7-membered heterocycloalkyl, bicyclic 5- to 11-membered heterocycloalkyl, phenyl, and 5- to 10-membered heteroaryl, said phenyl and 5- to 10-membered heteroaryl substituents themselves being optionally substituted one or two times, each substituent independently selected from a halogen atom or a group selected from cyano, methyl, ethyl, trifluoromethyl, methoxy, ethoxy, dimethylamino and trifluoromethoxy,

and wherein C_3-C_7-cycloalkyl, bicyclic C_5-C_{11}-cycloalkyl, adamantyl, monocyclic 4- to 7-membered heterocycloalkyl and bicyclic 5- to 11-membered heterocycloalkyl are optionally substituted one, two or three times, each substituent independently selected from a halogen atom or a group selected from cyano, oxo, hydroxy, C_1-C_4-alkyl, (C_1-C_4-alkyl)-C(=O)-, C_3-C_4-cycloalkyl and C_1-C_4-alkoxy,

and wherein said phenyl, naphthyl and 5- to 10-membered heteroaryl groups are optionally substituted one, two or three times, each substituent independently selected from a halogen atom or a group selected from cyano, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, -N(R^{22})(R^{23}) and -C(=O)-N(R^{24})(R^{25}),

R^{21} represents a hydrogen atom or a C_1-C_4-alkyl group,

or

R^{20} and R^{21}, together with the nitrogen atom to which they are attached, represent a monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group which is optionally benzocondensed, and which is optionally substituted one, two or three times, each substituent independently selected from a halogen atom or a group selected from cyano, oxo, hydroxy, C_1-C_4-alkyl, C_1-C_4-haloalkyl, (phenyl)-(C_1-C_3-alkyl)-, (C_1-C_4-alkyl)-C(=O)-, C_3-C_4-cycloalkyl, C_1-C_4-alkoxy, C_1-C_3-haloalkoxy, -N(R^{22})(R^{23}) and -C(=O)-N(R^{24})(R^{25});

R^{22} and R^{23} represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_2-alkyl and (C_1-C_2-alkyl)-C(=O)-;

R^{24} and R^{25} represent, independently from each occurrence, a hydrogen atom or a C_1-C_4-alkyl group, and

n represents an integer 0, 1, or 2,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

DEFINITIONS

The term "substituted" means that one or more hydrogen atoms on the designated atom or group are replaced with a selection from the indicated group, provided that the designated atom's normal valency under the existing circumstances is not exceeded. Combinations of substituents and/or variables are permissible.

The term "optionally substituted" means that the number of substituents can be equal to or different from zero. Unless otherwise indicated, it is possible that optionally substituted groups are substituted with as many optional substituents as can be accommodated by replacing a hydrogen atom with a non-hydrogen substituent on any available carbon or nitrogen atom. Commonly, it is possible for the number of optional substituents, when present, to be 1, 2, 3 or 4, in particular 1, 2 or 3.

When groups in the compounds according to the invention are substituted, it is possible for said groups to be mono-substituted or poly-substituted with substituent(s), unless otherwise specified. Within the scope of the present invention, the meanings of all groups which occur repeatedly are independent from one another. It is possible that groups in the compounds according to the invention are substituted with one, two or three identical or different substituents, particularly with one substituent.

As used herein, an oxo substituent represents an oxygen atom, which is bound to a carbon atom or to a sulfur atom via a double bond.

Should a composite substituent be composed of more than one part, *e.g.* (C_1-C_2-alkoxy)-(C_1-C_6-alkyl)-, it is possible for a given part to be attached at any suitable position of said composite substituent, *e.g.* it is possible for the C_1-C_2-alkoxy part to be attached to any suitable carbon atom of the C_1-C_6-alkyl part of said (C_1-C_2-alkoxy)-(C_1-C_6-alkyl)- group. A hyphen at the beginning or at the end of such a composite substituent indicates the point of attachment of said composite substituent to the rest of the molecule. Should a ring, comprising carbon atoms and optionally one or more heteroatoms, such as nitrogen, oxygen or sulfur atoms for example, be substituted with a substituent, it is possible for said substituent to be bound at any suitable position of said ring, be it bound to a suitable carbon atom and/or to a suitable heteroatom.

The term "comprising" when used in the specification includes "consisting of".

If within the present text any item is referred to as "as mentioned herein", it means that it may be mentioned anywhere in the present text.

The terms as mentioned in the present text have the following meanings:

The term "halogen atom" means a fluorine, chlorine, bromine or iodine atom, particularly a fluorine, chlorine or bromine atom.

The term "C_1-C_6-alkyl" means a linear or branched, saturated, monovalent hydrocarbon group having 1, 2, 3, 4, 5 or 6 carbon atoms, *e.g.* a methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl, isobutyl, *tert*-butyl, pentyl, isopentyl, 2-methylbutyl, 1-methylbutyl, 1-ethylpropyl, 1,2-dimethylpropyl, *neo*-pentyl, 1,1-dimethylpropyl, hexyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1-ethylbutyl, 2-ethylbutyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 2,3-dimethylbutyl, 1,2-dimethylbutyl or 1,3-dimethylbutyl group, or an isomer thereof. Particularly, said group has 1, 2, 3 or 4 carbon atoms ("C_1-C_4-alkyl"), *e.g.* a methyl, ethyl, propyl, isopropyl, butyl, sec-butyl isobutyl, or *tert*-butyl group, more particularly 1, 2 or 3 carbon atoms ("C_1-C_3-alkyl"), *e.g.* a methyl, ethyl, *n*-propyl or isopropyl group, more particularly 1 or 2 carbon atoms ("C_1-C_2-alkyl"), *e.g.* a methyl or ethyl group.

The term "C_1-C_4-hydroxyalkyl" means a linear or branched, saturated, monovalent hydrocarbon group in which the term "C_1-C_4-alkyl" is defined *supra*, and in which 1 or 2 hydrogen atoms are replaced with a hydroxy group, *e.g.* a hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 1,2-dihydroxyethyl, 3-hydroxypropyl, 2-hydroxypropyl, 1-hydroxypropyl, 1-hydroxypropan-2-yl, 2-hydroxypropan-2-yl, 2,3-dihydroxypropyl, 1,3-dihydroxypropan-2-yl, 3-hydroxy-2-methyl-propyl, 2-hydroxy-2-methyl-propyl, 1-hydroxy-2-methyl-propyl, 1-hydroxybutyl, 2-hydroxybutyl, 3-hydroxybutyl, 4-hydroxybutyl group, or an isomer thereof.

The term "C_1-C_6-haloalkyl" means a linear or branched, saturated, monovalent hydrocarbon group in which the term "C_1-C_6-alkyl" is as defined *supra*, and in which one or more of the hydrogen atoms are replaced, identically or differently, with a halogen atom. Particularly, said halogen atom is a fluorine atom. Said C_1-C_6-haloalkyl group is, for example, fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, 3,3,3-trifluoropropyl or 1,3-difluoropropan-2-yl.

The term "C_1-C_6-alkoxy" means a linear or branched, saturated, monovalent group of formula (C_1-C_6-alkyl)-O-, in which the term "C_1-C_6-alkyl" is as defined *supra*, *e.g.* a methoxy, ethoxy, *n*-propoxy, isopropoxy, *n*-butoxy, *sec*-butoxy, isobutoxy, *tert*-butoxy, pentyloxy, isopentyloxy or *n*-hexyloxy group, or an isomer thereof.

The term "C_1-C_6-haloalkoxy" means a linear or branched, saturated, monovalent C_1-C_6-alkoxy group, as defined *supra*, in which one or more of the hydrogen atoms is replaced, identically or differently, with a halogen atom. Particularly, said halogen atom is a fluorine atom. Said C_1-C_6-haloalkoxy group is, for example, fluoromethoxy, difluoromethoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy or pentafluoroethoxy.

The term "C_3-C_4-alkenyl" means a linear or branched, monovalent hydrocarbon group, which contains one or two double bonds, and which has 3 or 4 carbon atoms. Said alkenyl group is, for example, a prop-2-en-1-yl (or "allyl"), prop-1-en-1-yl, but-3-enyl, but-2-enyl or but-1-enyl group.

The term "C_3-C_4-alkynyl" means a linear or branched, monovalent hydrocarbon group which contains one triple bond, and which contains 3 or 4 carbon atoms. Said C_3-C_4-alkynyl group is, for example, a prop-1-ynyl, prop-2-ynyl (or "propargyl"), but-1-ynyl, but-2-ynyl or but-3-ynyl group.

The term "C_3-C_7-cycloalkyl" means a saturated, monovalent, monocyclic hydrocarbon ring which contains 3, 4, 5, 6 or 7 carbon ring atoms ("C_3-C_7-cycloalkyl"). Said C_3-C_7-cycloalkyl group is for example, a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl group.

The term "bicyclic C_6-C_{11}-cycloalkyl" means a spirocycloalkyl, fused C_6-C_{10}-cycloalkyl or bridged C_7-C_{10}-cycloalkyl group as defined below:

The term "spirocycloalkyl" means a bicyclic, saturated, monovalent C_5-C_{11} hydrocarbon group in which the two rings share one common ring carbon atom, and wherein said bicyclic hydrocarbon group contains 5, 6, 7, 8, 9, 10 or 11 carbon atoms, it being possible for said spirocycloalkyl group to be attached to the rest of the molecule via any one of the carbon atoms except the spiro carbon atom. Said spirocycloalkyl group is, for spiro[2.6]nonyl, spiro[3.3]heptyl, spiro[3.4]octyl, spiro[3.5]nonyl, spiro[3.6]decyl, spiro[4.4]nonyl, spiro[4.5]decyl, spiro[4.6]undecyl or spiro[5.5]undecyl.

The term "fused C_6-C_{10}-cycloalkyl" means a bicyclic, saturated, monovalent hydrocarbon group, in which the two rings share two adjacent ring atoms, such as bicyclo[4.2.0]octyl, octahydropentalenyl or decalinyl.

The term "bridged C_7-C_{10}-cycloalkyl" means a bicyclic, saturated, monovalent hydrocarbon group which the two rings share two common ring atoms which are not adjacent, *e.g.* bicyclo[2.2.1]heptyl (also known as norbornyl).

The term "bicyclic C_5-C_{11}-cycloalkyl" means a spirocycloalkyl, fused C_5-C_{10}-cycloalkyl or bridged C_5-C_{10}-cycloalkyl group as defined below:

The term "spirocycloalkyl" means a bicyclic, saturated, monovalent C_5-C_{11} hydrocarbon group in which the two rings share one common ring carbon atom, and wherein said bicyclic hydrocarbon group contains 5, 6, 7, 8, 9, 10 or 11 carbon atoms, it being possible for said spirocycloalkyl group to be attached to the rest of the molecule via any one of the carbon atoms except the spiro carbon atom. Said spirocycloalkyl group is, for spiro[2.6]nonyl, spiro[3.3]heptyl, spiro[3.4]octyl, spiro[3.5]nonyl, spiro[3.6]decyl, spiro[4.4]nonyl, spiro[4.5]decyl, spiro[4.6]undecyl or spiro[5.5]undecyl.

The term "fused C_5-C_{10}-cycloalkyl" means a bicyclic, saturated, monovalent hydrocarbon group, in which the two rings share two adjacent ring atoms, such as bicyclo[4.2.0]octyl, octahydropentalenyl or decalinyl.

The term "bridged C_5-C_{10}-cycloalkyl" means a bicyclic, saturated, monovalent hydrocarbon group which the two rings share two common ring atoms which are not adjacent, *e.g.* bicyclo[1.1.1]pentyl or bicyclo[2.2.1]heptyl (also known as norbornyl).

The term "monocyclic 4- to 7-membered heterocycloalkyl" means a monocyclic, saturated heterocycle with 4, 5, 6 or 7 ring atoms in total, which contains one or two identical or different ring heteroatoms from the series N, O and S.

Said monocyclic heterocycloalkyl group, without being limited thereto, can be a 4-membered ring, such as azetidinyl, oxetanyl or thietanyl, for example; or a 5-membered ring, such as tetrahydrofuranyl, 1,3-dioxolanyl, thiolanyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, 1,1-dioxidothiolanyl, 1,2-oxazolidinyl, 1,3-oxazolidinyl or 1,3-thiazolidinyl, for example; or a 6-membered ring, such as tetrahydropyranyl, tetrahydrothiopyranyl, piperidinyl, morpholinyl, dithianyl, thiomorpholinyl, piperazinyl, 1,3-dioxanyl, 1,4-dioxanyl or 1,2-oxazinanyl, for example, or a 7-membered ring, such as azepanyl, 1,4-diazepanyl or 1,4-oxazepanyl, for example.

The term "monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group" means a monocyclic, saturated heterocycle with 4, 5, 6 or 7 ring atoms in total, which contains one ring nitrogen atom and optionally one further ring heteroatom from the series N, O and S.

Said monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group, without being limited thereto, can be a 4-membered ring, such as azetidinyl, for example; or a 5-membered ring, such as pyrrolidinyl, imidazolidinyl, pyrazolidinyl, 1,2-oxazolidinyl, 1,3-oxazolidinyl or 1,3-thiazolidinyl, for example; or a 6-membered ring, such as piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, or 1,2-oxazinanyl, for example, or a 7-membered ring, such as azepanyl, 1,4-diazepanyl or 1,4-oxazepanyl, for example.

The term "monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group which is optionally benzocondensed" means a monocyclic, saturated heterocycle with 4, 5, 6 or 7 ring atoms in total, which contains one ring nitrogen atom and optionally one further ring heteroatom from the series N, O and S, in which two adjacent ring carbon atoms may be shared with a benzene ring optionally fused thereto, such group being one of the aforementioned monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl groups, such as pyrrolidinyl, piperidinyl, and the like, or benzocondensed groups *e.g.* 3,4-dihydroquinolin-1(2H)-yl, 3,4-dihydroisoquinolin-2(1H)-yl, 1,3-dihydro-2H-isoindol-2-yl or 2,3-dihydro-1H-indol-1-yl.

The term "bicyclic 6-11 membered heterocycloalkyl" means a 6- to 11-membered heterospirocycloalkyl, a 6- to 10-membered fused heterocycloalkyl or a 7- to 10-membered bridged heterocycloalkyl group as defined below:

The term "6- to 11-membered heterospirocycloalkyl" means a bicyclic, saturated heterocycle with 6, 7, 8, 9, 10 or 11 ring atoms in total, in which the two rings share one common ring carbon atom, which "heterospirocycloalkyl" contains one or two identical or different ring heteroatoms from the series: N, O, S; it being possible for said heterospirocycloalkyl group to be attached to the rest of the molecule via any one of the carbon atoms, except the spiro carbon atom, or, if present, a nitrogen atom.

Said heterospirocycloalkyl group is, for example, azaspiro[2.3]hexyl, azaspiro[3.3]heptyl, oxaazaspiro[3.3]heptyl, thiaazaspiro[3.3]heptyl, oxaspiro[3.3]heptyl, oxazaspiro[5.3]nonyl, oxazaspiro[4.3]octyl, azaspiro[4,5]decyl, oxazaspiro [5.5]undecyl, diazaspiro[3.3]heptyl, thiazaspiro[3.3]heptyl, thiazaspiro[4.3]octyl, azaspiro[5.5]undecyl, or one of the further homologous scaffolds such as spiro[3.4]-, spiro[4.4]-, spiro[2.4]-, spiro[2.5]-, spiro[2.6]-, spiro[3.5]-, spiro[3.6]-, spiro[4.5]- and spiro[4.6]-.

The term "a 6- to 10-membered fused heterocycloalkyl" means a bicyclic, saturated heterocycle with 6, 7, 8, 9 or 10 ring atoms in total, in which the two rings share two adjacent ring atoms, which "fused heterocycloalkyl" contains one or two identical or different ring heteroatoms from the series: N, O, S; it being possible for said fused heterocycloalkyl group to be attached to the rest of the molecule via any one of the carbon atoms or, if present, a nitrogen atom.

Said fused heterocycloalkyl group is, for example, azabicyclo[3.3.0]octyl, azabicyclo[4.3.0]nonyl, diazabicyclo[4.3.0]nonyl, oxazabicyclo[4.3.0]nonyl, thiazabicyclo[4.3.0]nonyl or azabicyclo[4.4.0]decyl.

The term "a 7- to 10-membered bridged heterocycloalkyl" means a bicyclic, saturated heterocycle with 7, 8, 9 or 10 ring atoms in total, in which the two rings share two common ring atoms which are not adjacent, which "bridged heterocycloalkyl" contains one or two identical or different ring heteroatoms from the series: N, O, S; it being possible for said bridged heterocycloalkyl group to be attached to the rest of the molecule via any one of the carbon atoms, except the spiro carbon atom, or, if present, a nitrogen atom.

Said bridged heterocycloalkyl group is, for example, azabicyclo[2.2.1]heptyl, oxazabicyclo[2.2.1]heptyl, thiazabicyclo[2.2.1]heptyl, diazabicyclo[2.2.1]heptyl, azabicyclo[2.2.2]octyl, diazabicyclo[2.2.2]octyl, oxazabicyclo[2.2.2]octyl, thiazabicyclo[2.2.2]octyl, azabicyclo[3.2.1]octyl, diazabicyclo[3.2.1]octyl, oxazabicyclo[3.2.1]octyl, thiazabicyclo[3.2.1]octyl, azabicyclo[3.3.1]nonyl, diazabicyclo[3.3.1]nonyl, oxazabicyclo[3.3.1]nonyl, thiazabicyclo[3.3.1]nonyl,

azabicyclo[4.2.1]nonyl, diazabicyclo[4.2.1]nonyl, oxazabicyclo[4.2.1]nonyl, thiazabicyclo[4.2.1]nonyl, azabicyclo[3.3.2]decyl, diazabicyclo[3.3.2]decyl, oxazabicyclo[3.3.2]decyl, thiazabicyclo[3.3.2]decyl or azabicyclo[4.2.2]decyl.

The term "bicyclic nitrogen containing 6-11 membered heterocycloalkyl" means a 6- to 11-membered heterospirocycloalkyl, 6- to 10-membered fused heterocycloalkyl or 7- to 10-membered bridged heterocycloalkyl group as defined *supra*, however containing one ring nitrogen atom and optionally one or two further ring heteroatoms from the series N, O and S; it being possible for said bicyclic nitrogen containing 6-11 membered heterocycloalkyl group to be attached to the rest of the molecule via a nitrogen atom or any one of the carbon atoms, except a spiro carbon atom.

The term "bicyclic 5-11 membered heterocycloalkyl" means a 5-11 membered heterospirocycloalkyl, a 5-11 membered fused heterocycloalkyl or a 5-11 membered bridged heterocycloalkyl group as defined below:

The term "5-11 membered heterospirocycloalkyl" means a bicyclic, saturated heterocycle with 5, 6, 7, 8, 9, 10 or 11 ring atoms in total, in which the two rings share one common ring carbon atom, which "heterospirocycloalkyl" contains one or two identical or different ring heteroatoms from the series: N, O, S; it being possible for said heterospirocycloalkyl group to be attached to the rest of the molecule via any one of the carbon atoms, except the spiro carbon atom, or, if present, a nitrogen atom.

Said heterospirocycloalkyl group is, for example, azaspiro[2.2]pentyl, azaspiro[2.3]hexyl, azaspiro[3.3]heptyl, oxaazaspiro[3.3]heptyl, thiaazaspiro[3.3]heptyl, oxaspiro[3.3]heptyl, oxazaspiro[5.3]nonyl, oxazaspiro[4.3]octyl, azaspiro[4,5]decyl, oxazaspiro [5.5]undecyl, diazaspiro[3.3]heptyl, thiazaspiro[3.3]heptyl, thiazaspiro[4.3]octyl, azaspiro[5.5]undecyl, or one of the further homologous scaffolds such as spiro[3.4]-, spiro[4.4]-, spiro[2.4]-, spiro[2.5]-, spiro[2.6]-, spiro[3.5]-, spiro[3.6]-, spiro[4.5]- and spiro[4.6]-.

The term "5-11 membered fused heterocycloalkyl" means a bicyclic, saturated heterocycle with 5, 6, 7, 8, 9 or 10 ring atoms in total, in which the two rings share two adjacent ring atoms, which "fused heterocycloalkyl" contains one or two identical or different ring heteroatoms from the series: N, O, S; it being possible for said fused heterocycloalkyl group to be attached to the rest of the molecule via any one of the carbon atoms or, if present, a nitrogen atom.

Said fused heterocycloalkyl group is, for example, azabicyclo[3.1.0]hexyl, azabicyclo[3.3.0]octyl, azabicyclo[4.3.0]nonyl, diazabicyclo[4.3.0]nonyl, oxazabicyclo[4.3.0]nonyl, thiazabicyclo[4.3.0]nonyl or azabicyclo[4.4.0]decyl.

The term "5-11 membered bridged heterocycloalkyl" means a bicyclic, saturated heterocycle with 5, 6, 7, 8, 9 or 10 ring atoms in total, in which the two rings share two

common ring atoms which are not adjacent, which "bridged heterocycloalkyl" contains one or two identical or different ring heteroatoms from the series: N, O, S; it being possible for said bridged heterocycloalkyl group to be attached to the rest of the molecule via any one of the carbon atoms, except the spiro carbon atom, or, if present, a nitrogen atom.

Said bridged heterocycloalkyl group is, for example, azabicyclo[2.2.1]heptyl, oxazabicyclo[2.2.1]heptyl, thiazabicyclo[2.2.1]heptyl, diazabicyclo[2.2.1]heptyl, azabicyclo[2.2.2]octyl, diazabicyclo[2.2.2]octyl, oxazabicyclo[2.2.2]octyl, thiazabicyclo[2.2.2]octyl, azabicyclo[3.2.1]octyl, diazabicyclo[3.2.1]octyl, oxazabicyclo[3.2.1]octyl, thiazabicyclo[3.2.1]octyl, azabicyclo[3.3.1]nonyl, diazabicyclo[3.3.1]nonyl, oxazabicyclo[3.3.1]nonyl, thiazabicyclo[3.3.1]nonyl, azabicyclo[4.2.1]nonyl, diazabicyclo[4.2.1]nonyl, oxazabicyclo[4.2.1]nonyl, thiazabicyclo[4.2.1]nonyl, azabicyclo[3.3.2]decyl, diazabicyclo[3.3.2]decyl, oxazabicyclo[3.3.2]decyl, thiazabicyclo[3.3.2]decyl or azabicyclo[4.2.2]decyl.

The term "bicyclic nitrogen containing 5-11 membered heterocycloalkyl" means a 5-11 membered heterospirocycloalkyl, 5-11 membered fused heterocycloalkyl or 5-11 membered bridged heterocycloalkyl group as defined *supra*, however containing one ring nitrogen atom and optionally one or two further ring heteroatoms from the series N, O and S; it being possible for said bicyclic nitrogen containing 5-11 membered heterocycloalkyl group to be attached to the rest of the molecule via a nitrogen atom or any one of the carbon atoms, except a spiro carbon atom.

The term "heteroaryl" means a monovalent, monocyclic or bicyclic aromatic ring having 5, 6, 8, 9 or 10 ring atoms (a "5- to 10-membered heteroaryl" group), which contains at least one ring heteroatom and optionally one, two or three further ring heteroatoms from the series: N, O and/or S, and which is bound via a ring carbon atom, or, if valency allows as *e.g.* in pyrrol-1-yl, a nitrogen atom.

Said heteroaryl group can be a 5-membered heteroaryl group, such as, for example, thienyl, furanyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl or tetrazolyl; or a 6-membered heteroaryl group, such as, for example, pyridinyl (herein also referred to as pyridyl), pyridazinyl, pyrimidinyl, pyrazinyl or triazinyl; or a 9-membered heteroaryl group, such as, for example, benzofuranyl, benzothienyl, benzoxazolyl, benzisoxazolyl, benzimidazolyl, benzothiazolyl, benzotriazolyl, thiazolopyridinyl, indazolyl, indolyl, isoindolyl, indolizinyl or purinyl; or a 10-membered heteroaryl group, such as, for example, quinolinyl, quinazolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinoxalinyl or pteridinyl.

In general, and unless otherwise mentioned, the heteroaryl or heteroarylene groups include all possible isomeric forms thereof, *e.g.*: tautomers and positional isomers with respect to the point of linkage to the rest of the molecule. Thus, for some illustrative non-restricting examples, the term pyridinyl includes pyridin-2-yl, pyridin-3-yl and pyridin-4-yl; or the term thienyl includes thien-2-yl and thien-3-yl.

The term "C_1-C_6", as used in the present text, *e.g.* in the context of the definition of "C_1-C_6-alkyl", "C_1-C_6-haloalkyl", "C_1-C_6-hydroxyalkyl", "C_1-C_6-alkoxy" or "C_1-C_6-haloalkoxy" means an alkyl group having a finite number of carbon atoms of 1 to 6, *i.e.* 1, 2, 3, 4, 5 or 6 carbon atoms.

Further, as used herein, the term "C_3-C_7", as used in the present text, *e.g.* in the context of the definition of "C_3-C_7-cycloalkyl", means a cycloalkyl group having a finite number of carbon atoms of 3 to 7, *i.e.* 3, 4, 5, 6 or 7 carbon atoms.

When a range of values is given, said range encompasses each value and sub-range within said range.

For example:

"C_1-C_6" encompasses C_1, C_2, C_3, C_4, C_5, C_6, C_1-C_6, C_1-C_5, C_1-C_4, C_1-C_3, C_1-C_2, C_2-C_6, C_2-C_5, C_2-C_4, C_2-C_3, C_3-C_6, C_3-C_5, C_3-C_4, C_4-C_6, C_4-C_5, and C_5-C_6;

"C_2-C_6" encompasses C_2, C_3, C_4, C_5, C_6, C_2-C_6, C_2-C_5, C_2-C_4, C_2-C_3, C_3-C_6, C_3-C_5, C_3-C_4, C_4-C_6, C_4-C_5, and C_5-C_6;

"C_3-C_6" encompasses C_3, C_4, C_5, C_6, C_3-C_6, C_3-C_5, C_3-C_4, C_4-C_6, C_4-C_5, and C_5-C_6.

As used herein, the term "leaving group" means an atom or a group of atoms that is displaced in a chemical reaction as stable species taking with it the bonding electrons. In particular, such a leaving group is selected from the group comprising: a halogen atom, in particular a fluorine atom, a chlorine atom, a bromine atom or an iodide atom, being displaced as halide, in particular fluoride, chloride, bromide or iodide; (methylsulfonyl)oxy, [(trifluoromethyl)sulfonyl]oxy, [(nonafluorobutyl)sulfonyl]oxy, (phenylsulfonyl)oxy, [(4-methylphenyl)sulfonyl]oxy, [(4-bromophenyl)sulfonyl]oxy, [(4-nitrophenyl)sulfonyl]oxy, [(2-nitrophenyl)sulfonyl]oxy, [(4-isopropylphenyl)sulfonyl]oxy, [(2,4,6-triisopropylphenyl)sulfonyl]oxy, [(2,4,6-trimethylphenyl)sulfonyl]oxy, [(4-*tert*-butylphenyl)sulfonyl]oxy and [(4-methoxyphenyl)sulfonyl]oxy.

As used herein, the term "dipolar aprotic solvent" means a solvent selected from acetone, acetonitrile, priopionitrile, dimethylsulfoxide, diethylsulfoxide, N,N-dimethylformamide, N,N-dimethylacetamide, N,N-diethylformamide, N,N-diethylacetamide, 1-methyl-2-pyrrolidinone, 1-ethyl-2-pyrrolidinone, 1-methyl-2-piperidinone and 1-ethyl-2-piperidinone, or mixtures thereof. Particularly, said dipolar aprotic solvent is acetonitrile, dimethylsulfoxide, N,N-dimethylformamide, N,N-dimethylacetamide or 1-methyl-2-pyrrolidinone.

As used herein, the term "room temperature" means a temperature in the range from 15 °C to 25 °C.

It is possible for the compounds of general formula (I) to exist as isotopic variants. The invention therefore includes one or more isotopic variant(s) of the compounds of general formula (I), particularly deuterium-containing compounds of general formula (I).

The term "Isotopic variant" of a compound or a reagent is defined as a compound exhibiting an unnatural proportion of one or more of the isotopes that constitute such a compound.

The term "Isotopic variant of the compound of general formula (I)" is defined as a compound of general formula (I) exhibiting an unnatural proportion of one or more of the isotopes that constitute such a compound.

The expression "unnatural proportion" means a proportion of such isotope which is higher than its natural abundance. The natural abundances of isotopes to be applied in this context are described in "Isotopic Compositions of the Elements 1997", Pure Appl. Chem., 70(1), 217-235, 1998.

Examples of such isotopes include stable and radioactive isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine, chlorine, bromine and iodine, such as ^{2}H (deuterium), ^{3}H (tritium), ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{17}O, ^{18}O, ^{32}P, ^{33}P, ^{33}S, ^{34}S, ^{35}S, ^{36}S, ^{18}F, ^{36}Cl, ^{82}Br, ^{123}I, ^{124}I, ^{125}I, ^{129}I and ^{131}I, respectively.

With respect to the treatment and/or prophylaxis of the disorders specified herein the isotopic variant(s) of the compounds of general formula (I) preferably contain deuterium ("deuterium-containing compounds of general formula (I)"). Isotopic variants of the compounds of general formula (I) in which one or more radioactive isotopes, such as ^{3}H or ^{14}C, are incorporated are useful e.g. in drug and/or substrate tissue distribution studies. These isotopes are particularly preferred for the ease of their incorporation and detectability. Positron emitting isotopes such as ^{18}F or ^{11}C may be incorporated into a compound of general formula (I). These isotopic variants of the compounds of general formula (I) are useful for in vivo imaging applications. Deuterium-containing and ^{13}C-containing compounds of general formula (I) can be used in mass spectrometry analyses in the context of preclinical or clinical studies.

Isotopic variants of the compounds of general formula (I) can generally be prepared by methods known to a person skilled in the art, such as those described in the schemes and/or examples herein, by substituting a reagent for an isotopic variant of said reagent, preferably for a deuterium-containing reagent. Depending on the desired sites of deuteration, in some cases deuterium from D_2O can be incorporated either directly into the compounds or into reagents that are useful for synthesizing such compounds. Deuterium gas is also a useful reagent for incorporating deuterium into molecules. Catalytic deuteration of olefinic bonds and acetylenic bonds is a rapid route for incorporation of deuterium. Metal catalysts (i.e. Pd, Pt, and Rh) in the

presence of deuterium gas can be used to directly exchange deuterium for hydrogen in functional groups containing hydrocarbons. A variety of deuterated reagents and synthetic building blocks are commercially available from companies such as for example C/D/N Isotopes, Quebec, Canada; Cambridge Isotope Laboratories Inc., Andover, MA, USA; and CombiPhos Catalysts, Inc., Princeton, NJ, USA.

The term "deuterium-containing compound of general formula (I)" is defined as a compound of general formula (I), in which one or more hydrogen atom(s) is/are replaced by one or more deuterium atom(s) and in which the abundance of deuterium at each deuterated position of the compound of general formula (I) is higher than the natural abundance of deuterium, which is about 0.015%. Particularly, in a deuterium-containing compound of general formula (I) the abundance of deuterium at each deuterated position of the compound of general formula (I) is higher than 10%, 20%, 30%, 40%, 50%, 60%, 70% or 80%, preferably higher than 90%, 95%, 96% or 97%, even more preferably higher than 98% or 99% at said position(s). It is understood that the abundance of deuterium at each deuterated position is independent of the abundance of deuterium at other deuterated position(s).

The selective incorporation of one or more deuterium atom(s) into a compound of general formula (I) may alter the physicochemical properties (such as for example acidity [C. L. Perrin, et al., J. Am. Chem. Soc., 2007, 129, 4490], basicity [C. L. Perrin et al., J. Am. Chem. Soc., 2005, 127, 9641], lipophilicity [B. Testa et al., Int. J. Pharm., 1984, 19(3), 271]) and/or the metabolic profile of the molecule and may result in changes in the ratio of parent compound to metabolites or in the amounts of metabolites formed. Such changes may result in certain therapeutic advantages and hence may be preferred in some circumstances. Reduced rates of metabolism and metabolic switching, where the ratio of metabolites is changed, have been reported (A. E. Mutlib et al., Toxicol. Appl. Pharmacol., 2000, 169, 102). These changes in the exposure to parent drug and metabolites can have important consequences with respect to the pharmacodynamics, tolerability and efficacy of a deuterium-containing compound of general formula (I). In some cases deuterium substitution reduces or eliminates the formation of an undesired or toxic metabolite and enhances the formation of a desired metabolite (e.g. Nevirapine: A. M. Sharma et al., Chem. Res. Toxicol., 2013, 26, 410; Efavirenz: A. E. Mutlib et al., Toxicol. Appl. Pharmacol., 2000, 169, 102). In other cases the major effect of deuteration is to reduce the rate of systemic clearance. As a result, the biological half-life of the compound is increased. The potential clinical benefits would include the ability to maintain similar systemic exposure with decreased peak levels and increased trough levels. This could result in lower side effects and enhanced efficacy, depending on the particular compound's pharmacokinetic/ pharmacodynamic relationship. ML-337 (C. J. Wenthur et al., J. Med. Chem., 2013, 56, 5208) and Odanacatib (K. Kassahun et al., WO2012/112363) are examples for this deuterium effect. Still other cases have been reported in which reduced rates of metabolism result in an increase

in exposure of the drug without changing the rate of systemic clearance (e.g. Rofecoxib: F. Schneider et al., Arzneim. Forsch. / Drug. Res., 2006, 56, 295; Telaprevir: F. Maltais et al., J. Med. Chem., 2009, 52, 7993). Deuterated drugs showing this effect may have reduced dosing requirements (e.g. lower number of doses or lower dosage to achieve the desired effect) and/or may produce lower metabolite loads.

A compound of general formula (I) may have multiple potential sites of attack for metabolism. To optimize the above-described effects on physicochemical properties and metabolic profile, deuterium-containing compounds of general formula (I) having a certain pattern of one or more deuterium-hydrogen exchange(s) can be selected. Particularly, the deuterium atom(s) of deuterium-containing compound(s) of general formula (I) is/are attached to a carbon atom and/or is/are located at those positions of the compound of general formula (I), which are sites of attack for metabolizing enzymes such as e.g. cytochrome P_{450}.

In another embodiment the present invention concerns a deuterium-containing compound of general formula (I) having 1, 2, 3 or 4 deuterium atoms, particularly with 1, 2 or 3 deuterium atoms.

Where the plural form of the word compounds, salts, polymorphs, hydrates, solvates and the like, is used herein, this is taken to mean also a single compound, salt, polymorph, isomer, hydrate, solvate or the like.

By "stable compound' or "stable structure" is meant a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

The compounds of the present invention optionally contain one or more asymmetric centres, depending upon the location and nature of the various substituents desired. It is possible that one or more asymmetric carbon atoms are present in the (R) or (S) configuration, which can result in racemic mixtures in the case of a single asymmetric centre, and in diastereomeric mixtures in the case of multiple asymmetric centres. In certain instances, it is possible that asymmetry also be present due to restricted rotation about a given bond, for example, the central bond adjoining two substituted aromatic rings of the specified compounds.

Preferred isomers are those which produce the more desirable biological activity. These separated, pure or partially purified isomers or racemic mixtures of the compounds of this invention are also included within the scope of the present invention. The purification and the separation of such materials can be accomplished by standard techniques known in the art.

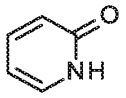
The optical isomers can be obtained by resolution of the racemic mixtures according to conventional processes, for example, by the formation of diastereoisomeric salts using an optically active acid or base or formation of covalent diastereomers. Examples of appropriate acids are tartaric, diacetyltartaric, ditoluoyltartaric and camphorsulfonic acid. Mixtures of

diastereoisomers can be separated into their individual diastereomers on the basis of their physical and/or chemical differences by methods known in the art, for example, by chromatography or fractional crystallisation. The optically active bases or acids are then liberated from the separated diastereomeric salts. A different process for separation of optical isomers involves the use of chiral chromatography (*e.g.*, HPLC columns using a chiral phase), with or without conventional derivatisation, optimally chosen to maximise the separation of the enantiomers. Suitable HPLC columns using a chiral phase are commercially available, such as those manufactured by Daicel, *e.g.*, Chiracel OD and Chiracel OJ, for example, among many others, which are all routinely selectable. Enzymatic separations, with or without derivatisation, are also useful. The optically active compounds of the present invention can likewise be obtained by chiral syntheses utilizing optically active starting materials.

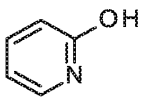
In order to distinguish different types of isomers from each other reference is made to IUPAC Rules Section E (Pure Appl Chem 45, 11-30, 1976).

The present invention includes all possible stereoisomers of the compounds of the present invention as single stereoisomers, or as any mixture of said stereoisomers, *e.g.* (R)- or (S)-isomers, in any ratio. Isolation of a single stereoisomer, *e.g.* a single enantiomer or a single diastereomer, of a compound of the present invention is achieved by any suitable state of the art method, such as chromatography, especially chiral chromatography, for example.

Further, it is possible for some of the compounds of the present invention to exist as tautomers. For example, the compounds of the present invention may contain a pyridone moiety and can exist as a pyridone, or as an hydroxypyridine, or even a mixture in any amount of the two tautomers, namely :



pyridone



hydroxypyridine

The present invention includes all possible tautomers of the compounds of the present invention as single tautomers, or as any mixture of said tautomers, in any ratio.

Further, the compounds of the present invention can exist as N-oxides, which are defined in that at least one nitrogen of the compounds of the present invention is oxidised. The present invention includes all such possible N-oxides.

The present invention also covers useful forms of the compounds of the present invention, such as metabolites, hydrates, solvates, prodrugs, salts, in particular pharmaceutically acceptable salts, and/or co-precipitates.

The compounds of the present invention can exist as a hydrate, or as a solvate, wherein the compounds of the present invention contain polar solvents, in particular water, methanol or ethanol for example, as structural element of the crystal lattice of the compounds. It is possible for the amount of polar solvents, in particular water, to exist in a stoichiometric or non-stoichiometric ratio. In the case of stoichiometric solvates, *e.g.* a hydrate, hemi-, (semi-), mono-, sesqui-, di-, tri-, tetra-, penta- *etc.* solvates or hydrates, respectively, are possible. The present invention includes all such hydrates or solvates.

Further, it is possible for the compounds of the present invention to exist in free form, *e.g.* as a free base, or as a free acid, or as a zwitterion, or to exist in the form of a salt. Said salt may be any salt, either an organic or inorganic addition salt, particularly any pharmaceutically acceptable organic or inorganic addition salt, which is customarily used in pharmacy, or which is used, for example, for isolating or purifying the compounds of the present invention.
The term "pharmaceutically acceptable salt" refers to an inorganic or organic acid addition salt of a compound of the present invention. For example, see S. M. Berge et al., "Pharmaceutical Salts," J. Pharm. Sci. 1977, 66, 1-19.

A suitable pharmaceutically acceptable salt of the compounds of the present invention may be, for example, an acid-addition salt of a compound of the present invention bearing a nitrogen atom, in a chain or in a ring, for example, which is sufficiently basic, such as an acid-addition salt with an inorganic acid, or "mineral acid", such as hydrochloric, hydrobromic, hydroiodic, sulfuric, sulfamic, bisulfuric, phosphoric, or nitric acid, for example, or with an organic acid, such as formic, acetic, acetoacetic, pyruvic, trifluoroacetic, propionic, butyric, hexanoic, heptanoic, undecanoic, lauric, benzoic, salicylic, 2-(4-hydroxybenzoyl)-benzoic, camphoric, cinnamic, cyclopentanepropionic, digluconic, 3-hydroxy-2-naphthoic, nicotinic, pamoic, pectinic, 3-phenylpropionic, pivalic, 2-hydroxyethanesulfonic, itaconic, trifluoromethanesulfonic, dodecylsulfuric, ethanesulfonic, benzenesulfonic, para-toluenesulfonic, methanesulfonic, 2-naphthalenesulfonic, naphthalinedisulfonic, camphorsulfonic acid, citric, tartaric, stearic, lactic, oxalic, malonic, succinic, malic, adipic, alginic, maleic, fumaric, D-gluconic, mandelic, ascorbic, glucoheptanoic, glycerophosphoric, aspartic, sulfosalicylic, or thiocyanic acid, for example.

Further, another suitably pharmaceutically acceptable salt of a compound of the present invention which is sufficiently acidic, is an alkali metal salt, for example a sodium or potassium

salt, an alkaline earth metal salt, for example a calcium, magnesium or strontium salt, or an aluminium or a zinc salt, or an ammonium salt derived from ammonia or from an organic primary, secondary or tertiary amine having 1 to 20 carbon atoms, such as ethylamine, diethylamine, triethylamine, ethyldiisopropylamine, monoethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, dimethylaminoethanol, diethylaminoethanol, tris(hydroxymethyl)aminomethane, procaine, dibenzylamine, *N*-methylmorpholine, arginine, lysine, 1,2-ethylenediamine, *N*-methylpiperidine, *N*-methyl-glucamine, *N,N*-dimethyl-glucamine, *N*-ethyl-glucamine, 1,6-hexanediamine, glucosamine, sarcosine, serinol, 2-amino-1,3-propanediol, 3-amino-1,2-propanediol, 4-amino-1,2,3-butanetriol, or a salt with a quarternary ammonium ion having 1 to 20 carbon atoms, such as tetramethylammonium, tetraethylammonium, tetra(*n*-propyl)ammonium, tetra(*n*-butyl)ammonium, *N*-benzyl-*N,N,N*-trimethylammonium, choline or benzalkonium.

Those skilled in the art will further recognise that it is possible for acid addition salts of the claimed compounds to be prepared by reaction of the compounds with the appropriate inorganic or organic acid via any of a number of known methods. Alternatively, alkali and alkaline earth metal salts of acidic compounds of the present invention are prepared by reacting the compounds of the present invention with the appropriate base via a variety of known methods.

The present invention includes all possible salts of the compounds of the present invention as single salts, or as any mixture of said salts, in any ratio.

In the present text, in particular in the "Experimental Section", for the synthesis of intermediates and of examples of the present invention, when a compound is mentioned as a salt form with the corresponding base or acid, the exact stoichiometric composition of said salt form, as obtained by the respective preparation and/or purification process, is, in most cases, unknown.

Unless specified otherwise, suffixes to chemical names or structural formulae relating to salts, such as "hydrochloride", "trifluoroacetate", "sodium salt", or "x HCl", "x CF_3COOH", "x Na^+", for example, mean a salt form, the stoichiometry of which salt form not being specified.

This applies analogously to cases in which synthesis intermediates or example compounds or salts thereof have been obtained, by the preparation and/or purification processes described, as solvates, such as hydrates, with (if defined) unknown stoichiometric composition.

Furthermore, the present invention includes all possible crystalline forms, or polymorphs, of the compounds of the present invention, either as single polymorph, or as a mixture of more than one polymorph, in any ratio.

Moreover, the present invention also includes prodrugs of the compounds according to the invention. The term "prodrugs" here designates compounds which themselves can be biologically active or inactive, but are converted (for example metabolically or hydrolytically) into compounds according to the invention during their residence time in the body.

The invention further includes all possible cyclodextrin clathrates, *i.e.* alpha-, beta-, or gamma-cyclodextrins, hydroxypropyl-beta-cyclodextrins, methylbetacyclodextrins.

In accordance with a second embodiment of the first aspect, the present invention covers compounds of general formula (I), *supra*, in which:

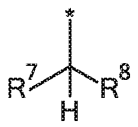
R^1 represents a phenyl or pyridinyl group optionally substituted, one, two, or three times, each substituent independently selected from a halogen atom or a group selected from hydroxy, cyano, nitro, C_1-C_4-alkyl, (phenyl)-(C_1-C_2-alkyl)-, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, (phenyl)-(C_1-C_2-alkoxy)-, C_1-C_4-haloalkoxy, -N(R^5)(R^6),

wherein the phenyl groups in said (phenyl)-(C_1-C_2-alkyl)- and (phenyl)-(C_1-C_2-alkoxy)- groups are optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a bromine atom, or a group selected from methyl, trifluoromethyl and methoxy,

or two substituents attached to adjacent carbon atoms of said phenyl or pyridinyl group together form a bivalent group selected from –-(CH_2)$_3$-, -(CH_2)$_4$-, -(CH_2)$_2$-O-, -(CH_2)$_3$-O-, -CH_2-O-CH_2-, -O-CH_2-O-, -O-CH_2-CH_2-O- and -O-CF_2-O-,

or

R^1 represents a pyrazolyl group optionally substituted one or two times, each substituent independently selected from a halogen atom or a group selected from cyano, C_1-C_2-alkyl, and C_1-C_2-alkoxy;

R^2 represents a group 

,

wherein "*" indicates the point of attachment to the nitrogen atom to which R^2 is attached;

R^3 represents a group selected from methyl and $-NH_2$;

R^4 represents a phenyl or pyridinyl group optionally substituted, one, two, or three times, each substituent independently selected from a halogen atom or a group selected from cyano, nitro, C_1-C_4-alkyl, (phenyl)-(C_1-C_2-alkyl)-, (5-membered heteroaryl)-(C_1-C_2-alkyl)-, (C_3-C_7-cycloalkyl)-(C_1-C_2-alkyl)-, ((R^9)O)-(C_1-C_4-alkyl)-, C_1-C_4-haloalkyl, C_3-C_7-cycloalkyl, $-OR^9$, $-N(R^{10})(R^{11})$, ((R^{10})(R^{11})N)-(C_1-C_3-alkyl)-, $-C(=O)-N(R^{12})(R^{13})$, $S(=O)_n-R^{14}$, $-C(=O)R^{14}$, $-C(=O)-OR^{17}$, and a 5-membered heteroaryl group which itself is optionally substituted with one or two methyl groups,

or two substituents attached to adjacent carbon atoms of said phenyl or pyridinyl group together form a bivalent group selected from $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_2-O-$, $-(CH_2)_3-O-$, $-CH_2-O-CH_2-$, $-O-CH_2-O-$, $-O-CH_2-CH_2-O-$ and $-O-CF_2-O-$;

R^5 and R^6 represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_2-alkyl and (C_1-C_2-alkyl)-C(=O)-,

or

R^5 and R^6, together with the nitrogen atom to which they are attached, represent a monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group which is optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a bromine atom, or a group selected from oxo, hydroxy, C_1-C_2-alkyl and (C_1-C_2-alkyl)-C(=O)-;

R^7 represents a hydrogen atom or a C_1-C_2-alkyl group;

R^8 represents a $-C(=O)-NH_2$ group;

R^9 represents a hydrogen atom or a group selected from C_1-C_4-alkyl, (phenyl)-(C_1-C_2-alkyl)-, C_1-C_4-haloalkyl, C_2-C_3-hydroxyalkyl, (C_1-C_2-alkoxy)-C_2-alkyl-, ((C_1-C_2-alkyl)-C(=O)-O)-C_2-alkyl-, $-C(R^{18})(R^{19})-C(=O)-OR^{17}$, $-C(R^{18})(R^{19})-C(=O)-N(R^{20})(R^{21})$, $-C(=O)-N(R^{20})(R^{21})$ and phenyl,

wherein the phenyl group within said (phenyl)-(C_1-C_2-alkyl)- group and said phenyl group itself are optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a bromine atom, or a group selected from cyano, methyl, trifluoromethyl and methoxy;

R^{10} and R^{11} represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_2-alkyl, C_1-C_2-haloalkyl, C_2-C_3-hydroxyalkyl, (C_1-C_2-alkoxy)-C_2-alkyl-, ((R^{22})(R^{23})N)-C_2-alkyl, (C_3-C_7-cycloalkyl)-(C_1-C_2-alkyl)-, (C_1-C_2-alkyl)-C(=O)-, C_3-C_7-cycloalkyl, (C_3-C_7-cycloalkyl)-C(=O)-, (phenyl)-(C_1-C_2-alkyl)-, (phenyl)-(C_1-C_2-alkyl)-C(=O)- and (phenyl)-(C_1-C_2-alkyl)-O-C(=O)-,

wherein C_3-C_7-cycloalkyl, and the C_3-C_7-cycloalkyl within said (C_3-C_7-cycloalkyl)-(C_1-C_2-alkyl)- and (C_3-C_7-cycloalkyl)-C(=O)- groups are optionally substituted one or two times, each substituent independently selected from a fluorine atom or a group selected from cyano, C_1-C_2-alkyl and C_1-C_2-haloalkyl,

and wherein the phenyl groups within said (phenyl)-(C_1-C_2-alkyl)-, (phenyl)-(C_1-C_2-alkyl)-C(=O)- and (phenyl)-(C_1-C_2-alkyl)-O-C(=O)- groups are optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a bromine atom, or a group selected from methyl, trifluoromethyl and methoxy,

or

R^{10} and R^{11}, together with the nitrogen atom to which they are attached, represent a monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group, or a bicyclic nitrogen containing 5- to 10-membered heterocycloalkyl group, which are optionally substituted one, two or three times, each substituent independently selected from a halogen atom or a group selected from cyano, oxo, hydroxy, C_1-C_2-alkyl, C_1-C_2-haloalkyl, (C_1-C_2-alkyl)-C(=O)-, C_1-C_2-alkoxy, -N(R^{22})(R^{23}), and a monocyclic 4- to 7-membered heterocycloalkyl group;

R^{12} and R^{13} represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-hydroxyalkyl, (C_1-C_4-alkoxy)-C_2-C_3-alkyl-, (C_1-C_4-haloalkoxy)-C_2-C_3-alkyl-, (phenoxy)-C_2-C_3-alkyl-, C_3-C_7-cycloalkyl, monocyclic 4- to 7-membered heterocycloalkyl and (phenyl)-(C_1-C_3-alkyl)-,

wherein C_3-C_7-cycloalkyl and monocyclic 4- to 7-membered heterocycloalkyl are optionally substituted one or two times, each substituent independently selected from a halogen atom or a group selected from oxo, C_1-C_2-alkyl and (C_1-C_2-alkyl)-C(=O)-,

and wherein the phenyl groups within said (phenoxy)-C_2-C_3-alkyl- group and said (phenyl)-(C_1-C_3-alkyl)- group are optionally substituted one or two times, each substituent independently selected from fluorine atom, a chlorine atom and a bromine atom, or a group selected from cyano, methyl, trifluoromethyl and methoxy,

or

R^{12} and R^{13}, together with the nitrogen atom to which they are attached, represent a monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group which is optionally substituted one or two times, each substituent independently selected from a halogen atom or a group selected from oxo, C_1-C_2-alkyl and (C_1-C_2-alkyl)-C(=O)-;

R^{14} represents a group selected from C_1-C_2-alkyl, C_1-C_2-haloalkyl and phenyl,

wherein the phenyl group is optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a bromine atom, or a group selected from methyl, trifluoromethyl and methoxy;

R^{17} represents a C_1-C_4-alkyl group;

R^{18} and R^{19} represent, independently from each occurrence, a hydrogen atom or a C_1-C_2-alkyl group;

R^{20} represents a hydrogen atom or a group selected from C_1-C_6-alkyl, C_3-C_4-alkenyl, C_3-C_4-alkynyl, C_1-C_3-alkoxy, C_3-C_7-cycloalkyl, bicyclic C_5-C_{11}-cycloalkyl, adamantyl, monocyclic 4- to 7-membered heterocycloalkyl, bicyclic 5- to 10-membered heterocycloalkyl, phenyl, naphthyl, and 5- to 10-membered heteroaryl,

wherein said C_1-C_6-alkyl group is optionally substituted one, two or three times, each substituent independently selected from a halogen atom or a group selected from hydroxy, cyano, C_1-C_3-alkoxy, -N(R^{22})(R^{23}), C_3-C_7-cycloalkyl, bicyclic C_5-C_{11}-cycloalkyl, adamantyl, monocyclic 4- to 7-membered heterocycloalkyl, bicyclic 5- to 10-membered heterocycloalkyl, phenyl, and 5- to 10-membered heteroaryl, said phenyl and 5- to 10-membered heteroaryl substituents themselves being optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a bromine atom, or a group selected from methyl, trifluoromethyl and methoxy,

and wherein C_3-C_7-cycloalkyl, bicyclic C_5-C_{11}-cycloalkyl, adamantyl, monocyclic 4- to 7-membered heterocycloalkyl, bicyclic 5- to 10-membered heterocycloalkyl are optionally substituted one or two or three times, each substituent independently selected from a halogen atom or a group selected from cyano, oxo, hydroxy, C_1-C_2-alkyl and (C_1-C_2-alkyl)-C(=O)-,

and wherein said phenyl, naphthyl and 5- to 10-membered heteroaryl groups are optionally substituted one, two or three times, each substituent independently

selected from a halogen atom or a group selected from cyano, C_1-C_2-alkyl, C_1-C_2-haloalkyl, C_1-C_2-alkoxy, C_1-C_2-haloalkoxy, -N(R^{22})(R^{23}) and -C(=O)-N(R^{24})(R^{25}),

R^{21} represents a hydrogen atom or a C_1-C_2-alkyl group,

or

R^{20} and R^{21}, together with the nitrogen atom to which they are attached, represent a monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group which is optionally benzocondensed, and which is optionally substituted one, two or three times, each substituent independently selected from a halogen atom or a group selected from cyano, oxo, hydroxy, C_1-C_2-alkyl, C_1-C_2-haloalkyl, (phenyl)-(C_1-C_2-alkyl)-, (C_1-C_2-alkyl)-C(=O)-, C_3-C_4-cycloalkyl, C_1-C_2-alkoxy, C_1-C_2-haloalkoxy, -N(R^{22})(R^{23}) and -C(=O)-N(R^{24})(R^{25});

R^{22} and R^{23} represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_2-alkyl and (C_1-C_2-alkyl)-C(=O)-;

R^{24} and R^{25} represent, independently from each occurrence, a hydrogen atom or a C_1-C_2-alkyl group, and

n represents an integer 0, 1, or 2,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

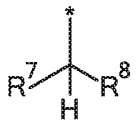
In accordance with a third embodiment of the first aspect, the present invention covers compounds of general formula (I), *supra*, in which:

R^1 represents a phenyl or pyridinyl group optionally substituted, one, two, or three times, each substituent independently selected from a fluorine atom, a chlorine atom and a bromine atom, or a group selected from hydroxy, cyano, C_1-C_4-alkyl, C_1-C_2-fluoroalkyl, C_1-C_2-alkoxy, (phenyl)-(C_1-C_2-alkoxy)-, C_1-C_2-fluoroalkoxy and -N(R^5)(R^6),

or two substituents attached to adjacent carbon atoms of said phenyl or pyridinyl group together form a bivalent group selected from –$(CH_2)_3$-, -O-CH_2-O- and -O-CF_2-O-,

or

R^1 represents a pyrazolyl group optionally substituted with one methyl group;

R^2 represents a group  ,

wherein "*" indicates the point of attachment to the nitrogen atom to which R^2 is attached;

R^3 represents a group selected from methyl and $-NH_2$;

R^4 represents a phenyl or pyridinyl group optionally substituted, one, two, or three times, each substituent independently selected from a halogen atom or a group selected from cyano, C_1-C_3-alkyl, $((R^9)O)$-(C_1-C_3-alkyl)-, C_1-C_3-fluoroalkyl, $-OR^9$, $-N(R^{10})(R^{11})$, $-C(=O)-N(R^{12})(R^{13})$, $S(=O)_n-R^{14}$ and $-C(=O)-OR^{17}$,

or two substituents attached to adjacent carbon atoms of said phenyl or pyridinyl group together form a bivalent group selected from $-(CH_2)_3-$, $-O-CH_2-O-$ and $-O-CF_2-O-$;

R^5 and R^6 represent, independently from each occurrence, a hydrogen atom or a C_1-C_2-alkyl group,

or

R^5 and R^6, together with the nitrogen atom to which they are attached, represent a monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group which is optionally substituted one or two times, each substituent independently selected from a fluorine atom or a group selected from hydroxy and C_1-C_2-alkyl;

R^7 represents a hydrogen atom or a C_1-C_2-alkyl group;

R^8 represents a $-C(=O)-NH_2$ group;

R^9 represents a hydrogen atom or a group selected from C_1-C_2-alkyl, benzyl, C_1-C_2-fluoroalkyl, C_2-hydroxyalkyl, (C_1-C_2-alkoxy)-C_2-alkyl-, ((C_1-C_2-alkyl)-C(=O)-O)-C_2-alkyl-, $-C(R^{18})(R^{19})-C(=O)-OR^{17}$, $-C(R^{18})(R^{19})-C(=O)-N(R^{20})(R^{21})$, $-C(=O)-N(R^{20})(R^{21})$ and phenyl,

wherein the phenyl group within said benzyl group and said phenyl group itself are optionally substituted one or two times, each substituent independently selected from a fluorine atom and a chlorine atom, or a group selected from cyano and methyl;

R^{10} and R^{11} represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_2-alkyl, C_1-C_2-fluoroalkyl, (C_3-C_5-cycloalkyl)-(C_1-C_2-alkyl)- (C_1-C_2-alkyl)-C(=O)-, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-(C=O)-, (phenyl)-(C_1-C_2-alkyl)-, (phenyl)-(C_1-C_2-alkyl)-C(=O)- and (phenyl)-(C_1-C_2-alkyl)-O-C(=O)-,

wherein C_3-C_7-cycloalkyl, and the C_3-C_5-cycloalkyl within said (C_3-C_5-cycloalkyl)-(C_1-C_2-alkyl)- and the C_3-C_7-cycloalkyl within the C_3-C_7-cycloalkyl-(C=O)- groups are optionally substituted one or two times, each substituent independently selected from a fluorine atom or a group selected from cyano, C_1-C_2-alkyl and C_1-C_2-fluoroalkyl,

and wherein the phenyl groups within said (phenyl)-(C_1-C_2-alkyl)-, (phenyl)-(C_1-C_2-alkyl)-C(=O)- and (phenyl)-(C_1-C_2-alkyl)-O-C(=O)- groups are optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a methyl group,

or

R^{10} and R^{11}, together with the nitrogen atom to which they are attached, represent a monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group which is optionally substituted one or two times, each substituent independently selected from a fluorine atom or a group selected from cyano, oxo, C_1-C_2-alkyl, C_1-C_2-fluoroalkyl and (C_1-C_2-alkyl)-C(=O)-;

R^{12} and R^{13} represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_4-alkyl, C_1-C_4-fluoroalkyl, C_1-C_4-hydroxyalkyl, (C_1-C_4-alkoxy)-C_2-C_3-alkyl-, (C_1-C_2-fluoroalkoxy)-C_2-C_3-alkyl-, (phenoxy)-C_2-C_3-alkyl-, C_3-C_7-cycloalkyl, monocyclic 4- to 7-membered heterocycloalkyl and (phenyl)-(C_1-C_2-alkyl)-,

wherein C_3-C_7-cycloalkyl and monocyclic 4- to 7-membered heterocycloalkyl are optionally substituted one or two times, each substituent independently selected from a fluorine atom or a group selected from oxo, C_1-C_2-alkyl and (C_1-C_2-alkyl)-C(=O)-,

and wherein the phenyl groups within said (phenoxy)-C_2-C_3-alkyl- group and said (phenyl)-(C_1-C_2-alkyl)- group are optionally substituted one or two times, each substituent independently selected from a fluorine atom and a chlorine atom, or a group selected from methyl, trifluoromethyl and methoxy,

or

R^{12} and R^{13}, together with the nitrogen atom to which they are attached, represent a monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group which is optionally

substituted one or two times, each substituent independently selected from a halogen atom or a group selected from oxo, C_1-C_2-alkyl and (C_1-C_2-alkyl)-C(=O)-;

R^{14} represents a group selected from methyl and trifluoromethyl;

R^{17} represents a C_1-C_2-alkyl group;

R^{18} and R^{19} represent, independently from each occurrence, a hydrogen atom or a methyl group;

R^{20} represents a hydrogen atom or a group selected from optionally substituted C_1-C_3-alkyl, unsubstituted C_4-C_6-alkyl, prop-2-ynyl, methoxy, C_3-C_6-cycloalkyl, adamantyl, monocyclic 4- to 7-membered heterocycloalkyl, phenyl, and 5- to 10-membered heteroaryl,

wherein said C_1-C_3-alkyl group is optionally substituted one, two or three times, each substituent independently selected from a halogen atom or a group selected from hydroxy, cyano, C_1-C_3-alkoxy, -N(R^{22})(R^{23}), C_3-C_6-cycloalkyl, adamantyl, monocyclic 4- to 7-membered heterocycloalkyl, phenyl, and 5- to 10-membered heteroaryl, said phenyl and 5- to 10-membered heteroaryl substituents themselves being optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a methyl group,

and wherein said C_3-C_6-cycloalkyl, adamantyl and monocyclic 4- to 7-membered heterocycloalkyl groups are optionally substituted one or two or three times, each substituent independently selected from a fluorine atom or a group selected from oxo, C_1-C_2-alkyl and (C_1-C_2-alkyl)-C(=O)-,

and wherein said phenyl and 5- to 10-membered heteroaryl groups are optionally substituted one, two or three times, each substituent independently selected from a fluorine atom and a chlorine atom or a group selected from cyano, C_1-C_2-alkyl, C_1-C_2-fluoroalkyl, C_1-C_2-alkoxy, C_1-C_2-fluoroalkoxy, -N(R^{22})(R^{23}) and -C(=O)-N(R^{24})(R^{25}),

R^{21} represents a hydrogen atom or a C_1-C_2-alkyl group,

or

R^{20} and R^{21}, together with the nitrogen atom to which they are attached, represent a monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group which is optionally benzocondensed, and which is optionally substituted one, two or three times, each substituent independently selected from a halogen atom or a group selected from cyano,

oxo, hydroxy, C_1-C_2-alkyl, C_1-C_2-fluoroalkyl, benzyl, (C_1-C_2-alkyl)-C(=O)-, C_3-C_4-cycloalkyl, C_1-C_2-alkoxy, C_1-C_2-fluoroalkoxy, -N(R^{22})(R^{23}) and -C(=O)-N(R^{24})(R^{25});

R^{22} and R^{23} represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_2-alkyl and (C_1-C_2-alkyl)-C(=O)-;

R^{24} and R^{25} represent, independently from each occurrence, a hydrogen atom or a C_1-C_2-alkyl group, and

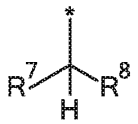
n represents an integer 2,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In accordance with a fourth embodiment of the first aspect, the present invention covers compounds of general formula (I), *supra*, in which:

R^1 represents a phenyl or pyridinyl group optionally substituted, one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a bromine atom, or a group selected from cyano, methyl, difluoromethyl, trifluoromethyl, methoxy, benzyloxy, difluoromethoxy and trifluoromethoxy,

or two substituents attached to adjacent carbon atoms of said phenyl or pyridinyl group together form a bivalent group -O-CF_2-O-;

R^2 represents a group  ,

wherein "*" indicates the point of attachment to the nitrogen atom to which R^2 is attached;

R^3 represents a group selected from methyl and -NH_2;

R^4 represents a phenyl or pyridinyl group optionally substituted, one or two times, each substituent independently selected from a halogen atom or a group selected from C_1-C_2-alkyl, C_1-C_2-fluoroalkyl, -OR^9, -N(R^{10})(R^{11}), -C(=O)-N(R^{12})(R^{13}) and -C(=O)-OR^{17};

R^7 represents a hydrogen atom or a C_1-C_2-alkyl group;

R^8 represents a -C(=O)-NH_2 group;

R^9 represents a hydrogen atom or a group selected from C_1-C_2-alkyl, benzyl, C_1-C_2-fluoroalkyl, (C_1-C_2-alkoxy)-C_2-alkyl-, ((C_1-C_2-alkyl)-C(=O)-O)-C_2-alkyl-, -C(R^{18})(R^{19})-C(=O)-N(R^{20})(R^{21}), -C(=O)-N(R^{20})(R^{21}) and phenyl,

wherein the phenyl group within said benzyl group and said phenyl group itself are optionally substituted one or two times, each substituent independently selected from a fluorine atom and a chlorine atom, or a group selected from cyano and methyl;

R^{10} and R^{11} represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_2-alkyl, (C_3-C_5-cycloalkyl)-(C_1-C_2-alkyl)-, C_3-C_7-cycloalkyl and (phenyl)-(C_1-C_2-alkyl)-O-C(=O)-,

wherein C_3-C_7-cycloalkyl, and the C_3-C_5-cycloalkyl within said (C_3-C_5-cycloalkyl)-(C_1-C_2-alkyl)- group are optionally substituted one or two times, each substituent independently selected from a fluorine atom or a group selected from cyano, methyl and C_1-fluoroalkyl,

and wherein the phenyl group within said (phenyl)-(C_1-C_2-alkyl)-O-C(=O)- group is optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a methyl group,

or

R^{10} and R^{11}, together with the nitrogen atom to which they are attached, represent a monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group which is optionally substituted one or two times, each substituent independently selected from a fluorine atom or a group selected from cyano, methyl and C_1-fluoroalkyl;

R^{12} and R^{13} represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_4-alkyl, C_1-C_2-fluoroalkyl, C_1-C_2-hydroxyalkyl, (C_1-C_4-alkoxy)-C_2-C_3-alkyl-, (C_1-C_2-fluoroalkoxy)-C_2-C_3-alkyl-, (phenoxy)-C_2-C_3-alkyl-, C_3-C_7-cycloalkyl and (phenyl)-(C_1-C_2-alkyl)-,

wherein C_3-C_7-cycloalkyl is optionally substituted one or two times, each substituent independently selected from a fluorine atom or a methyl group,

and wherein the phenyl groups within said (phenoxy)-C_2-C_3-alkyl- group and said (phenyl)-(C_1-C_2-alkyl)- group are optionally substituted one or two times, each substituent independently selected from a fluorine atom and a chlorine atom, or a group selected from methyl, trifluoromethyl and methoxy;

R^{17} represents a C_1-C_2-alkyl group;

R^{18} and R^{19} represent, independently from each occurrence, a hydrogen atom or a methyl group;

R^{20} represents a hydrogen atom or a group selected from C_1-C_3-alkyl and phenyl,

wherein said C_1-C_3-alkyl group is optionally substituted one or two times, each substituent independently selected from a fluorine atom or a group selected from hydroxy, C_1-C_3-alkoxy and phenyl, said phenyl itself being optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a methyl group,

and wherein said phenyl group is optionally substituted one, two or three times, each substituent independently selected from a fluorine atom and a chlorine atom or a group selected from methyl, trifluoromethyl, methoxy and trifluoromethoxy, and

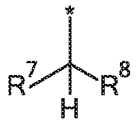
R^{21} represents a hydrogen atom or a C_1-C_2-alkyl group,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In accordance with a fifth embodiment of the first aspect, the present invention covers compounds of general formula (I), *supra*, in which:

R^1 represents a phenyl or pyridinyl group optionally substituted, one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a bromine atom, or a group selected from cyano, difluoromethyl, trifluoromethyl, methoxy, benzyloxy, difluoromethoxy and trifluoromethoxy,

or two substituents attached to adjacent carbon atoms of said phenyl or pyridinyl group together form a bivalent group -O-CF_2-O-;

R^2 represents a group  ,

wherein "*" indicates the point of attachment to the nitrogen atom to which R^2 is attached;

R^3 represents a group selected from methyl and -NH_2;

R^4 represents a phenyl or pyridinyl group optionally substituted, one or two times, each substituent independently selected from a halogen atom or a group selected from C_1-C_2-alkyl, C_1-C_2-fluoroalkyl, -OR^9, -$N(R^{10})(R^{11})$, -$C(=O)$-$N(R^{12})(R^{13})$ and -$C(=O)$-OR^{17};

R^7 represents a hydrogen atom or a C_1-C_2-alkyl group;

R^8 represents a -C(=O)-NH_2 group;

R^9 represents a hydrogen atom or a group selected from C_1-C_2-alkyl, benzyl, C_1-C_2-fluoroalkyl, (C_1-C_2-alkoxy)-C_2-alkyl-, ((C_1-C_2-alkyl)-C(=O)-O)-C_2-alkyl-, -C(R^{18})(R^{19})-C(=O)-N(R^{20})(R^{21}), -C(=O)-N(R^{20})(R^{21}) and phenyl,

wherein the phenyl group within said benzyl group and said phenyl group itself are optionally substituted one or two times, each substituent independently selected from a fluorine atom and a chlorine atom, or a group selected from cyano and methyl;

R^{10} and R^{11} represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_2-alkyl, (C_3-C_5-cycloalkyl)-(C_1-C_2-alkyl)-, C_3-C_7-cycloalkyl and (phenyl)-(C_1-C_2-alkyl)-O-C(=O)-,

wherein C_3-C_7-cycloalkyl, and the C_3-C_5-cycloalkyl within said (C_3-C_5-cycloalkyl)-(C_1-C_2-alkyl)- group are optionally substituted one or two times, each substituent independently selected from a fluorine atom or a group selected from cyano, methyl and C_1-fluoroalkyl,

and wherein the phenyl group within said (phenyl)-(C_1-C_2-alkyl)-O-C(=O)- group is optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a methyl group,

or

R^{10} and R^{11}, together with the nitrogen atom to which they are attached, represent a monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group which is optionally substituted one or two times, each substituent independently selected from a fluorine atom or a group selected from cyano, methyl and C_1-fluoroalkyl;

R^{12} and R^{13} represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_4-alkyl, C_1-C_2-fluoroalkyl, C_1-C_2-hydroxyalkyl, (C_1-C_4-alkoxy)-C_2-C_3-alkyl-, (C_1-C_2-fluoroalkoxy)-C_2-C_3-alkyl-, (phenoxy)-C_2-C_3-alkyl-, C_3-C_7-cycloalkyl and (phenyl)-(C_1-C_2-alkyl)-,

wherein C_3-C_7-cycloalkyl is optionally substituted one or two times, each substituent independently selected from a fluorine atom or a methyl group,

and wherein the phenyl groups within said (phenoxy)-C_2-C_3-alkyl- group and said (phenyl)-(C_1-C_2-alkyl)- group are optionally substituted one or two times, each substituent independently selected from a fluorine atom and a chlorine atom, or a group selected from methyl, trifluoromethyl and methoxy;

R^{17} represents a C_1-C_2-alkyl group;

R^{18} and R^{19} represent, independently from each occurrence, a hydrogen atom or a methyl group;

R^{20} represents a hydrogen atom or a group selected from C_1-C_3-alkyl and phenyl,

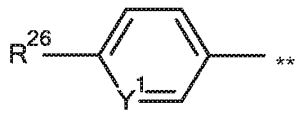
wherein said C_1-C_3-alkyl group is optionally substituted one or two times, each substituent independently selected from a fluorine atom or a group selected from hydroxy, C_1-C_3-alkoxy and phenyl, said phenyl itself being optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a methyl group,

and wherein said phenyl group is optionally substituted one, two or three times, each substituent independently selected from a fluorine atom and a chlorine atom or a group selected from methyl, trifluoromethyl, methoxy and trifluoromethoxy, and

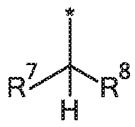
R^{21} represents a hydrogen atom or a C_1-C_2-alkyl group,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In accordance with a sixth embodiment of the first aspect, the present invention covers compounds of general formula (I), *supra*, in which:

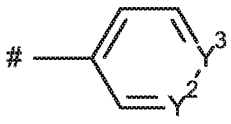
R^1 represents a group  ,

wherein "**" indicates the point of attachment to the nitrogen atom to which R^1 is attached;

R^2 represents a group  ,

wherein "*" indicates the point of attachment to the nitrogen atom to which R^2 is attached;

R^3 represents a group selected from methyl and $-NH_2$;

R^4 represents a group 

wherein "#" indicates the point of attachment to the carbonyl group to which R^4 is attached;

R^7 represents a hydrogen atom or a C_1-C_2-alkyl group;

R^8 represents a -C(=O)-NH_2 group;

R^9 represents a hydrogen atom or a group selected from C_1-C_2-alkyl, benzyl, C_1-C_2-fluoroalkyl, (C_1-C_2-alkoxy)-C_2-alkyl-, ((C_1-C_2-alkyl)-C(=O)-O)-C_2-alkyl-, -C(R^{18})(R^{19})-C(=O)-N(R^{20})(R^{21}), -C(=O)-N(R^{20})(R^{21}) and phenyl,

wherein the phenyl group within said benzyl group and said phenyl group itself are optionally substituted one or two times, each substituent independently selected from a fluorine atom and a chlorine atom, or a group selected from cyano and methyl;

R^{10} and R^{11} represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_2-alkyl, C_3-C_7-cycloalkyl and (benzyl)-O-C(=O)-,

wherein C_3-C_7-cycloalkyl is optionally substituted one or two times, each substituent independently selected from a fluorine atom or a group selected from methyl and trifluoromethyl,

and wherein the phenyl group within said (benzyl)-O-C(=O)- group is optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a methyl group,

or

R^{10} and R^{11}, together with the nitrogen atom to which they are attached, represent a monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group which is optionally substituted one or two times, each substituent independently selected from a fluorine atom or a group selected from cyano, methyl and trifluoromethyl;

R^{12} and R^{13} represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_4-alkyl, C_1-C_2-fluoroalkyl, C_1-C_2-hydroxyalkyl, (C_1-C_4-alkoxy)-C_2-alkyl-, (C_1-C_2-fluoroalkoxy)-C_2-alkyl-, (phenoxy)-C_2-alkyl-, C_3-C_7-cycloalkyl and (phenyl)-(C_1-C_2-alkyl)-,

wherein the phenyl groups within said (phenoxy)-C_2-alkyl- group and said (phenyl)-(C_1-C_2-alkyl)- group are optionally substituted one or two times, each substituent independently selected from fluorine atom and a chlorine atom, or a group selected from methyl, trifluoromethyl and methoxy;

R^{17} represents a C_1-C_2-alkyl group;

R^{18} and R^{19} represent, independently from each occurrence, a hydrogen atom or a methyl group;

R^{20} represents a group selected from benzyl and phenyl,

wherein said phenyl group, and the phenyl group within said benzyl group, is optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a methyl group,

R^{21} represents a hydrogen atom or a methyl group,

Y^1 represents -C(H)=, -C(F)=, -C(Cl)=, -C(CN)= or -N=;

Y^2 represents -C(H)= or -N=;

Y^3 represents -C(R^{27})= or -N=,

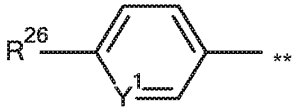
with the proviso that if Y^2 represents -N=, Y^3 represents -C(R^{27})=, and if Y^3 represents -N=, Y^2 represents -C(H)=;

R^{26} represents a fluorine atom, a chlorine atom or a bromine atom, or a group selected from methyl, difluoromethyl, trifluoromethyl, methoxy, benzyloxy, difluoromethoxy and trifluoromethoxy, and

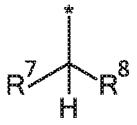
R^{27} represents a halogen atom or a group selected from C_1-C_2-alkyl, C_1-C_2-fluoroalkyl, -OR^9, -N(R^{10})(R^{11}), -C(=O)-N(R^{12})(R^{13}) and -C(=O)-OR^{17},

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In accordance with a seventh embodiment of the first aspect, the present invention covers compounds of general formula (I), *supra*, in which:

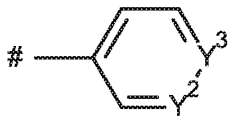
R^1 represents a group  ,

wherein "**" indicates the point of attachment to the nitrogen atom to which R^1 is attached;

R^2 represents a group  ,

wherein "*" indicates the point of attachment to the nitrogen atom to which R^2 is attached;

R^3 represents a group selected from methyl and $-NH_2$;

R^4 represents a group 

wherein "#" indicates the point of attachment to the carbonyl group to which R^4 is attached;

R^7 represents a hydrogen atom or a C_1-C_2-alkyl group;

R^8 represents a $-C(=O)-NH_2$ group;

R^9 represents a hydrogen atom or a group selected from C_1-C_2-alkyl, benzyl, C_1-C_2-fluoroalkyl and phenyl,

wherein the phenyl group within said benzyl group and said phenyl group itself are optionally substituted one or two times, each substituent independently selected from a fluorine atom and a chlorine atom, or a group selected from cyano and methyl;

R^{10} and R^{11} represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_2-alkyl and (benzyl)-O-C(=O)-,

and wherein the phenyl group within said (benzyl)-O-C(=O)- group is optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a methyl group,

or

R^{10} and R^{11}, together with the nitrogen atom to which they are attached, represent a monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group which is optionally substituted one or two times, each substituent independently selected from a fluorine atom or a group selected from cyano, methyl and trifluoromethyl;

R^{12} and R^{13} represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_2-alkyl, (C_1-C_4-alkoxy)-C_2-alkyl-, (C_1-C_2-fluoroalkoxy)-C_2-alkyl-, (phenoxy)-C_2-alkyl-, C_3-C_7-cycloalkyl and (phenyl)-(C_1-C_2-alkyl)-;

Y^1 represents -C(H)=, -C(F)=, -C(Cl)= or -N=;

Y^2 represents -C(H)= or -N=;

Y^3 represents $-C(R^{27})=$ or -N=,

with the proviso that if Y^2 represents -N=, Y^3 represents $-C(R^{27})=$, and if Y^3 represents -N=, Y^2 represents -C(H)=;

R^{26} represents a fluorine atom, a chlorine atom or a bromine atom, or a group selected from difluoromethyl, methoxy, benzyloxy, difluoromethoxy and trifluoromethoxy, and

R^{27} represents a halogen atom or a group selected from $-OR^9$, $-N(R^{10})(R^{11})$ and $-C(=O)-N(R^{12})(R^{13})$,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In accordance with an eigth embodiment of the first aspect, the present invention covers compounds of general formula (I):

in which :

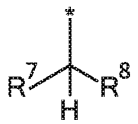
R^1 represents a phenyl or 6-membered heteroaryl group optionally substituted, one, two, or three times, each substituent independently selected from a halogen atom or a group selected from cyano, nitro, C_1-C_6-alkyl, (phenyl)-(C_1-C_3-alkyl)-, C_1-C_6-haloalkyl, C_1-C_6-alkoxy, (phenyl)-(C_1-C_3-alkoxy)-, C_1-C_6-haloalkoxy, $-N(R^5)(R^6)$,

wherein the phenyl groups in said (phenyl)-(C_1-C_3-alkyl)- and (phenyl)-(C_1-C_3-alkoxy)-groups are optionally substituted one or two times, each substituent independently selected from a halogen atom or a group selected from cyano, methyl, ethyl, trifluoromethyl, methoxy, ethoxy, dimethylamino and trifluoromethoxy,

or two substituents attached to adjacent carbon atoms of said phenyl or 6-membered heteroaryl group together form a bivalent group selected from $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_2-O-$, $-(CH_2)_3-O-$, $-CH_2-O-CH_2-$, $-(CH_2)_2-O-CH_2-$, $-O-CH_2-O-$, $-O-CH_2-CH_2-O-$, $-O-CF_2-O-$, $-O-CH_2-CF_2-O-$, and $-O-CF_2-CF_2-O-$,

or

R^1 represents a 5-membered heteroaryl group optionally substituted one or two times, each substituent independently selected from a halogen atom or a group selected from cyano, C_1-C_3-alkyl, and C_1-C_3-alkoxy;

R^2 represents a group  ,

wherein "*" indicates the point of attachment to the nitrogen atom to which R^2 is attached;

R^3 represents a group selected from methyl and $-NH_2$;

R^4 represents a phenyl or 6-membered heteroaryl group optionally substituted, one, two, or three times, each substituent independently selected from a halogen atom or a group selected from cyano, nitro, C_1-C_6-alkyl, (phenyl)-(C_1-C_3-alkyl)-, (5-membered heteroaryl)-(C_1-C_3-alkyl)-, C_1-C_6-hydroxyalkyl, C_1-C_6-haloalkyl, $-OR^9$, $-N(R^{10})(R^{11})$, $-C(=O)-N(R^{12})(R^{13})$, $S(=O)_n-R^{14}$, and a 5-membered heteroaryl group which itself is optionally substituted with one or two methyl groups,

or two substituents attached to adjacent carbon atoms of said phenyl or 6-membered heteroaryl group together form a bivalent group selected from $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_2-O-$, $-(CH_2)_3-O-$, $-CH_2-O-CH_2-$, $-(CH_2)_2-O-CH_2-$, $-O-CH_2-O-$, $-O-CH_2-CH_2-O-$, $-O-CF_2-O-$, $-O-CH_2-CF_2-O-$, and $-O-CF_2-CF_2-O-$;

R^5 and R^6 represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_4-alkyl, (C_1-C_4-alkyl)-C(=O)-, C_3-C_4-cycloalkyl and (phenyl)-(C_1-C_3-alkyl)-,

or

R^5 and R^6, together with the nitrogen atom to which they are attached, represent a monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group which is optionally substituted one, two or three times, each substituent independently selected from a halogen atom or a group selected from oxo, hydroxy, C_1-C_4-alkyl, (C_1-C_4-alkyl)-C(=O)-, C_3-C_4-cycloalkyl and C_1-C_4-alkoxy;

R^7 represents a hydrogen atom or a C_1-C_2-alkyl group;

R^8 represents a group selected from $-C(=O)-NH_2$ and $-S(=O)_2-NH_2$;

R^9 represents a hydrogen atom or a group selected from C_1-C_6-alkyl, (phenyl)-(C_1-C_3-alkyl)-, C_1-C_6-haloalkyl, C_2-C_4-hydroxyalkyl, (C_1-C_3-alkoxy)-C_2-C_3-alkyl-, ((C_1-C_3-alkyl)-C(=O)-O)-C_2-C_3-alkyl-, $-C(R^{18})(R^{19})-C(=O)-OR^{17}$, $-C(R^{18})(R^{19})-C(=O)-N(R^{20})(R^{21})$ and phenyl,

wherein the phenyl group within said (phenyl)-(C_1-C_3-alkyl)- group and said phenyl group itself are optionally substituted one or two times, each substituent independently selected from a halogen atom or a group selected from cyano, methyl, ethyl, trifluoromethyl, methoxy, ethoxy, dimethylamino and trifluoromethoxy;

R^{10} and R^{11} represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_2-C_4-hydroxyalkyl, (C_1-C_3-alkoxy)-C_2-C_3-alkyl-, ((R^{22})(R^{23})N)-C_2-C_3-alkyl, (C_1-C_4-alkyl)-C(=O)-, C_3-C_7-cycloalkyl, (C_3-C_7-cycloalkyl)-C(=O)-, (phenyl)-(C_1-C_3-alkyl)-, (phenyl)-(C_1-C_3-alkyl)-C(=O)- and (phenyl)-(C_1-C_3-alkyl)-O-C(=O)-,

wherein the phenyl groups within said (phenyl)-(C_1-C_3-alkyl)-, (phenyl)-(C_1-C_3-alkyl)-C(=O)- and (phenyl)-(C_1-C_3-alkyl)-O-C(=O)- groups are optionally substituted one or two times, each substituent independently selected from a halogen atom or a group selected from cyano, methyl, ethyl, trifluoromethyl, methoxy, ethoxy, dimethylamino and trifluoromethoxy,

or

R^{10} and R^{11}, together with the nitrogen atom to which they are attached, represent a monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group, or a bicyclic nitrogen containing 6- to 11-membered heterocycloalkyl group, which are optionally substituted one, two or three times, each substituent independently selected from a halogen atom or a group selected from cyano, oxo, hydroxy, C_1-C_4-alkyl, C_1-C_4-haloalkyl, (C_1-C_4-alkyl)-C(=O)-, C_3-C_7-cycloalkyl, C_1-C_4-alkoxy, -N(R^{22})(R^{23}), and a monocyclic 4- to 7-membered heterocycloalkyl group;

R^{12} and R^{13} represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-hydroxyalkyl, (C_1-C_3-alkoxy)-C_2-C_3-alkyl-, C_3-C_7-cycloalkyl, monocyclic 4- to 7-membered heterocycloalkyl and (phenyl)-(C_1-C_3-alkyl)-,

wherein C_3-C_7-cycloalkyl and monocyclic 4- to 7-membered heterocycloalkyl are optionally substituted one, two or three times, each substituent independently selected from a halogen atom or a group selected from oxo, hydroxy, C_1-C_4-alkyl, (C_1-C_4-alkyl)-C(=O)-, C_3-C_4-cycloalkyl and C_1-C_4-alkoxy,

or

R^{12} and R^{13}, together with the nitrogen atom to which they are attached, represent a monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group which is optionally substituted one, two or three times, each substituent independently selected from a halogen atom or a group selected from oxo, hydroxy, C_1-C_4-alkyl, (C_1-C_4-alkyl)-C(=O)-, C_3-C_4-cycloalkyl and C_1-C_4-alkoxy;

R^{14} represents a group selected from C_1-C_4-alkyl and C_1-C_4-haloalkyl;

R^{17} represents a C_1-C_4-alkyl group;

R^{18} and R^{19} represent, independently from each occurrence, a hydrogen atom or a C_1-C_4-alkyl group;

R^{20} represents a hydrogen atom or a group selected from C_1-C_6-alkyl, C_3-C_4-alkenyl, C_3-C_4-alkynyl, C_1-C_3-alkoxy, C_3-C_7-cycloalkyl, bicyclic C_6-C_{11}-cycloalkyl, adamantyl, monocyclic 4- to 7-membered heterocycloalkyl, bicyclic 6- to 11-membered heterocycloalkyl, phenyl, naphthyl, and 5- to 10-membered heteroaryl,

wherein said C_1-C_6-alkyl group is optionally substituted one, two or three times, each substituent independently selected from a halogen atom or a group selected from hydroxy, cyano, C_1-C_3-alkoxy, -$N(R^{22})(R^{23})$, C_3-C_7-cycloalkyl, bicyclic C_6-C_{11}-cycloalkyl, adamantyl, monocyclic 4- to 7-membered heterocycloalkyl, bicyclic 6- to 11-membered heterocycloalkyl, phenyl, and 5- to 10-membered heteroaryl, said phenyl and 5- to 10-membered heteroaryl substituents themselves being optionally substituted one or two times, each substituent independently selected from a halogen atom or a group selected from cyano, methyl, ethyl, trifluoromethyl, methoxy, ethoxy, dimethylamino and trifluoromethoxy,

wherein C_3-C_7-cycloalkyl, bicyclic C_6-C_{11}-cycloalkyl, adamantyl, monocyclic 4- to 7-membered heterocycloalkyl and bicyclic 6- to 11-membered heterocycloalkyl are optionally substituted one, two or three times, each substituent independently selected from a halogen atom or a group selected from cyano, oxo, hydroxy, C_1-C_4-alkyl, (C_1-C_4-alkyl)-C(=O)-, C_3-C_4-cycloalkyl and C_1-C_4-alkoxy,

and wherein said phenyl, naphthyl and 5- to 10-membered heteroaryl groups are optionally substituted one, two or three times, each substituent independently selected from a halogen atom or a group selected from cyano, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, -$N(R^{22})(R^{23})$ and -C(=O)-$N(R^{24})(R^{25})$,

R^{21} represents a hydrogen atom or a C_1-C_4-alkyl group,

or

R^{20} and R^{21}, together with the nitrogen atom to which they are attached, represent a monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group which is optionally benzocondensed, and which is optionally substituted one, two or three times, each substituent independently selected from a halogen atom or a group selected from cyano, oxo, hydroxy, C_1-C_4-alkyl, C_1-C_4-haloalkyl, (phenyl)-(C_1-C_3-alkyl)-, (C_1-C_4-alkyl)-C(=O)-, C_3-C_4-cycloalkyl, C_1-C_4-alkoxy, C_1-C_3-haloalkoxy, -$N(R^{22})(R^{23})$ and -C(=O)-$N(R^{24})(R^{25})$;

R^{22} and R^{23} represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_2-alkyl and (C_1-C_2-alkyl)-C(=O)-;

R^{24} and R^{25} represent, independently from each occurrence, a hydrogen atom or a C_1-C_4-alkyl group, and

n represents an integer 0, 1, or 2,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In accordance with a ninth embodiment of the first aspect, the present invention covers compounds of general formula (I), *supra*, in which:

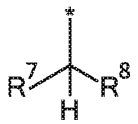
R^1 represents a phenyl or pyridinyl group optionally substituted, one, two, or three times, each substituent independently selected from a halogen atom or a group selected from cyano, nitro, C_1-C_4-alkyl, (phenyl)-(C_1-C_2-alkyl)-, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, (phenyl)-(C_1-C_2-alkoxy)-, C_1-C_4-haloalkoxy, -N(R^5)(R^6),

wherein the phenyl groups in said (phenyl)-(C_1-C_2-alkyl)- and (phenyl)-(C_1-C_2-alkoxy)-groups are optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a bromine atom, or a group selected from methyl, trifluoromethyl and methoxy,

or two substituents attached to adjacent carbon atoms of said phenyl or pyridinyl group together form a bivalent group selected from –$(CH_2)_3$-, -$(CH_2)_4$-, -$(CH_2)_2$-O-, -$(CH_2)_3$-O-, -CH_2-O-CH_2-, -O-CH_2-O-, -O-CH_2-CH_2-O- and -O-CF_2-O-,

or

R^1 represents a pyrazolyl group optionally substituted one or two times, each substituent independently selected from a halogen atom or a group selected from cyano, C_1-C_2-alkyl, and C_1-C_2-alkoxy;

R^2 represents a group  ,

wherein "*" indicates the point of attachment to the nitrogen atom to which R^2 is attached;

R^3 represents a group selected from methyl and $-NH_2$;

R^4 represents a phenyl or pyridinyl group optionally substituted, one, two, or three times, each substituent independently selected from a halogen atom or a group selected from cyano, nitro, C_1-C_4-alkyl, (phenyl)-(C_1-C_2-alkyl)-, (5-membered heteroaryl)-(C_1-C_2-alkyl)-, C_1-C_4-hydroxyalkyl, C_1-C_4-haloalkyl, $-OR^9$, $-N(R^{10})(R^{11})$, $-C(=O)-N(R^{12})(R^{13})$, $S(=O)_n-R^{14}$, and a 5-membered heteroaryl group which itself is optionally substituted with one or two methyl groups,

or two substituents attached to adjacent carbon atoms of said phenyl or pyridinyl group together form a bivalent group selected from $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_2-O-$, $-(CH_2)_3-O-$, $-CH_2-O-CH_2-$, $-O-CH_2-O-$, $-O-CH_2-CH_2-O-$ and $-O-CF_2-O-$;

R^5 and R^6 represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_2-alkyl and (C_1-C_2-alkyl)-C(=O)-,

or

R^5 and R^6, together with the nitrogen atom to which they are attached, represent a monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group which is optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a bromine atom, or a group selected from oxo, hydroxy, C_1-C_2-alkyl and (C_1-C_2-alkyl)-C(=O)-;

R^7 represents a hydrogen atom or a C_1-C_2-alkyl group;

R^8 represents a $-C(=O)-NH_2$ group;

R^9 represents a hydrogen atom or a group selected from C_1-C_4-alkyl, (phenyl)-(C_1-C_2-alkyl)-, C_1-C_4-haloalkyl, C_2-C_3-hydroxyalkyl, (C_1-C_2-alkoxy)-C_2-alkyl-, ((C_1-C_2-alkyl)-C(=O)-O)-C_2-alkyl-, $-C(R^{18})(R^{19})-C(=O)-OR^{17}$, $-C(R^{18})(R^{19})-C(=O)-N(R^{20})(R^{21})$ and phenyl,

wherein the phenyl group within said (phenyl)-(C_1-C_2-alkyl)- group and said phenyl group itself are optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a bromine atom, or a group selected from methyl, trifluoromethyl and methoxy;

R^{10} and R^{11} represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_2-alkyl, C_1-C_2-haloalkyl, C_2-C_3-hydroxyalkyl, (C_1-C_2-alkoxy)-C_2-alkyl-, ((R^{22})(R^{23})N)-C_2-alkyl, (C_1-C_2-alkyl)-C(=O)-, C_3-C_5-cycloalkyl, (C_3-C_5-cycloalkyl)-C(=O)-, (phenyl)-(C_1-C_2-alkyl)-, (phenyl)-(C_1-C_2-alkyl)-C(=O)- and (phenyl)-(C_1-C_2-alkyl)-O-C(=O)-,

wherein the phenyl groups within said (phenyl)-(C_1-C_2-alkyl)-, (phenyl)-(C_1-C_2-alkyl)-C(=O)- and (phenyl)-(C_1-C_2-alkyl)-O-C(=O)- groups are optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a bromine atom, or a group selected from methyl, trifluoromethyl and methoxy,

or

R^{10} and R^{11}, together with the nitrogen atom to which they are attached, represent a monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group, or a bicyclic nitrogen containing 6- to 10-membered heterocycloalkyl group, which are optionally substituted one, two or three times, each substituent independently selected from a halogen atom or a group selected from cyano, oxo, hydroxy, C_1-C_2-alkyl, C_1-C_2-haloalkyl, (C_1-C_2-alkyl)-C(=O)-, C_1-C_2-alkoxy, -N(R^{22})(R^{23}), and a monocyclic 4- to 7-membered heterocycloalkyl group;

R^{12} and R^{13} represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-hydroxyalkyl, (C_1-C_2-alkoxy)-C_2-C_3-alkyl-, C_3-C_7-cycloalkyl, monocyclic 4- to 7-membered heterocycloalkyl and (phenyl)-(C_1-C_3-alkyl)-,

wherein C_3-C_7-cycloalkyl and monocyclic 4- to 7-membered heterocycloalkyl are optionally substitueted one or two times, each substituent independently selected from a halogen atom or a group selected from oxo, C_1-C_2-alkyl and (C_1-C_2-alkyl)-C(=O)-,

or

R^{12} and R^{13}, together with the nitrogen atom to which they are attached, represent a monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group which is optionally substituted one or two times, each substituent independently selected from a halogen atom or a group selected from oxo, C_1-C_2-alkyl and (C_1-C_2-alkyl)-C(=O)-;

R^{14} represents a group selected from C_1-C_2-alkyl and C_1-C_2-haloalkyl;

R^{17} represents a C_1-C_4-alkyl group;

R^{18} and R^{19} represent, independently from each occurrence, a hydrogen atom or a C_1-C_2-alkyl group;

R^{20} represents a hydrogen atom or a group selected from C_1-C_6-alkyl, C_3-C_4-alkenyl, C_3-C_4-alkynyl, C_1-C_3-alkoxy, C_3-C_7-cycloalkyl, bicyclic C_6-C_{11}-cycloalkyl, adamantyl, monocyclic 4- to 7-membered heterocycloalkyl, bicyclic 6- to 10-membered heterocycloalkyl, phenyl, naphthyl, and 5- to 10-membered heteroaryl,

wherein said C_1-C_6-alkyl group is optionally substituted one, two or three times, each substituent independently selected from a halogen atom or a group selected from hydroxy, cyano, C_1-C_3-alkoxy, -$N(R^{22})(R^{23})$, C_3-C_7-cycloalkyl, bicyclic C_6-C_{11}-cycloalkyl, adamantyl, monocyclic 4- to 7-membered heterocycloalkyl, bicyclic 6- to 10-membered heterocycloalkyl, phenyl, and 5- to 10-membered heteroaryl, said phenyl and 5- to 10-membered heteroaryl substituents themselves being optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a bromine atom, or a group selected from methyl, trifluoromethyl and methoxy,

wherein C_3-C_7-cycloalkyl, bicyclic C_6-C_{11}-cycloalkyl, adamantyl, monocyclic 4- to 7-membered heterocycloalkyl, bicyclic 6- to 10-membered heterocycloalkyl are optionally substituted one or two or three times, each substituent independently selected from a halogen atom or a group selected from cyano, oxo, hydroxy, C_1-C_2-alkyl and (C_1-C_2-alkyl)-C(=O)-,

and wherein said phenyl, naphthyl and 5- to 10-membered heteroaryl groups are optionally substituted one, two or three times, each substituent independently selected from a halogen atom or a group selected from cyano, C_1-C_2-alkyl, C_1-C_2-haloalkyl, C_1-C_2-alkoxy, C_1-C_2-haloalkoxy, -$N(R^{22})(R^{23})$ and -C(=O)-$N(R^{24})(R^{25})$,

R^{21} represents a hydrogen atom or a C_1-C_2-alkyl group,

or

R^{20} and R^{21}, together with the nitrogen atom to which they are attached, represent a monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group which is optionally benzocondensed, and which is optionally substituted one, two or three times, each substituent independently selected from a halogen atom or a group selected from cyano, oxo, hydroxy, C_1-C_2-alkyl, C_1-C_2-haloalkyl, (phenyl)-(C_1-C_2-alkyl)-, (C_1-C_2-alkyl)-C(=O)-, C_3-C_4-cycloalkyl, C_1-C_2-alkoxy, C_1-C_2-haloalkoxy, -$N(R^{22})(R^{23})$ and -C(=O)-$N(R^{24})(R^{25})$;

R^{22} and R^{23} represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_2-alkyl and (C_1-C_2-alkyl)-C(=O)-;

R^{24} and R^{25} represent, independently from each occurrence, a hydrogen atom or a C_1-C_2-alkyl group, and

n represents an integer 0, 1, or 2,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

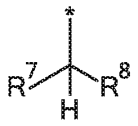
In accordance with a tenth embodiment of the first aspect, the present invention covers compounds of general formula (I), *supra*, in which:

R^1 represents a phenyl or pyridinyl group optionally substituted, one, two, or three times, each substituent independently selected from a fluorine atom, a chlorine atom and a bromine atom, or a group selected from cyano, C_1-C_4-alkyl, C_1-C_2-fluoroalkyl, C_1-C_2-alkoxy, C_1-C_2-fluoroalkoxy, -N(R^5)(R^6),

or two substituents attached to adjacent carbon atoms of said phenyl or pyridinyl group together form a bivalent group selected from –$(CH_2)_3$-, -O-CH_2-O- and -O-CF_2-O-,

or

R^1 represents a pyrazolyl group optionally substituted with one methyl group,

R^2 represents a group  ,

wherein "*" indicates the point of attachment to the nitrogen atom to which R^2 is attached;

R^3 represents a group selected from methyl and -NH_2;

R^4 represents a phenyl or pyridinyl group optionally substituted, one, two, or three times, each substituent independently selected from a fluorine atom, a chlorine atom and a bromine atom, or a group selected from cyano, C_1-C_3-alkyl, C_1-C_3-hydroxyalkyl, C_1-C_3-fluoroalkyl, -OR^9, -N(R^{10})(R^{11}), -C(=O)-N(R^{12})(R^{13}) and S(=O)$_n$-R^{14},

or two substituents attached to adjacent carbon atoms of said phenyl or pyridinyl group together form a bivalent group selected from –$(CH_2)_3$-, -O-CH_2-O- and -O-CF_2-O-;

R^5 and R^6 represent, independently from each occurrence, a hydrogen atom or a C_1-C_2-alkyl group,

or

R^5 and R^6, together with the nitrogen atom to which they are attached, represent a monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group which is optionally substituted one or two times, each substituent independently selected from a fluorine atom or a group selected from hydroxy and C_1-C_2-alkyl;

R^7 represents a hydrogen atom or a C_1-C_2-alkyl group;

R^8 represents a -C(=O)-NH_2 group;

R^9 represents a hydrogen atom or a group selected from C_1-C_2-alkyl, benzyl, C_1-C_2-fluoroalkyl, (C_1-C_2-alkoxy)-C_2-alkyl-, ((C_1-C_2-alkyl)-C(=O)-O)-C_2-alkyl-, -C(R^{18})(R^{19})-C(=O)-OR^{17}, -C(R^{18})(R^{19})-C(=O)-N(R^{20})(R^{21}) and phenyl,

wherein the phenyl group within said benzyl group and said phenyl group itself are optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a methyl group;

R^{10} and R^{11} represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_2-alkyl, C_1-C_2-fluoroalkyl, (C_1-C_2-alkyl)-C(=O)-, (phenyl)-(C_1-C_2-alkyl)-, (phenyl)-(C_1-C_2-alkyl)-C(=O)- and (phenyl)-(C_1-C_2-alkyl)-O-C(=O)-,

wherein the phenyl groups within said (phenyl)-(C_1-C_2-alkyl)-, (phenyl)-(C_1-C_2-alkyl)-C(=O)- and (phenyl)-(C_1-C_2-alkyl)-O-C(=O)- groups are optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a methyl group,

or

R^{10} and R^{11}, together with the nitrogen atom to which they are attached, represent a monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group which is optionally substituted one or two times, each substituent independently selected from a fluorine atom or a group selected from oxo, C_1-C_2-alkyl, C_1-C_2-fluoroalkyl and (C_1-C_2-alkyl)-C(=O)-;

R^{12} and R^{13} represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_4-alkyl, C_1-C_4-fluoroalkyl, C_3-C_7-cycloalkyl, monocyclic 4- to 7-membered heterocycloalkyl and (phenyl)-(C_1-C_2-alkyl)-,

wherein C_3-C_7-cycloalkyl and monocyclic 4- to 7-membered heterocycloalkyl are optionally substitueted one or two times, each substituent independently selected from a fluorine atom or a group selected from oxo, C_1-C_2-alkyl and (C_1-C_2-alkyl)-C(=O)-,

or

R^{12} and R^{13}, together with the nitrogen atom to which they are attached, represent a monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group which is optionally substituted one or two times, each substituent independently selected from a halogen atom or a group selected from oxo, C_1-C_2-alkyl and (C_1-C_2-alkyl)-C(=O)-;

R^{14} represents a group selected from methyl and trifluoromethyl;

R^{17} represents a C_1-C_2-alkyl group;

R^{18} and R^{19} represent, independently from each occurrence, a hydrogen atom or a methyl group;

R^{20} represents a hydrogen atom or a group selected from optionally substituted C_1-C_3-alkyl, unsubstituted C_4-C_6-alkyl, prop-2-ynyl, methoxy, C_3-C_6-cycloalkyl, adamantyl, monocyclic 4- to 7-membered heterocycloalkyl, phenyl, and 5- to 10-membered heteroaryl,

wherein said C_1-C_3-alkyl group is optionally substituted one, two or three times, each substituent independently selected from a halogen atom or a group selected from hydroxy, cyano, C_1-C_3-alkoxy, -N(R^{22})(R^{23}), C_3-C_6-cycloalkyl, adamantyl, monocyclic 4- to 7-membered heterocycloalkyl, phenyl, and 5- to 10-membered heteroaryl, said phenyl and 5- to 10-membered heteroaryl substituents themselves being optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a methyl group,

wherein said C_3-C_6-cycloalkyl, adamantyl and monocyclic 4- to 7-membered heterocycloalkyl groups are optionally substituted one or two or three times, each substituent independently selected from a fluorine atom or a group selected from oxo, C_1-C_2-alkyl and (C_1-C_2-alkyl)-C(=O)-,

and wherein said phenyl and 5- to 10-membered heteroaryl groups are optionally substituted one, two or three times, each substituent independently selected from a fluorine atom and a chlorine atom or a group selected from cyano, C_1-C_2-alkyl, C_1-C_2-fluoroalkyl, C_1-C_2-alkoxy, C_1-C_2-haloalkoxy, -N(R^{22})(R^{23}) and -C(=O)-N(R^{24})(R^{25}),

R^{21} represents a hydrogen atom or a C_1-C_2-alkyl group,

or

R^{20} and R^{21}, together with the nitrogen atom to which they are attached, represent a monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group which is optionally benzocondensed, and which is optionally substituted one, two or three times, each substituent independently selected from a halogen atom or a group selected from cyano, oxo, hydroxy, C_1-C_2-alkyl, C_1-C_2-fluoroalkyl, benzyl, (C_1-C_2-alkyl)-C(=O)-, C_3-C_4-cycloalkyl, C_1-C_2-alkoxy, C_1-C_2-haloalkoxy, -N(R^{22})(R^{23}) and -C(=O)-N(R^{24})(R^{25});

R^{22} and R^{23} represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_2-alkyl and (C_1-C_2-alkyl)-C(=O)-;

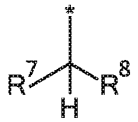
R^{24} and R^{25} represent, independently from each occurrence, a hydrogen atom or a C_1-C_2-alkyl group, and

n represents an integer 2,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In accordance with an eleventh embodiment of the first aspect, the present invention covers compounds of general formula (I), *supra*, in which:

R^1 represents a phenyl or pyridinyl group optionally substituted, one or two times, each substituent independently selected from a fluorine atom and a chlorine atom, or a group selected from cyano, C_1-C_2-alkyl, C_1-C_2-fluoroalkyl, C_1-C_2-alkoxy, C_1-C_2-fluoroalkoxy;

R^2 represents a group  ,

wherein "*" indicates the point of attachment to the nitrogen atom to which R^2 is attached;

R^3 represents a group selected from methyl and $-NH_2$;

R^4 represents a phenyl or pyridinyl group optionally substituted, one or two times, each substituent independently selected from a fluorine atom and a chlorine atom, or a group selected from C_1-C_2-alkyl, C_1-C_2-fluoroalkyl, $-OR^9$;

R^7 represents a hydrogen atom or a C_1-C_2-alkyl group;

R^8 represents a $-C(=O)-NH_2$ group, and

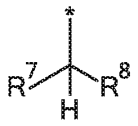
R^9 represents a group selected from C_1-C_2-alkyl, benzyl, C_1-C_2-fluoroalkyl, (C_1-C_2-alkoxy)-C_2-alkyl- and phenyl,

wherein the phenyl group within said benzyl group and said phenyl group itself are optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a methyl group;

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In accordance with a twelfth embodiment of the first aspect, the present invention covers compounds of general formula (I), *supra*, in which:

R^1 represents a phenyl or pyridinyl group optionally substituted, one or two times, each substituent independently selected from a fluorine atom and a chlorine atom, or a group selected from cyano, C_1-C_2-fluoroalkyl, C_1-C_2-alkoxy, C_1-C_2-fluoroalkoxy;

R^2 represents a group  ,

wherein "*" indicates the point of attachment to the nitrogen atom to which R^2 is attached;

R^3 represents a group selected from methyl and $-NH_2$;

R^4 represents a phenyl or pyridinyl group optionally substituted, one or two times, each substituent independently selected from a fluorine atom and a chlorine atom, or a group selected from C_1-C_2-alkyl, C_1-C_2-fluoroalkyl, $-OR^9$;

R^7 represents a hydrogen atom or a C_1-C_2-alkyl group;

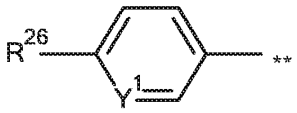
R^8 represents a $-C(=O)-NH_2$ group, and

R^9 represents a group selected from C_1-C_2-alkyl, benzyl, C_1-C_2-fluoroalkyl, (C_1-C_2-alkoxy)-C_2-alkyl- and phenyl,

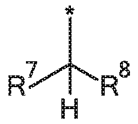
wherein the phenyl group within said benzyl group and said phenyl group itself are optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a methyl group;

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In accordance with a thirteenth embodiment of the first aspect, the present invention covers compounds of general formula (I), *supra*, in which:

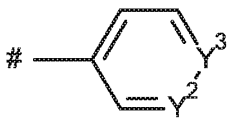
R^1 represents a group 

wherein "**" indicates the point of attachment to the nitrogen atom to which R^1 is attached;

R^2 represents a group  ,

wherein "*" indicates the point of attachment to the nitrogen atom to which R^2 is attached;

R^3 represents a group selected from methyl and $-NH_2$;

R^4 represents a group 

wherein "#" indicates the point of attachment to the carbonyl group to which R^4 is attached;

R^7 represents a hydrogen atom or a C_1-C_2-alkyl group;

R^8 represents a $-C(=O)-NH_2$ group;

Y^1 represents -C(H)=, -C(F)=, -C(Cl)=, -C(CN)= or -N=;

Y^2 represents -C(H)= and -N=;

Y^3 represents -C(R^{27})= and -N=,

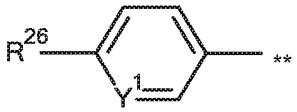
with the proviso that if Y^2 represents -N=, Y^3 represents -C(R^{27})=, and if Y^3 represents -N=, Y^2 represents -C(H)=;

R^{26} represents a fluorine atom, a chlorine atom, or a group selected from C_1-C_2-alkyl, C_1-C_2-fluoroalkyl, C_1-C_2-alkoxy and C_1-C_2-fluoroalkoxy, and

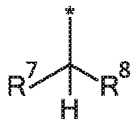
R^{27} represents a fluorine atom, a chlorine atom, or a group selected from C_1-C_2-alkoxy, benzyloxy and C_1-C_2-fluoroalkoxy,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In accordance with a fourteenth embodiment of the first aspect, the present invention covers compounds of general formula (I), *supra*, in which:

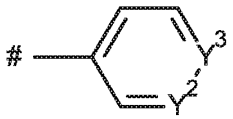
R^1 represents a group 

wherein "**" indicates the point of attachment to the nitrogen atom to which R^1 is attached;

R^2 represents a group  ,

wherein "*" indicates the point of attachment to the nitrogen atom to which R^2 is attached;

R^3 represents a group selected from methyl and -NH_2;

R^4 represents a group 

wherein "#" indicates the point of attachment to the carbonyl group to which R^4 is attached;

R^7 represents a hydrogen atom or a C_1-C_2-alkyl group;

R^8 represents a -C(=O)-NH_2 group;

Y^1 represents -C(H)=, -C(F)=, -C(Cl)=, -C(CN)= or -N=;

Y^2 represents -C(H)= or -N=;

Y^3 represents -C(R^{27})= or -N=,

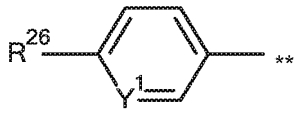
with the proviso that if Y^2 represents -N=, Y^3 represents -C(R^{27})=, and if Y^3 represents -N=, Y^2 represents -C(H)=;

R^{26} represents a fluorine atom, a chlorine atom, or a group selected from C_1-C_2-alkyl, C_1-C_2-fluoroalkyl, C_1-C_2-alkoxy and C_1-C_2-fluoroalkoxy, and

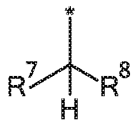
R^{27} represents a fluorine atom, a chlorine atom, or a group selected from C_1-C_2-alkoxy, benzyloxy and C_1-C_2-fluoroalkoxy,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In accordance with a fifteenth embodiment of the first aspect, the present invention covers compounds of general formula (I), *supra*, in which:

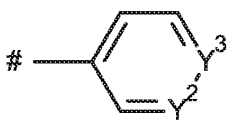
R^1 represents a group 

wherein "**" indicates the point of attachment to the nitrogen atom to which R^1 is attached;

R^2 represents a group  ,

wherein "*" indicates the point of attachment to the nitrogen atom to which R^2 is attached;

R^3 represents a group selected from methyl and -NH_2;

R^4 represents a group 

wherein "#" indicates the point of attachment to the carbonyl group to which R^4 is attached;

R^7 represents a hydrogen atom or a C_1-C_2-alkyl group;

R^8 represents a -C(=O)-NH_2 group;

Y^1 represents -C(H)=, -C(F)= or -N=;

Y^2 represents -C(H)= and -N=;

Y^3 represents -C(R^{27})= and -N=,

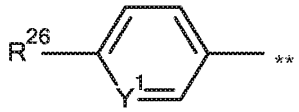
with the proviso that if Y^2 represents -N=, Y^3 represents -C(R^{27})=, and if Y^3 represents -N=, Y^2 represents -C(H)=;

R^{26} represents a fluorine atom, a chlorine atom, or a group selected from methyl, difluoromethyl, trifluoromethyl, methoxy, difluoromethoxy and trifluoromethoxy, and

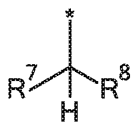
R^{27} represents a chlorine atom, or a group selected from methoxy, benzyloxy, difluoromethoxy and trifluoromethoxy,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In accordance with a sixteenth embodiment of the first aspect, the present invention covers compounds of general formula (I), *supra*, in which:

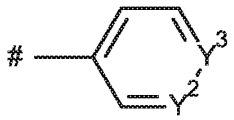
R^1 represents a group 

wherein "**" indicates the point of attachment to the nitrogen atom to which R^1 is attached;

R^2 represents a group  ,

wherein "*" indicates the point of attachment to the nitrogen atom to which R^2 is attached;

R^3 represents a group selected from methyl and -NH_2;



R^4 represents a group

wherein "#" indicates the point of attachment to the carbonyl group to which R^4 is attached;

R^7 represents a hydrogen atom or a C_1-C_2-alkyl group;

R^8 represents a -C(=O)-NH_2 group;

Y^1 represents -C(H)=, -C(F)= or -N=;

Y^2 represents -C(H)= or -N=;

Y^3 represents -C(R^{27})= or -N=,

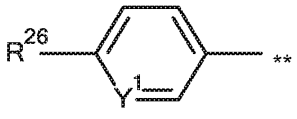
with the proviso that if Y^2 represents -N=, Y^3 represents -C(R^{27})=, and if Y^3 represents -N=, Y^2 represents -C(H)=;

R^{26} represents a fluorine atom, a chlorine atom, or a group selected from methyl, difluoromethyl, trifluoromethyl, methoxy, difluoromethoxy and trifluoromethoxy, and

R^{27} represents a chlorine atom, or a group selected from methoxy, benzyloxy, difluoromethoxy and trifluoromethoxy,

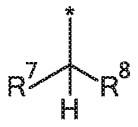
and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In accordance with a seventeenth embodiment of the first aspect, the present invention covers compounds of general formula (I), *supra*, in which:



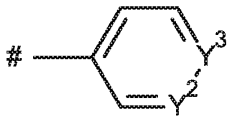
R^1 represents a group

wherein "**" indicates the point of attachment to the nitrogen atom to which R^1 is attached;

R^2 represents a group  ,

wherein "*" indicates the point of attachment to the nitrogen atom to which R^2 is attached;

R^3 represents a $-NH_2$ group;

R^4 represents a group 

wherein "#" indicates the point of attachment to the carbonyl group to which R^4 is attached;

R^7 represents a hydrogen atom or a C_1-C_2-alkyl group;

R^8 represents a $-C(=O)-NH_2$ group;

Y^1 represents -C(H)=, -C(F)=, -C(Cl)=, -C(CN)= or -N=;

Y^2 represents -C(H)= and -N=;

Y^3 represents $-C(R^{27})=$ and -N=,

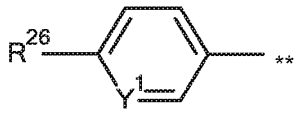
with the proviso that if Y^2 represents -N=, Y^3 represents $-C(R^{27})=$, and if Y^3 represents -N=, Y^2 represents -C(H)=;

R^{26} represents a fluorine atom, a chlorine atom, or a group selected from C_1-C_2-alkyl, C_1-C_2-fluoroalkyl, C_1-C_2-alkoxy and C_1-C_2-fluoroalkoxy, and

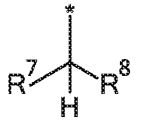
R^{27} represents a fluorine atom, a chlorine atom, or a group selected from C_1-C_2-alkoxy, benzyloxy and C_1-C_2-fluoroalkoxy ,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In accordance with an eighteenth embodiment of the first aspect, the present invention covers compounds of general formula (I), *supra*, in which:

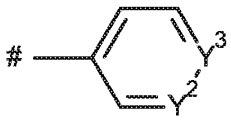
R^1 represents a group 

wherein "**" indicates the point of attachment to the nitrogen atom to which R^1 is attached;

R^2 represents a group  ,

wherein "*" indicates the point of attachment to the nitrogen atom to which R^2 is attached;

R^3 represents a $-NH_2$ group;

R^4 represents a group 

wherein "#" indicates the point of attachment to the carbonyl group to which R^4 is attached;

R^7 represents a hydrogen atom or a C_1-C_2-alkyl group;

R^8 represents a $-C(=O)-NH_2$ group;

Y^1 represents -C(H)=, -C(F)=, -C(Cl)=, -C(CN)= or -N=;

Y^2 represents -C(H)= or -N=;

Y^3 represents $-C(R^{27})=$ or -N=,

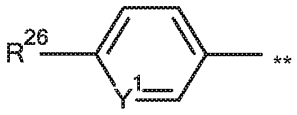
with the proviso that if Y^2 represents -N=, Y^3 represents $-C(R^{27})=$, and if Y^3 represents -N=, Y^2 represents -C(H)=;

R^{26} represents a fluorine atom, a chlorine atom, or a group selected from C_1-C_2-alkyl, C_1-C_2-fluoroalkyl, C_1-C_2-alkoxy and C_1-C_2-fluoroalkoxy, and

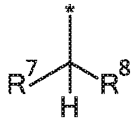
R^{27} represents a fluorine atom, a chlorine atom, or a group selected from C_1-C_2-alkoxy, benzyloxy and C_1-C_2-fluoroalkoxy ,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In accordance with a nineteenth embodiment of the first aspect, the present invention covers compounds of general formula (I), *supra*, in which:

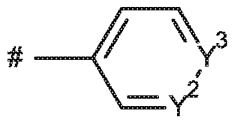
R^1 represents a group 

wherein "**" indicates the point of attachment to the nitrogen atom to which R^1 is attached;

R^2 represents a group  ,

wherein "*" indicates the point of attachment to the nitrogen atom to which R^2 is attached;

R^3 represents a $-NH_2$ group;

R^4 represents a group 

wherein "#" indicates the point of attachment to the carbonyl group to which R^4 is attached;

R^7 represents a hydrogen atom or a C_1-C_2-alkyl group;

R^8 represents a $-C(=O)-NH_2$ group;

Y^1 represents -C(H)=, -C(F)= or -N=;

Y^2 represents -C(H)= and -N=;

Y^3 represents $-C(R^{27})=$ and -N=,

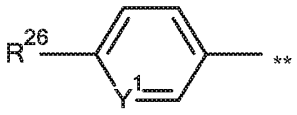
with the proviso that if Y^2 represents -N=, Y^3 represents $-C(R^{27})=$, and if Y^3 represents -N=, Y^2 represents -C(H)=;

R^{26} represents a fluorine atom, a chlorine atom, or a group selected from methyl, difluoromethyl, trifluoromethyl, methoxy, difluoromethoxy and trifluoromethoxy, and

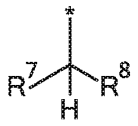
R^{27} represents a chlorine atom, or a group selected from methoxy, benzyloxy, difluoromethoxy and trifluoromethoxy,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In accordance with a twentieth embodiment of the first aspect, the present invention covers compounds of general formula (I), *supra*, in which:

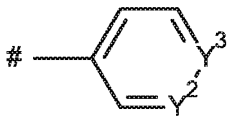
R^1 represents a group 

wherein "**" indicates the point of attachment to the nitrogen atom to which R^1 is attached;

R^2 represents a group  ,

wherein "*" indicates the point of attachment to the nitrogen atom to which R^2 is attached;

R^3 represents a $-NH_2$ group;

R^4 represents a group 

wherein "#" indicates the point of attachment to the carbonyl group to which R^4 is attached;

R^7 represents a hydrogen atom or a C_1-C_2-alkyl group;

R^8 represents a $-C(=O)-NH_2$ group;

Y^1 represents -C(H)=, -C(F)= or -N=;

Y^2 represents -C(H)= or -N=;

Y^3 represents -C(R^{27})= or -N=,

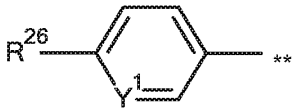
with the proviso that if Y^2 represents -N=, Y^3 represents -C(R^{27})=, and if Y^3 represents -N=, Y^2 represents -C(H)=;

R^{26} represents a fluorine atom, a chlorine atom, or a group selected from methyl, difluoromethyl, trifluoromethyl, methoxy, difluoromethoxy and trifluoromethoxy, and

R^{27} represents a chlorine atom, or a group selected from methoxy, benzyloxy, difluoromethoxy and trifluoromethoxy,

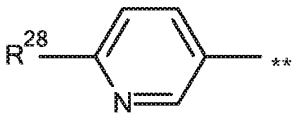
and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In accordance with a twenty-first embodiment of the first aspect, the present invention covers compounds of general formula (I), *supra*, in which:

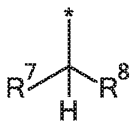
R^1 represents a group  ,

wherein "**" indicates the point of attachment to the nitrogen atom to which R^1 is attached,

or

R^1 represents a group  ,

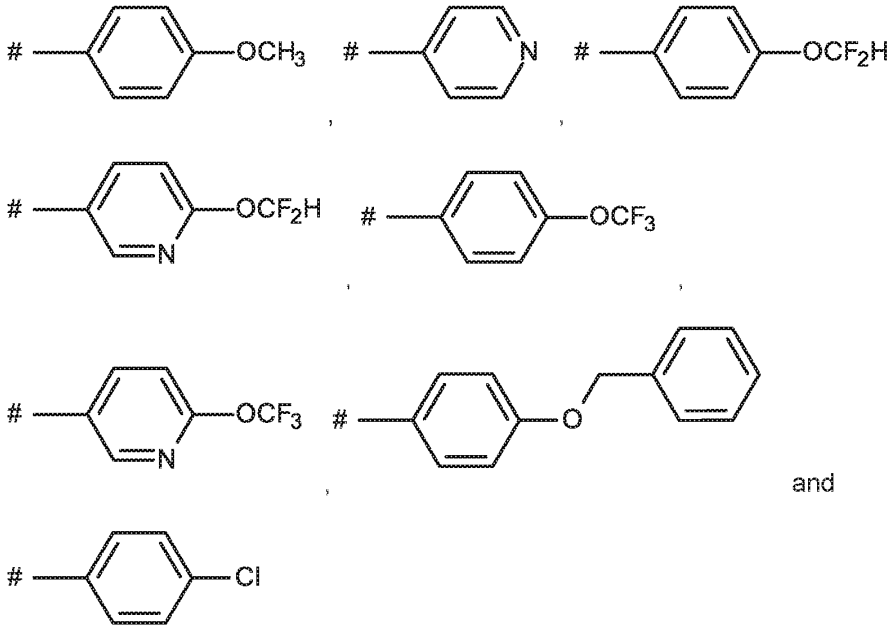
wherein "**" indicates the point of attachment to the nitrogen atom to which R^1 is attached;

R^2 represents a group  ,

wherein "*" indicates the point of attachment to the nitrogen atom to which R^2 is attached;

R^3 represents a group selected from methyl and -NH_2;

R^4 represents a group selected from



and

wherein "#" indicates the point of attachment to the carbonyl group to which R^4 is attached;

R^7 represents a methyl group;

R^8 represents a -C(=O)-NH_2 group;

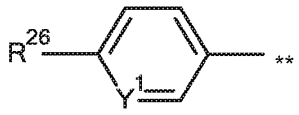
Y^1 represents -C(H)= or-C(F)=;

R^{26} represents a fluorine atom, a chlorine atom, or a group selected from difluoromethyl, trifluoromethyl, methoxy, difluoromethoxy and trifluoromethoxy;

R^{28} represents a group selected from methyl, difluoromethyl, trifluoromethyl, methoxy, difluoromethoxy and trifluoromethoxy;

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In accordance with a twenty-second embodiment of the first aspect, the present invention covers compounds of general formula (I), *supra*, in which:

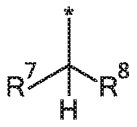
R^1 represents a group  ,

wherein "**" indicates the point of attachment to the nitrogen atom to which R^1 is attached,

or

R^1 represents a group  ,

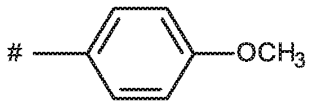
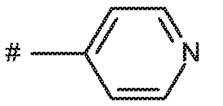
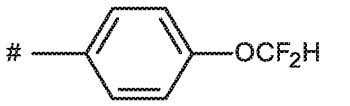
wherein "**" indicates the point of attachment to the nitrogen atom to which R^1 is attached;

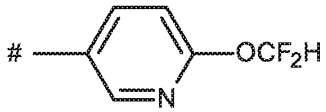
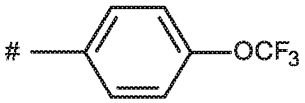
R^2 represents a group  ,

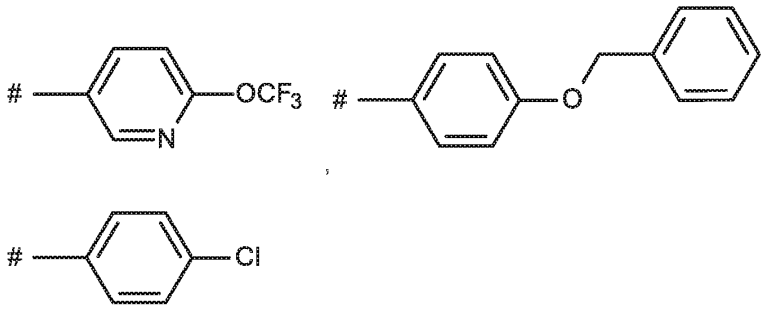
wherein "*" indicates the point of attachment to the nitrogen atom to which R^2 is attached;

R^3 represents a $-NH_2$ group;

R^4 represents a group selected from

 ,  ,  ,

 ,  ,



and

,

wherein "#" indicates the point of attachment to the carbonyl group to which R^4 is attached;

R^7 represents a methyl group;

R^8 represents a -C(=O)-NH_2 group;

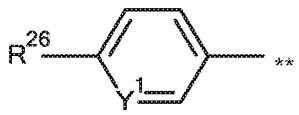
Y^1 represents -C(H)= or-C(F)=;

R^{26} represents a fluorine atom, a chlorine atom, or a group selected from difluoromethyl, trifluoromethyl, methoxy, difluoromethoxy and trifluoromethoxy;

R^{28} represents a group selected from methyl, difluoromethyl, trifluoromethyl, methoxy, difluoromethoxy and trifluoromethoxy;

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In accordance with a twenty-third embodiment of the first aspect, the present invention covers compounds of general formula (I), *supra*, in which:

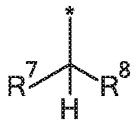
R^1 represents a group  ,

wherein "**" indicates the point of attachment to the nitrogen atom to which R^1 is attached,

or



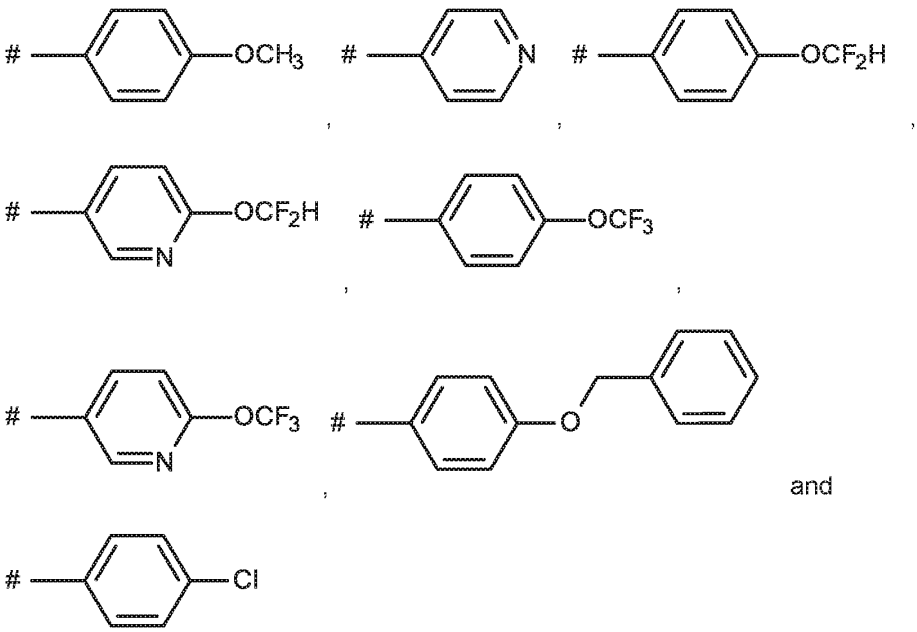
R^1 represents a group , wherein "**" indicates the point of attachment to the nitrogen atom to which R^1 is attached;



R^2 represents a group , wherein "*" indicates the point of attachment to the nitrogen atom to which R^2 is attached;

R^3 represents a methyl group;

R^4 represents a group selected from



, wherein "#" indicates the point of attachment to the carbonyl group to which R^4 is attached;

R^7 represents a methyl group;

R^8 represents a -C(=O)-NH_2 group;

Y^1 represents -C(H)= or-C(F)=;

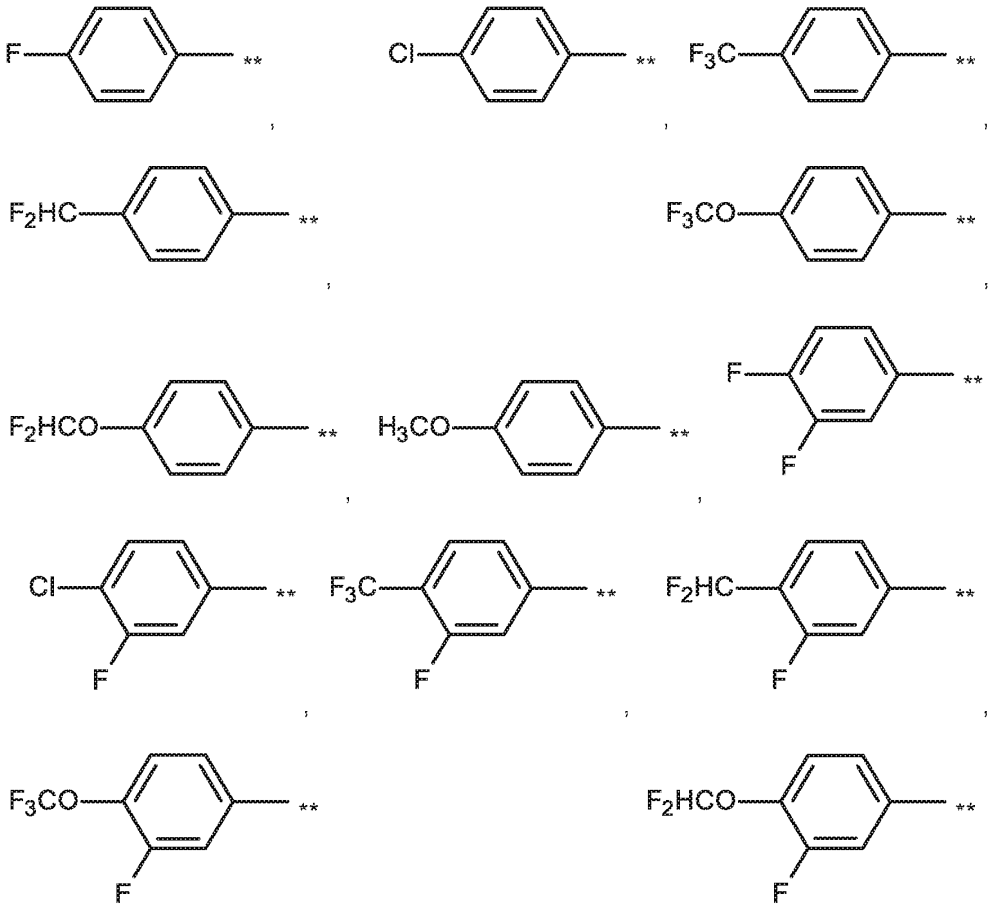
R^{26} represents a fluorine atom, a chlorine atom, or a group selected from difluoromethyl, trifluoromethyl, methoxy, difluoromethoxy and trifluoromethoxy;

R^{28} represents a group selected from methyl, difluoromethyl, trifluoromethyl, methoxy, difluoromethoxy and trifluoromethoxy;

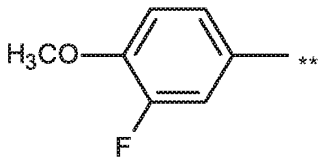
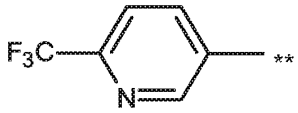
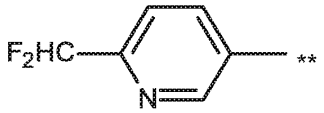
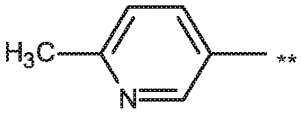
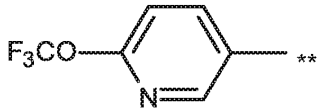
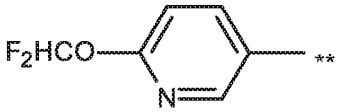
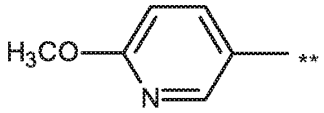
and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In accordance with a twenty-fourth embodiment of the first aspect, the present invention covers compounds of general formula (I), *supra*, in which:

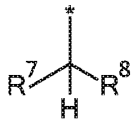
R^1 represents a group selected from



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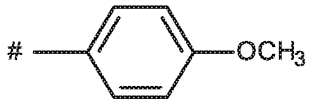
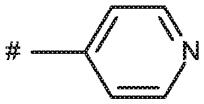
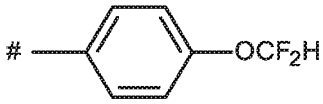
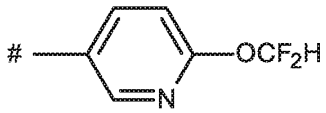
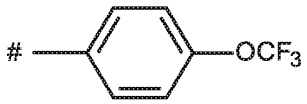
wherein "**" indicates the point of attachment to the nitrogen atom to which R^1 is attached;

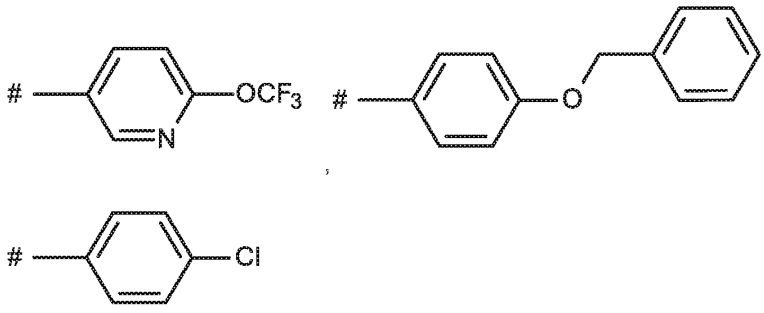
R^2 represents a group  ,

wherein "*" indicates the point of attachment to the nitrogen atom to which R^2 is attached;

R^3 represents a $-NH_2$ group;

R^4 represents a group selected from


,

,

;

,

,



and

wherein "#" indicates the point of attachment to the carbonyl group to which R^4 is attached;

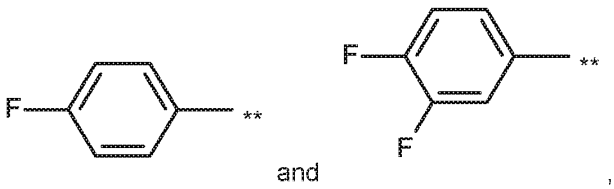
R^7 represents a methyl group;

R^8 represents a -C(=O)-NH_2 group;

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

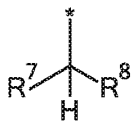
In accordance with a twenty-fifth embodiment of the first aspect, the present invention covers compounds of general formula (I), *supra*, in which:

R^1 represents a group selected from



and

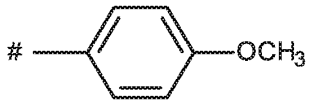
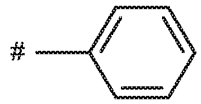
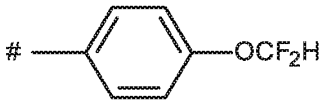
wherein "**" indicates the point of attachment to the nitrogen atom to which R^1 is attached;

R^2 represents a group  ,

wherein "*" indicates the point of attachment to the nitrogen atom to which R^2 is attached;

R^3 represents a methyl group;

R^4 represents a group selected from


, 
and 
,

wherein "#" indicates the point of attachment to the carbonyl group to which R^4 is attached;

R^7 represents a methyl group;

R^8 represents a -C(=O)-NH_2 group;

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

FURTHER EMBODIMENTS OF THE FIRST ASPECT OF THE PRESENT INVENTION

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^1 represents a phenyl or pyridinyl group optionally substituted, one, two, or three times, each substituent independently selected from a halogen atom or a group selected from hydroxy, cyano, nitro, C_1-C_4-alkyl, (phenyl)-(C_1-C_2-alkyl)-, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, (phenyl)-(C_1-C_2-alkoxy)-, C_1-C_4-haloalkoxy, -N(R^5)(R^6),

wherein the phenyl groups in said (phenyl)-(C_1-C_2-alkyl)- and (phenyl)-(C_1-C_2-alkoxy)- groups are optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a bromine atom, or a group selected from methyl, trifluoromethyl and methoxy,

or two substituents attached to adjacent carbon atoms of said phenyl or pyridinyl group together form a bivalent group selected from –-(CH_2)$_3$-, -(CH_2)$_4$-, -(CH_2)$_2$-O-, -(CH_2)$_3$-O-, -CH_2-O-CH_2-, -O-CH_2-O-, -O-CH_2-CH_2-O- and -O-CF_2-O-,

or

R^1 represents a pyrazolyl group optionally substituted one or two times, each substituent independently selected from a halogen atom or a group selected from cyano, C_1-C_2-alkyl, and C_1-C_2-alkoxy,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^1 represents a phenyl or pyridinyl group optionally substituted, one, two, or three times, each substituent independently selected from a halogen atom or a group selected from hydroxy, cyano, nitro, C_1-C_4-alkyl, (phenyl)-(C_1-C_2-alkyl)-, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, (phenyl)-(C_1-C_2-alkoxy)-, C_1-C_4-haloalkoxy, -N(R^5)(R^6),

wherein the phenyl groups in said (phenyl)-(C_1-C_2-alkyl)- and (phenyl)-(C_1-C_2-alkoxy)- groups are optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a bromine atom, or a group selected from methyl, trifluoromethyl and methoxy,

or two substituents attached to adjacent carbon atoms of said phenyl or pyridinyl group together form a bivalent group selected from –$(CH_2)_3$-, -$(CH_2)_4$-, -$(CH_2)_2$-O-, -$(CH_2)_3$-O-, -CH_2-O-CH_2-, -O-CH_2-O-, -O-CH_2-CH_2-O- and -O-CF_2-O-,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^1 represents a phenyl or pyridinyl group optionally substituted, one, two, or three times, each substituent independently selected from a halogen atom or a group selected from hydroxy, cyano, nitro, (phenyl)-(C_1-C_2-alkyl)-, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, (phenyl)-(C_1-C_2-alkoxy)-, C_1-C_4-haloalkoxy, -N(R^5)(R^6),

wherein the phenyl groups in said (phenyl)-(C_1-C_2-alkyl)- and (phenyl)-(C_1-C_2-alkoxy)- groups are optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a bromine atom, or a group selected from methyl, trifluoromethyl and methoxy,

or two substituents attached to adjacent carbon atoms of said phenyl or pyridinyl group together form a bivalent group selected from –$(CH_2)_3$-, -$(CH_2)_4$-, -$(CH_2)_2$-O-, -$(CH_2)_3$-O-, -CH_2-O-CH_2-, -O-CH_2-O-, -O-CH_2-CH_2-O- and -O-CF_2-O-,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^1 represents a phenyl or pyridinyl group optionally substituted, one, two, or three times, each substituent independently selected from a halogen atom or a group selected from cyano, nitro, C_1-C_4-alkyl, (phenyl)-(C_1-C_2-alkyl)-, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, (phenyl)-(C_1-C_2-alkoxy)-, C_1-C_4-haloalkoxy, -N(R^5)(R^6),

wherein the phenyl groups in said (phenyl)-(C_1-C_2-alkyl)- and (phenyl)-(C_1-C_2-alkoxy)- groups are optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a bromine atom, or a group selected from methyl, trifluoromethyl and methoxy,

or two substituents attached to adjacent carbon atoms of said phenyl or pyridinyl group together form a bivalent group selected from –$(CH_2)_3$-, -$(CH_2)_4$-, -$(CH_2)_2$-O-, -$(CH_2)_3$-O-, -CH_2-O-CH_2-, -O-CH_2-O-, -O-CH_2-CH_2-O- and -O-CF_2-O-,

or

R^1 represents a pyrazolyl group optionally substituted one or two times, each substituent independently selected from a halogen atom or a group selected from cyano, C_1-C_2-alkyl, and C_1-C_2-alkoxy,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^1 represents a phenyl or pyridinyl group optionally substituted, one, two, or three times, each substituent independently selected from a halogen atom or a group selected from cyano, nitro, C_1-C_4-alkyl, (phenyl)-(C_1-C_2-alkyl)-, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, (phenyl)-(C_1-C_2-alkoxy)-, C_1-C_4-haloalkoxy, -N(R^5)(R^6),

wherein the phenyl groups in said (phenyl)-(C_1-C_2-alkyl)- and (phenyl)-(C_1-C_2-alkoxy)- groups are optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a bromine atom, or a group selected from methyl, trifluoromethyl and methoxy,

or two substituents attached to adjacent carbon atoms of said phenyl or pyridinyl group together form a bivalent group selected from –$(CH_2)_3$-, -$(CH_2)_4$-, -$(CH_2)_2$-O-, -$(CH_2)_3$-O-, -CH_2-O-CH_2-, -O-CH_2-O-, -O-CH_2-CH_2-O- and -O-CF_2-O-,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^1 represents a phenyl or pyridinyl group optionally substituted, one, two, or three times, each substituent independently selected from a halogen atom or a group selected from cyano, nitro, (phenyl)-(C_1-C_2-alkyl)-, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, (phenyl)-(C_1-C_2-alkoxy)-, C_1-C_4-haloalkoxy, -N(R^5)(R^6),

wherein the phenyl groups in said (phenyl)-(C_1-C_2-alkyl)- and (phenyl)-(C_1-C_2-alkoxy)- groups are optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a bromine atom, or a group selected from methyl, trifluoromethyl and methoxy,

or two substituents attached to adjacent carbon atoms of said phenyl or pyridinyl group together form a bivalent group selected from –-(CH_2)$_3$-, -(CH_2)$_4$-, -(CH_2)$_2$-O-, -(CH_2)$_3$-O-, -CH_2-O-CH_2-, -O-CH_2-O-, -O-CH_2-CH_2-O- and -O-CF_2-O-,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^1 represents a phenyl or pyridinyl group optionally substituted, one, two, or three times, each substituent independently selected from a fluorine atom, a chlorine atom and a bromine atom, or a group selected from hydroxy, cyano, C_1-C_4-alkyl, C_1-C_2-fluoroalkyl, C_1-C_2-alkoxy, (phenyl)-(C_1-C_2-alkoxy)-, C_1-C_2-fluoroalkoxy and -N(R^5)(R^6),

or two substituents attached to adjacent carbon atoms of said phenyl or pyridinyl group together form a bivalent group selected from –-(CH_2)$_3$-, -O-CH_2-O- and -O-CF_2-O-,

or

R^1 represents a pyrazolyl group optionally substituted with one methyl group,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^1 represents a phenyl or pyridinyl group optionally substituted, one, two, or three times, each substituent independently selected from a fluorine atom, a chlorine atom and a bromine atom, or a group selected from hydroxy, cyano, C_1-C_4-alkyl, C_1-C_2-fluoroalkyl, C_1-C_2-alkoxy, (phenyl)-(C_1-C_2-alkoxy)-, C_1-C_2-fluoroalkoxy and -N(R^5)(R^6),

or two substituents attached to adjacent carbon atoms of said phenyl or pyridinyl group together form a bivalent group selected from –$(CH_2)_3$-, -O-CH_2-O- and -O-CF_2-O-,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^1 represents a phenyl or pyridinyl group optionally substituted, one, two, or three times, each substituent independently selected from a fluorine atom, a chlorine atom and a bromine atom, or a group selected from hydroxy, cyano, C_1-C_2-fluoroalkyl, C_1-C_2-alkoxy, (phenyl)-(C_1-C_2-alkoxy)-, C_1-C_2-fluoroalkoxy and -N(R^5)(R^6),

or two substituents attached to adjacent carbon atoms of said phenyl or pyridinyl group together form a bivalent group selected from –$(CH_2)_3$-, -O-CH_2-O- and -O-CF_2-O-,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^1 represents a phenyl group optionally substituted, one, two, or three times, each substituent independently selected from a fluorine atom, a chlorine atom and a bromine atom, or a group selected from hydroxy, cyano, C_1-C_4-alkyl, C_1-C_2-fluoroalkyl, C_1-C_2-alkoxy, (phenyl)-(C_1-C_2-alkoxy)-, C_1-C_2-fluoroalkoxy and -N(R^5)(R^6),

or two substituents attached to adjacent carbon atoms of said phenyl group together form a bivalent group selected from –$(CH_2)_3$-, -O-CH_2-O- and -O-CF_2-O-,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^1 represents a phenyl group optionally substituted, one, two, or three times, each substituent independently selected from a fluorine atom, a chlorine atom and a bromine atom, or a group selected from hydroxy, cyano, C_1-C_2-fluoroalkyl, C_1-C_2-alkoxy, (phenyl)-(C_1-C_2-alkoxy)-, C_1-C_2-fluoroalkoxy and -N(R^5)(R^6),

or two substituents attached to adjacent carbon atoms of said phenyl group together form a bivalent group selected from –$(CH_2)_3$-, -O-CH_2-O- and -O-CF_2-O-,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^1 represents a pyridinyl group optionally substituted, one, two, or three times, each substituent independently selected from a fluorine atom, a chlorine atom and a bromine atom, or a group selected from hydroxy, cyano, C_1-C_4-alkyl, C_1-C_2-fluoroalkyl, C_1-C_2-alkoxy, (phenyl)-(C_1-C_2-alkoxy)-, C_1-C_2-fluoroalkoxy and -N(R^5)(R^6),

or two substituents attached to adjacent carbon atoms of said pyridinyl group together form a bivalent group selected from –$(CH_2)_3$-, -O-CH_2-O- and -O-CF_2-O-,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^1 represents a phenyl or pyridinyl group optionally substituted, one, two, or three times, each substituent independently selected from a fluorine atom, a chlorine atom and a bromine atom, or a group selected from cyano, C_1-C_4-alkyl, C_1-C_2-fluoroalkyl, C_1-C_2-alkoxy, C_1-C_2-fluoroalkoxy, -N(R^5)(R^6),

or two substituents attached to adjacent carbon atoms of said phenyl or pyridinyl group together form a bivalent group selected from –$(CH_2)_3$-, -O-CH_2-O- and -O-CF_2-O-,

or

R^1 represents a pyrazolyl group optionally substituted with one methyl group,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^1 represents a phenyl or pyridinyl group optionally substituted, one, two, or three times, each substituent independently selected from a fluorine atom, a chlorine atom and a bromine atom, or a group selected from cyano, C_1-C_4-alkyl, C_1-C_2-fluoroalkyl, C_1-C_2-alkoxy, C_1-C_2-fluoroalkoxy, -N(R^5)(R^6),

or two substituents attached to adjacent carbon atoms of said phenyl or pyridinyl group together form a bivalent group selected from –$(CH_2)_3$-, -O-CH_2-O- and -O-CF_2-O-,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^1 represents a phenyl or pyridinyl group optionally substituted, one, two, or three times, each substituent independently selected from a fluorine atom, a chlorine atom and a bromine atom, or a group selected from cyano, C_1-C_2-fluoroalkyl, C_1-C_2-alkoxy, C_1-C_2-fluoroalkoxy, -N(R^5)(R^6),

or two substituents attached to adjacent carbon atoms of said phenyl or pyridinyl group together form a bivalent group selected from –$(CH_2)_3$-, -O-CH_2-O- and -O-CF_2-O-,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^1 represents a phenyl group optionally substituted, one, two, or three times, each substituent independently selected from a fluorine atom, a chlorine atom and a bromine atom, or a group selected from cyano, C_1-C_4-alkyl, C_1-C_2-fluoroalkyl, C_1-C_2-alkoxy, C_1-C_2-fluoroalkoxy, -N(R^5)(R^6),

or two substituents attached to adjacent carbon atoms of said phenyl or pyrdinyl group together form a bivalent group selected from –$(CH_2)_3$-, -O-CH_2-O- and -O-CF_2-O-,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^1 represents a phenyl group optionally substituted, one, two, or three times, each substituent independently selected from a fluorine atom, a chlorine atom and a bromine atom, or a group selected from cyano, C_1-C_2-fluoroalkyl, C_1-C_2-alkoxy, C_1-C_2-fluoroalkoxy, -N(R^5)(R^6),

or two substituents attached to adjacent carbon atoms of said phenyl group together form a bivalent group selected from –$(CH_2)_3$-, -O-CH_2-O- and -O-CF_2-O-,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^1 represents a pyridinyl group optionally substituted, one, two, or three times, each substituent independently selected from a fluorine atom, a chlorine atom and a bromine atom, or a group selected from cyano, C_1-C_4-alkyl, C_1-C_2-fluoroalkyl, C_1-C_2-alkoxy, C_1-C_2-fluoroalkoxy, -N(R^5)(R^6),

or two substituents attached to adjacent carbon atoms of said phenyl or pyridinyl group together form a bivalent group selected from –$(CH_2)_3$-, -O-CH_2-O- and -O-CF_2-O-,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^1 represents a phenyl or pyridinyl group optionally substituted, one or two times, each substituent independently selected from a fluorine atom and a chlorine atom, or a group selected from C_1-C_2-alkyl, C_1-C_2-fluoroalkyl, C_1-C_2-alkoxy, C_1-C_2-fluoroalkoxy,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^1 represents a phenyl or pyridinyl group optionally substituted, one or two times, each substituent independently selected from a fluorine atom and a chlorine atom, or a group selected from C_1-C_2-fluoroalkyl, C_1-C_2-alkoxy, C_1-C_2-fluoroalkoxy,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^1 represents a phenyl group optionally substituted, one or two times, each substituent independently selected from a fluorine atom and a chlorine atom, or a group selected from cyano, C_1-C_2-alkyl, C_1-C_2-fluoroalkyl, C_1-C_2-alkoxy, C_1-C_2-fluoroalkoxy,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^1 represents a phenyl group optionally substituted, one or two times, each substituent independently selected from a fluorine atom and a chlorine atom, or a group selected from C_1-C_2-alkyl, C_1-C_2-fluoroalkyl, C_1-C_2-alkoxy, C_1-C_2-fluoroalkoxy,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^1 represents a phenyl group optionally substituted, one or two times, each substituent independently selected from a fluorine atom and a chlorine atom, or a group selected from cyano, C_1-C_2-fluoroalkyl, C_1-C_2-alkoxy, C_1-C_2-fluoroalkoxy,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^1 represents a phenyl group optionally substituted, one or two times, each substituent independently selected from a fluorine atom and a chlorine atom, or a group selected from C_1-C_2-fluoroalkyl, C_1-C_2-alkoxy, C_1-C_2-fluoroalkoxy,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^1 represents a pyridinyl group optionally substituted, one or two times, each substituent independently selected from a fluorine atom and a chlorine atom, or a group selected from C_1-C_2-alkyl, C_1-C_2-fluoroalkyl, C_1-C_2-alkoxy, C_1-C_2-fluoroalkoxy,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^1 represents a phenyl or pyridinyl group optionally substituted, one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a bromine atom, or a group selected from cyano, methyl, difluoromethyl, trifluoromethyl, methoxy, benzyloxy, difluoromethoxy and trifluoromethoxy,

or two substituents attached to adjacent carbon atoms of said phenyl or pyridinyl group together form a bivalent group -O-CF_2-O-,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^1 represents a phenyl or pyridinyl group optionally substituted, one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a bromine atom, or a group selected from cyano, difluoromethyl, trifluoromethyl, methoxy, benzyloxy, difluoromethoxy and trifluoromethoxy,

or two substituents attached to adjacent carbon atoms of said phenyl or pyridinyl group together form a bivalent group -O-CF_2-O-,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^1 represents a phenyl group optionally substituted, one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a bromine atom, or a group selected from cyano, methyl, difluoromethyl, trifluoromethyl, methoxy, benzyloxy, difluoromethoxy and trifluoromethoxy,

or two substituents attached to adjacent carbon atoms of said phenyl group together form a bivalent group -O-CF_2-O-,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^1 represents a phenyl group optionally substituted, one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a bromine atom, or a group selected from cyano, difluoromethyl, trifluoromethyl, methoxy, benzyloxy, difluoromethoxy and trifluoromethoxy,

or two substituents attached to adjacent carbon atoms of said phenyl group together form a bivalent group -O-CF_2-O-,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^1 represents a pyridinyl group optionally substituted, one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a bromine atom, or a group selected from cyano, methyl, difluoromethyl, trifluoromethyl, methoxy, benzyloxy, difluoromethoxy and trifluoromethoxy,

or two substituents attached to adjacent carbon atoms of said pyridinyl group together form a bivalent group -O-CF_2-O-,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^1 represents a phenyl or pyridinyl group optionally substituted, one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a bromine atom, or a group selected from methyl, difluoromethyl, trifluoromethyl, methoxy, benzyloxy, difluoromethoxy and trifluoromethoxy,

or two substituents attached to adjacent carbon atoms of said phenyl or pyridinyl group together form a bivalent group -O-CF_2-O-,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^1 represents a phenyl or pyridinyl group optionally substituted, one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a bromine atom, or a group selected from difluoromethyl, trifluoromethyl, methoxy, benzyloxy, difluoromethoxy and trifluoromethoxy,

or two substituents attached to adjacent carbon atoms of said phenyl or pyridinyl group together form a bivalent group -O-CF_2-O-,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^1 represents a phenyl group optionally substituted, one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a bromine atom, or a group selected from methyl, difluoromethyl, trifluoromethyl, methoxy, benzyloxy, difluoromethoxy and trifluoromethoxy,

or two substituents attached to adjacent carbon atoms of said phenyl group together form a bivalent group -O-CF_2-O-,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^1 represents a phenyl group optionally substituted, one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a bromine atom, or a group selected from difluoromethyl, trifluoromethyl, methoxy, benzyloxy, difluoromethoxy and trifluoromethoxy,

or two substituents attached to adjacent carbon atoms of said phenyl group together form a bivalent group -O-CF_2-O-,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

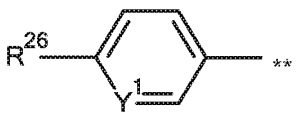
In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^1 represents a pyridinyl group optionally substituted, one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a bromine atom, or a group selected from methyl, difluoromethyl, trifluoromethyl, methoxy, benzyloxy, difluoromethoxy and trifluoromethoxy,

or two substituents attached to adjacent carbon atoms of said pyridinyl group together form a bivalent group -O-CF_2-O-,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

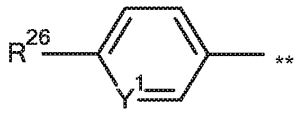
In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^1 represents a group 

wherein "**" indicates the point of attachment to the nitrogen atom to which R^1 is attached,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^1 represents a group 

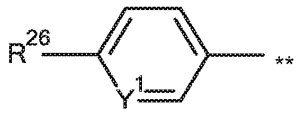
wherein "**" indicates the point of attachment to the nitrogen atom to which R^1 is attached;

Y^1 represents -C(H)=, -C(F)=, -C(Cl)=, -C(CN)= or -N=;

R^{26} represents a fluorine atom, a chlorine atom or a bromine atom, or a group selected from methyl, difluoromethyl, trifluoromethyl, methoxy, benzyloxy, difluoromethoxy and trifluoromethoxy,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^1 represents a group 

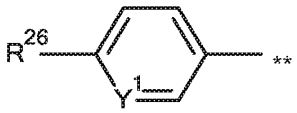
wherein "**" indicates the point of attachment to the nitrogen atom to which R^1 is attached;

Y^1 represents -C(H)=, -C(F)=, -C(Cl)=, -C(CN)= or -N=;

R^{26} represents a fluorine atom, a chlorine atom or a bromine atom, or a group selected from difluoromethyl, trifluoromethyl, methoxy, benzyloxy, difluoromethoxy and trifluoromethoxy,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:



R^1 represents a group

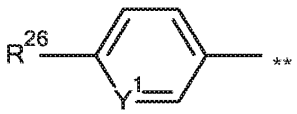
wherein "**" indicates the point of attachment to the nitrogen atom to which R^1 is attached;

Y^1 represents -C(H)=, -C(F)= or -N=;

R^{26} represents a fluorine atom, a chlorine atom, or a group selected from C_1-C_2-alkyl, C_1-C_2-fluoroalkyl, C_1-C_2-alkoxy and C_1-C_2-fluoroalkoxy,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:



R^1 represents a group

wherein "**" indicates the point of attachment to the nitrogen atom to which R^1 is attached;

Y^1 represents -C(H)=, -C(F)= or -N=;

R^{26} represents a fluorine atom, a chlorine atom, or a group selected from C_1-C_2-fluoroalkyl, C_1-C_2-alkoxy and C_1-C_2-fluoroalkoxy,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:



R^1 represents a group

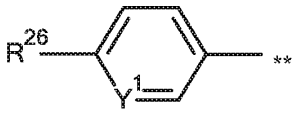
wherein "**" indicates the point of attachment to the nitrogen atom to which R^1 is attached;

Y^1 represents -C(H)=, -C(F)=, -C(Cl)= or -N=;

R^{26} represents a fluorine atom, a chlorine atom or a bromine atom, or a group selected from difluoromethyl, methoxy, benzyloxy, difluoromethoxy and trifluoromethoxy,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^1 represents a group  ,

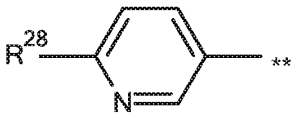
wherein "**" indicates the point of attachment to the nitrogen atom to which R^1 is attached,

Y^1 represents -C(H)= or-C(F)=, and

R^{26} represents a fluorine atom, a chlorine atom, or a group selected from difluoromethyl, trifluoromethyl, methoxy, difluoromethoxy and trifluoromethoxy,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^1 represents a group  ,

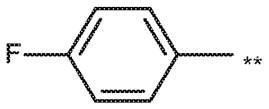
wherein "**" indicates the point of attachment to the nitrogen atom to which R^1 is attached, and

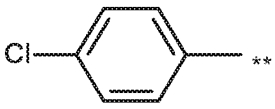
R^{28} represents a group selected from methyl, difluoromethyl, trifluoromethyl, methoxy, difluoromethoxy and trifluoromethoxy,

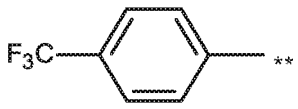
and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

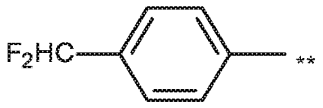
In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

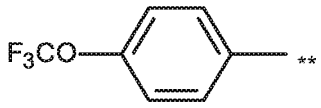
R^1 represents a group selected from



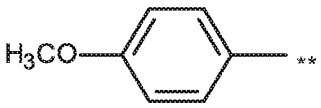
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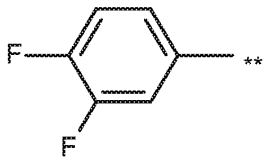
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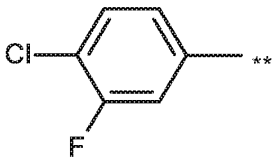
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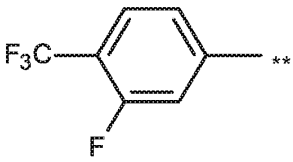
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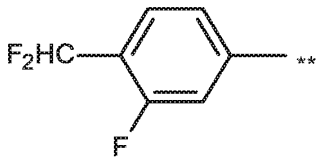
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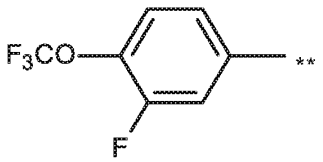

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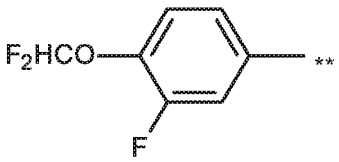
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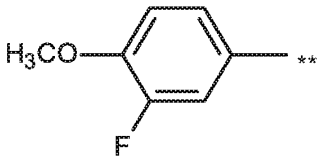
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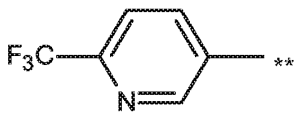
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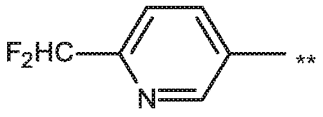
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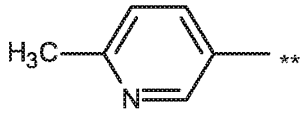
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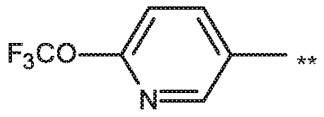
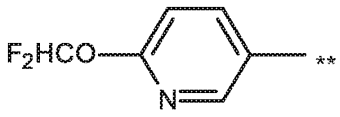
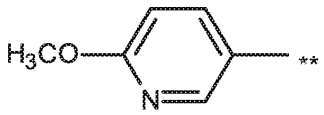
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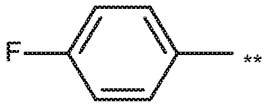
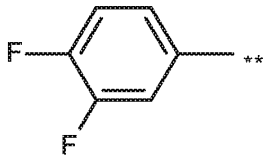




wherein "**" indicates the point of attachment to the nitrogen atom to which R^1 is attached,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

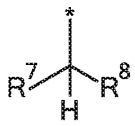
R^1 represents a group selected from


and


wherein "**" indicates the point of attachment to the nitrogen atom to which R^1 is attached,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^2 represents a group  ,

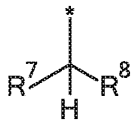
wherein "*" indicates the point of attachment to the nitrogen atom to which R^2 is attached;

R^7 represents a hydrogen atom or a C_1-C_2-alkyl group;

R^8 represents a -C(=O)-NH_2 group,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^2 represents a group  ,

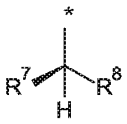
wherein "*" indicates the point of attachment to the nitrogen atom to which R^2 is attached;

R^7 represents a C_1-C_2-alkyl group;

R^8 represents a -C(=O)-NH_2 group,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^2 represents a group  ,

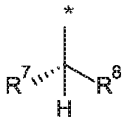
wherein "*" indicates the point of attachment to the nitrogen atom to which R^2 is attached;

R^7 represents a C_1-C_2-alkyl group;

R^8 represents a -C(=O)-NH_2 group,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^2 represents a group  ,

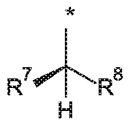
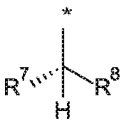
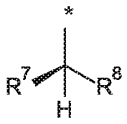
wherein "*" indicates the point of attachment to the nitrogen atom to which R^2 is attached;

R^7 represents a C_1-C_2-alkyl group;

R^8 represents a -C(=O)-NH_2 group,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers isomeric mixtures of compounds of formula (I), *supra*, in which:

R^2 represents a group  and  , in a ratio of about 99:1 and higher, in favour of  ,

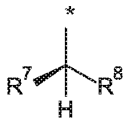
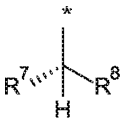
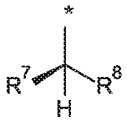
wherein "*" indicates the point of attachment to the nitrogen atom to which R^2 is attached;

R^7 represents a C_1-C_2-alkyl group;

R^8 represents a -C(=O)-NH_2 group,

and tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers isomeric mixtures of compounds of formula (I), *supra*, in which:

R^2 represents a group  and  , in a ratio of about 98:2 and higher, in favour of  ,

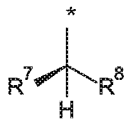
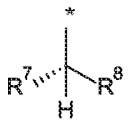
wherein "*" indicates the point of attachment to the nitrogen atom to which R^2 is attached;

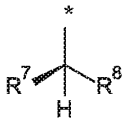
R^7 represents a C_1-C_2-alkyl group;

R^8 represents a -C(=O)-NH_2 group,

and tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers isomeric mixtures of compounds of formula (I), *supra*, in which:

R^2 represents a group  and  , in a ratio of about 95:5 and higher,

in favour of  ,

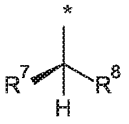
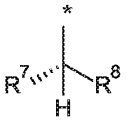
wherein "*" indicates the point of attachment to the nitrogen atom to which R^2 is attached;

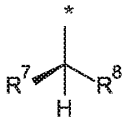
R^7 represents a C_1-C_2-alkyl group;

R^8 represents a -C(=O)-NH_2 group,

and tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers isomeric mixtures of compounds of formula (I), *supra*, in which:

R^2 represents a group  and  , in a ratio of about 90:10 and higher,

in favour of  ,

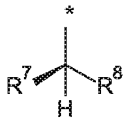
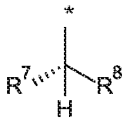
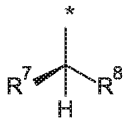
wherein "*" indicates the point of attachment to the nitrogen atom to which R^2 is attached;

R^7 represents a C_1-C_2-alkyl group;

R^8 represents a -C(=O)-NH_2 group,

and tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers isomeric mixtures of compounds of formula (I), *supra*, in which:

R^2 represents a group  and  , in a ratio of about 80:20 and higher, in favour of  ,

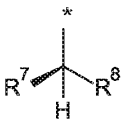
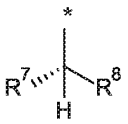
wherein "*" indicates the point of attachment to the nitrogen atom to which R^2 is attached;

R^7 represents a C_1-C_2-alkyl group;

R^8 represents a -C(=O)-NH_2 group,

and tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers isomeric mixtures of compounds of formula (I), *supra*, in which:

R^2 represents a group  and  , in a ratio of about 50:50, that is, racemic mixtures in case of compounds featuring no further element of chirality,

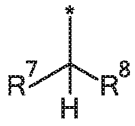
wherein "*" indicates the point of attachment to the nitrogen atom to which R^2 is attached;

R^7 represents a C_1-C_2-alkyl group;

R^8 represents a -C(=O)-NH_2 group,

and tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^2 represents a group  ,

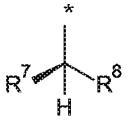
wherein "*" indicates the point of attachment to the nitrogen atom to which R^2 is attached;

R^7 represents a methyl group;

R^8 represents a -C(=O)-NH_2 group,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^2 represents a group  ,

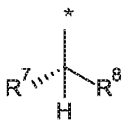
wherein "*" indicates the point of attachment to the nitrogen atom to which R^2 is attached;

R^7 represents a methyl group;

R^8 represents a -C(=O)-NH_2 group,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^2 represents a group  ,

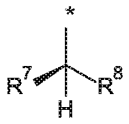
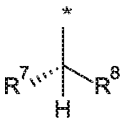
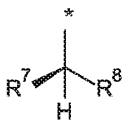
wherein "*" indicates the point of attachment to the nitrogen atom to which R^2 is attached;

R^7 represents a methyl group;

R^8 represents a -C(=O)-NH_2 group,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers isomeric mixtures of compounds of formula (I), *supra*, in which:

R^2 represents a group  and  , in a ratio of about 99:1 and higher, in favour of  ,

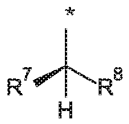
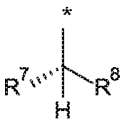
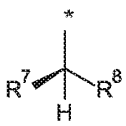
wherein "*" indicates the point of attachment to the nitrogen atom to which R^2 is attached;

R^7 represents a methyl group;

R^8 represents a -C(=O)-NH_2 group,

and tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers isomeric mixtures of compounds of formula (I), *supra*, in which:

R^2 represents a group  and  , in a ratio of about 98:2 and higher, in favour of  ,

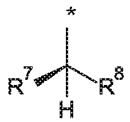
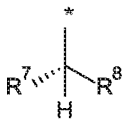
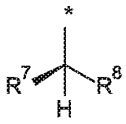
wherein "*" indicates the point of attachment to the nitrogen atom to which R^2 is attached;

R^7 represents a methyl group;

R^8 represents a -C(=O)-NH_2 group,

and tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers isomeric mixtures of compounds of formula (I), *supra*, in which:

R^2 represents a group  and  , in a ratio of about 95:5 and higher, in favour of  ,

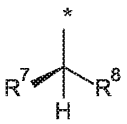
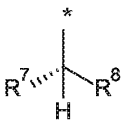
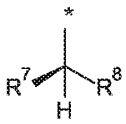
wherein "*" indicates the point of attachment to the nitrogen atom to which R^2 is attached;

R^7 represents a methyl group;

R^8 represents a -C(=O)-NH_2 group,

and tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers isomeric mixtures of compounds of formula (I), *supra*, in which:

R^2 represents a group  and  , in a ratio of about 90:10 and higher, in favour of  ,

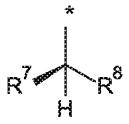
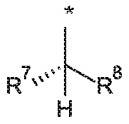
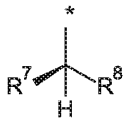
wherein "*" indicates the point of attachment to the nitrogen atom to which R^2 is attached;

R^7 represents a methyl group;

R^8 represents a -C(=O)-NH_2 group,

and tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers isomeric mixtures of compounds of formula (I), *supra*, in which:

R^2 represents a group  and  , in a ratio of about 80:20 and higher, in favour of  ,

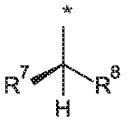
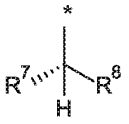
wherein "*" indicates the point of attachment to the nitrogen atom to which R^2 is attached;

R^7 represents a methyl group;

R^8 represents a -C(=O)-NH_2 group,

and tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers isomeric mixtures of compounds of formula (I), *supra*, in which:

R^2 represents a group  and  , in a ratio of about 50:50, that is, racemic mixtures in case of compounds featuring no further element of chirality,

wherein "*" indicates the point of attachment to the nitrogen atom to which R^2 is attached;

R^7 represents a methyl group;

R^8 represents a -C(=O)-NH_2 group,

and tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^3 represents a group selected from methyl and -NH_2,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^3 represents a $-NH_2$ group,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^3 represents a methyl group,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^4 represents a phenyl or pyridinyl group optionally substituted, one, two, or three times, each substituent independently selected from a halogen atom or a group selected from cyano, nitro, C_1-C_4-alkyl, (phenyl)-(C_1-C_2-alkyl)-, (5-membered heteroaryl)-(C_1-C_2-alkyl)-, (C_3-C_7-cycloalkyl)-(C_1-C_2-alkyl)-, ((R^9)O)-(C_1-C_4-alkyl)-, C_1-C_4-haloalkyl, C_3-C_7-cycloalkyl, $-OR^9$, $-N(R^{10})(R^{11})$, $((R^{10})(R^{11})N)$-(C_1-C_3-alkyl)-, $-C(=O)-N(R^{12})(R^{13})$, $S(=O)_n-R^{14}$, $-C(=O)R^{14}$, $-C(=O)-OR^{17}$, and a 5-membered heteroaryl group which itself is optionally substituted with one or two methyl groups,

or two substituents attached to adjacent carbon atoms of said phenyl or pyridinyl group together form a bivalent group selected from $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_2-O-$, $-(CH_2)_3-O-$, $-CH_2-O-CH_2-$, $-O-CH_2-O-$, $-O-CH_2-CH_2-O-$ and $-O-CF_2-O-$,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^4 represents a phenyl or pyridinyl group optionally substituted, one, two, or three times, each substituent independently selected from a halogen atom or a group selected from cyano, nitro, C_1-C_4-alkyl, (phenyl)-(C_1-C_2-alkyl)-, (5-membered heteroaryl)-(C_1-C_2-alkyl)-

, C_1-C_4-hydroxyalkyl, C_1-C_4-haloalkyl, -OR^9, -$N(R^{10})(R^{11})$, -$C(=O)$-$N(R^{12})(R^{13})$, $S(=O)_n$-R^{14}, and a 5-membered heteroaryl group which itself is optionally substituted with one or two methyl groups,

or two substituents attached to adjacent carbon atoms of said phenyl or pyridinyl group together form a bivalent group selected from –$(CH_2)_3$-, -$(CH_2)_4$-, -$(CH_2)_2$-O-, -$(CH_2)_3$-O-, -CH_2-O-CH_2-, -O-CH_2-O-, -O-CH_2-CH_2-O- and -O-CF_2-O-,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^4 represents a phenyl or pyridinyl group optionally substituted, one, two, or three times, each substituent independently selected from a halogen atom or a group selected from cyano, C_1-C_3-alkyl, ((R^9)O)-(C_1-C_3-alkyl)-, C_1-C_3-fluoroalkyl, -OR^9, -$N(R^{10})(R^{11})$, -$C(=O)$-$N(R^{12})(R^{13})$, $S(=O)_n$-R^{14} and -$C(=O)$-OR^{17},

or two substituents attached to adjacent carbon atoms of said phenyl or pyridinyl group together form a bivalent group selected from –$(CH_2)_3$-, -O-CH_2-O- and -O-CF_2-O-,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^4 represents a phenyl group optionally substituted, one, two, or three times, each substituent independently selected from a halogen atom or a group selected from cyano, C_1-C_3-alkyl, ((R^9)O)-(C_1-C_3-alkyl)-, C_1-C_3-fluoroalkyl, -OR^9, -$N(R^{10})(R^{11})$, -$C(=O)$-$N(R^{12})(R^{13})$, $S(=O)_n$-R^{14} and -$C(=O)$-OR^{17},

or two substituents attached to adjacent carbon atoms of said phenyl or pyridinyl group together form a bivalent group selected from –$(CH_2)_3$-, -O-CH_2-O- and -O-CF_2-O-,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^4 represents a pyridinyl group optionally substituted, one, two, or three times, each substituent independently selected from a halogen atom or a group selected from cyano, C_1-C_3-alkyl, $((R^9)O)$-(C_1-C_3-alkyl)-, C_1-C_3-fluoroalkyl, $-OR^9$, $-N(R^{10})(R^{11})$, $-C(=O)-N(R^{12})(R^{13})$, $S(=O)_n-R^{14}$ and $-C(=O)-OR^{17}$,

or two substituents attached to adjacent carbon atoms of said phenyl or pyridinyl group together form a bivalent group selected from $-(CH_2)_3-$, $-O-CH_2-O-$ and $-O-CF_2-O-$,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^4 represents a phenyl group optionally substituted, one, two, or three times, each substituent independently selected from a fluorine atom, a chlorine atom and a bromine atom, or a group selected from cyano, C_1-C_3-alkyl, C_1-C_3-hydroxyalkyl C_1-C_3-fluoroalkyl, $-OR^9$, $-N(R^{10})(R^{11})$, $-C(=O)-N(R^{12})(R^{13})$ and $S(=O)_n-R^{14}$,

or two substituents attached to adjacent carbon atoms of said phenyl group together form a bivalent group selected from $-(CH_2)_3-$, $-O-CH_2-O-$ and $-O-CF_2-O-$,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^4 represents a pyridinyl group optionally substituted, one, two, or three times, each substituent independently selected from a fluorine atom, a chlorine atom and a bromine atom, or a group selected from cyano, C_1-C_3-alkyl, C_1-C_3-hydroxyalkyl, C_1-C_3-fluoroalkyl, $-OR^9$, $-N(R^{10})(R^{11})$, $-C(=O)-N(R^{12})(R^{13})$ and $S(=O)_n-R^{14}$,

or two substituents attached to adjacent carbon atoms of said pyridinyl group together form a bivalent group selected from $-(CH_2)_3-$, $-O-CH_2-O-$ and $-O-CF_2-O-$,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^4 represents a phenyl or pyridinyl group optionally substituted, one or two times, each substituent independently selected from a fluorine atom and a chlorine atom, or a group selected from C_1-C_2-alkyl, C_1-C_2-fluoroalkyl, -OR^9;

R^9 represents a group selected from C_1-C_2-alkyl, benzyl, C_1-C_2-fluoroalkyl, (C_1-C_2-alkoxy)-C_2-alkyl- and phenyl,

wherein the phenyl group within said benzyl group and said phenyl group itself are optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a methyl group,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^4 represents a phenyl or pyridinyl group optionally substituted, one or two times, each substituent independently selected from a halogen atom or a group selected from C_1-C_2-alkyl, C_1-C_2-fluoroalkyl, -OR^9, -$N(R^{10})(R^{11})$, -$C(=O)$-$N(R^{12})(R^{13})$ and -$C(=O)$-OR^{17};

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^4 represents a phenyl group optionally substituted, one or two times, each substituent independently selected from a halogen atom or a group selected from C_1-C_2-alkyl, C_1-C_2-fluoroalkyl, -OR^9, -$N(R^{10})(R^{11})$, -$C(=O)$-$N(R^{12})(R^{13})$ and -$C(=O)$-OR^{17};

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^4 represents a pyridinyl group optionally substituted, one or two times, each substituent independently selected from a halogen atom or a group selected from C_1-C_2-alkyl, C_1-C_2-fluoroalkyl, $-OR^9$, $-N(R^{10})(R^{11})$, $-C(=O)-N(R^{12})(R^{13})$ and $-C(=O)-OR^{17}$;

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^4 represents a phenyl or pyridinyl group optionally substituted, one or two times, each substituent independently selected from a fluorine atom and a chlorine atom, or a group selected from C_1-C_2-alkyl, C_1-C_2-fluoroalkyl, $-OR^9$,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^4 represents a phenyl group optionally substituted, one or two times, each substituent independently selected from a fluorine atom and a chlorine atom, or a group selected from C_1-C_2-alkyl, C_1-C_2-fluoroalkyl, $-OR^9$;

R^9 represents a group selected from C_1-C_2-alkyl, benzyl, C_1-C_2-fluoroalkyl, (C_1-C_2-alkoxy)-C_2-alkyl- and phenyl,

wherein the phenyl group within said benzyl group and said phenyl group itself are optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a methyl group,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^4 represents a phenyl group optionally substituted, one or two times, each substituent independently selected from a fluorine atom and a chlorine atom, or a group selected from C_1-C_2-alkyl, C_1-C_2-fluoroalkyl, -OR^9,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^4 represents a pyridinyl group optionally substituted, one or two times, each substituent independently selected from a fluorine atom and a chlorine atom, or a group selected from C_1-C_2-alkyl, C_1-C_2-fluoroalkyl, -OR^9;

R^9 represents a group selected from C_1-C_2-alkyl, benzyl, C_1-C_2-fluoroalkyl, (C_1-C_2-alkoxy)-C_2-alkyl- and phenyl,

wherein the phenyl group within said benzyl group and said phenyl group itself are optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a methyl group,

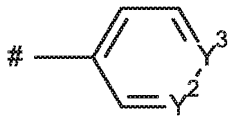
and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^4 represents a pyridinyl group optionally substituted, one or two times, each substituent independently selected from a fluorine atom and a chlorine atom, or a group selected from C_1-C_2-alkyl, C_1-C_2-fluoroalkyl, -OR^9,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:



R^4 represents a group

wherein "#" indicates the point of attachment to the carbonyl group to which R^4 is attached;

Y^2 represents -C(H)= or -N=;

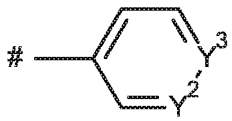
Y^3 represents -C(R^{27})= or -N=,

with the proviso that if Y^2 represents -N=, Y^3 represents -C(R^{27})=, and if Y^3 represents -N=, Y^2 represents -C(H)=;

R^{27} represents a halogen atom or a group selected from C_1-C_2-alkyl, C_1-C_2-fluoroalkyl, -OR^9, -N(R^{10})(R^{11}), -C(=O)-N(R^{12})(R^{13}) and -C(=O)-OR^{17},

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:



R^4 represents a group

wherein "#" indicates the point of attachment to the carbonyl group to which R^4 is attached;

Y^2 represents -C(H)= or -N=;

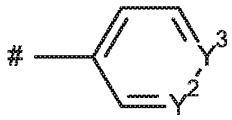
Y^3 represents -C(R^{27})= or -N=,

with the proviso that if Y^2 represents -N=, Y^3 represents -C(R^{27})=, and if Y^3 represents -N=, Y^2 represents -C(H)=;

R^{27} represents a fluorine atom, a chlorine atom, or a group selected from C_1-C_2-alkoxy, benzyloxy and C_1-C_2-fluoroalkoxy,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^4 represents a group 

wherein "#" indicates the point of attachment to the carbonyl group to which R^4 is attached;

Y^2 represents -C(H)= and -N=;

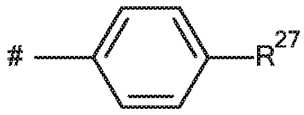
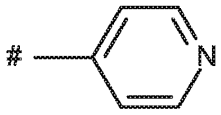
Y^3 represents -C(R^{27})= and -N=,

with the proviso that if Y^2 represents -N=, Y^3 represents -C(R^{27})=, and if Y^3 represents -N=, Y^2 represents -C(H)=;

R^{27} represents a fluorine atom, a chlorine atom, or a group selected from C_1-C_2-alkoxy, benzyloxy and C_1-C_2-fluoroalkoxy,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

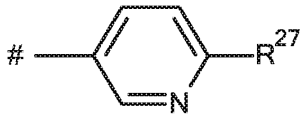
R^4 represents a group  or 

wherein "#" indicates the point of attachment to the carbonyl group to which R^4 is attached;

R^{27} represents a fluorine atom, a chlorine atom, or a group selected from C_1-C_2-alkoxy, benzyloxy and C_1-C_2-fluoroalkoxy,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:



R^4 represents a group

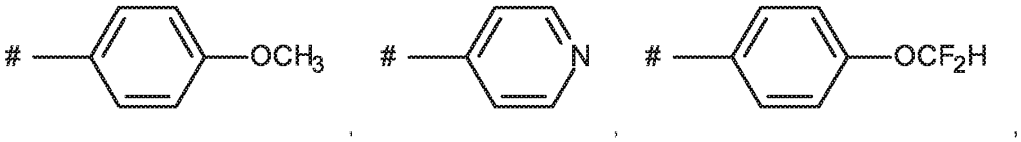
wherein "#" indicates the point of attachment to the carbonyl group to which R^4 is attached;

R^{27} represents a fluorine atom, a chlorine atom, or a group selected from C_1-C_2-alkoxy, benzyloxy and C_1-C_2-fluoroalkoxy,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

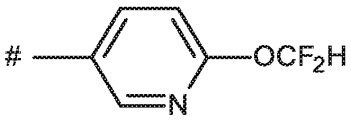
R^4 represents a group selected from:



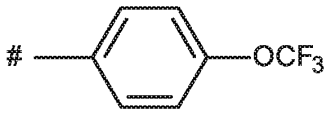
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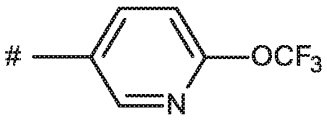
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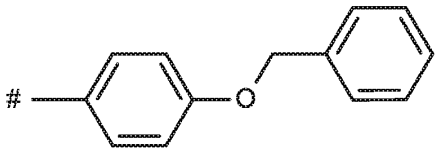
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and



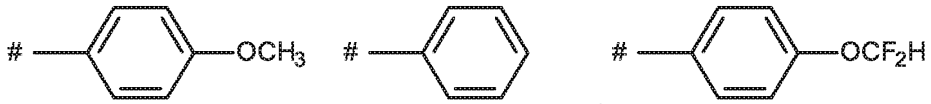
,

wherein "#" indicates the point of attachment to the carbonyl group to which R^4 is attached,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^4 represents a group selected from:



wherein "#" indicates the point of attachment to the carbonyl group to which R^4 is attached,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^5 and R^6 represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_2-alkyl and (C_1-C_2-alkyl)-C(=O)-,

or

R^5 and R^6, together with the nitrogen atom to which they are attached, represent a monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group which is optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a bromine atom, or a group selected from oxo, hydroxy, C_1-C_2-alkyl and (C_1-C_2-alkyl)-C(=O)-,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^5 and R^6 represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_2-alkyl and (C_1-C_2-alkyl)-C(=O)-,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^5 and R^6, together with the nitrogen atom to which they are attached, represent a monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group which is optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a bromine atom, or a group selected from oxo, hydroxy, C_1-C_2-alkyl and (C_1-C_2-alkyl)-C(=O)-,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^5 and R^6 represent, independently from each occurrence, a hydrogen atom or a C_1-C_2-alkyl group,

or

R^5 and R^6, together with the nitrogen atom to which they are attached, represent a monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group which is optionally substituted one or two times, each substituent independently selected from a fluorine atom or a group selected from hydroxy and C_1-C_2-alkyl,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^5 and R^6 represent, independently from each occurrence, a hydrogen atom or a C_1-C_2-alkyl group,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^5 and R^6, together with the nitrogen atom to which they are attached, represent a monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group which is optionally substituted one or two times, each substituent independently selected from a fluorine atom or a group selected from hydroxy and C_1-C_2-alkyl,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^7 represents a hydrogen atom,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^7 represents a methyl group,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^7 represents an ethyl group,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^7 represents a hydrogen atom or a C_1-C_2-alkyl group;

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^9 represents a hydrogen atom or a group selected from C_1-C_4-alkyl, (phenyl)-(C_1-C_2-alkyl)-, C_1-C_4-haloalkyl, C_2-C_3-hydroxyalkyl, (C_1-C_2-alkoxy)-C_2-alkyl-, ((C_1-C_2-alkyl)-C(=O)-O)-C_2-alkyl-, -$C(R^{18})(R^{19})$-C(=O)-OR^{17}, -$C(R^{18})(R^{19})$-C(=O)-$N(R^{20})(R^{21})$, -C(=O)-$N(R^{20})(R^{21})$ and phenyl,

wherein the phenyl group within said (phenyl)-(C_1-C_2-alkyl)- group and said phenyl group itself are optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a bromine atom, or a group selected from cyano, methyl, trifluoromethyl and methoxy,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^9 represents a hydrogen atom or a group selected from C_1-C_4-alkyl, (phenyl)-(C_1-C_2-alkyl)-, C_1-C_4-haloalkyl, C_2-C_3-hydroxyalkyl, (C_1-C_2-alkoxy)-C_2-alkyl-, ((C_1-C_2-alkyl)-C(=O)-O)-C_2-alkyl-, -$C(R^{18})(R^{19})$-C(=O)-OR^{17}, -$C(R^{18})(R^{19})$-C(=O)-$N(R^{20})(R^{21})$ and phenyl,

wherein the phenyl group within said (phenyl)-(C_1-C_2-alkyl)- group and said phenyl group itself are optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a bromine atom, or a group selected from methyl, trifluoromethyl and methoxy,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^9 represents a hydrogen atom or a group selected from C_1-C_2-alkyl, benzyl, C_1-C_2-fluoroalkyl, C_2-hydroxyalkyl, (C_1-C_2-alkoxy)-C_2-alkyl-, ((C_1-C_2-alkyl)-C(=O)-O)-C_2-alkyl-, -$C(R^{18})(R^{19})$-C(=O)-OR^{17}, -$C(R^{18})(R^{19})$-C(=O)-$N(R^{20})(R^{21})$, -C(=O)-$N(R^{20})(R^{21})$ and phenyl,

wherein the phenyl group within said benzyl group and said phenyl group itself are optionally substituted one or two times, each substituent independently selected from a fluorine atom and a chlorine atom, or a group selected from cyano and methyl,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^9 represents a hydrogen atom or a group selected from C_1-C_2-alkyl, benzyl, C_1-C_2-fluoroalkyl, (C_1-C_2-alkoxy)-C_2-alkyl-, ((C_1-C_2-alkyl)-C(=O)-O)-C_2-alkyl-, -C(R^{18})(R^{19})-C(=O)-OR^{17}, -C(R^{18})(R^{19})-C(=O)-N(R^{20})(R^{21}) and phenyl,

wherein the phenyl group within said benzyl group and said phenyl group itself are optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a methyl group,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^9 represents a group selected from C_1-C_2-alkyl, benzyl, C_1-C_2-fluoroalkyl, (C_1-C_2-alkoxy)-C_2-alkyl- and phenyl,

wherein the phenyl group within said benzyl group and said phenyl group itself are optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a methyl group;

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^9 represents a hydrogen atom or a group selected from C_1-C_2-alkyl, benzyl, C_1-C_2-fluoroalkyl, (C_1-C_2-alkoxy)-C_2-alkyl-, ((C_1-C_2-alkyl)-C(=O)-O)-C_2-alkyl-, -C(R^{18})(R^{19})-C(=O)-N(R^{20})(R^{21}), -C(=O)-N(R^{20})(R^{21}) and phenyl,

wherein the phenyl group within said benzyl group and said phenyl group itself are optionally substituted one or two times, each substituent independently selected from a fluorine atom and a chlorine atom, or a group selected from cyano and methyl,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^9 represents a hydrogen atom or a group selected from C_1-C_2-alkyl, benzyl, C_1-C_2-fluoroalkyl and phenyl,

wherein the phenyl group within said benzyl group and said phenyl group itself are optionally substituted one or two times, each substituent independently selected from a fluorine atom and a chlorine atom, or a group selected from cyano and methyl,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{10} and R^{11} represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_2-alkyl, C_1-C_2-haloalkyl, C_2-C_3-hydroxyalkyl, (C_1-C_2-alkoxy)-C_2-alkyl-, ((R^{22})(R^{23})N)-C_2-alkyl, (C_3-C_7-cycloalkyl)-(C_1-C_2-alkyl)-, (C_1-C_2-alkyl)-C(=O)-, C_3-C_7-cycloalkyl, (C_3-C_7-cycloalkyl)-C(=O)-, (phenyl)-(C_1-C_2-alkyl)-, (phenyl)-(C_1-C_2-alkyl)-C(=O)- and (phenyl)-(C_1-C_2-alkyl)-O-C(=O)-,

wherein C_3-C_7-cycloalkyl, and the C_3-C_7-cycloalkyl within said (C_3-C_7-cycloalkyl)-(C_1-C_2-alkyl)- and (C_3-C_7-cycloalkyl)-C(=O)- groups are optionally substituted one or two times, each substituent independently selected from a fluorine atom or a group selected from cyano, C_1-C_2-alkyl and C_1-C_2-haloalkyl,

and wherein the phenyl groups within said (phenyl)-(C_1-C_2-alkyl)-, (phenyl)-(C_1-C_2-alkyl)-C(=O)- and (phenyl)-(C_1-C_2-alkyl)-O-C(=O)- groups are optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a bromine atom, or a group selected from methyl, trifluoromethyl and methoxy,

or

R^{10} and R^{11}, together with the nitrogen atom to which they are attached, represent a monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group, or a bicyclic nitrogen containing 5- to 10-membered heterocycloalkyl group, which are optionally substituted one, two or three times, each substituent independently selected from a halogen atom or a group selected from cyano, oxo, hydroxy, C_1-C_2-alkyl, C_1-C_2-haloalkyl, (C_1-C_2-alkyl)-C(=O)-, C_1-C_2-alkoxy, -N(R^{22})(R^{23}), and a monocyclic 4- to 7-membered heterocycloalkyl group,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{10} and R^{11} represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_2-alkyl, C_1-C_2-haloalkyl, C_2-C_3-hydroxyalkyl, (C_1-C_2-alkoxy)-C_2-alkyl-, ((R^{22})(R^{23})N)-C_2-alkyl, (C_3-C_7-cycloalkyl)-(C_1-C_2-alkyl)-, (C_1-C_2-alkyl)-C(=O)-, C_3-C_7-cycloalkyl, (C_3-C_7-cycloalkyl)-C(=O)-, (phenyl)-(C_1-C_2-alkyl)-, (phenyl)-(C_1-C_2-alkyl)-C(=O)- and (phenyl)-(C_1-C_2-alkyl)-O-C(=O)-,

wherein C_3-C_7-cycloalkyl, and the C_3-C_7-cycloalkyl within said (C_3-C_7-cycloalkyl)-(C_1-C_2-alkyl)- and (C_3-C_7-cycloalkyl)-C(=O)- groups are optionally substituted one or two times, each substituent independently selected from a fluorine atom or a group selected from cyano, C_1-C_2-alkyl and C_1-C_2-haloalkyl,

and wherein the phenyl groups within said (phenyl)-(C_1-C_2-alkyl)-, (phenyl)-(C_1-C_2-alkyl)-C(=O)- and (phenyl)-(C_1-C_2-alkyl)-O-C(=O)- groups are optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a bromine atom, or a group selected from methyl, trifluoromethyl and methoxy,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{10} and R^{11}, together with the nitrogen atom to which they are attached, represent a monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group, or a bicyclic nitrogen containing 5- to 10-membered heterocycloalkyl group, which are optionally substituted one, two or three times, each substituent independently selected from a halogen atom or

a group selected from cyano, oxo, hydroxy, C_1-C_2-alkyl, C_1-C_2-haloalkyl, (C_1-C_2-alkyl)-C(=O)-, C_1-C_2-alkoxy, -N(R^{22})(R^{23}), and a monocyclic 4- to 7-membered heterocycloalkyl group,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{10} and R^{11} represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_2-alkyl, C_1-C_2-haloalkyl, C_2-C_3-hydroxyalkyl, (C_1-C_2-alkoxy)-C_2-alkyl-, ((R^{22})(R^{23})N)-C_2-alkyl, (C_1-C_2-alkyl)-C(=O)-, C_3-C_5-cycloalkyl, (C_3-C_5-cycloalkyl)-C(=O)-, (phenyl)-(C_1-C_2-alkyl)-, (phenyl)-(C_1-C_2-alkyl)-C(=O)- and (phenyl)-(C_1-C_2-alkyl)-O-C(=O)-,

wherein the phenyl groups within said (phenyl)-(C_1-C_2-alkyl)-, (phenyl)-(C_1-C_2-alkyl)-C(=O)- and (phenyl)-(C_1-C_2-alkyl)-O-C(=O)- groups are optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a bromine atom, or a group selected from methyl, trifluoromethyl and methoxy,

or

R^{10} and R^{11}, together with the nitrogen atom to which they are attached, represent a monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group, or a bicyclic nitrogen containing 6- to 10-membered heterocycloalkyl group, which are optionally substituted one, two or three times, each substituent independently selected from a halogen atom or a group selected from cyano, oxo, hydroxy, C_1-C_2-alkyl, C_1-C_2-haloalkyl, (C_1-C_2-alkyl)-C(=O)-, C_1-C_2-alkoxy, -N(R^{22})(R^{23}), and a monocyclic 4- to 7-membered heterocycloalkyl group,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{10} and R^{11} represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_2-alkyl, C_1-C_2-haloalkyl, C_2-C_3-hydroxyalkyl, (C_1-C_2-alkoxy)-C_2-alkyl-, ((R^{22})(R^{23})N)-C_2-alkyl, (C_1-C_2-alkyl)-C(=O)-, C_3-C_5-cycloalkyl, (C_3-C_5-cycloalkyl)-C(=O)-,

(phenyl)-(C_1-C_2-alkyl)-, (phenyl)-(C_1-C_2-alkyl)-C(=O)- and (phenyl)-(C_1-C_2-alkyl)-O-C(=O)-,

wherein the phenyl groups within said (phenyl)-(C_1-C_2-alkyl)-, (phenyl)-(C_1-C_2-alkyl)-C(=O)- and (phenyl)-(C_1-C_2-alkyl)-O-C(=O)- groups are optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a bromine atom, or a group selected from methyl, trifluoromethyl and methoxy,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{10} and R^{11}, together with the nitrogen atom to which they are attached, represent a monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group, or a bicyclic nitrogen containing 6- to 10-membered heterocycloalkyl group, which are optionally substituted one, two or three times, each substituent independently selected from a halogen atom or a group selected from cyano, oxo, hydroxy, C_1-C_2-alkyl, C_1-C_2-haloalkyl, (C_1-C_2-alkyl)-C(=O)-, C_1-C_2-alkoxy, -N(R^{22})(R^{23}), and a monocyclic 4- to 7-membered heterocycloalkyl group,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{10} and R^{11} represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_2-alkyl, C_1-C_2-fluoroalkyl, (C_3-C_5-cycloalkyl)-(C_1-C_2-alkyl)- (C_1-C_2-alkyl)-C(=O)-, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-(C=O)-, (phenyl)-(C_1-C_2-alkyl)-, (phenyl)-(C_1-C_2-alkyl)-C(=O)- and (phenyl)-(C_1-C_2-alkyl)-O-C(=O)-,

wherein C_3-C_7-cycloalkyl, and the C_3-C_5-cycloalkyl within said (C_3-C_5-cycloalkyl)-(C_1-C_2-alkyl)- and the C_3-C_7-cycloalkyl within the C_3-C_7-cycloalkyl-(C=O)- groups are optionally substituted one or two times, each substituent independently selected from a fluorine atom or a group selected from cyano, C_1-C_2-alkyl and C_1-C_2-fluoroalkyl,

and wherein the phenyl groups within said (phenyl)-(C_1-C_2-alkyl)-, (phenyl)-(C_1-C_2-alkyl)-C(=O)- and (phenyl)-(C_1-C_2-alkyl)-O-C(=O)- groups are optionally substituted

one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a methyl group,

or

R^{10} and R^{11}, together with the nitrogen atom to which they are attached, represent a monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group which is optionally substituted one or two times, each substituent independently selected from a fluorine atom or a group selected from cyano, oxo, C_1-C_2-alkyl, C_1-C_2-fluoroalkyl and (C_1-C_2-alkyl)-C(=O)-,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{10} and R^{11} represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_2-alkyl, C_1-C_2-fluoroalkyl, (C_3-C_5-cycloalkyl)-(C_1-C_2-alkyl)- (C_1-C_2-alkyl)-C(=O)-, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-(C=O)-, (phenyl)-(C_1-C_2-alkyl)-, (phenyl)-(C_1-C_2-alkyl)-C(=O)- and (phenyl)-(C_1-C_2-alkyl)-O-C(=O)-,

wherein C_3-C_7-cycloalkyl, and the C_3-C_5-cycloalkyl within said (C_3-C_5-cycloalkyl)-(C_1-C_2-alkyl)- and the C_3-C_7-cycloalkyl within the C_3-C_7-cycloalkyl-(C=O)- groups are optionally substituted one or two times, each substituent independently selected from a fluorine atom or a group selected from cyano, C_1-C_2-alkyl and C_1-C_2-fluoroalkyl,

and wherein the phenyl groups within said (phenyl)-(C_1-C_2-alkyl)-, (phenyl)-(C_1-C_2-alkyl)-C(=O)- and (phenyl)-(C_1-C_2-alkyl)-O-C(=O)- groups are optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a methyl group,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{10} and R^{11}, together with the nitrogen atom to which they are attached, represent a monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group which is optionally substituted one or two times, each substituent independently selected from a fluorine

atom or a group selected from cyano, oxo, C_1-C_2-alkyl, C_1-C_2-fluoroalkyl and (C_1-C_2-alkyl)-C(=O)-,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{10} and R^{11} represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_2-alkyl, C_1-C_2-fluoroalkyl, (C_1-C_2-alkyl)-C(=O)-, (phenyl)-(C_1-C_2-alkyl)-, (phenyl)-(C_1-C_2-alkyl)-C(=O)- and (phenyl)-(C_1-C_2-alkyl)-O-C(=O)-,

wherein the phenyl groups within said (phenyl)-(C_1-C_2-alkyl)-, (phenyl)-(C_1-C_2-alkyl)-C(=O)- and (phenyl)-(C_1-C_2-alkyl)-O-C(=O)- groups are optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a methyl group,

or

R^{10} and R^{11}, together with the nitrogen atom to which they are attached, represent a monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group which is optionally substituted one or two times, each substituent independently selected from a fluorine atom or a group selected from oxo, C_1-C_2-alkyl, C_1-C_2-fluoroalkyl and (C_1-C_2-alkyl)-C(=O)-,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{10} and R^{11} represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_2-alkyl, C_1-C_2-fluoroalkyl, (C_1-C_2-alkyl)-C(=O)-, (phenyl)-(C_1-C_2-alkyl)-, (phenyl)-(C_1-C_2-alkyl)-C(=O)- and (phenyl)-(C_1-C_2-alkyl)-O-C(=O)-,

wherein the phenyl groups within said (phenyl)-(C_1-C_2-alkyl)-, (phenyl)-(C_1-C_2-alkyl)-C(=O)- and (phenyl)-(C_1-C_2-alkyl)-O-C(=O)- groups are optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a methyl group,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{10} and R^{11}, together with the nitrogen atom to which they are attached, represent a monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group which is optionally substituted one or two times, each substituent independently selected from a fluorine atom or a group selected from oxo, C_1-C_2-alkyl, C_1-C_2-fluoroalkyl and (C_1-C_2-alkyl)-C(=O)-,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{10} and R^{11} represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_2-alkyl, (C_3-C_5-cycloalkyl)-(C_1-C_2-alkyl)-, C_3-C_7-cycloalkyl and (phenyl)-(C_1-C_2-alkyl)-O-C(=O)-,

wherein C_3-C_7-cycloalkyl, and the C_3-C_5-cycloalkyl within said (C_3-C_5-cycloalkyl)-(C_1-C_2-alkyl)- group are optionally substituted one or two times, each substituent independently selected from a fluorine atom or a group selected from cyano, methyl and C_1-fluoroalkyl,

and wherein the phenyl group within said (phenyl)-(C_1-C_2-alkyl)-O-C(=O)- group is optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a methyl group,

or

R^{10} and R^{11}, together with the nitrogen atom to which they are attached, represent a monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group which is optionally substituted one or two times, each substituent independently selected from a fluorine atom or a group selected from cyano, methyl and C_1-fluoroalkyl,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{10} and R^{11} represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_2-alkyl, (C_3-C_5-cycloalkyl)-(C_1-C_2-alkyl)-, C_3-C_7-cycloalkyl and (phenyl)-(C_1-C_2-alkyl)-O-C(=O)-,

wherein C_3-C_7-cycloalkyl, and the C_3-C_5-cycloalkyl within said (C_3-C_5-cycloalkyl)-(C_1-C_2-alkyl)- group are optionally substituted one or two times, each substituent independently selected from a fluorine atom or a group selected from cyano, methyl and C_1-fluoroalkyl,

and wherein the phenyl group within said (phenyl)-(C_1-C_2-alkyl)-O-C(=O)- group is optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a methyl group,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{10} and R^{11}, together with the nitrogen atom to which they are attached, represent a monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group which is optionally substituted one or two times, each substituent independently selected from a fluorine atom or a group selected from cyano, methyl and C_1-fluoroalkyl,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{10} and R^{11} represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_2-alkyl, C_3-C_7-cycloalkyl and (benzyl)-O-C(=O)-,

wherein C_3-C_7-cycloalkyl is optionally substituted one or two times, each substituent independently selected from a fluorine atom or a group selected from methyl and trifluoromethyl,

and wherein the phenyl group within said (benzyl)-O-C(=O)- group is optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a methyl group,

or

R^{10} and R^{11}, together with the nitrogen atom to which they are attached, represent a monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group which is optionally substituted one or two times, each substituent independently selected from a fluorine atom or a group selected from cyano, methyl and trifluoromethyl,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{10} and R^{11} represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_2-alkyl, C_3-C_7-cycloalkyl and (benzyl)-O-C(=O)-,

wherein C_3-C_7-cycloalkyl is optionally substituted one or two times, each substituent independently selected from a fluorine atom or a group selected from methyl and trifluoromethyl,

and wherein the phenyl group within said (benzyl)-O-C(=O)- group is optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a methyl group,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{10} and R^{11}, together with the nitrogen atom to which they are attached, represent a monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group which is optionally substituted one or two times, each substituent independently selected from a fluorine atom or a group selected from cyano, methyl and trifluoromethyl,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{10} and R^{11} represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_2-alkyl and (benzyl)-O-C(=O)-,

and wherein the phenyl group within said (benzyl)-O-C(=O)- group is optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a methyl group,

or

R^{10} and R^{11}, together with the nitrogen atom to which they are attached, represent a monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group which is optionally substituted one or two times, each substituent independently selected from a fluorine atom or a group selected from cyano, methyl and trifluoromethyl,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{10} and R^{11} represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_2-alkyl and (benzyl)-O-C(=O)-,

and wherein the phenyl group within said (benzyl)-O-C(=O)- group is optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a methyl group,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{12} and R^{13} represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-hydroxyalkyl, (C_1-C_4-alkoxy)-C_2-C_3-alkyl-, (C_1-C_4-haloalkoxy)-C_2-C_3-alkyl-, (phenoxy)-C_2-C_3-alkyl-, C_3-C_7-cycloalkyl, monocyclic 4- to 7-membered heterocycloalkyl and (phenyl)-(C_1-C_3-alkyl)-,

wherein C_3-C_7-cycloalkyl and monocyclic 4- to 7-membered heterocycloalkyl are optionally substituted one or two times, each substituent independently selected from a halogen atom or a group selected from oxo, C_1-C_2-alkyl and (C_1-C_2-alkyl)-C(=O)-,

and wherein the phenyl groups within said (phenoxy)-C_2-C_3-alkyl- group and said (phenyl)-(C_1-C_3-alkyl)- group are optionally substituted one or two times, each substituent independently selected from fluorine atom, a chlorine atom and a bromine atom, or a group selected from cyano, methyl, trifluoromethyl and methoxy,

or

R^{12} and R^{13}, together with the nitrogen atom to which they are attached, represent a monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group which is optionally substituted one or two times, each substituent independently selected from a halogen atom or a group selected from oxo, C_1-C_2-alkyl and (C_1-C_2-alkyl)-C(=O)-,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{12} and R^{13} represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-hydroxyalkyl, (C_1-C_4-alkoxy)-C_2-C_3-alkyl-, (C_1-C_4-haloalkoxy)-C_2-C_3-alkyl-, (phenoxy)-C_2-C_3-alkyl-, C_3-C_7-cycloalkyl, monocyclic 4- to 7-membered heterocycloalkyl and (phenyl)-(C_1-C_3-alkyl)-,

wherein C_3-C_7-cycloalkyl and monocyclic 4- to 7-membered heterocycloalkyl are optionally substituted one or two times, each substituent independently selected from a halogen atom or a group selected from oxo, C_1-C_2-alkyl and (C_1-C_2-alkyl)-C(=O)-,

and wherein the phenyl groups within said (phenoxy)-C_2-C_3-alkyl- group and said (phenyl)-(C_1-C_3-alkyl)- group are optionally substituted one or two times, each substituent independently selected from fluorine atom, a chlorine atom and a bromine atom, or a group selected from cyano, methyl, trifluoromethyl and methoxy,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{12} and R^{13}, together with the nitrogen atom to which they are attached, represent a monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group which is optionally substituted one or two times, each substituent independently selected from a halogen atom or a group selected from oxo, C_1-C_2-alkyl and (C_1-C_2-alkyl)-C(=O)-,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{12} and R^{13} represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-hydroxyalkyl, (C_1-C_2-alkoxy)-C_2-C_3-alkyl-, C_3-C_7-cycloalkyl, monocyclic 4- to 7-membered heterocycloalkyl and (phenyl)-(C_1-C_3-alkyl)-,

wherein C_3-C_7-cycloalkyl and monocyclic 4- to 7-membered heterocycloalkyl are optionally substitueted one or two times, each substituent independently selected from a halogen atom or a group selected from oxo, C_1-C_2-alkyl and (C_1-C_2-alkyl)-C(=O)-,

or

R^{12} and R^{13}, together with the nitrogen atom to which they are attached, represent a monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group which is optionally substituted one or two times, each substituent independently selected from a halogen atom or a group selected from oxo, C_1-C_2-alkyl and (C_1-C_2-alkyl)-C(=O)-,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{12} and R^{13} represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-hydroxyalkyl, (C_1-C_2-alkoxy)-C_2-C_3-alkyl-, C_3-C_7-cycloalkyl, monocyclic 4- to 7-membered heterocycloalkyl and (phenyl)-(C_1-C_3-alkyl)-,

wherein C_3-C_7-cycloalkyl and monocyclic 4- to 7-membered heterocycloalkyl are optionally substitueted one or two times, each substituent independently selected from a halogen atom or a group selected from oxo, C_1-C_2-alkyl and (C_1-C_2-alkyl)-C(=O)-,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{12} and R^{13}, together with the nitrogen atom to which they are attached, represent a monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group which is optionally substituted one or two times, each substituent independently selected from a halogen atom or a group selected from oxo, C_1-C_2-alkyl and (C_1-C_2-alkyl)-C(=O)-,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{12} and R^{13} represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_4-alkyl, C_1-C_4-fluoroalkyl, C_1-C_4-hydroxyalkyl, (C_1-C_4-alkoxy)-C_2-C_3-alkyl-, (C_1-C_2-fluoroalkoxy)-C_2-C_3-alkyl-, (phenoxy)-C_2-C_3-alkyl-, C_3-C_7-cycloalkyl, monocyclic 4- to 7-membered heterocycloalkyl and (phenyl)-(C_1-C_2-alkyl)-,

wherein C_3-C_7-cycloalkyl and monocyclic 4- to 7-membered heterocycloalkyl are optionally substituted one or two times, each substituent independently selected from a fluorine atom or a group selected from oxo, C_1-C_2-alkyl and (C_1-C_2-alkyl)-C(=O)-,

and wherein the phenyl groups within said (phenoxy)-C_2-C_3-alkyl- group and said (phenyl)-(C_1-C_2-alkyl)- group are optionally substituted one or two times, each substituent independently selected from a fluorine atom and a chlorine atom, or a group selected from methyl, trifluoromethyl and methoxy,

or

R^{12} and R^{13}, together with the nitrogen atom to which they are attached, represent a monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group which is optionally substituted one

or two times, each substituent independently selected from a halogen atom or a group selected from oxo, C_1-C_2-alkyl and (C_1-C_2-alkyl)-C(=O)-,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{12} and R^{13} represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_4-alkyl, C_1-C_4-fluoroalkyl, C_1-C_4-hydroxyalkyl, (C_1-C_4-alkoxy)-C_2-C_3-alkyl-, (C_1-C_2-fluoroalkoxy)-C_2-C_3-alkyl-, (phenoxy)-C_2-C_3-alkyl-, C_3-C_7-cycloalkyl, monocyclic 4- to 7-membered heterocycloalkyl and (phenyl)-(C_1-C_2-alkyl)-,

wherein C_3-C_7-cycloalkyl and monocyclic 4- to 7-membered heterocycloalkyl are optionally substituted one or two times, each substituent independently selected from a fluorine atom or a group selected from oxo, C_1-C_2-alkyl and (C_1-C_2-alkyl)-C(=O)-,

and wherein the phenyl groups within said (phenoxy)-C_2-C_3-alkyl- group and said (phenyl)-(C_1-C_2-alkyl)- group are optionally substituted one or two times, each substituent independently selected from a fluorine atom and a chlorine atom, or a group selected from methyl, trifluoromethyl and methoxy,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{12} and R^{13} represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_4-alkyl, C_1-C_4-fluoroalkyl, C_3-C_7-cycloalkyl, monocyclic 4- to 7-membered heterocycloalkyl and (phenyl)-(C_1-C_2-alkyl)-,

wherein C_3-C_7-cycloalkyl and monocyclic 4- to 7-membered heterocycloalkyl are optionally substitueted one or two times, each substituent independently selected from a fluorine atom or a group selected from oxo, C_1-C_2-alkyl and (C_1-C_2-alkyl)-C(=O)-,

or

R^{12} and R^{13}, together with the nitrogen atom to which they are attached, represent a monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group which is optionally

substituted one or two times, each substituent independently selected from a halogen atom or a group selected from oxo, C_1-C_2-alkyl and (C_1-C_2-alkyl)-C(=O)-,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{12} and R^{13} represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_4-alkyl, C_1-C_4-fluoroalkyl, C_3-C_7-cycloalkyl, monocyclic 4- to 7-membered heterocycloalkyl and (phenyl)-(C_1-C_2-alkyl)-,

wherein C_3-C_7-cycloalkyl and monocyclic 4- to 7-membered heterocycloalkyl are optionally substitueted one or two times, each substituent independently selected from a fluorine atom or a group selected from oxo, C_1-C_2-alkyl and (C_1-C_2-alkyl)-C(=O)-,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{12} and R^{13}, together with the nitrogen atom to which they are attached, represent a monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group which is optionally substituted one or two times, each substituent independently selected from a halogen atom or a group selected from oxo, C_1-C_2-alkyl and (C_1-C_2-alkyl)-C(=O)-,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{12} and R^{13} represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_4-alkyl, C_1-C_2-fluoroalkyl, C_1-C_2-hydroxyalkyl, (C_1-C_4-alkoxy)- C_2-C_3-alkyl-, (C_1-C_2-fluoroalkoxy)-C_2-C_3-alkyl-, (phenoxy)-C_2-C_3-alkyl-, C_3-C_7-cycloalkyl and (phenyl)-(C_1-C_2-alkyl)-,

wherein C_3-C_7-cycloalkyl is optionally substituted one or two times, each substituent independently selected from a fluorine atom or a methyl group,

and wherein the phenyl groups within said (phenoxy)-C_2-C_3-alkyl- group and said (phenyl)-(C_1-C_2-alkyl)- group are optionally substituted one or two times, each substituent independently selected from a fluorine atom and a chlorine atom, or a group selected from methyl, trifluoromethyl and methoxy,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{12} and R^{13} represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_4-alkyl, C_1-C_2-fluoroalkyl, C_1-C_2-hydroxyalkyl, (C_1-C_4-alkoxy)-C_2-alkyl-, (C_1-C_2-fluoroalkoxy)-C_2-alkyl-, (phenoxy)-C_2-alkyl-, C_3-C_7-cycloalkyl and (phenyl)-(C_1-C_2-alkyl)-,

wherein the phenyl groups within said (phenoxy)-C_2-alkyl- group and said (phenyl)-(C_1-C_2-alkyl)- group are optionally substituted one or two times, each substituent independently selected from fluorine atom and a chlorine atom, or a group selected from methyl, trifluoromethyl and methoxy,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{12} and R^{13} represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_2-alkyl, (C_1-C_4-alkoxy)-C_2-alkyl-, (C_1-C_2-fluoroalkoxy)-C_2-alkyl-, (phenoxy)-C_2-alkyl-, C_3-C_7-cycloalkyl and (phenyl)-(C_1-C_2-alkyl)-,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{14} represents a group selected from C_1-C_2-alkyl, C_1-C_2-haloalkyl and phenyl,

wherein the phenyl group is optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a bromine atom, or a group selected from methyl, trifluoromethyl and methoxy,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{14} represents a group selected from C_1-C_2-alkyl, C_1-C_2-haloalkyl and phenyl,

wherein the phenyl group is optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a bromine atom, or a group selected from methyl, trifluoromethyl and methoxy,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{14} represents a group selected from C_1-C_2-alkyl and C_1-C_2-haloalkyl,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{14} represents a group selected from methyl and trifluoromethyl,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{14} represents a methyl group,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{17} represents a C_1-C_4-alkyl group,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{17} represents a C_1-C_3-alkyl group,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{17} represents a C_1-C_2-alkyl group,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{17} represents a methyl group,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{17} represents an ethyl group,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{18} and R^{19} represent, independently from each occurrence, a hydrogen atom or a C_1-C_2-alkyl group,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{18} and R^{19} represent, independently from each occurrence, a hydrogen atom or a methyl group,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{18} and R^{19} both represent a methyl group,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{18} and R^{19} both represent a hydrogen atom,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{18} represents a hydrogen atom and R^{19} represents a methyl group,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{20} represents a hydrogen atom or a group selected from C_1-C_6-alkyl, C_3-C_4-alkenyl, C_3-C_4-alkynyl, C_1-C_3-alkoxy, C_3-C_7-cycloalkyl, bicyclic C_6-C_{11}-cycloalkyl, adamantyl, monocyclic 4- to 7-membered heterocycloalkyl, bicyclic 6- to 10-membered heterocycloalkyl, phenyl, naphthyl, and 5- to 10-membered heteroaryl,

wherein said C_1-C_6-alkyl group is optionally substituted one, two or three times, each substituent independently selected from a halogen atom or a group selected from hydroxy, cyano, C_1-C_3-alkoxy, -N(R^{22})(R^{23}), C_3-C_7-cycloalkyl, bicyclic C_6-C_{11}-cycloalkyl, adamantyl, monocyclic 4- to 7-membered heterocycloalkyl, bicyclic 6- to 10-membered heterocycloalkyl, phenyl, and 5- to 10-membered heteroaryl, said phenyl and 5- to 10-membered heteroaryl substituents themselves being optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a bromine atom, or a group selected from methyl, trifluoromethyl and methoxy,

wherein C_3-C_7-cycloalkyl, bicyclic C_6-C_{11}-cycloalkyl, adamantyl, monocyclic 4- to 7-membered heterocycloalkyl, bicyclic 6- to 10-membered heterocycloalkyl are optionally substituted one or two or three times, each substituent independently selected from a halogen atom or a group selected from cyano, oxo, hydroxy, C_1-C_2-alkyl and (C_1-C_2-alkyl)-C(=O)-,

and wherein said phenyl, naphthyl and 5- to 10-membered heteroaryl groups are optionally substituted one, two or three times, each substituent independently selected from a halogen atom or a group selected from cyano, C_1-C_2-alkyl, C_1-C_2-haloalkyl, C_1-C_2-alkoxy, C_1-C_2-haloalkoxy, -N(R^{22})(R^{23}) and -C(=O)-N(R^{24})(R^{25}),

R^{21} represents a hydrogen atom or a C_1-C_2-alkyl group,

or

R^{20} and R^{21}, together with the nitrogen atom to which they are attached, represent a monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group which is optionally benzocondensed, and which is optionally substituted one, two or three times, each substituent independently selected from a halogen atom or a group selected from cyano, oxo, hydroxy, C_1-C_2-alkyl, C_1-C_2-haloalkyl, (phenyl)-(C_1-C_2-alkyl)-, (C_1-C_2-alkyl)-C(=O)-, C_3-C_4-cycloalkyl, C_1-C_2-alkoxy, C_1-C_2-haloalkoxy, -N(R^{22})(R^{23}) and -C(=O)-N(R^{24})(R^{25});

R^{22} and R^{23} represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_2-alkyl and (C_1-C_2-alkyl)-C(=O)-;

R^{24} and R^{25} represent, independently from each occurrence, a hydrogen atom or a C_1-C_2-alkyl group,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{20} represents a hydrogen atom or a group selected from C_1-C_6-alkyl, C_3-C_4-alkenyl, C_3-C_4-alkynyl, C_1-C_3-alkoxy, C_3-C_7-cycloalkyl, bicyclic C_6-C_{11}-cycloalkyl, adamantyl, monocyclic 4- to 7-membered heterocycloalkyl, bicyclic 6- to 10-membered heterocycloalkyl, phenyl, naphthyl, and 5- to 10-membered heteroaryl,

wherein said C_1-C_6-alkyl group is optionally substituted one, two or three times, each substituent independently selected from a halogen atom or a group selected from hydroxy, cyano, C_1-C_3-alkoxy, -N(R^{22})(R^{23}), C_3-C_7-cycloalkyl, bicyclic C_6-C_{11}-cycloalkyl, adamantyl, monocyclic 4- to 7-membered heterocycloalkyl, bicyclic 6- to 10-membered heterocycloalkyl, phenyl, and 5- to 10-membered heteroaryl, said phenyl and 5- to 10-membered heteroaryl substituents themselves being optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a bromine atom, or a group selected from methyl, trifluoromethyl and methoxy,

wherein C_3-C_7-cycloalkyl, bicyclic C_6-C_{11}-cycloalkyl, adamantyl, monocyclic 4- to 7-membered heterocycloalkyl, bicyclic 6- to 10-membered heterocycloalkyl are optionally substituted one or two or three times, each substituent independently selected from a halogen atom or a group selected from cyano, oxo, hydroxy, C_1-C_2-alkyl and (C_1-C_2-alkyl)-C(=O)-,

and wherein said phenyl, naphthyl and 5- to 10-membered heteroaryl groups are optionally substituted one, two or three times, each substituent independently selected from a halogen atom or a group selected from cyano, C_1-C_2-alkyl, C_1-C_2-haloalkyl, C_1-C_2-alkoxy, C_1-C_2-haloalkoxy, -N(R^{22})(R^{23}) and -C(=O)-N(R^{24})(R^{25}),

R^{21} represents a hydrogen atom or a C_1-C_2-alkyl group,

R^{22} and R^{23} represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_2-alkyl and (C_1-C_2-alkyl)-C(=O)-;

R^{24} and R^{25} represent, independently from each occurrence, a hydrogen atom or a C_1-C_2-alkyl group,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{20} and R^{21}, together with the nitrogen atom to which they are attached, represent a monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group which is optionally benzocondensed, and which is optionally substituted one, two or three times, each substituent independently selected from a halogen atom or a group selected from cyano, oxo, hydroxy, C_1-C_2-alkyl, C_1-C_2-haloalkyl, (phenyl)-(C_1-C_2-alkyl)-, (C_1-C_2-alkyl)-C(=O)-, C_3-C_4-cycloalkyl, C_1-C_2-alkoxy, C_1-C_2-haloalkoxy, -N(R^{22})(R^{23}) and -C(=O)-N(R^{24})(R^{25});

R^{22} and R^{23} represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_2-alkyl and (C_1-C_2-alkyl)-C(=O)-;

R^{24} and R^{25} represent, independently from each occurrence, a hydrogen atom or a C_1-C_2-alkyl group,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{20} represents a hydrogen atom or a group selected from C_1-C_6-alkyl, C_3-C_4-alkenyl, C_3-C_4-alkynyl, C_1-C_3-alkoxy, C_3-C_7-cycloalkyl, bicyclic C_5-C_{11}-cycloalkyl, adamantyl, monocyclic 4- to 7-membered heterocycloalkyl, bicyclic 5- to 10-membered heterocycloalkyl, phenyl, naphthyl, and 5- to 10-membered heteroaryl,

wherein said C_1-C_6-alkyl group is optionally substituted one, two or three times, each substituent independently selected from a halogen atom or a group selected from hydroxy, cyano, C_1-C_3-alkoxy, -N(R^{22})(R^{23}), C_3-C_7-cycloalkyl, bicyclic C_5-C_{11}-cycloalkyl, adamantyl, monocyclic 4- to 7-membered heterocycloalkyl, bicyclic 5- to 10-membered heterocycloalkyl, phenyl, and 5- to 10-membered heteroaryl, said phenyl and 5- to 10-membered heteroaryl substituents themselves being optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a bromine atom, or a group selected from methyl, trifluoromethyl and methoxy,

and wherein C_3-C_7-cycloalkyl, bicyclic C_5-C_{11}-cycloalkyl, adamantyl, monocyclic 4- to 7-membered heterocycloalkyl, bicyclic 5- to 10-membered heterocycloalkyl are optionally substituted one or two or three times, each substituent independently selected from a halogen atom or a group selected from cyano, oxo, hydroxy, C_1-C_2-alkyl and (C_1-C_2-alkyl)-C(=O)-,

and wherein said phenyl, naphthyl and 5- to 10-membered heteroaryl groups are optionally substituted one, two or three times, each substituent independently selected from a halogen atom or a group selected from cyano, C_1-C_2-alkyl, C_1-C_2-haloalkyl, C_1-C_2-alkoxy, C_1-C_2-haloalkoxy, -N(R^{22})(R^{23}) and -C(=O)-N(R^{24})(R^{25}), and

R^{21} represents a hydrogen atom or a C_1-C_2-alkyl group,

or

R^{20} and R^{21}, together with the nitrogen atom to which they are attached, represent a monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group which is optionally benzocondensed, and which is optionally substituted one, two or three times, each substituent independently selected from a halogen atom or a group selected from cyano, oxo, hydroxy, C_1-C_2-alkyl, C_1-C_2-haloalkyl, (phenyl)-(C_1-C_2-alkyl)-, (C_1-C_2-alkyl)-C(=O)-, C_3-C_4-cycloalkyl, C_1-C_2-alkoxy, C_1-C_2-haloalkoxy, -N(R^{22})(R^{23}) and -C(=O)-N(R^{24})(R^{25}),

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{20} represents a hydrogen atom or a group selected from C_1-C_6-alkyl, C_3-C_4-alkenyl, C_3-C_4-alkynyl, C_1-C_3-alkoxy, C_3-C_7-cycloalkyl, bicyclic C_5-C_{11}-cycloalkyl, adamantyl, monocyclic 4- to 7-membered heterocycloalkyl, bicyclic 5- to 10-membered heterocycloalkyl, phenyl, naphthyl, and 5- to 10-membered heteroaryl,

wherein said C_1-C_6-alkyl group is optionally substituted one, two or three times, each substituent independently selected from a halogen atom or a group selected from hydroxy, cyano, C_1-C_3-alkoxy, -N(R^{22})(R^{23}), C_3-C_7-cycloalkyl, bicyclic C_5-C_{11}-cycloalkyl, adamantyl, monocyclic 4- to 7-membered heterocycloalkyl, bicyclic 5- to 10-membered heterocycloalkyl, phenyl, and 5- to 10-membered heteroaryl, said phenyl and 5- to 10-membered heteroaryl substituents themselves being optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a bromine atom, or a group selected from methyl, trifluoromethyl and methoxy,

and wherein C_3-C_7-cycloalkyl, bicyclic C_5-C_{11}-cycloalkyl, adamantyl, monocyclic 4- to 7-membered heterocycloalkyl, bicyclic 5- to 10-membered heterocycloalkyl are optionally substituted one or two or three times, each substituent independently selected from a halogen atom or a group selected from cyano, oxo, hydroxy, C_1-C_2-alkyl and (C_1-C_2-alkyl)-C(=O)-,

and wherein said phenyl, naphthyl and 5- to 10-membered heteroaryl groups are optionally substituted one, two or three times, each substituent independently selected from a halogen atom or a group selected from cyano, C_1-C_2-alkyl, C_1-C_2-haloalkyl, C_1-C_2-alkoxy, C_1-C_2-haloalkoxy, -N(R^{22})(R^{23}) and -C(=O)-N(R^{24})(R^{25}), and

R^{21} represents a hydrogen atom or a C_1-C_2-alkyl group,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{20} represents a hydrogen atom or a group selected from C_1-C_6-alkyl, C_3-C_4-alkenyl, C_3-C_4-alkynyl, C_1-C_3-alkoxy, C_3-C_7-cycloalkyl, bicyclic C_6-C_{11}-cycloalkyl, adamantyl, monocyclic 4- to 7-membered heterocycloalkyl, bicyclic 6- to 10-membered heterocycloalkyl, phenyl, naphthyl, and 5- to 10-membered heteroaryl,

wherein said C_1-C_6-alkyl group is optionally substituted one, two or three times, each substituent independently selected from a halogen atom or a group selected from hydroxy, cyano, C_1-C_3-alkoxy, -N(R^{22})(R^{23}), C_3-C_7-cycloalkyl, bicyclic C_6-C_{11}-cycloalkyl, adamantyl, monocyclic 4- to 7-membered heterocycloalkyl, bicyclic 6- to 10-membered heterocycloalkyl, phenyl, and 5- to 10-membered heteroaryl, said phenyl and 5- to 10-membered heteroaryl substituents themselves being optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a bromine atom, or a group selected from methyl, trifluoromethyl and methoxy,

wherein C_3-C_7-cycloalkyl, bicyclic C_6-C_{11}-cycloalkyl, adamantyl, monocyclic 4- to 7-membered heterocycloalkyl, bicyclic 6- to 10-membered heterocycloalkyl are optionally substituted one or two or three times, each substituent independently selected from a halogen atom or a group selected from cyano, oxo, hydroxy, C_1-C_2-alkyl and (C_1-C_2-alkyl)-C(=O)-,

and wherein said phenyl, naphthyl and 5- to 10-membered heteroaryl groups are optionally substituted one, two or three times, each substituent independently

selected from a halogen atom or a group selected from cyano, C_1-C_2-alkyl, C_1-C_2-haloalkyl, C_1-C_2-alkoxy, C_1-C_2-haloalkoxy, -N(R^{22})(R^{23}) and -C(=O)-N(R^{24})(R^{25}),

R^{21} represents a hydrogen atom or a C_1-C_2-alkyl group,

or

R^{20} and R^{21}, together with the nitrogen atom to which they are attached, represent a monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group which is optionally benzocondensed, and which is optionally substituted one, two or three times, each substituent independently selected from a halogen atom or a group selected from cyano, oxo, hydroxy, C_1-C_2-alkyl, C_1-C_2-haloalkyl, (phenyl)-(C_1-C_2-alkyl)-, (C_1-C_2-alkyl)-C(=O)-, C_3-C_4-cycloalkyl, C_1-C_2-alkoxy, C_1-C_2-haloalkoxy, -N(R^{22})(R^{23}) and -C(=O)-N(R^{24})(R^{25});

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{20} represents a hydrogen atom or a group selected from C_1-C_6-alkyl, C_3-C_4-alkenyl, C_3-C_4-alkynyl, C_1-C_3-alkoxy, C_3-C_7-cycloalkyl, bicyclic C_6-C_{11}-cycloalkyl, adamantyl, monocyclic 4- to 7-membered heterocycloalkyl, bicyclic 6- to 10-membered heterocycloalkyl, phenyl, naphthyl, and 5- to 10-membered heteroaryl,

wherein said C_1-C_6-alkyl group is optionally substituted one, two or three times, each substituent independently selected from a halogen atom or a group selected from hydroxy, cyano, C_1-C_3-alkoxy, -N(R^{22})(R^{23}), C_3-C_7-cycloalkyl, bicyclic C_6-C_{11}-cycloalkyl, adamantyl, monocyclic 4- to 7-membered heterocycloalkyl, bicyclic 6- to 10-membered heterocycloalkyl, phenyl, and 5- to 10-membered heteroaryl, said phenyl and 5- to 10-membered heteroaryl substituents themselves being optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a bromine atom, or a group selected from methyl, trifluoromethyl and methoxy,

wherein C_3-C_7-cycloalkyl, bicyclic C_6-C_{11}-cycloalkyl, adamantyl, monocyclic 4- to 7-membered heterocycloalkyl, bicyclic 6- to 10-membered heterocycloalkyl are optionally substituted one or two or three times, each substituent independently selected from a halogen atom or a group selected from cyano, oxo, hydroxy, C_1-C_2-alkyl and (C_1-C_2-alkyl)-C(=O)-,

and wherein said phenyl, naphthyl and 5- to 10-membered heteroaryl groups are optionally substituted one, two or three times, each substituent independently

selected from a halogen atom or a group selected from cyano, C_1-C_2-alkyl, C_1-C_2-haloalkyl, C_1-C_2-alkoxy, C_1-C_2-haloalkoxy, -N(R^{22})(R^{23}) and -C(=O)-N(R^{24})(R^{25}),

R^{21} represents a hydrogen atom or a C_1-C_2-alkyl group,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{20} and R^{21}, together with the nitrogen atom to which they are attached, represent a monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group which is optionally benzocondensed, and which is optionally substituted one, two or three times, each substituent independently selected from a halogen atom or a group selected from cyano, oxo, hydroxy, C_1-C_2-alkyl, C_1-C_2-haloalkyl, (phenyl)-(C_1-C_2-alkyl)-, (C_1-C_2-alkyl)-C(=O)-, C_3-C_4-cycloalkyl, C_1-C_2-alkoxy, C_1-C_2-haloalkoxy, -N(R^{22})(R^{23}) and -C(=O)-N(R^{24})(R^{25});

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{20} represents a hydrogen atom or a group selected from optionally substituted C_1-C_3-alkyl, unsubstituted C_4-C_6-alkyl, prop-2-ynyl, methoxy, C_3-C_6-cycloalkyl, adamantyl, monocyclic 4- to 7-membered heterocycloalkyl, phenyl, and 5- to 10-membered heteroaryl,

wherein said C_1-C_3-alkyl group is optionally substituted one, two or three times, each substituent independently selected from a halogen atom or a group selected from hydroxy, cyano, C_1-C_3-alkoxy, -N(R^{22})(R^{23}), C_3-C_6-cycloalkyl, adamantyl, monocyclic 4- to 7-membered heterocycloalkyl, phenyl, and 5- to 10-membered heteroaryl, said phenyl and 5- to 10-membered heteroaryl substituents themselves being optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a methyl group,

wherein said C_3-C_6-cycloalkyl, adamantyl and monocyclic 4- to 7-membered heterocycloalkyl groups are optionally substituted one or two or three times, each substituent independently selected from a fluorine atom or a group selected from oxo, C_1-C_2-alkyl and (C_1-C_2-alkyl)-C(=O)-,

and wherein said phenyl and 5- to 10-membered heteroaryl groups are optionally substituted one, two or three times, each substituent independently selected from a fluorine atom and a chlorine atom or a group selected from cyano, C_1-C_2-alkyl, C_1-C_2-fluoroalkyl, C_1-C_2-alkoxy, C_1-C_2-haloalkoxy, -N(R^{22})(R^{23}) and -C(=O)-N(R^{24})(R^{25}),

R^{21} represents a hydrogen atom or a C_1-C_2-alkyl group,

or

R^{20} and R^{21}, together with the nitrogen atom to which they are attached, represent a monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group which is optionally benzocondensed, and which is optionally substituted one, two or three times, each substituent independently selected from a halogen atom or a group selected from cyano, oxo, hydroxy, C_1-C_2-alkyl, C_1-C_2-fluoroalkyl, benzyl, (C_1-C_2-alkyl)-C(=O)-, C_3-C_4-cycloalkyl, C_1-C_2-alkoxy, C_1-C_2-haloalkoxy, -N(R^{22})(R^{23}) and -C(=O)-N(R^{24})(R^{25});

R^{22} and R^{23} represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_2-alkyl and (C_1-C_2-alkyl)-C(=O)-;

R^{24} and R^{25} represent, independently from each occurrence, a hydrogen atom or a C_1-C_2-alkyl group,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{20} represents a hydrogen atom or a group selected from optionally substituted C_1-C_3-alkyl, unsubstituted C_4-C_6-alkyl, prop-2-ynyl, methoxy, C_3-C_6-cycloalkyl, adamantyl, monocyclic 4- to 7-membered heterocycloalkyl, phenyl, and 5- to 10-membered heteroaryl,

wherein said C_1-C_3-alkyl group is optionally substituted one, two or three times, each substituent independently selected from a halogen atom or a group selected from hydroxy, cyano, C_1-C_3-alkoxy, -N(R^{22})(R^{23}), C_3-C_6-cycloalkyl, adamantyl, monocyclic 4- to 7-membered heterocycloalkyl, phenyl, and 5- to 10-membered heteroaryl, said phenyl and 5- to 10-membered heteroaryl substituents themselves being optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a methyl group,

wherein said C_3-C_6-cycloalkyl, adamantyl and monocyclic 4- to 7-membered heterocycloalkyl groups are optionally substituted one or two or three times, each

substituent independently selected from a fluorine atom or a group selected from oxo, C_1-C_2-alkyl and (C_1-C_2-alkyl)-C(=O)-,

and wherein said phenyl and 5- to 10-membered heteroaryl groups are optionally substituted one, two or three times, each substituent independently selected from a fluorine atom and a chlorine atom or a group selected from cyano, C_1-C_2-alkyl, C_1-C_2-fluoroalkyl, C_1-C_2-alkoxy, C_1-C_2-haloalkoxy, -N(R^{22})(R^{23}) and -C(=O)-N(R^{24})(R^{25}),

R^{21} represents a hydrogen atom or a C_1-C_2-alkyl group,

R^{22} and R^{23} represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_2-alkyl and (C_1-C_2-alkyl)-C(=O)-;

R^{24} and R^{25} represent, independently from each occurrence, a hydrogen atom or a C_1-C_2-alkyl group,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{20} and R^{21}, together with the nitrogen atom to which they are attached, represent a monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group which is optionally benzocondensed, and which is optionally substituted one, two or three times, each substituent independently selected from a halogen atom or a group selected from cyano, oxo, hydroxy, C_1-C_2-alkyl, C_1-C_2-fluoroalkyl, benzyl, (C_1-C_2-alkyl)-C(=O)-, C_3-C_4-cycloalkyl, C_1-C_2-alkoxy, C_1-C_2-haloalkoxy, -N(R^{22})(R^{23}) and -C(=O)-N(R^{24})(R^{25});

R^{22} and R^{23} represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_2-alkyl and (C_1-C_2-alkyl)-C(=O)-;

R^{24} and R^{25} represent, independently from each occurrence, a hydrogen atom or a C_1-C_2-alkyl group,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{20} represents a hydrogen atom or a group selected from optionally substituted C_1-C_3-alkyl, unsubstituted C_4-C_6-alkyl, prop-2-ynyl, methoxy, C_3-C_6-cycloalkyl, adamantyl,

monocyclic 4- to 7-membered heterocycloalkyl, phenyl, and 5- to 10-membered heteroaryl,

wherein said C_1-C_3-alkyl group is optionally substituted one, two or three times, each substituent independently selected from a halogen atom or a group selected from hydroxy, cyano, C_1-C_3-alkoxy, -N(R^{22})(R^{23}), C_3-C_6-cycloalkyl, adamantyl, monocyclic 4- to 7-membered heterocycloalkyl, phenyl, and 5- to 10-membered heteroaryl, said phenyl and 5- to 10-membered heteroaryl substituents themselves being optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a methyl group,

wherein said C_3-C_6-cycloalkyl, adamantyl and monocyclic 4- to 7-membered heterocycloalkyl groups are optionally substituted one or two or three times, each substituent independently selected from a fluorine atom or a group selected from oxo, C_1-C_2-alkyl and (C_1-C_2-alkyl)-C(=O)-,

and wherein said phenyl and 5- to 10-membered heteroaryl groups are optionally substituted one, two or three times, each substituent independently selected from a fluorine atom and a chlorine atom or a group selected from cyano, C_1-C_2-alkyl, C_1-C_2-fluoroalkyl, C_1-C_2-alkoxy, C_1-C_2-haloalkoxy, -N(R^{22})(R^{23}) and -C(=O)-N(R^{24})(R^{25}),

R^{21} represents a hydrogen atom or a C_1-C_2-alkyl group,

or

R^{20} and R^{21}, together with the nitrogen atom to which they are attached, represent a monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group which is optionally benzocondensed, and which is optionally substituted one, two or three times, each substituent independently selected from a halogen atom or a group selected from cyano, oxo, hydroxy, C_1-C_2-alkyl, C_1-C_2-fluoroalkyl, benzyl, (C_1-C_2-alkyl)-C(=O)-, C_3-C_4-cycloalkyl, C_1-C_2-alkoxy, C_1-C_2-haloalkoxy, -N(R^{22})(R^{23}) and -C(=O)-N(R^{24})(R^{25}),

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{20} represents a hydrogen atom or a group selected from optionally substituted C_1-C_3-alkyl, unsubstituted C_4-C_6-alkyl, prop-2-ynyl, methoxy, C_3-C_6-cycloalkyl, adamantyl, monocyclic 4- to 7-membered heterocycloalkyl, phenyl, and 5- to 10-membered heteroaryl,

wherein said C_1-C_3-alkyl group is optionally substituted one, two or three times, each substituent independently selected from a halogen atom or a group selected from hydroxy, cyano, C_1-C_3-alkoxy, -N(R^{22})(R^{23}), C_3-C_6-cycloalkyl, adamantyl, monocyclic 4- to 7-membered heterocycloalkyl, phenyl, and 5- to 10-membered heteroaryl, said phenyl and 5- to 10-membered heteroaryl substituents themselves being optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a methyl group,

wherein said C_3-C_6-cycloalkyl, adamantyl and monocyclic 4- to 7-membered heterocycloalkyl groups are optionally substituted one or two or three times, each substituent independently selected from a fluorine atom or a group selected from oxo, C_1-C_2-alkyl and (C_1-C_2-alkyl)-C(=O)-,

and wherein said phenyl and 5- to 10-membered heteroaryl groups are optionally substituted one, two or three times, each substituent independently selected from a fluorine atom and a chlorine atom or a group selected from cyano, C_1-C_2-alkyl, C_1-C_2-fluoroalkyl, C_1-C_2-alkoxy, C_1-C_2-haloalkoxy, -N(R^{22})(R^{23}) and -C(=O)-N(R^{24})(R^{25}),

R^{21} represents a hydrogen atom or a C_1-C_2-alkyl group,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{20} and R^{21}, together with the nitrogen atom to which they are attached, represent a monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group which is optionally benzocondensed, and which is optionally substituted one, two or three times, each substituent independently selected from a halogen atom or a group selected from cyano, oxo, hydroxy, C_1-C_2-alkyl, C_1-C_2-fluoroalkyl, benzyl, (C_1-C_2-alkyl)-C(=O)-, C_3-C_4-cycloalkyl, C_1-C_2-alkoxy, C_1-C_2-haloalkoxy, -N(R^{22})(R^{23}) and -C(=O)-N(R^{24})(R^{25}),

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{20} represents a hydrogen atom or a group selected from optionally substituted C_1-C_3-alkyl, unsubstituted C_4-C_6-alkyl, prop-2-ynyl, methoxy, C_3-C_6-cycloalkyl, adamantyl,

monocyclic 4- to 7-membered heterocycloalkyl, phenyl, and 5- to 10-membered heteroaryl,

wherein said C_1-C_3-alkyl group is optionally substituted one, two or three times, each substituent independently selected from a halogen atom or a group selected from hydroxy, cyano, C_1-C_3-alkoxy, -N(R^{22})(R^{23}), C_3-C_6-cycloalkyl, adamantyl, monocyclic 4- to 7-membered heterocycloalkyl, phenyl, and 5- to 10-membered heteroaryl, said phenyl and 5- to 10-membered heteroaryl substituents themselves being optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a methyl group,

and wherein said C_3-C_6-cycloalkyl, adamantyl and monocyclic 4- to 7-membered heterocycloalkyl groups are optionally substituted one or two or three times, each substituent independently selected from a fluorine atom or a group selected from oxo, C_1-C_2-alkyl and (C_1-C_2-alkyl)-C(=O)-,

and wherein said phenyl and 5- to 10-membered heteroaryl groups are optionally substituted one, two or three times, each substituent independently selected from a fluorine atom and a chlorine atom or a group selected from cyano, C_1-C_2-alkyl, C_1-C_2-fluoroalkyl, C_1-C_2-alkoxy, C_1-C_2-fluoroalkoxy, -N(R^{22})(R^{23}) and -C(=O)-N(R^{24})(R^{25}),

R^{21} represents a hydrogen atom or a C_1-C_2-alkyl group,

or

R^{20} and R^{21}, together with the nitrogen atom to which they are attached, represent a monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group which is optionally benzocondensed, and which is optionally substituted one, two or three times, each substituent independently selected from a halogen atom or a group selected from cyano, oxo, hydroxy, C_1-C_2-alkyl, C_1-C_2-fluoroalkyl, benzyl, (C_1-C_2-alkyl)-C(=O)-, C_3-C_4-cycloalkyl, C_1-C_2-alkoxy, C_1-C_2-fluoroalkoxy, -N(R^{22})(R^{23}) and -C(=O)-N(R^{24})(R^{25}),

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{20} represents a hydrogen atom or a group selected from optionally substituted C_1-C_3-alkyl, unsubstituted C_4-C_6-alkyl, prop-2-ynyl, methoxy, C_3-C_6-cycloalkyl, adamantyl, monocyclic 4- to 7-membered heterocycloalkyl, phenyl, and 5- to 10-membered heteroaryl,

wherein said C_1-C_3-alkyl group is optionally substituted one, two or three times, each substituent independently selected from a halogen atom or a group selected from hydroxy, cyano, C_1-C_3-alkoxy, -N(R^{22})(R^{23}), C_3-C_6-cycloalkyl, adamantyl, monocyclic 4- to 7-membered heterocycloalkyl, phenyl, and 5- to 10-membered heteroaryl, said phenyl and 5- to 10-membered heteroaryl substituents themselves being optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a methyl group,

and wherein said C_3-C_6-cycloalkyl, adamantyl and monocyclic 4- to 7-membered heterocycloalkyl groups are optionally substituted one or two or three times, each substituent independently selected from a fluorine atom or a group selected from oxo, C_1-C_2-alkyl and (C_1-C_2-alkyl)-C(=O)-,

and wherein said phenyl and 5- to 10-membered heteroaryl groups are optionally substituted one, two or three times, each substituent independently selected from a fluorine atom and a chlorine atom or a group selected from cyano, C_1-C_2-alkyl, C_1-C_2-fluoroalkyl, C_1-C_2-alkoxy, C_1-C_2-fluoroalkoxy, -N(R^{22})(R^{23}) and -C(=O)-N(R^{24})(R^{25}),

R^{21} represents a hydrogen atom or a C_1-C_2-alkyl group,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{20} and R^{21}, together with the nitrogen atom to which they are attached, represent a monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group which is optionally benzocondensed, and which is optionally substituted one, two or three times, each substituent independently selected from a halogen atom or a group selected from cyano, oxo, hydroxy, C_1-C_2-alkyl, C_1-C_2-fluoroalkyl, benzyl, (C_1-C_2-alkyl)-C(=O)-, C_3-C_4-cycloalkyl, C_1-C_2-alkoxy, C_1-C_2-fluoroalkoxy, -N(R^{22})(R^{23}) and -C(=O)-N(R^{24})(R^{25}),

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{20} represents a hydrogen atom or a group selected from C_1-C_3-alkyl and phenyl,

wherein said C_1-C_3-alkyl group is optionally substituted one or two times, each substituent independently selected from a fluorine atom or a group selected from hydroxy, C_1-C_3-alkoxy and phenyl, said phenyl itself being optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a methyl group,

and wherein said phenyl group is optionally substituted one, two or three times, each substituent independently selected from a fluorine atom and a chlorine atom or a group selected from methyl, trifluoromethyl, methoxy and trifluoromethoxy;

R^{21} represents a hydrogen atom or a C_1-C_2-alkyl group,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{20} represents a group selected from benzyl and phenyl,

wherein said phenyl group, and the phenyl group within said benzyl group, is optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a methyl group,

R^{21} represents a hydrogen atom or a methyl group,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{22} and R^{23} represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_2-alkyl and (C_1-C_2-alkyl)-C(=O)-,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{22} and R^{23} represent, independently from each occurrence, a hydrogen atom or a group selected from methyl and (CH_3)-C(=O)-,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{24} and R^{25} represent, independently from each occurrence, a hydrogen atom or a C_1-C_2-alkyl group,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{24} and R^{25} represent, independently from each occurrence, a hydrogen atom or a methyl group,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{26} represents a fluorine atom, a chlorine atom, or a group selected from C_1-C_2-alkyl, C_1-C_2-fluoroalkyl, C_1-C_2-alkoxy and C_1-C_2-fluoroalkoxy,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{26} represents a fluorine atom, a chlorine atom or a bromine atom, or a group selected from methyl, difluoromethyl, trifluoromethyl, methoxy, benzyloxy, difluoromethoxy and trifluoromethoxy,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{26} represents a fluorine atom, a chlorine atom, or a group selected from methyl, difluoromethyl, trifluoromethyl, methoxy, difluoromethoxy and trifluoromethoxy,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{26} represents a fluorine atom, a chlorine atom or a bromine atom, or a group selected from difluoromethyl, methoxy, benzyloxy, difluoromethoxy and trifluoromethoxy,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{26} represents a fluorine atom, a chlorine atom, or a group selected from difluoromethyl, trifluoromethyl, methoxy, difluoromethoxy and trifluoromethoxy,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{27} represents a halogen atom or a group selected from C_1-C_2-alkyl, C_1-C_2-fluoroalkyl, $-OR^9$, $-N(R^{10})(R^{11})$, $-C(=O)-N(R^{12})(R^{13})$ and $-C(=O)-OR^{17}$,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{27} represents a fluorine atom, a chlorine atom, or a group selected from C_1-C_2-alkoxy, benzyloxy and C_1-C_2-fluoroalkoxy,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{27} represents a halogen atom or a group selected from $-OR^9$, $-N(R^{10})(R^{11})$ and $-C(=O)-N(R^{12})(R^{13})$,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

R^{27} represents a chlorine atom, or a group selected from methoxy, benzyloxy, difluoromethoxy and trifluoromethoxy,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

n represents an integer 0, 1, or 2,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

n represents an integer 0 or 2,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

n represents an integer 0,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

n represents an integer 2,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

Y^1 represents -C(H)=, -C(F)=, -C(Cl)=, -C(CN)= or -N=,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

Y^1 represents -C(H)=, -C(F)=, -C(Cl)= or -N=;

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

Y^1 represents -C(H)=, -C(F)= or -N=,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

Y^1 represents -C(H)= or -C(F)=,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

Y^1 represents -C(H)=,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

Y^1 represents -C(Cl)=,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

Y^1 represents -C(F)=,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

Y^1 represents -N=,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

Y^2 represents -C(H)= or -N=,

Y^3 represents -C(R^{27})= or -N=,

with the proviso that if Y^2 represents -N=, Y^3 represents -C(R^{27})=, and if Y^3 represents -N=, Y^2 represents -C(H)=,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

Y^2 represents -C(H)= and -N=,

Y^3 represents -C(R^{27})= and -N=,

with the proviso that if Y^2 represents -N=, Y^3 represents -C(R^{27})=, and if Y^3 represents -N=, Y^2 represents -C(H)=,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

Y^2 represents -N=;

Y^3 represents -C(R^{27})=,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

Y^2 represents -C(H)=;

Y^3 represents -N=,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a further embodiment of the first aspect, the present invention covers compounds of formula (I), *supra*, in which:

Y^2 represents -C(H)=;

Y^3 represents -C(R^{27})=,

and stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, and mixtures of same.

In a particular further embodiment of the first aspect, the present invention covers combinations of two or more of the above mentioned embodiments under the heading "further embodiments of the first aspect of the present invention".

The present invention covers any sub-combination within any embodiment or aspect of the present invention of compounds of general formula (I), *supra*.

The present invention covers the compounds of general formula (I) which are disclosed in the Example Section of this text, *infra*.

The compounds of general formula (I) of the present invention can be converted to any salt, preferably pharmaceutically acceptable salts, as described herein, by any method which is known to the person skilled in the art. Similarly, any salt of a compound of general formula (I) of the present invention can be converted into the free compound, by any method which is known to the person skilled in the art.

Compounds of general formula (I) of the present invention demonstrate a valuable pharmacological spectrum of action, which could not have been predicted. Compounds of the present invention have surprisingly been found to effectively inhibit DGKζ and it is possible therefore that said compounds be used for the treatment or prophylaxis of diseases, preferably conditions with dysregulated immune responses, particularly cancer or other disorders associated with aberrant DGKζ signaling, in mammals, including humans.

Disorders and conditions particularly suitable for treatment with an DGKζ inhibitor of the present invention are liquid and solid tumours, such as cancers of the breast, respiratory tract, brain, reproductive organs, digestive tract, urinary tract, eye, liver, skin, head and neck, thyroid, parathyroid and their distant metastases. Those disorders also include lymphomas, sarcomas, and leukaemias.

Examples of breast cancers include, but are not limited to, triple negative breast cancer, invasive ductal carcinoma, invasive lobular carcinoma, ductal carcinoma *in situ*, and lobular carcinoma *in situ*.

Examples of cancers of the respiratory tract include, but are not limited to, small-cell and non-small-cell lung carcinoma, as well as bronchial adenoma and pleuropulmonary blastoma.

Examples of brain cancers include, but are not limited to, brain stem and hypophtalmic glioma, cerebellar and cerebral astrocytoma, glioblastoma, medulloblastoma, ependymoma, as well as neuroectodermal and pineal tumour.

Tumours of the male reproductive organs include, but are not limited to, prostate and testicular cancer.

Tumours of the female reproductive organs include, but are not limited to, endometrial, cervical, ovarian, vaginal, and vulvar cancer, as well as sarcoma of the uterus.

Examples of ovarian cancer include, but are not limited to serous tumour, endometrioid tumour, mucinous cystadenocarcinoma, granulosa cell tumour, Sertoli-Leydig cell tumour and arrhenoblastoma.

Examples of cervical cancer include, but are not limited to squamous cell carcinoma, adenocarcinoma, adenosquamous carcinoma, small cell carcinoma, neuroendocrine tumour, glassy cell carcinoma and villoglandular adenocarcinoma.

Tumours of the digestive tract include, but are not limited to, anal, colon, colorectal, esophageal, gallbladder, gastric, pancreatic, rectal, small-intestine, and salivary gland cancers.

Examples of esophageal cancer include, but are not limited to esophageal cell carcinomas and adenocarcinomas, as well as squamous cell carcinomas, leiomyosarcoma, malignant melanoma, rhabdomyosarcoma and lymphoma.

Examples of gastric cancer include, but are not limited to intestinal type and diffuse type gastric adenocarcinoma.

Examples of pancreatic cancer include, but are not limited to ductal adenocarcinoma, adenosquamous carcinomas and pancreatic endocrine tumours.

Tumours of the urinary tract include, but are not limited to, bladder, penile, kidney, renal pelvis, ureter, urethral and human papillary renal cancers.

Examples of kidney cancer include, but are not limited to renal cell carcinoma, urothelial cell carcinoma, juxtaglomerular cell tumour (reninoma), angiomyolipoma, renal oncocytoma, Bellini duct carcinoma, clear-cell sarcoma of the kidney, mesoblastic nephroma and Wilms' tumour.

Examples of bladder cancer include, but are not limited to transitional cell carcinoma, squamous cell carcinoma, adenocarcinoma, sarcoma and small cell carcinoma.

Eye cancers include, but are not limited to, intraocular melanoma and retinoblastoma.

Examples of liver cancers include, but are not limited to, hepatocellular carcinoma (liver cell carcinomas with or without fibrolamellar variant), cholangiocarcinoma (intrahepatic bile duct carcinoma), and mixed hepatocellular cholangiocarcinoma.

Skin cancers include, but are not limited to, squamous cell carcinoma, Kaposi's sarcoma, malignant melanoma, Merkel cell skin cancer, and non-melanoma skin cancer.

Head-and-neck cancers include, but are not limited to, squamous cell cancer of the head and neck, laryngeal, hypopharyngeal, nasopharyngeal, oropharyngeal cancer, salivary gland cancer, lip and oral cavity cancer and squamous cell.

Lymphomas include, but are not limited to, AIDS-related lymphoma, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, Burkitt lymphoma, Hodgkin's disease, and lymphoma of the central nervous system.

Sarcomas include, but are not limited to, sarcoma of the soft tissue, osteosarcoma, malignant fibrous histiocytoma, lymphosarcoma, and rhabdomyosarcoma.

Leukemias include, but are not limited to, acute myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, and hairy cell leukemia.

The term "treating" or "treatment" as stated throughout this document is used conventionally, for example the management or care of a subject for the purpose of combating, alleviating, reducing, relieving, improving the condition of a disease or disorder, such as a carcinoma.

The compounds of the present invention can be used in particular in therapy and prevention, *i.e.* prophylaxis, of tumour growth and metastases, especially in solid tumours of all indications and stages with or without pre-treatment of the tumour growth.

Generally, the use of chemotherapeutic agents and/or anti-cancer agents in combination with a compound or pharmaceutical composition of the present invention will serve to:

1. yield better efficacy in reducing the growth of a tumour or even eliminate the tumour as compared to administration of either agent alone,
2. provide for the administration of lesser amounts of the administered chemotherapeutic agents,
3. provide for a chemotherapeutic treatment that is well tolerated in the patient with fewer deleterious pharmacological complications than observed with single agent chemotherapies and certain other combined therapies,
4. provide for treating a broader spectrum of different cancer types in mammals, especially humans,
5. provide for a higher response rate among treated patients,
6. provide for a longer survival time among treated patients compared to standard chemotherapy treatments,
7. provide a longer time for tumour progression, and/or
8. yield efficacy and tolerability results at least as good as those of the agents used alone, compared to known instances where other cancer agent combinations produce antagonistic effects.

In addition, the compounds of general formula (I) of the present invention can also be used in combination with radiotherapy and/or surgical intervention.

In a further embodiment of the present invention, the compounds of general formula (I) of the present invention are used in combination with radiation: *i.e.* radiation treatment sensitizes cancers to anti-tumor immune responses by induction of tumor cell death and subsequent presentation of tumor neoantigens to tumor-reactive Tcells. As DGKζ is enhancing the antigen specific activation of T cells, the overall effect results in a much stronger cancer cell attack as compared to irradiation treatment alone.
Thus, the present invention also provides a method of killing a tumor, wherein conventional radiation therapy is employed previous to administering one or more of the compounds of the present invention.

The compounds of the present invention can be administered as the sole pharmaceutical agent or in combination with one or more other pharmaceutically active ingredients where the combination causes no unacceptable adverse effects. The present invention also covers such

pharmaceutical combinations. For example, the compounds of the present invention can be combined with:

131I-chTNT, abarelix, abemaciclib, abiraterone, acalabrutinib, aclarubicin, adalimumab, ado-trastuzumab emtansine, afatinib, aflibercept, aldesleukin, alectinib, alemtuzumab, alendronic acid, alitretinoin, alpharadin, altretamine, amifostine, aminoglutethimide, hexyl aminolevulinate, amrubicin, amsacrine, anastrozole, ancestim, anethole dithiolethione, anetumab ravtansine, angiotensin II, antithrombin III, apalutamide, aprepitant, arcitumomab, arglabin, arsenic trioxide, asparaginase, atezolizumab, avelumab, axicabtagene ciloleucel, axitinib, azacitidine, basiliximab, belotecan, bendamustine, besilesomab, belinostat, bevacizumab, bexarotene, bicalutamide, bisantrene, bleomycin, blinatumomab, bortezomib, bosutinib, buserelin, brentuximab vedotin, brigatinib, busulfan, cabazitaxel, cabozantinib, calcitonine, calcium folinate, calcium levofolinate, capecitabine, capromab, carbamazepine carboplatin, carboquone, carfilzomib, carmofur, carmustine, catumaxomab, celecoxib, celmoleukin, cemiplimab, ceritinib, cetuximab, chlorambucil, chlormadinone, chlormethine, cidofovir, cinacalcet, cisplatin, cladribine, clodronic acid, clofarabine, cobimetinib, copanlisib, crisantaspase, crizotinib, cyclophosphamide, cyproterone, cytarabine, dacarbazine, dactinomycin, daratumumab, darbepoetin alfa, dabrafenib, dasatinib, daunorubicin, decitabine, degarelix, denileukin diftitox, denosumab, depreotide, deslorelin, dianhydrogalactitol, dexrazoxane, dibrospidium chloride, dianhydrogalactitol, diclofenac, dinutuximab, docetaxel, dolasetron, doxifluridine, doxorubicin, doxorubicin + estrone, dronabinol, durvalumab, eculizumab, edrecolomab, elimusertib (BAY1895344), elliptinium acetate, elotuzumab, eltrombopag, enasidenib, endostatin, enocitabine, enzalutamide, epirubicin, epitiostanol, epoetin alfa, epoetin beta, epoetin zeta, eptaplatin, eribulin, erlotinib, esomeprazole, estradiol, estramustine, ethinylestradiol, etoposide, everolimus, exemestane, fadrozole, fentanyl, filgrastim, fluoxymesterone, floxuridine, fludarabine, fluorouracil, flutamide, folinic acid, formestane, fosaprepitant, fotemustine, fulvestrant, gadobutrol, gadoteridol, gadoteric acid meglumine, gadoversetamide, gadoxetic acid, gallium nitrate, ganirelix, gefitinib, gemcitabine, gemtuzumab, Glucarpidase, glutoxim, GM-CSF, goserelin, granisetron, granulocyte colony stimulating factor, histamine dihydrochloride, histrelin, hydroxycarbamide, I-125 seeds, lansoprazole, ibandronic acid, ibritumomab tiuxetan, ibrutinib, idarubicin, ifosfamide, imatinib, imiquimod, improsulfan, indisetron, incadronic acid, ingenol mebutate, inotuzumab ozogamicin, interferon alfa, interferon beta, interferon gamma, iobitridol, iobenguane (123I), iomeprol, ipilimumab, irinotecan, Itraconazole, ixabepilone, ixazomib, lanreotide, lansoprazole, lapatinib, lasocholine, lenalidomide, lenvatinib, lenograstim, lentinan, letrozole, leuprorelin, levamisole, levonorgestrel, levothyroxine sodium, lisuride, lobaplatin, lomustine, lonidamine, lutetium Lu 177 dotatate, masoprocol, medroxyprogesterone, megestrol, melarsoprol, melphalan, mepitiostane, mercaptopurine, mesna, methadone, methotrexate, methoxsalen, methylaminolevulinate, methylprednisolone, methyltestosterone, metirosine, midostaurin, mifamurtide, miltefosine, miriplatin, mitobronitol, mitoguazone,

mitolactol, mitomycin, mitotane, mitoxantrone, mogamulizumab, molgramostim, mopidamol, morphine hydrochloride, morphine sulfate, mvasi, nabilone, nabiximols, nafarelin, naloxone + pentazocine, naltrexone, nartograstim, necitumumab, nedaplatin, nelarabine, neratinib, neridronic acid, netupitant/palonosetron, nivolumab, pentetreotide, nilotinib, nilutamide, nimorazole, nimotuzumab, nimustine, nintedanib, niraparib, nitracrine, nivolumab, obinutuzumab, octreotide, ofatumumab, olaparib, olaratumab, omacetaxine mepesuccinate, omeprazole, ondansetron, oprelvekin, orgotein, orilotimod, osimertinib, oxaliplatin, oxycodone, oxymetholone, ozogamicine, p53 gene therapy, paclitaxel, palbociclib, palifermin, palladium-103 seed, palonosetron, pamidronic acid, panitumumab, panobinostat, pantoprazole, pazopanib, pegaspargase, PEG-epoetin beta (methoxy PEG-epoetin beta), pembrolizumab, pegfilgrastim, peginterferon alfa-2b, pemetrexed, pentazocine, pentostatin, peplomycin, Perflubutane, perfosfamide, Pertuzumab, picibanil, pilocarpine, pirarubicin, pixantrone, plerixafor, plicamycin, poliglusam, polyestradiol phosphate, polyvinylpyrrolidone + sodium hyaluronate, polysaccharide-K, pomalidomide, ponatinib, porfimer sodium, pralatrexate, prednimustine, prednisone, procarbazine, procodazole, propranolol, quinagolide, rabeprazole, racotumomab, radium-223 chloride, radotinib, raloxifene, raltitrexed, ramosetron, ramucirumab, ranimustine, rasburicase, razoxane, refametinib, regorafenib, ribociclib, risedronic acid, rhenium-186 etidronate, rituximab, rolapitant, romidepsin, romiplostim, romurtide, rucaparib, samarium (153Sm) lexidronam, sargramostim, sarilumab, satumomab, secretin, siltuximab, sipuleucel-T, sizofiran, sobuzoxane, sodium glycididazole, sonidegib, sorafenib, stanozolol, streptozocin, sunitinib, talaporfin, talimogene laherparepvec, tamibarotene, tamoxifen, tapentadol, tasonermin, teceleukin, technetium (99mTc) nofetumomab merpentan, 99mTc-HYNIC-[Tyr3]-octreotide, tegafur, tegafur + gimeracil + oteracil, temoporfin, temozolomide, temsirolimus, teniposide, testosterone, tetrofosmin, thalidomide, thiotepa, thymalfasin, thyrotropin alfa, tioguanine, tisagenlecleucel, tislelizumab, tocilizumab, topotecan, toremifene, tositumomab, trabectedin, trametinib, tramadol, trastuzumab, trastuzumab emtansine, treosulfan, tretinoin, trifluridine + tipiracil, trilostane, triptorelin, trametinib, trofosfamide, thrombopoietin, tryptophan, ubenimex, valatinib, valrubicin, vandetanib, vapreotide, vemurafenib, vinblastine, vincristine, vindesine, vinflunine, vinorelbine, vismodegib, vorinostat, vorozole, yttrium-90 glass microspheres, zinostatin, zinostatin stimalamer, zoledronic acid, zorubicin.

The compounds of the invention can further be combined with other reagents targeting the immune system, such as immune checkpoint inhibitors, e.g. aPD-1/-L1 axis antagonists.

PD-1, along with its ligands PD-L1 and PD-L2, function as negative regulators of T cell activation. PD-L1 is overexpressed in many cancers and overexpression of PD-1 often occurs concomitantly in tumor infiltrating T cells. This results in attenuation of T cell activation and

evasion of immune surveillance, which contributes to impaired antitumor immune responses. (M. E. Keir et al., Annu. Rev. Immunol. 2008, 26, 677-704).

In accordance with a further aspect, the present invention covers combinations comprising one or more of the compounds of general formula (I), as described herein, or stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, particularly pharmaceutically acceptable salts thereof, or mixtures of same, and one or more immune checkpoint inhibitors. Preferably, the immune checkpoint inhibitor is a aPD-1/-L1 axis antagonist.

The compounds of the invention can further be combined with inhibitors of DGKα, such as those inhibitors of DGKα disclosed in WO2020/006016, WO2020/006018 and WO 2021/041588. As DGKα in T cells operates in a similar fashion as DGKζ, a dual inhibition profoundly enhances T cell effector functions compared with cells with deletion of either DGK isoform alone or wild-type cells. (M. J. Riese et al. Cancer Res. (2013), 73(12); p. 3566–77).

The compounds of the invention can further be combined with chimeric antigen receptor T cells (CAR-T cells), such as Axicabtagen-Ciloleucel or Tisagenlecleucel. The activity of CAR-T cells can be suppressed by the tumor micro environment (TME). Knock out of DGKs by techniques such as Crispr had been shown to enhance CAR-T cell activity in a suppressive TME (I. Y. Jung et al., Mol. Cells 2018, 41 (8), 717-723).

In accordance with a further aspect, the present invention covers combinations comprising one or more compounds of general formula (I), as described herein, or stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, particularly pharmaceutically acceptable salts thereof, or mixtures of same, with chimeric antigen receptor T cells, (CAR-T cells), CAR-NKT cells or CAR-NK cells.
Preferably, the chimeric antigen receptor T cells (CAR-T cells) are Axicabtagen-Ciloleucel or Tisagenlecleucel.

The present invention further provides the use of the compounds according to the invention for expansion of T cells including CAR-T and tumor infiltrated lymphocytes *ex-vivo*.

In accordance with a further aspect, the present invention covers compounds of general formula (I), as described herein, or stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, particularly pharmaceutically acceptable salts thereof, or mixtures of same, for use in the expansion of T cells including CAR-T cells, CAR-NKT cells or CAR-NK cells and tumor infiltrated lymphocytes *ex-vivo*.

Hence, the present invention also relates to the use of the compounds according to the invention for the expansion of T cells, including CAR-T cell, CAR-NKT cells or CAR-NK cells and tumor infiltrated lymphocytes, *ex-vivo*.

The present invention also comprises an *ex-vivo* method for the expansion of T cells, including CAR-T cells, CAR-NKT cells or CAR-NK cells and tumor infiltrated lymphocytes, contacting said T cells with compounds according to the invention.

Compounds of the present invention can be utilized to inhibit, block, reduce or decrease DGKζ activity resulting in the modulation of dysregulated immune responses e.g. to block immunosuppression and increase immune cell activation and infiltration in the context of cancer and cancer immunotherapy that will eventually lead to reduction of tumour growth.
This method comprises administering to a mammal in need thereof, including a human, an amount of a compound of this invention, or a pharmaceutically acceptable salt, isomer, polymorph, metabolite, hydrate, solvate or ester thereof; which is effective to treat the disorder.
The present invention also provides methods of treating a variety of other disorders wherein DGKζ is involved such as, but not limited to, disorders with dysregulated immune responses, inflammation, vaccination for infection & cancer, virus infections, lymphoproliferative disorders, asthma, eye diseases, and type 2 diabetes/ insulin resistance.
These disorders have been well characterized in humans, but also exist with a similar etiology in other mammals, and can be treated by administering pharmaceutical compositions of the present invention.

In accordance with a further aspect, the present invention covers compounds of general formula (I), as described *supra*, or stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, particularly pharmaceutically acceptable salts thereof, or mixtures of same, for use in the treatment or prophylaxis of diseases, in particular cancer or conditions with dysregulated immune responses or other disorders associated with aberrant DGKζ signaling.

The pharmaceutical activity of the compounds according to the invention can be explained by their activity as DGKζ inhibitors.

In accordance with a further aspect, the present invention covers the use of compounds of general formula (I), as described *supra*, or stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, particularly pharmaceutically acceptable salts thereof, or mixtures of same, for the treatment or prophylaxis of diseases, in particular cancer or conditions with dysregulated immune responses or other disorders associated with aberrant DGKζ signaling, particularly liquid and solid tumours.

In accordance with a further aspect, the present invention covers the compounds of general formula (I), as described *supra*, or stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, particularly pharmaceutically acceptable salts thereof, or mixtures of same, for the use in the treatment or prophylaxis of diseases, in particular cancer or conditions with dysregulated immune responses or other disorders associated with aberrant DGKζ signaling, particularly liquid and solid tumours.

In accordance with a further aspect, the present invention covers the use of compounds of general formula (I), as described *supra*, or stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, particularly pharmaceutically acceptable salts thereof, or mixtures of same, in a method of treatment or prophylaxis of diseases, in particular cancer or conditions with dysregulated immune responses or other disorders associated with aberrant DGKζ signaling, particularly liquid and solid tumours.

In accordance with a further aspect, the present invention covers the use of a compound of general formula (I), as described *supra*, or stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, particularly pharmaceutically acceptable salts thereof, or mixtures of same, in a method of treatment or prophylaxis of diseases, in particular cancer or conditions with dysregulated immune responses or other disorders associated with aberrant DGKζ signaling, particularly liquid and solid tumours.

In accordance with a further aspect, the present invention covers use of a compound of general formula (I), as described *supra*, or stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, particularly pharmaceutically acceptable salts thereof, or mixtures of same, for the preparation of a pharmaceutical composition, preferably a medicament, for the prophylaxis or treatment of diseases, in particular cancer or conditions with dysregulated immune responses or other disorders associated with aberrant DGKζ signaling, particularly liquid and solid tumours.

In accordance with a further aspect, the present invention covers a method of treatment or prophylaxis of diseases, in particular cancer or conditions with dysregulated immune responses or other disorders associated with aberrant DGKζ signaling, particularly liquid and solid tumours, using an effective amount of a compound of general formula (I), as described *supra*, or stereoisomers, tautomers, N-oxides, hydrates, solvates, and salts thereof, particularly pharmaceutically acceptable salts thereof, or mixtures of same.

In accordance with a further aspect, the present invention covers pharmaceutical compositions, in particular a medicament, comprising a compound of general formula (I), as described *supra*,

or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, a salt thereof, particularly a pharmaceutically acceptable salt, or a mixture of same, and one or more excipients), in particular one or more pharmaceutically acceptable excipient(s). Conventional procedures for preparing such pharmaceutical compositions in appropriate dosage forms can be utilized.

The present invention furthermore covers pharmaceutical compositions, in particular medicaments, which comprise at least one compound according to the invention, conventionally together with one or more pharmaceutically suitable excipients, and to their use for the above mentioned purposes.

It is possible for the compounds according to the invention to have systemic and/or local activity. For this purpose, they can be administered in a suitable manner, such as, for example, via the oral, parenteral, pulmonary, nasal, sublingual, lingual, buccal, rectal, vaginal, dermal, transdermal, conjunctival, otic route or as an implant or stent.
For these administration routes, it is possible for the compounds according to the invention to be administered in suitable administration forms.

For oral administration, it is possible to formulate the compounds according to the invention to dosage forms known in the art that deliver the compounds of the invention rapidly and/or in a modified manner, such as, for example, tablets (uncoated or coated tablets, for example with enteric or controlled release coatings that dissolve with a delay or are insoluble), orally-disintegrating tablets, films/wafers, films/lyophylisates, capsules (for example hard or soft gelatine capsules), sugar-coated tablets, granules, pellets, powders, emulsions, suspensions, aerosols or solutions. It is possible to incorporate the compounds according to the invention in crystalline and/or amorphised and/or dissolved form into said dosage forms.

Parenteral administration can be effected with avoidance of an absorption step (for example intravenous, intraarterial, intracardial, intraspinal or intralumbal) or with inclusion of absorption (for example intramuscular, subcutaneous, intracutaneous, percutaneous or intraperitoneal). Administration forms which are suitable for parenteral administration are, inter alia, preparations for injection and infusion in the form of solutions, suspensions, emulsions, lyophylisates or sterile powders.

Examples which are suitable for other administration routes are pharmaceutical forms for inhalation [inter alia powder inhalers, nebulizers], nasal drops, nasal solutions, nasal sprays; tablets/films/wafers/capsules for lingual, sublingual or buccal administration; suppositories; eye drops, eye ointments, eye baths, ocular inserts, ear drops, ear sprays, ear powders, ear-rinses, ear tampons; vaginal capsules, aqueous suspensions (lotions, mixturae agitandae), lipophilic

suspensions, emulsions, ointments, creams, transdermal therapeutic systems (such as, for example, patches), milk, pastes, foams, dusting powders, implants or stents.

The compounds according to the invention can be incorporated into the stated administration forms. This can be effected in a manner known per se by mixing with pharmaceutically suitable excipients. Pharmaceutically suitable excipients include, inter alia,

- fillers and carriers (for example cellulose, microcrystalline cellulose (such as, for example, Avicel®), lactose, mannitol, starch, calcium phosphate (such as, for example, Di-Cafos®)),
- ointment bases (for example petroleum jelly, paraffins, triglycerides, waxes, wool wax, wool wax alcohols, lanolin, hydrophilic ointment, polyethylene glycols),
- bases for suppositories (for example polyethylene glycols, cacao butter, hard fat),
- solvents (for example water, ethanol, isopropanol, glycerol, propylene glycol, medium chain-length triglycerides fatty oils, liquid polyethylene glycols, paraffins),
- surfactants, emulsifiers, dispersants or wetters (for example sodium dodecyl sulfate), lecithin, phospholipids, fatty alcohols (such as, for example, Lanette®), sorbitan fatty acid esters (such as, for example, Span®), polyoxyethylene sorbitan fatty acid esters (such as, for example, Tween®), polyoxyethylene fatty acid glycerides (such as, for example, Cremophor®), polyoxethylene fatty acid esters, polyoxyethylene fatty alcohol ethers, glycerol fatty acid esters, poloxamers (such as, for example, Pluronic®),
- buffers, acids and bases (for example phosphates, carbonates, citric acid, acetic acid, hydrochloric acid, sodium hydroxide solution, ammonium carbonate, trometamol, triethanolamine),
- isotonicity agents (for example glucose, sodium chloride),
- adsorbents (for example highly-disperse silicas),
- viscosity-increasing agents, gel formers, thickeners and/or binders (for example polyvinylpyrrolidone, methylcellulose, hydroxypropylmethylcellulose, hydroxypropyl-cellulose, carboxymethylcellulose-sodium, starch, carbomers, polyacrylic acids (such as, for example, Carbopol®); alginates, gelatine),
- disintegrants (for example modified starch, carboxymethylcellulose-sodium, sodium starch glycolate (such as, for example, Explotab®), cross- linked polyvinylpyrrolidone, croscarmellose-sodium (such as, for example, AcDiSol®)),
- flow regulators, lubricants, glidants and mould release agents (for example magnesium stearate, stearic acid, talc, highly-disperse silicas (such as, for example, Aerosil®)),

- coating materials (for example sugar, shellac) and film formers for films or diffusion membranes which dissolve rapidly or in a modified manner (for example polyvinylpyrrolidones (such as, for example, Kollidon®), polyvinyl alcohol, hydroxypropylmethylcellulose, hydroxypropylcellulose, ethylcellulose, hydroxypropyl-methylcellulose phthalate, cellulose acetate, cellulose acetate phthalate, polyacrylates, polymethacrylates such as, for example, Eudragit®)),
- capsule materials (for example gelatine, hydroxypropylmethylcellulose),
- synthetic polymers (for example polylactides, polyglycolides, polyacrylates, polymethacrylates (such as, for example, Eudragit®), polyvinylpyrrolidones (such as, for example, Kollidon®), polyvinyl alcohols, polyvinyl acetates, polyethylene oxides, polyethylene glycols and their copolymers and blockcopolymers),
- plasticizers (for example polyethylene glycols, propylene glycol, glycerol, triacetine, triacetyl citrate, dibutyl phthalate),
- penetration enhancers,
- stabilisers (for example antioxidants such as, for example, ascorbic acid, ascorbyl palmitate, sodium ascorbate, butylhydroxyanisole, butylhydroxytoluene, propyl gallate),
- preservatives (for example parabens, sorbic acid, thiomersal, benzalkonium chloride, chlorhexidine acetate, sodium benzoate),
- colourants (for example inorganic pigments such as, for example, iron oxides, titanium dioxide),
- flavourings, sweeteners, flavour- and/or odour-masking agents.

The present invention furthermore relates to a pharmaceutical composition which comprise at least one compound according to the invention, conventionally together with one or more pharmaceutically suitable excipient(s), and to their use according to the present invention.

In accordance with another aspect, the present invention covers pharmaceutical combinations, in particular medicaments, comprising at least one compound of general formula (I) of the present invention and at least one or more further active ingredients, in particular for the treatment and/or prophylaxis of cancer or conditions with dysregulated immune responses or other disorders associated with aberrant DGKζ signaling, particularly liquid and solid tumours.

Particularly, the present invention covers a pharmaceutical combination, which comprises:

- one or more first active ingredients, in particular compounds of general formula (I) as defined *supra,* and
- one or more further active ingredients, in particular in particular immune checkpoint inhibitors.

The term "combination" in the present invention is used as known to persons skilled in the art, it being possible for said combination to be a fixed combination, a non-fixed combination or a kit-of-parts.

A "fixed combination" in the present invention is used as known to persons skilled in the art and is defined as a combination wherein, for example, a first active ingredient, such as one or more compounds of general formula (I) of the present invention, and a further active ingredient are present together in one unit dosage or in one single entity. One example of a "fixed combination" is a pharmaceutical composition wherein a first active ingredient and a further active ingredient are present in admixture for simultaneous administration, such as in a formulation. Another example of a "fixed combination" is a pharmaceutical combination wherein a first active ingredient and a further active ingredient are present in one unit without being in admixture.

A non-fixed combination or "kit-of-parts" in the present invention is used as known to persons skilled in the art and is defined as a combination wherein a first active ingredient and a further active ingredient are present in more than one unit. One example of a non-fixed combination or kit-of-parts is a combination wherein the first active ingredient and the further active ingredient are present separately. It is possible for the components of the non-fixed combination or kit-of-parts to be administered separately, sequentially, simultaneously, concurrently or chronologically staggered.

Based upon standard laboratory techniques known to evaluate compounds useful for the treatment of cancer or conditions with dysregulated immune responses or other disorders associated with aberrant DGKζ signaling, by standard toxicity tests and by standard pharmacological assays for the determination of treatment of the conditions identified above in mammals, and by comparison of these results with the results of known active ingredients or medicaments that are used to treat these conditions, the effective dosage of the compounds of the present invention can readily be determined for treatment of each desired indication. The amount of the active ingredient to be administered in the treatment of one of these conditions can vary widely according to such considerations as the particular compound and dosage unit employed, the mode of administration, the period of treatment, the age and sex of the patient treated, and the nature and extent of the condition treated.

The total amount of the active ingredient to be administered will generally range from about 0.001 mg/kg to about 200 mg/kg body weight per day, and preferably from about 0.01 mg/kg to about 20 mg/kg body weight per day. Clinically useful dosing schedules will range from one to three times a day dosing to once every four weeks dosing. In addition, it is possible for "drug holidays", in which a patient is not dosed with a drug for a certain period of time, to be beneficial to the overall balance between pharmacological effect and tolerability. It is possible for a unit dosage to contain from about 0.5 mg to about 1500 mg of active ingredient, and can be administered one or more times per day or less than once a day. The average daily dosage for administration by injection, including intravenous, intramuscular, subcutaneous and parenteral injections, and use of infusion techniques will preferably be from 0.01 to 200 mg/kg of total body weight. The average daily rectal dosage regimen will preferably be from 0.01 to 200 mg/kg of total body weight. The average daily vaginal dosage regimen will preferably be from 0.01 to 200 mg/kg of total body weight. The average daily topical dosage regimen will preferably be from 0.1 to 200 mg administered between one to four times daily. The transdermal concentration will preferably be that required to maintain a daily dose of from 0.01 to 200 mg/kg. The average daily inhalation dosage regimen will preferably be from 0.01 to 100 mg/kg of total body weight.

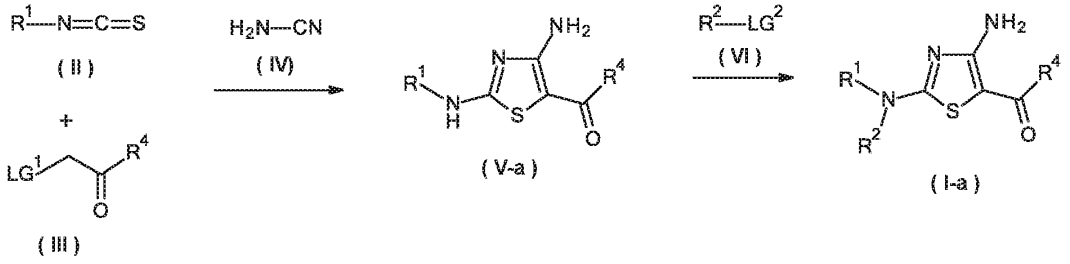
Of course the specific initial and continuing dosage regimen for each patient will vary according to the nature and severity of the condition as determined by the attending diagnostician, the activity of the specific compound employed, the age and general condition of the patient, time of administration, route of administration, rate of excretion of the drug, drug combinations, and the like. The desired mode of treatment and number of doses of a compound of the present invention or a pharmaceutically acceptable salt or ester or composition thereof can be ascertained by those skilled in the art using conventional treatment tests.

General syntheses of compounds of the present invention

The compounds according to the invention of general formula (I) can be prepared according to the following Schemes 1, 2, 3 and 4. The schemes and procedures described below illustrate synthetic routes to the compounds of general formula (I) of the invention and are not intended to be limiting. It is clear to the person skilled in the art that the order of transformations as exemplified in Schemes 1, 2, 3 and 4 can be modified in various ways. The order of transformations exemplified in these schemes is therefore not intended to be limiting. In addition, modification of any of the substituents, R^1, R^2, R^3 or R^4 can be achieved before and/or after the exemplified transformations. These modifications can be such as the introduction of protecting groups, cleavage of protecting groups, reduction or oxidation of functional groups, halogenation, metallation, substitution, or coupling reactions such as amide couplings (couplings of carboxylic

acids with amines) or transition metal catalysed coupling reactions (such as the well-known Suzuki coupling) known to the person skilled in the art. These transformations include those which introduce a functionality which allows for further modification of substituents. Appropriate protecting groups and their introduction and cleavage are well-known to the person skilled in the art (see for example T.W. Greene and P.G.M. Wuts in *Protective Groups in Organic Synthesis*, 3rd edition, Wiley 1999). Specific examples are described in the subsequent paragraphs.

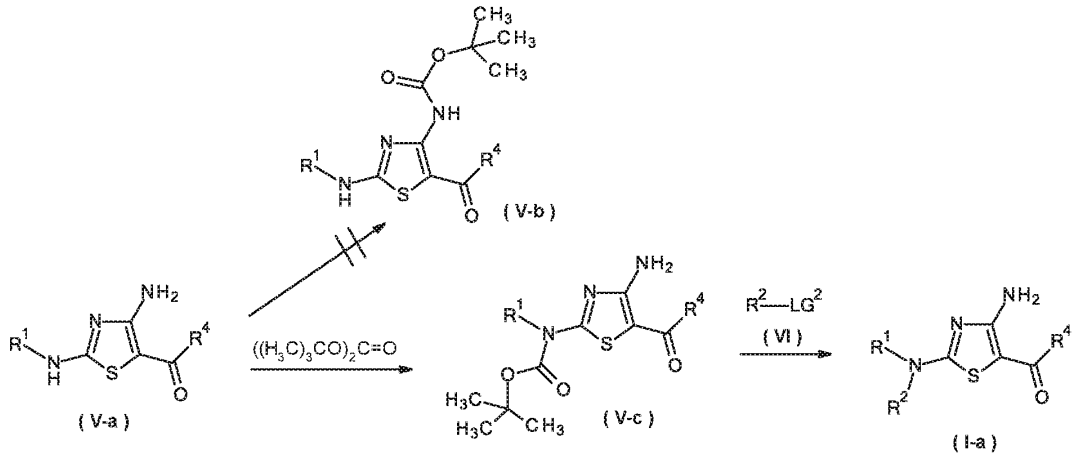
Suitable routes for the preparation of compounds of formulae (I-a) and (I-b), which are sub-sets of general formula (I), which when taken together they form, and for the preparation of compounds of formula (I-c) which, in turn constitutes a sub-set of formula (I-a), are described in Schemes 1, 2, 3 and 4.



Scheme 1: Route for the preparation of compounds of formula (I-a), a sub-set of general formula (I) in which R^3 represents an amino group, from isothiocyanates of formula (II) and ketones of formula (III).

Compounds of formula (I-a), which constitutes a sub-set of general formula (I) in which R^3 represents an amino group, can be prepared from isothiocyanates of formula (II), in which R^1 has the meaning as given for general formula (I), and ketones of formula (III), in which R^4 has the meaning as given for general formula (I), and in which LG^1 represents a leaving group as defined herein, preferably a chlorine, bromine, or iodine atom, more preferably a bromine atom, by reacting with cyanamide (IV), in the presence of a non-nucleophilic base, preferably 1,8-diazabicyclo(5.4.0)undec-7-ene (herein also being referred to as DBU, CAS-RN 6674-22-2), in a dipolar aprotic solvent as defined herein, preferably acetonitrile, at a temperature in the range from 0°C to 50 °C, preferably 15°C to 30°C, more preferably at room temperature, for a time in the range from 1 hour to 100 hours, preferably from 1 hour to 10 hours, more preferably from 2 hours to 4 hours, to give intermediate compounds of formula (V-a). Said intermediate compounds of formula (V-a) can subsequently be reacted with compounds of formula (VI), in which R^2 has the meaning as given for general formula (I), and in which LG^2 represents a leaving group as defined herein, preferably a chlorine, bromine, or iodine atom, or a (methylsulfonyl)oxy or [(4-methylphenyl)sulfonyl]oxy group, more preferably a bromine atom, in a dipolar aprotic

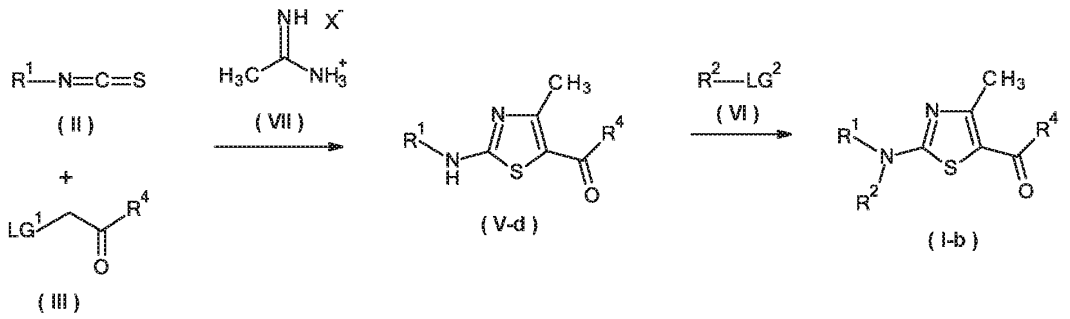
solvent as defined herein, preferably N,N-dimethylformamide, at a temperature in the range from 60°C to 120 °C, preferably 80°C to 100°C, more preferably 90°C, for a time in the range from 30 minutes to 24 hours, preferably from 1 hour to 4 hours, more preferably 2 hours, to give compounds of the present invention, of formula (I-a). Said conversion of intermediate compounds of formula (V-a) into compounds of the present invention of formula (I-a) by reacting with compounds of formula (VI) can also be accomplished advantageously in a dipolar aprotic solvent as defined herein, preferably N,N-dimethylformamide, at a temperature in the range from 0°C to 60 °C, preferably 10°C to 40°C, more preferably at room temperature as defined herein, for a time in the range from 6 hours to 48 hours, preferably from 12 hour to 24 hours. Specific examples are described in the Experimental Section. As indicated in the introductory paragraph of this section, substituents, *e.g.* those attached to R^1 and R^4, can be modified by various methods known to the person skilled in the art during this synthesis route or on the final step. Specific examples are described in the Experimental Section.



Scheme 2: Alternative route for the preparation of compounds of formula (I-a), a sub-set of general formula (I) in which R^3 represents an amino group, from intermediates of formula (V-a).

The reaction between intermediates of the formula (V-a) and compounds of formula (VI) proceeds selectively at the nitrogen atom attached to C-2 of the thiazole, not involving the -NH_2 group attached to C-4. As shown in Scheme 2, this also applies to the analogous reaction with di-tert-butyl dicarbonate which gives compounds of formula (V-c) but not compounds of formula (V-b), said compounds of formula (V-c) being converted, upon reaction with compounds of formula (VI), in which R^2 has the meaning as given for general formula (I), and in which LG^2 represents a leaving group as defined herein, preferably a chlorine, bromine, or iodine atom, more preferably a bromine atom, in a dipolar aprotic solvent as defined herein, preferably N,N-

dimethylformamide, at a temperature in the range from 60°C to 120 °C, preferably 80°C to 100°C, more preferably 90°C, for a time in the range from 30 minutes to 24 hours, preferably from 1 hour to 4 hours, more preferably 2 hours, into compounds of the present invention, of formula (I-a), likewise. Specific examples are described in the Experimental Section.



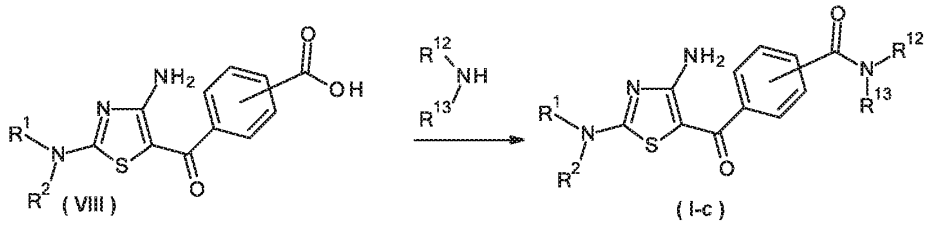
Scheme 3: Route for the preparation of compounds of formula (I-b), a sub-set of general formula (I) in which R^3 represents a methyl group, from isothiocyanates of formula (II) and ketones of formula (III).

Compounds of formula (I-b), which constitutes a sub-set of general formula (I) in which R^3 represents a methyl group, can be prepared from isothiocyanates of formula (II), in which R^1 has the meaning as given for general formula (I), and ketones of formula (III), in which R^4 has the meaning as given for general formula (I), and in which LG^1 represents a leaving group as defined herein, preferably a chlorine, bromine, or iodine atom, more preferably a bromine atom, by reacting with a salt of ethanimidamide of formula (VII), in which X^- represents a monovalent anion, preferably chloride, bromide, iodide or acetate, more preferably chloride, in the presence of a non-nucleophilic base, preferably 1,8-diazabicyclo(5.4.0)undec-7-ene (herein also being referred to as DBU, CAS-RN 6674-22-2), in a dipolar aprotic solvent as defined herein, preferably acetonitrile, at a temperature in the range from 0°C to 50 °C, preferably 15°C to 30°C, more preferably at room temperature, for a time in the range from 1 hour to 100 hours, preferably from 1 hour to 10 hours, more preferably from 2 hours to 4 hours, to give intermediate compounds of formula (V-d). Said intermediate compounds of formula (V-d) can subsequently be reacted with compounds of formula (VI), in which R^2 has the meaning as given for general formula (I), and in which LG^2 represents a leaving group as defined herein, preferably a chlorine, bromine, or iodine atom, or a (methylsulfonyl)oxy or [(4-methylphenyl)sulfonyl]oxy group, more preferably a bromine atom, in a dipolar aprotic solvent as defined herein, preferably N,N-dimethylformamide, at a temperature in the range from 60°C to 120 °C, preferably 80°C to 100°C, more preferably 90°C, for a time in the range from 30 minutes to 24 hours, preferably

from 1 hour to 4 hours, more preferably 2 hours, to give compounds of the present invention, of formula (I-b). Specific examples are described in the Experimental Section.

Compounds of formulae (II), (III), (IV), (VI), and (VII) are largely commercially available or can be prepared using methods known to the person skilled in the art, see *e.g.* F. Calderon et al. Journal of Medicinal Chemistry 2017, 60 (16), 6880 – 6896, for the preparation of isothiocyanates of formula (II); see also the synthesis protocols of Intermediates 200-208 in the Experimental Section, or Y. Xing et al. European Journal of Organic Chemistry 2017, 2017 (4), 781 – 785; A. Wu et al. Tetrahedron 2013, 69 (31), 6392 – 6398, for the preparation of ketones of formula (III); see also the synthesis protocols of Intermediates 198 and 199 in the Experimental Section.

Alternatively, compounds of formula (I-a), which constitutes a sub-set of general formula (I) in which R^3 represents an amino group, can be prepared from precursors in which the R^4 group substituted with a group not covered within the definition of R^4 (such as a carboxy group), which however allows for establishing R^4 groups featuring diverse substituents from a common precursor, such as carboxamides of formula (I-c) (Scheme 4).



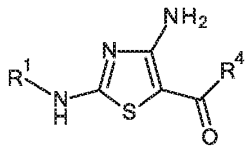
Scheme 4: Route for the preparation of further compounds of the invention, of formula (I-c), from advanced intermediate compounds of formula (VIII).

Scheme 4 exemplifies (without any limitation to the invention) the conversions of advanced intermediates of formula (VIII), which can be prepared using the methods described in the preceding Schemes, in combination with well-established methods such as the saponification of carboxylic esters, Thus, carboxylic acid derivatives of formula (VIII) can be reacted in well-known amide coupling reactions with amines $(R^{12})(R^{13})NH$, in the presence of a coupling reagent such as HATU and a tertiary amine such as triethylamine or N,N-diisopropylethylamine, and optionally in the presence of DMAP, in a dipolar aprotic solvent as defined herein, preferably N,N-dimethylformamide, at a temperature in the range from 0°C to 50 °C, preferably at room temperature as defined herein, for a time in the range from 2 hours to 24 hours, preferably from

12 hour to 20 hours, to give carboxamide compounds of the invention, of formula (I-c). Specific examples are described in the Experimental Section.

In accordance with a second aspect, the present invention covers methods of preparing compounds of formulae (I-a) and (I-b), which are sub-sets of general formula (I), *supra*, which when taken together they form.

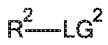
In accordance with a second embodiment of the second aspect, said methods comprise the step of allowing an intermediate compound of formula (V-a) :



(V-a)

in which R^1 and R^4 are as defined for the compound of general formula (I) as defined *supra*,

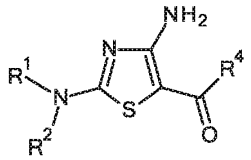
to react with a compound of formula (VI) :



(VI),

in which R^2 is as defined for the compound of general formula (I) as defined *supra*, and in which LG^2 represents a leaving group as defined herein,

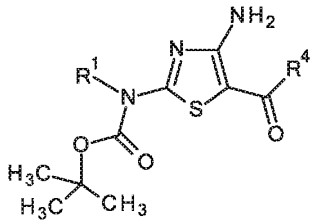
thereby giving a compound of formula (I-a) :



(I-a),

in which R^1, R^2 and R^4 are as defined *supra*.

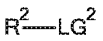
In accordance with a third embodiment of the second aspect, the present invention covers methods of preparing compounds of formula (I-a), said methods comprising the step of allowing an intermediate compound of formula (V-c) :



(V-c)

in which R^1 and R^4 are as defined for the compound of general formula (I) as defined *supra*,

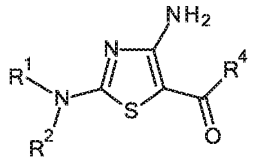
to react with a compound of formula (VI) :



(VI),

in which R^2 is as defined for the compound of general formula (I) as defined *supra*, and in which LG^2 represents a leaving group as defined herein,

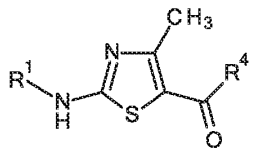
thereby giving a compound of formula (I-a) :



(I-a),

in which R^1, R^2 and R^4 are as defined *supra*.

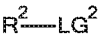
In accordance with a fourth embodiment of the second aspect, the present invention covers methods of preparing compounds of formula (I-b), said methods comprising the step of allowing an intermediate compound of formula (V-d) :



(V-d)

in which R^1 and R^4 are as defined for the compound of general formula (I) as defined *supra*,

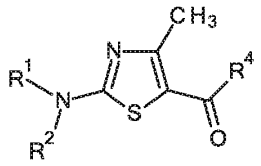
to react with a compound of formula (VI) :



(VI),

in which R^2 is as defined for the compound of general formula (I) as defined *supra*, and in which LG^2 represents a leaving group as defined herein,

thereby giving a compound of formula (I-b) :

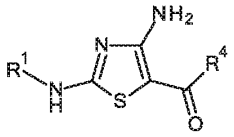


(I-b),

in which R^1, R^2 and R^4 are as defined *supra*.

In accordance with a third aspect, the present invention covers methods of preparing compounds of formulae (I-a) and (I-b), which are sub-sets of general formula (I), *supra*, which when taken together they form.

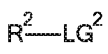
In accordance with a second embodiment of the third aspect, said methods comprise the step of allowing an intermediate compound of formula (V-a) :



(V-a)

in which R^1 and R^4 are as defined for the compound of general formula (I) as defined *supra*,

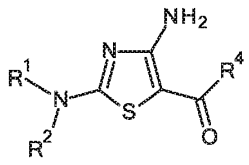
to react with a compound of formula (VI) :



(VI),

in which R^2 is as defined for the compound of general formula (I) as defined *supra*, and in which LG^2 represents a leaving group as defined herein,

thereby giving a compound of formula (I-a) :

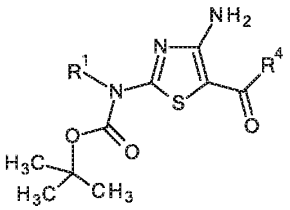


(I-a),

in which R^1, R^2 and R^4 are as defined *supra*,

then optionally converting said compound into solvates, salts and/or solvates of such salts using the corresponding (i) solvents and/or (ii) bases or acids.

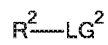
In accordance with a third embodiment of the third aspect, the present invention covers methods of preparing compounds of formula (I-a), said methods comprising the step of allowing an intermediate compound of formula (V-c) :



(V-c)

in which R^1 and R^4 are as defined for the compound of general formula (I) as defined *supra*,

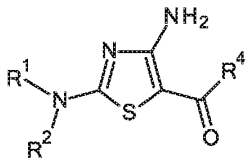
to react with a compound of formula (VI) :



(VI),

in which R^2 is as defined for the compound of general formula (I) as defined *supra*, and in which LG^2 represents a leaving group as defined herein,

thereby giving a compound of formula (I-a) :

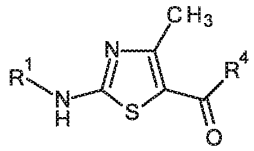


(I-a),

in which R^1, R^2 and R^4 are as defined *supra*,

then optionally converting said compound into solvates, salts and/or solvates of such salts using the corresponding (i) solvents and/or (ii) bases or acids.

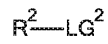
In accordance with a fourth embodiment of the third aspect, the present invention covers methods of preparing compounds of formula (I-b), said methods comprising the step of allowing an intermediate compound of formula (V-d) :



(V-d)

in which R^1 and R^4 are as defined for the compound of general formula (I) as defined *supra*,

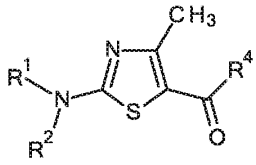
to react with a compound of formula (VI) :



(VI),

in which R^2 is as defined for the compound of general formula (I) as defined *supra*, and in which LG^2 represents a leaving group as defined herein,

thereby giving a compound of formula (I-b) :



(I-b),

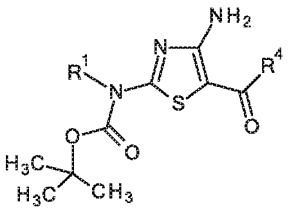
in which R^1, R^2 and R^4 are as defined *supra*,

then optionally converting said compound into solvates, salts and/or solvates of such salts using the corresponding (i) solvents and/or (ii) bases or acids.

The present invention covers methods of preparing compounds of the present invention of general formula (I), said methods comprising the steps as described in the Experimental Section herein.

In accordance with a fourth aspect, the present invention covers intermediate compounds which are useful for the preparation of the compounds of formulae (I-a) and (I-b), which are sub-sets of general formula (I), *supra*, which when taken together they form.

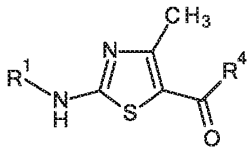
In accordance with a second embodiment of the fourth aspect, the present invention covers the intermediate compounds of formula (V-c) :



(V-c)

in which R^1 and R^4 are as defined for the compound of general formula (I) *supra*.

In accordance with a third embodiment of the fourth aspect, the present invention covers the intermediate compounds of formula (V-d) :

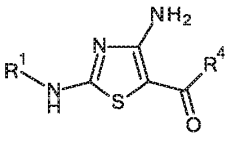


(V-d)

in which R^1 and R^4 are as defined for the compound of general formula (I) *supra*.

In accordance with a fifth aspect, the present invention covers the use of intermediate compounds for the preparation of the compounds of formulae (I-a) and (I-b), which are sub-sets of general formula (I), *supra*, which when taken together they form.

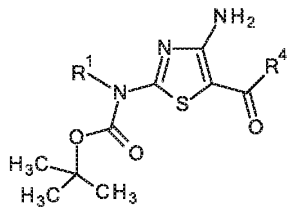
In accordance with a second embodiment of the fifth aspect, the present invention covers the intermediate compounds of formula (V-a) :



(V-a)

in which R^1 and R^4 are as defined for the compound of general formula (I) *supra*, for the preparation of a compound of formula (I-a) as defined *supra*.

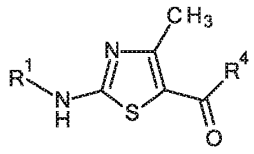
In accordance with a third embodiment of the fifth aspect, the present invention covers the intermediate compounds of formula (V-c) :



(V-c)

in which R^1 and R^4 are as defined for the compound of general formula (I) *supra*, for the preparation of a compound of formula (I-a) as defined *supra*.

In accordance with a fourth embodiment of the fifth aspect, the present invention covers the intermediate compounds of formula (V-d) :



(V-d)

in which R^1 and R^4 are as defined for the compound of general formula (I) *supra*, for the preparation of a compound of formula (I-b) as defined *supra*.

The present invention covers intermediate compounds which are disclosed in the Example Section of this text, *infra*.

The present invention covers the use of intermediate compounds which are disclosed in the Example Section of this text, *infra*.

The present invention covers any sub-combination within any embodiment or aspect of the present invention of intermediate compounds of formulae (V-a), (V-c) and (V-d), *supra*.

Description of the Figures

Figure 1: DGKz_hu_1 encoding human DGKζ M1 to V928 plus N-terminal Flag-Tag, as described under SEQ ID No. 1.

Figure 2: SIINFEKL amino acid sequence, as described under SEQ ID No. 2.

Figure 3: OVA-30 peptide sequence, as described under SEQ ID No. 3.

Figure 4: FLAG-Tag, as described under SEQ ID No. 4.

Figure 5: Kozak sequence for translation initiation, as described under SEQ ID No. 5.

Figure 6: 50% thermal ellipsoids of Example 49.2, Molecule 1. F171 and F151 represents the two refined positions for the 180° disorder over the C13-C16 axis.

Figure 7: 50% thermal ellipsoids of Example 59.1, Molecule 1

Figure 8: 50% thermal ellipsoids of Example 61.2, Molecule 1

Figure 9: 50% thermal ellipsoids of Example 62.2, Molecule 1

EXPERIMENTAL SECTION – GENERAL PART

NMR peak forms are stated as they appear in the spectra, possible higher order effects have not been considered. The multiplicities are stated according to the signal form which appears in the spectrum, NMR-spectroscopic effects of a higher order were not taken into consideration. Multiplicity of the NMR signals: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, br = broad signal, m = multiplet. NMR signals: shift in [ppm]. Combinations of multiplicity could be e.g. dd = doublet from doublet.

Chemical names were generated using software programs such as the ACD/Name batch version 14.05 from ACD/Labs and BioVia Draw 2019 Version 19.1 NET, and chemical names were adapted if needed. In some cases generally accepted names of commercially available reagents were used in place of chemical names generated using abovementioned software programs.

All reagents the synthesis of which is not described in the experimental part were purchased commercially, or said reagents are known compounds or can be formed from known compounds by known methods by a person skilled in the art.

Table 1 lists the abbreviations used in this paragraph and in the Examples section as far as they are not explained within the text body. Other abbreviations have their meanings customary *per se* to the skilled person.

Table 1: Abbreviations

$CDCl_3$	deuterochloroform
DAD	diode array detector
SQD	single quadrupole detector
Azura UVD	single variable wavelength UV detector for HPLC
DMF	N,N-dimethylformamide
DMSO-d6	deuterated dimethyl sulphoxide
DMSO	dimethyl sulphoxide
ELSD	evaporative light scattering detector
ESIpos	electrospray ionization positive
Expl.	example
HATU	(7-aza-1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HPLC	high-pressure liquid chromatography
LC-MS	liquid chromatography coupled with mass spectrometry
mL	milliliter
min	minute(s)
MTBE	methyl *tert*-butyl ether
RP-HPLC	reverse-phase high-pressure liquid chromatography
Rt	retention time
rt	room temperature
sat.	saturated
THF	tetrahydrofurane
EtOAc	ethyl acetate
TLC	thin layer chromatography
rac	racemic
µM	micromolar

M	molar
UPLC	Ultra high performance chromatography
UPLC-MS	Ultra high performance chromatography coupled with mass spectrometry
BEH	ethylene bridged hybrid
CSH	charged surface hybrid
UV	ultra violet
CAS-RN	chemical abstracts service registry number
NMR	nuclear magnetic resonance
MHz	Megahertz

Analytical UPLC-MS Standard Procedures

Method 1 / acidic

Instrument: Waters Acquity UPLC-MS SQD 3001; column: Acquity UPLC BEH C18 1.7 50x2.1mm; eluent A: water + 0.1 vol% formic acid, eluent B: acetonitrile; gradient: 0-1.6 min 1-99% B, 1.6-2.0 min 99% B; flow 0.8 mL/min; temperature: 60°C; injection: 2 µL; DAD scan: 210-400 nm; ELSD

Method 2 / basic

Instrument: Waters Acquity UPLC-MS SQD 3001; column: Acquity UPLC BEH C18 1.7 50x2.1mm; eluent A: water + 0.2 vol% aqueous ammonia (32%), eluent B: acetonitrile; gradient: 0-1.6 min 1-99% B, 1.6-2.0 min 99% B; flow 0.8 mL/min; temperature: 60°C; injection: 2 µL; DAD scan: 210-400 nm; ELSD

Method 3 / basic

Instrument: Waters Acquity UPLC-MS SingleQuad; Column: Acquity UPLC CSH C18 1.7µm 50x2.1mm; eluent A: water + 0.2 vol % aqueous ammonia (32%), eluent B: acetonitrile; gradient: 0-1.6 min 1-99% B, 1.6-2.0 min 99% B; flow 0.8 mL/min; temperature: 60 °C; DAD scan: 210-400 nm.

Optical Rotation

Optical rotations were measured with a JASCO Polarimeter 2000 using the solvent and concentration stated in each case at 20°C, wavelength 589 nm, integration time 10 s, layer thickness 100 mm.

Compound purification - General

The example compounds and intermediates produced according to the methods of the invention may require purification. Purification of organic compounds is well known to the person skilled in the art and there may be several ways of purifying the same compound. In some cases, no purification may be necessary. In some cases, the compounds may be purified by crystallization. In some cases, impurities may be stirred out using a suitable solvent. In some cases, the compounds may be purified by chromatography, particularly flash column chromatography, using for example prepacked silica gel cartridges, e.g. Biotage SNAP cartidges KP-Sil® or KP-NH® in combination with a Biotage autopurifier system (SP4® or Isolera Four®) and eluents such as gradients of hexane/ethyl acetate or dichloromethane/methanol. In some cases, the compounds may be purified by preparative HPLC using for example a Waters autopurifier system equipped with a diode array detector and/or on-line electrospray ionization mass spectrometer in combination with a suitable prepacked reverse phase column and eluents such as gradients of water and acetonitrile which may contain additives such as trifluoroacetic acid, formic acid or aqueous ammonia.

In some cases, purification methods as described above can provide those compounds of the present invention which possess a sufficiently basic or acidic functionality in the form of a salt, such as, in the case of a compound of the present invention which is sufficiently basic, a trifluoroacetate or formate salt for example, or, in the case of a compound of the present invention which is sufficiently acidic, an ammonium salt for example. A salt of this type can either be transformed into its free base or free acid form, respectively, by various methods known to the person skilled in the art, or be used as salts in subsequent biological assays. It is to be understood that the specific form (e.g. salt, free base etc.) of a compound of the present invention as isolated and as described herein is not necessarily the only form in which said compound can be applied to a biological assay in order to quantify the specific biological activity.

Specific methods are described below, and in the respective protocols describing the preparations of example compounds and intermediates.

Preparative HPLC

Instrument: pump: Labomatic HD-3000, head HDK 280, low pressure gradient module ND-B1000; manual injection valve: Rheodyne 3725i038; detector: Knauer Azura UVD 2.15; collector: Labomatic Labocol Vario-4000; column: Chromatorex RP C-18 10 µm, 125x30mm;

eluent; gradient; UV-Detection. Eluent: solvent A: water + 0.1 vol% formic acid (99%; acidic) or 0.2 vol% aqueous ammonia (32%, basic) , solvent B: acetonitrile; flow 150 mL/min.

Gradients:

Method A: 0.00-0.50 min 1% B, 0.50–6.00 min 1-25% B, 6.00-6.10 min 25-100% B, 6.10-8.00 min 100% B

Method B: 0.00-0.50 min 10% B, 0.50–6.00 min 10-50% B, 6.00-6.10 min 50-100% B, 6.10-8.00 min 100% B

Method C: 0.00-0.50 min 15% B, 0.50–6.00 min 15-55% B, 6.00-6.10 min 55-100% B, 6.10-8.00 min 100% B

Method D: 0.00-0.50 min 30% B, 0.50–6.00 min 30-70% B, 6.00-6.10 min 70-100% B, 6.10-8.00 min 100% B

Method E: 0.00-0.50 min 40% B, 0.50–6.00 min 40-80% B, 6.00-6.10 min 80-100% B, 6.10-8.00 min 100% B

Method F:

Instrument: Waters autopurification system; column: Waters CSH C18 5µ 100x30mm; eluent A: water + 0.1 Vol-% aqueous ammonia (32%), eluent B: acetonitrile, DAD scan: 210-400 nm; MS Instrument: QDA (Waters); Collector-Trigger: DAD-MS flow rate: 60 mL/min

Chiral HPLC and stereochemistry assignments

Separations of stereoisomeric mixtures, such as racemic compounds, by chiral HPLC can result in the isolation of single stereoisomers without known configuration of the respective stereogenic centres in the isolated isomers. In the following, the full chemical names of all such separated isomers obtained from an isomeric mixture, including (R) and (S) configurations, are listed in alphabetical order together with all respective intermediate or example numbers, followed by the individual isomers with data on their analytics, isolation and yield, followed by descriptors such as "(enantiomer 1)", "(stereoisomer 2)", and the like. Likewise, example compounds obtained from starting materials being single stereoisomers of unknown absolute configuration are disclosed herein in an analogous fashion. The order of the full chemical names (including (R) and (S) configurations) cannot be construed as to encode for any correlation to the individual intermediate or example numbers.

Preparative flash chromatography

Instrument: Biotage Isolera Four; pump: Dual-Piston; flow rate: 1 to 200 mL/min; internal detector: 200-400 nm (variable UV detector); solvent inlets: 4; cartridges: Biotage SNAP

Ultra™, sizes: 10 g, 25 g, 50 g, 100 g, 340 g, media: Biotage® HP-Sphere - 25 micron spherical silica, resolution: minimum 7000 N/m (plates per meter) typical 10 000 N/m; solvent A: hexane, solvent B: ethyl acetate, solvent C: dichlormethane, solvent D: ethanol; solvent E: methanol; UV collection modes: single/dual/λ-All wavelengths (variable UV); fractionation modes: volume, threshold, threshold with volume, low slope, medium slope, custom slope or via external detection

Method X: gradient with solvent A and B, λ-all

Method Y: gradient with solvent C and D, λ-all

Method Z: gradient with solvent C and E, λ-all

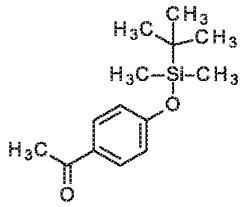
The various aspects of the invention described in this application are illustrated by the following examples which are not meant to limit the invention in any way.

The example testing experiments described herein serve to illustrate the present invention and the invention is not limited to the examples given.

EXPERIMENTAL SECTION – PREPARATION OF INTERMEDIATES

Intermediate 1

1-(4-{[tert-butyl(dimethyl)silyl]oxy}phenyl)ethan-1-one

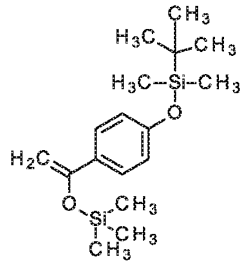


1-(4-Hydroxyphenyl)ethan-1-one (2.00 g, 14.7 mmol) was provided in dichloromethane (25 mL) at 0°C. 4-dimethylaminopyridine (100 mg, 819 µmol; CAS-RN 1122-58-3) and imidazole (2.00 g, 29.4 mmol; CAS-RN 288-32-4) were added. To the mixture was added dropwise a solution of tert-butyl(chloro)dimethylsilane (3.32 g, 22.0 mmol) dichloromethane. The reaction mixture was stirred for 2 h at rt. The mixture was poured into aqueous sodiumbicarbonate solution and extracted with dichloromethane. The organic layer was washed with water, dried and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, hexane / ethyl acetate gradient 0-10 %) to give 3.7 g (96 % yield) of the title compound.

^{1}H-NMR (400 MHz, CHLOROFORM-*d*): δ ppm = 0.23 (s, 6 H), 0.99 (s, 9 H), 2.55 (s, 3 H), 6.85 - 6.89 (m, 2 H), 7.86 - 7.90 (m, 2 H)

Intermediate 2

tert-butyl(dimethyl)(4-{1-[(trimethylsilyl)oxy]ethenyl}phenoxy)silane

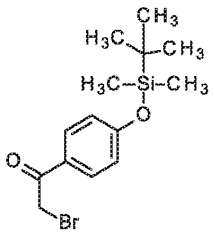


Lithium diisopropylamide solution in tetrahydrofurane (1.5 mL, 2.0 M, 3.0 mmol; CAS-RN 4111-54-0) was provided under argon at – 70°C, and 1-(4-{[tert-butyl(dimethyl)silyl]oxy}phenyl)ethan-1-one (500 mg, 2.00 mmol, Intermediate 1) was added. The mixture was allowed to warm to 0°C and was stirred for 30 min at 0°C. Chlorotrimethylsilane (1.6 mL, 13 mmol; CAS-RN 75-77-4) was added and the reaction mixture was stirred for 4 h at rt. The mixture was poured into water/brine and extracted with methyl tert-butylether. The combined organic layer was washed with brine, dried and concentrated under reduced pressure to give 700 mg (98 % yield) of the title compound as a yellow oil.

^{1}H-NMR (400 MHz, CHLOROFORM-*d*): δ ppm = 0.07 (s, 9 H), 0.77 - 0.82 (m, 15 H), 4.13 - 4.15 (m, 1 H), 4.60 (d, *J*=1.77 Hz, 1 H), 6.57 - 6.61 (m, 2 H), 7.24 - 7.29 (m, 2 H).

Intermediate 3

2-bromo-1-(4-{[tert-butyl(dimethyl)silyl]oxy}phenyl)ethan-1-one



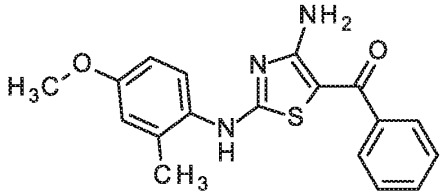
Tert-butyl(dimethyl)(4-{1-[(trimethylsilyl)oxy]ethenyl}phenoxy)silane (695 mg, 2.15 mmol; Intermediate 2) was provided at 0 °C in tetrahydrofurane (57 mL) and N-bromosuccinimide (460 mg, 2.59 mmol; CAS-RN 128-08-5) was added. The reaction mixture was stirred overnight at rt. The mixture was treated with water/brine and extracted with ethyl acetate. The combined organic layer was washed with brine, dried and concentrated under reduced pressure. The residue was purified by flash chromatography (silica, hexane / ethyl acetate gradient 0-10 %) to give 460 mg (62 % yield) of the title compound.

^{1}H-NMR (400 MHz, CHLOROFORM-*d*): δ ppm = 0.24 - 0.26 (m, 6 H), 0.99 (s, 9 H), 4.40 (s, 2 H), 6.90 (d, *J*=8.87 Hz, 2 H), 7.91 (d, *J*=8.87 Hz, 2 H).

LC-MS (method 2): R_t = 1.58 min; MS (ESIpos): m/z = 329.2 $[M+H]^+$

Intermediate 4

[4-amino-2-(4-methoxy-2-methyl-anilino)thiazol-5-yl]-phenyl-methanone



1-Isothiocyanato-4-methoxy-2-methylbenzene (225.1 mg, 1.26 mmol) was dissolved in acetonitrile (25 mL) followed by the addition of 1,8-diazabicyclo(5.4.0)undec-7-ene (190 mg, 1.26 mmol) and cyanamide (63.4 mg, 1.51 mmol). After stirring for 45 min at rt further 1,8-diazabicyclo(5.4.0)undec-7-ene (96 mg, 0.62 mmol) and 2-bromo-1-phenylethanone (225 mg, 1.26 mmol) were added. The reaction mixture was stirred at rt overnight. The suspension was treated with water and the precipitate was isolated by filtration, washed with water and some ethyl acetate and dried by lyophilization to give 351 mg (78 % yield) of the title compound.

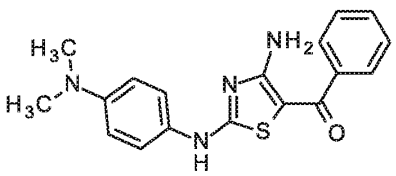
^{1}H-NMR: (400 MHz, DMSO-*d*6): δ ppm = 2.19 (s, 3 H), 3.74 (s, 3 H), 6.78 (dd, *J*=8.62, 2.79 Hz, 1 H), 6.88 (d, *J*=2.79 Hz, 1 H), 7.26 (d, *J*=8.62 Hz, 1 H), 7.34 - 7.47 (m, 3 H), 7.50 - 7.62 (m, 2 H), 7.75 - 8.52 (m, 2 H), 9.90 - 10.16 (br s, 1 H).

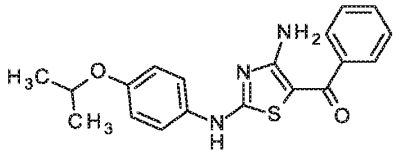
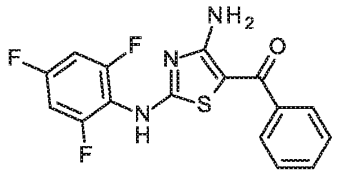
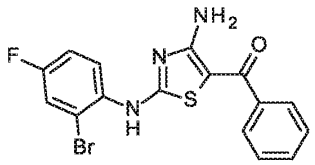
LC-MS (method 2) Rt = 1.09 min; MS (ESIpos): m/z = 340.1 $[M+H]^+$

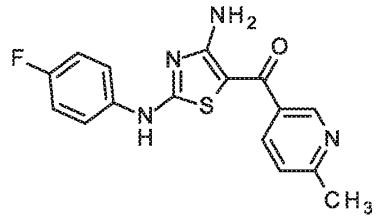
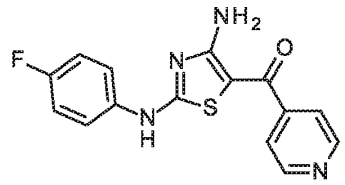
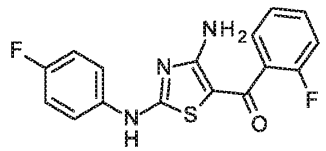
The following intermediates were prepared from commercial starting materials stated in Table 2, below, using the procedure as for Intermediate 4, followed by purification by chromatography if needed. If no purification is specified, the respective title compound was isolated as crude product.

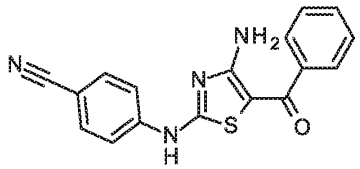
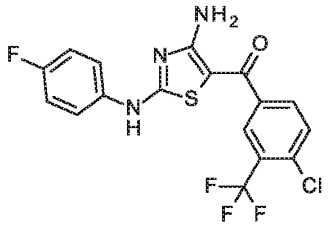
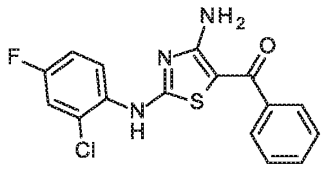
The crude product was either purified by RP-HPLC (methods A-D depending on polarity) or by preparative flash chromatography (methods X, Y or Z depending on polarity) if necessary. In case of a missing precipitation, the reaction mixture was extracted three times with ethyl acetate. The combined organic phases were dried over sodium sulfate, filtrated and evaporated to dryness. The crude product was purified by chromatography as stated in Table 2.

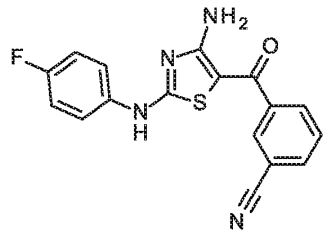
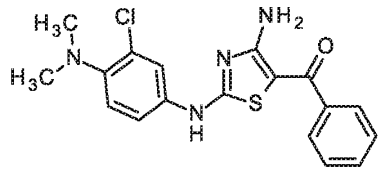
Table 2: Intermediates 5 – 77

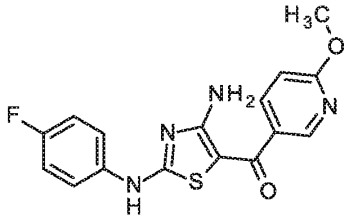
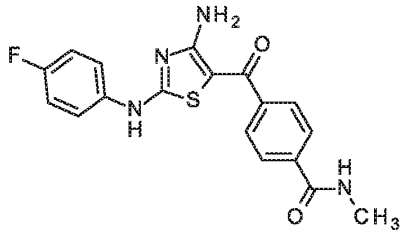
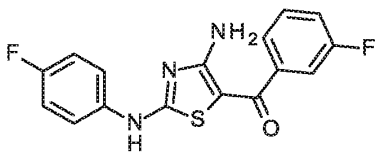
Inter-mediate number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
5	 [4-amino-2-[4-(dimethylamino)anilino]thiazol-5-yl]-phenyl-methanone	4-isothiocyanato-N,N-dimethylaniline; 2-bromo-1-phenylethanone	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 2.87 (s, 6 H), 6.72 (d, *J*=9.13 Hz, 2 H), 7.30 (br d, *J*=8.36Hz, 2 H), 7.38 - 7.51 (m, 3 H), 7.61 (dd, *J*=7.48, 2.15 Hz, 2 H), 7.82 - 8.55 (m, 2 H), 10.32 - 10.58 (br s, 1 H). LC-MS (method 1) Rt = 1.00 min; MS (ESIpos): m/z = 339.3 $[M+H]^+$ RP-HPLC (method C, acidic) 10 % yield

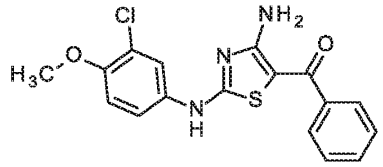
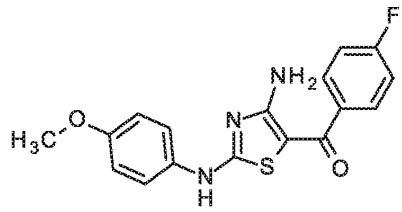
Inter-mediate number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
6	 [4-amino-2-(4-isopropoxyanilino)thiazol-5-yl]-phenyl-methanone	1-isopropoxy-4-isothiocyanatobenzene; 2-bromo-1-phenylethanone	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.24 (d, *J*=6.08 Hz, 6 H), 4.56 (spt, *J*=6.04 Hz, 1 H), 6.88 - 6.95 (m, 2 H), 7.42 - 7.49 (m, 5 H), 7.61 - 7.67 (m, 2 H), 7.89 - 8.41 (m, 2 H), 10.57 - 10.61 (br s, 1 H). LC-MS (method 1) Rt = 1.24 min; MS (ESIpos): m/z = 354.8 $[M+H]^+$ RP-HPLC (method D, acidic) 66 % yield
7	 [4-amino-2-(2,4,6-trifluoroanilino)thiazol-5-yl]-phenyl-methanone	1,3,5-trifluoro-2-isothiocyanatobenzene; 2-bromo-1-phenylethanone	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 7.38 (m, 2 H), 7.43 - 7.52 (m, 3 H), 7.63 (m, 2 H), 7.97 - 8.42 (m, 2 H), 10.22 - 10.38 (br s, 1 H). LC-MS (method 2) Rt = 0.81 min; MS (ESIpos): m/z = 350.5 $[M+H]^+$ RP-HPLC (method C, basic) 68 % yield
8	 [4-amino-2-(2-bromo-4-fluoro-anilino)thiazol-5-yl]-phenyl-methanone	2-bromo-4-fluoro-1-isothiocyanatobenzene; 2-bromo-1-phenylethanone	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 7.33 (td, *J*=8.55, 2.91 Hz, 1 H), 7.39 - 7.51 (m, 3 H), 7.61 (dd, *J*=7.48, 1.90 Hz, 2 H), 7.66 - 7.75 (m, 2 H), 7.96 - 8.45 (m, 2 H), 10.20 - 10.49 (br s, 1 H). LC-MS (method 2) Rt = 0.81 min; MS (ESIpos): m/z = 350.5 $[M+H]^+$ RP-HPLC (method C, basic) 33 % yield

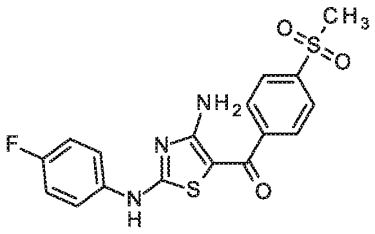
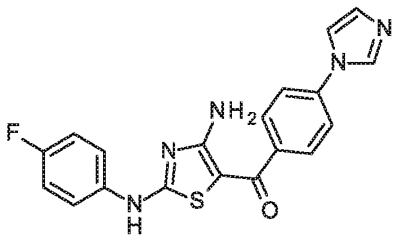
Inter-mediate number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
9	 [4-amino-2-(4-fluoroanilino)thiazol-5-yl]-(6-methyl-3-pyridyl)methanone	1-fluoro-4-isothiocyanatobenzene; 2-chloro-1-(6-methylpyridin-3-yl)ethanone	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 2.52 (s, 3 H), 7.22 (t, *J*=8.87 Hz, 2 H), 7.36 (d, *J*=7.86 Hz, 1 H), 7.60 - 7.67 (m, 2 H), 7.92 (dd, *J*=7.86, 2.28 Hz, 1 H), 8.14 - 8.48 (m, 2 H), 8.72 (d, *J*=2.03 Hz, 1 H), 10.87 (s, 1 H). LC-MS (method 2) Rt = 0.86 min; MS (ESIpos): m/z = 329.2 $[M+H]^+$ 72 % yield
10	 [4-amino-2-(4-fluoroanilino)thiazol-5-yl]-(4-pyridyl)methanone	1-fluoro-4-isothiocyanatobenzene; 2-bromo-1-(4-pyridyl)ethanone; hydrobromide (1:1)	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 7.20 - 7.26 (m, 2 H), 7.54 - 7.59 (m, 1 H), 7.56 - 7.58 (m, 1 H), 7.60 - 7.67 (m, 2 H), 8.27 - 8.47 (m, 2 H), 8.70 (d, *J*=5.83 Hz, 2 H), 10.83 - 11.02 (br s, 1 H). LC-MS (method 2) Rt = 0.77 min; MS (ESIpos): m/z = 315.1 $[M+H]^+$ 76 % yield
11	 [4-amino-2-(4-fluoroanilino)thiazol-5-yl]-(2-fluorophenyl)methanone	1-fluoro-4-isothiocyanatobenzene; 2-bromo-1-(2-fluorophenyl)ethanone	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 7.21 (t, *J*=8.87 Hz, 2 H), 7.24 - 7.31 (m, 2 H), 7.44 - 7.53 (m, 2 H), 7.55 - 7.63 (m, 2 H), 8.16 (br s, 2 H), 10.79 (s, 1 H). LC-MS (method 2) Rt = 0.97 min; MS (ESIpos): m/z = 332.3 $[M+H]^+$ 92 % yield

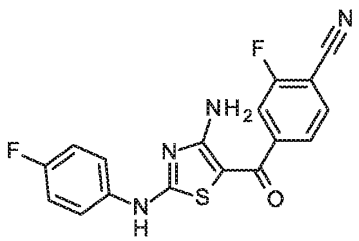
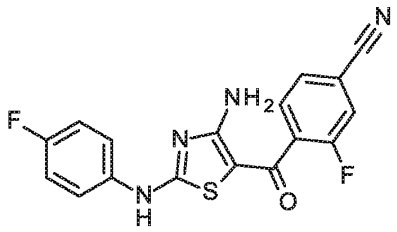
Inter-mediate number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
12	 4-[(4-amino-5-benzoyl-thiazol-2-yl)amino]benzonitrile	4-isothiocyanatobenzonitrile; 2-bromo-1-phenylethanone	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 7.45 - 7.52 (m, 3 H), 7.68 (dd, *J*=7.73, 1.65 Hz, 2 H), 7.81 (s, 4 H), 8.17 - 8.40 (m, 2 H), 11.08 - 11.35 (br s, 1 H). LC-MS (method 2) Rt = 0.92 min; MS (ESIpos): m/z = 321.1 $[M+H]^+$ 56 % yield
13	 [4-amino-2-(4-fluoroanilino)thiazol-5-yl]-[4-chloro-3-(trifluoromethyl)phenyl]methanone	1-fluoro-4-isothiocyanatobenzene; 2-bromo-1-[4-chloro-3-(trifluoromethyl)phenyl]ethanone	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 7.22 (t, *J*=8.87 Hz, 2 H), 7.66 (br d, *J*=4.06 Hz, 2 H), 7.87 (s, 1 H), 7.95 - 8.01 (m, 1 H), 8.07 (s, 1 H), 8.28 - 8.49 (m, 2 H), 10.90 - 10.96 (br s, 1 H). LC-MS (method 2) Rt = 1.26 min; MS (ESIpos): m/z = 416.2 $[M+H]^+$ RP-HPLC (method D, basic) 31 % yield
14	 [4-amino-2-(2-chloro-4-fluoro-anilino)thiazol-5-yl]-phenyl-methanone	2-chloro-4-fluoro-1-isothiocyanatobenzene; 2-bromo-1-phenylethanone	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 7.25 - 7.31 (m, 1 H), 7.41 - 7.50 (m, 3 H), 7.58 (dd, *J*=8.49, 2.91 Hz, 1 H), 7.60 - 7.66 (m, 2 H), 7.81 (dd, *J*=9.12, 5.83 Hz, 1 H), 8.17 (br s, 2 H), 10.36 (br s, 1 H). LC-MS (method 2) Rt = 1.00 min; MS (ESIpos): m/z = 348.5 $[M+H]^+$ RP-HPLC (method C, basic) 67 % yield

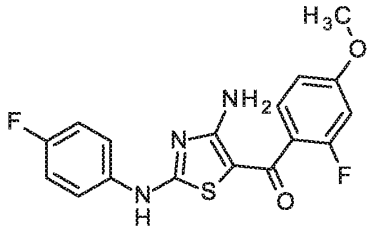
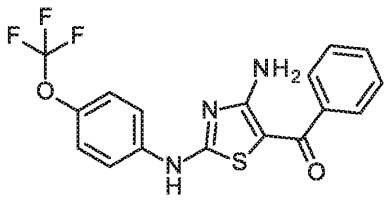
Inter-mediate number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
15	 3-[4-amino-2-(4-fluoroanilino)thiazole-5-carbonyl]benzonitrile	1-fluoro-4-isothiocyanatobenzene; 3-(bromoacetyl)benzonitrile	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 7.22 (t, *J*=8.87 Hz, 2 H), 7.61 - 7.66 (m, 2 H), 7.69 (t, *J*=7.98 Hz, 1 H), 7.97 (dd, *J*=7.86, 1.77 Hz, 2 H), 8.06 (t, *J*=1.52 Hz, 1 H), 8.33 (br s, 2 H), 10.81 - 10.97 (m, 1 H). LC-MS (method 2) Rt = 0.97 min; MS (ESIpos): m/z = 339.2 $[M+H]^+$ 78 % yield
16	 [4-amino-2-[3-chloro-4-(dimethylamino)anilino]thiazol-5-yl]-phenyl-methanone	2-chloro-4-isothiocyanato-N,N-dimethylaniline; 2-bromo-1-phenylethanone	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 2.68 (s, 6 H), 7.14 (d, *J*=8.87 Hz, 1 H), 7.34 (dd, *J*=8.62, 2.53 Hz, 1 H), 7.42 - 7.50 (m, 3 H), 7.60 - 7.69 (m, 2 H), 7.69 - 7.74 (m, 1 H), 8.22 (br s, 2 H), 10.58 (br s, 1 H). LC-MS (method 2) Rt = 1.14 min; MS (ESIpos): m/z = 373.2 $[M+H]^+$ RP-HPLC (method D, basic) 66 % yield

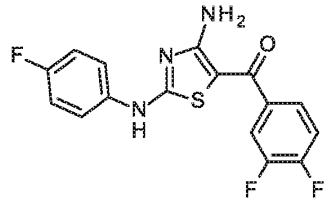
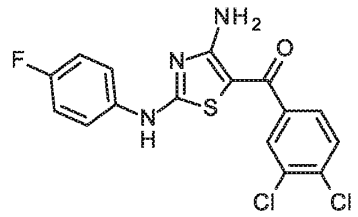
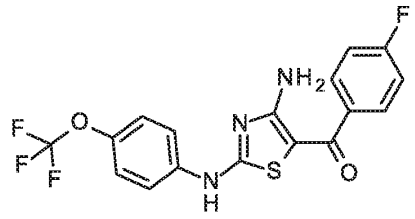
Inter-mediate number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
17	 [4-amino-2-(4-fluoroanilino)thiazol-5-yl]-(6-methoxy-3-pyridyl)methanone	1-fluoro-4-isothiocyanatobenzene; 2-bromo-1-(6-methoxypyridin-3-yl)ethanone	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 3.91 (s, 3 H), 6.91 (dd, *J*=8.49, 0.63 Hz, 1 H), 7.19 - 7.26 (m, 2 H), 7.62 - 7.66 (m, 2 H), 7.98 (dd, *J*=8.62, 2.53 Hz, 1 H), 8.24 (br s, 2 H), 8.51 (dd, *J*=2.53, 0.76 Hz, 1 H), 10.85 (br s, 1 H). LC-MS (method 1) Rt = 1.09 min; MS (ESIpos): m/z = 345.2 $[M+H]^+$ 72 % yield
18	 4-[4-amino-2-(4-fluoroanilino)thiazole-5-carbonyl]-N-methyl-benzamide	1-fluoro-4-isothiocyanatobenzene; 4-(bromoacetyl)-N-methylbenzamide	LC-MS (method 2) Rt = 0.79 min; MS (ESIpos): m/z = 371.2 $[M+H]^+$ RP-HPLC (method C, basic) 31 % yield
19	 [4-amino-2-(4-fluoroanilino)thiazol-5-yl]-(3-fluorophenyl)methanone	1-fluoro-4-isothiocyanatobenzene; 2-bromo-1-(3-fluorophenyl)ethanone	LC-MS (method 2) Rt = 1.03 min; MS (ESIpos): m/z = 332.2 [M+H]+ RP-HPLC (method D, basic) 13 % yield

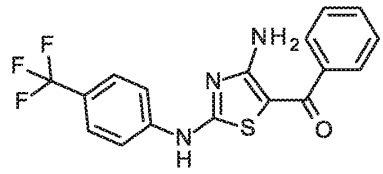
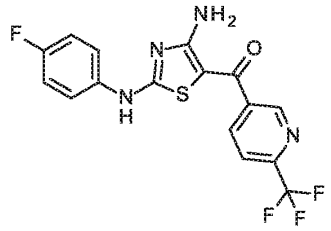
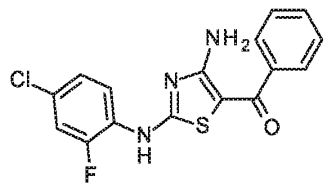
Inter-mediate number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
20	 [4-amino-2-(3-chloro-4-methoxy-anilino)thiazol-5-yl]-phenyl-methanone	2-chloro-4-isothiocyanato-1-methoxybenzene; 2-bromo-1-phenylethanone	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 3.83 (s, 3 H), 7.15 (d, *J*=8.87 Hz, 1 H), 7.41 (dd, *J*=8.87, 2.79 Hz, 1 H), 7.44 - 7.51 (m, 3 H), 7.62 - 7.69 (m, 2 H), 7.82 (d, *J*=2.03 Hz, 1 H), 8.27 (br s, 2 H), 10.71 (s, 1 H). LC-MS (method 2) Rt = 0.98 min; MS (ESIpos): m/z = 360.2 $[M+H]^+$ 39 % yield
21	 [4-amino-2-(4-methoxyanilino)thiazol-5-yl]-(4-fluorophenyl)methanone	1-isothiocyanato-4-methoxybenzene; 2-bromo-1-(4-fluorophenyl)ethanone	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 3.74 (s, 3 H), 6.94 (d, *J*=8.87 Hz, 2 H), 7.28 (t, *J*=8.87 Hz, 2 H), 7.45 (br d, *J*=8.62 Hz, 2 H), 7.67 - 7.73 (m, 2 H), 7.89 - 8.50 (m, 2 H), 10.64 (br s, 1 H). LC-MS (method 2) Rt = 1.09 min; MS (ESIpos): m/z = 344.5 $[M+H]^+$ preparative flash chromatography (method Y, 1-10%) 66 % yield

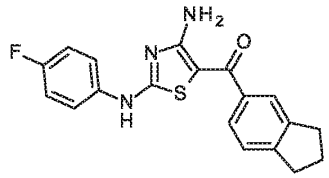
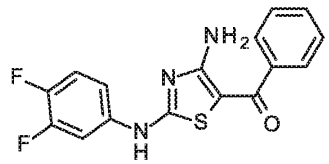
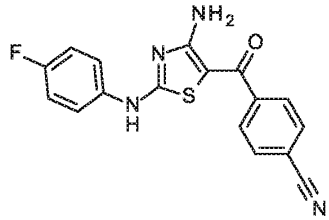
Inter-mediate number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
22	 [4-amino-2-(4-fluoroanilino)thiazol-5-yl]-(4-methylsulfonylphenyl)methanone	1-fluoro-4-isothiocyanatobenzene; 2-bromo-1-[4-(methylsulfonyl)phenyl]ethanone	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 3.28 (s, 3 H), 7.22 (t, *J*=8.87 Hz, 2 H), 7.60 - 7.65 (m, 2 H), 7.88 (d, *J*=8.62 Hz, 2 H), 8.00 - 8.04 (m, 2 H), 8.31 (br s, 2 H), 9.20 (s, 1 H). LC-MS (method 2) Rt = 0.83 min; MS (ESIpos): m/z = 392.2 $[M+H]^+$ 92 % yield
23	 [4-amino-2-(4-fluoroanilino)thiazol-5-yl]-(4-imidazol-1-ylphenyl)methanone	1-fluoro-4-isothiocyanatobenzene; 2-bromo-1-[4-(1H-imidazol-1-yl)phenyl]ethanone	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 7.14 - 7.15 (m, 1 H), 7.22 (t, *J*=8.87 Hz, 2 H), 7.58 - 7.69 (m, 2 H), 7.75 - 7.82 (m, 4 H), 7.84 (t, *J*=1.39 Hz, 1 H), 8.00 - 8.56 (m, 2 H), 8.37 (t, *J*=1.14 Hz, 1 H), 10.84 (br s, 1 H). LC-MS (method 2) Rt = 0.88 min; MS (ESIpos): m/z = 380.2 $[M+H]^+$ RP-HPLC (method C, basic) 16 % yield

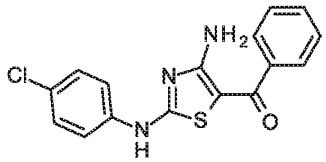
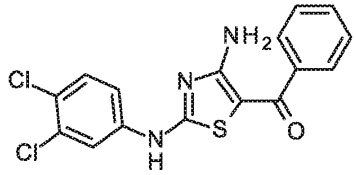
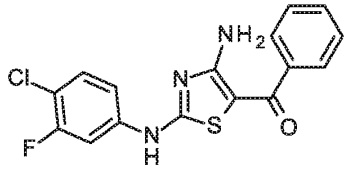
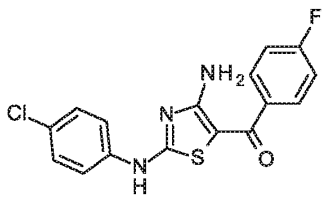
Inter-mediate number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
24	 4-[4-amino-2-(4-fluoroanilino)thiazole-5-carbonyl]-2-fluoro-benzonitrile	1-fluoro-4-isothiocyanatobenzene; 4-(bromoacetyl)-2-fluorobenzonitrile	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 7.22 (t, *J*=8.87 Hz, 2 H), 7.58 - 7.63 (m, 2 H), 7.65 (dd, *J*=7.98, 1.39 Hz, 1 H), 7.72 (dd, *J*=9.76, 1.39 Hz, 1 H), 8.04 (dd, *J*=7.86, 6.59 Hz, 1 H), 8.39 (br s, 2 H), 10.92 (br s, 1 H). LC-MS (method 2) Rt = 0.92 min; MS (ESIpos): m/z = 357.2 $[M+H]^+$ RP-HPLC (method C, basic) 5 % yield
25	 4-[4-amino-2-(4-fluoroanilino)thiazole-5-carbonyl]-3-fluoro-benzonitrile	1-fluoro-4-isothiocyanatobenzene; 4-(bromoacetyl)-3-fluorobenzonitrile	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 7.23 (t, *J*=8.87 Hz, 2 H), 7.60 - 7.67 (m, 3 H), 7.73 (dd, *J*=9.89, 1.27 Hz, 1 H), 8.05 (dd, *J*=7.86, 6.59 Hz, 1 H), 8.41 (br s, 2 H), 10.94 (br s, 1 H). LC-MS (method 2) Rt = 0.92 min; MS (ESIpos): m/z = 357.2 $[M+H]^+$ RP-HPLC (method D, acidic) 13 % yield

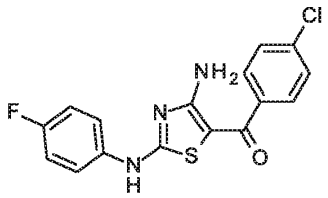
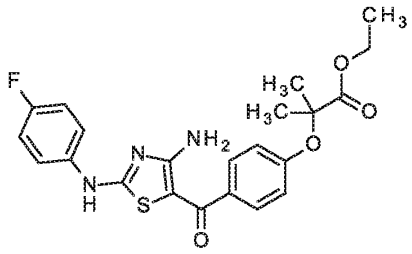
Inter-mediate number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
26	 [4-amino-2-(4-fluoroanilino)thiazol-5-yl]-(2-fluoro-4-methoxy-phenyl)methanone	1-fluoro-4-isothiocyanatobenzene; 2-bromo-1-(2-fluoro-4-methoxyphenyl)ethanone	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 3.81 (s, 3 H), 6.83 (dd, *J*=8.49, 2.41 Hz, 1 H), 6.89 (dd, *J*=12.29, 2.41 Hz, 1 H), 7.21 (t, *J*=8.87 Hz, 2 H), 7.42 (t, *J*=8.49 Hz, 1 H), 7.56 - 7.63 (m, 2 H), 7.99 - 8.17 (br s, 2 H), 10.77 (br s, 1 H). LC-MS (method 1) Rt = 1.13 min; MS (ESIpos): m/z = 362.4 $[M+H]^+$ 81 % yield
27	 [4-amino-2-[4-(trifluoromethoxy)anilino]thiazol-5-yl]-phenyl-methanone	1-isothiocyanato-4-(trifluoromethoxy)benzene; 2-bromo-1-phenylethanone	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 7.38 (d, *J*=8.36 Hz, 2 H), 7.45 - 7.52 (m, 3 H), 7.67 (dd, *J*=7.60, 1.77 Hz, 2 H), 7.74 (d, *J*=9.13 Hz, 2 H), 8.03 - 8.37 (br s, 2 H), 10.94 (br s, 1 H). LC-MS (method 1) Rt = 1.13 min; MS (ESIpos): m/z = 380.5 $[M+H]^+$ preparative flash chromatography (method X, 25-90%) 21 % yield

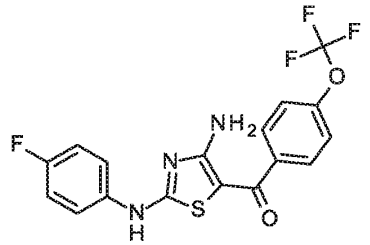
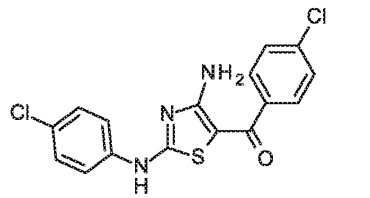
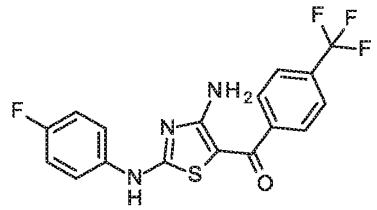
Inter-mediate number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
28	 [4-amino-2-(4-fluoroanilino)thiazol-5-yl]-(3,4-difluorophenyl)methanone	1-fluoro-4-isothiocyanatobenzene; 2-chloro-1-(3,4-difluorophenyl)ethanone	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 7.22 (t, *J*=8.87 Hz, 2 H), 7.52 - 7.58 (m, 2 H), 7.61 - 7.73 (m, 3 H), 8.06 - 8.52 (br s, 2 H), 10.87 (br s, 1 H). LC-MS (method 2) Rt = 1.13 min; MS (ESIpos): m/z = 350.2 $[M+H]^+$ RP-HPLC (method D, basic) 34 % yield
29	 [4-amino-2-(4-fluoroanilino)thiazol-5-yl]-(3,4-dichlorophenyl)methanone	1-fluoro-4-isothiocyanatobenzene; 2-bromo-1-(3,4-dichlorophenyl)ethanone	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 7.19 (t, *J*=8.87 Hz, 2 H), 7.56 (br s, 2 H), 7.63 (dd, *J*=8.36, 2.03 Hz, 1 H), 7.73 (d, *J*=8.36 Hz, 1 H), 7.84 (d, *J*=1.77 Hz, 1 H), 8.03 - 8.58 (m, 2 H), 10.83 (br s, 1 H). LC-MS (method 2) Rt = 1.22 min; MS (ESIneg): m/z = 380.3 $[M-H]^+$ RP-HPLC (method D, basic) 32 % yield
30	 [4-amino-2-[4-(trifluoromethoxy)anilino]thiazol-5-yl]-(4-fluorophenyl)methanone	1-isothiocyanato-4-(trifluoromethoxy)benzene; 2-bromo-1-(4-fluorophenyl)ethanone	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 7.31 (t, *J*=8.87 Hz, 2 H), 7.37 (d, *J*=8.36 Hz, 2 H), 7.70 - 7.77 (m, 4 H), 8.07 - 8.34 (br s, 2 H), 10.98 (br s, 1 H). LC-MS (method 2) Rt = 1.20 min; MS (ESIpos): m/z = 398.2 $[M+H]^+$ 89 % yield

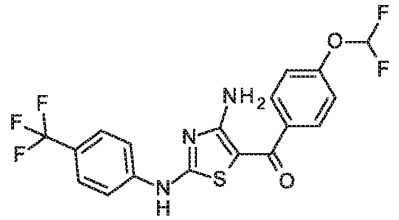
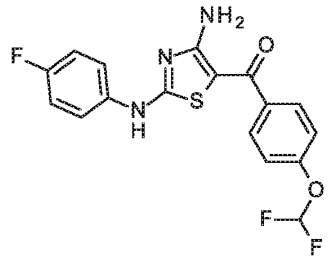
Inter-mediate number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
31	 [4-amino-2-[4-(trifluoromethyl)anilino]thiazol-5-yl]-phenyl-methanone	1-isothiocyanato-4-(trifluoromethyl)benzene; 2-bromo-1-phenylethanone	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 7.45 - 7.52 (m, 3 H), 7.66 - 7.73 (m, 4 H), 7.83 (br d, *J*=8.36 Hz, 2 H), 8.24 (br s, 2 H), 11.13 (br s, 1 H). LC-MS (method 2) Rt = 1.14 min; MS (ESIpos): m/z = 364.2 $[M+H]^+$ 85 % yield
32	 [4-amino-2-(4-fluoroanilino)thiazol-5-yl]-[6-(trifluoromethyl)-3-pyridyl]methanone	1-fluoro-4-isothiocyanatobenzene; 2-bromo-1-[6-(trifluoromethyl)pyridin-3-yl]ethanone	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 7.22 (t, *J*=8.87 Hz, 2 H), 7.55 - 7.64 (m, 2 H), 8.02 (d, *J*=7.86 Hz, 1 H), 8.39 (br s, 1 H), 8.29 (dd, *J*=7.86, 1.77 Hz, 2 H), 8.99 (d, *J*=1.77 Hz, 1 H), 10.95 (br s, 1 H). LC-MS (method 2) Rt = 1.03 min; MS (ESIpos): m/z = 383.1 $[M+H]^+$ RP-HPLC (method C, basic) 97 % yield
33	 [4-amino-2-(4-chloro-2-fluoro-anilino)thiazol-5-yl]-phenyl-methanone	4-chloro-2-fluoro-1-isothiocyanatobenzene; 2-bromo-1-phenylethanone	LC-MS (method 2) Rt = 0.97 min; MS (ESIpos): m/z = 348.2 $[M+H]^+$ 94 % yield

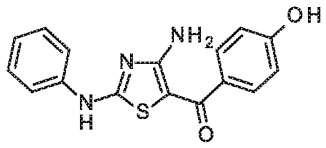
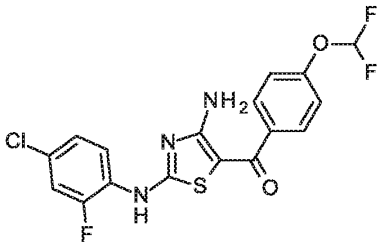
Inter-mediate number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
34	 [4-amino-2-(4-fluoroanilino)thiazol-5-yl]-indan-5-yl-methanone	1-fluoro-4-isothiocyanatobenzene; 2-bromo-1-(2,3-dihydro-1H-inden-5-yl)ethanone	LC-MS (method 2) Rt = 1.25 min; MS (ESIpos): m/z = 354.5 $[M+H]^+$ 89 % yield
35	 [4-amino-2-(3,4-difluoroanilino)thiazol-5-yl]-phenyl-methanone	1,2-difluoro-4-isothiocyanatobenzene; 2-bromo-1-phenylethanone	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 7.21 – 7.28 (m, 1 H), 7.38 - 7.54 (m, 4 H), 7.63 - 7.72 (m, 2 H), 7.90 - 8.02 (m, 1 H), 8.10 - 8.46 (br s, 2 H), 10.86 - 11.07 (br s, 1 H). LC-MS (method 2) Rt = 1.05 min; MS (ESIpos): m/z = 332.2 $[M+H]^+$ 76 % yield
36	 4-[4-amino-2-(4-fluoroanilino)thiazole-5-carbonyl]benzonitrile	1-fluoro-4-isothiocyanatobenzene; 4-(bromoacetyl)benzonitrile	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 7.22 (t, *J*=8.87 Hz, 2 H), 7.62 (br dd, *J*=8.87, 4.82 Hz, 2 H), 7.80 (d, *J*=8.36 Hz, 2 H), 7.95 (d, *J*=1.00 Hz, 2 H), 8.32 (br s, 2 H), 10.84 - 10.95 (br s, 1 H). LC-MS (method 2) Rt = 0.97 min; MS (ESIpos): m/z = 339.2 $[M+H]^+$ 84 % yield

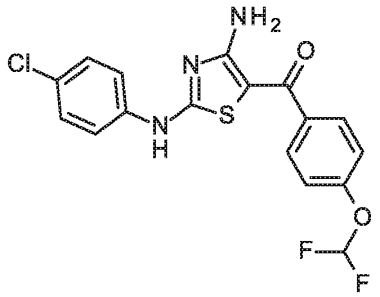
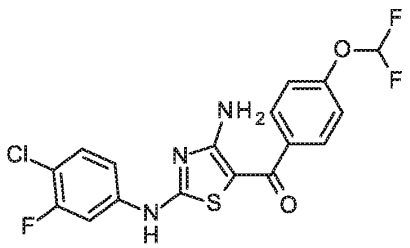
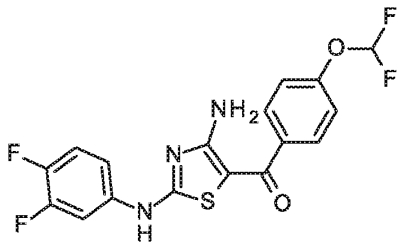
Inter-mediate number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
37	 [4-amino-2-(4-chloroanilino)thiazol-5-yl]-phenyl-methanone	1-chloro-4-isothiocyanatobenzene; 2-bromo-1-phenylethanone	LC-MS (method 1) Rt = 1.23 min; MS (ESIneg): m/z = 328.3 $[M-H]^+$ 100 % yield
38	 [4-amino-2-(3,4-dichloroanilino)thiazol-5-yl]-phenyl-methanone	1,2-dichloro-4-isothiocyanatobenzene; 2-bromo-1-phenylethanone	LC-MS (method 1) Rt = 1.32 min; MS (ESIneg): m/z = 362.3 $[M-H]^+$ preparative flash chromatography (method X, 10-80%) 65 % yield
39	 [4-amino-2-(4-chloro-3-fluoro-anilino)thiazol-5-yl]-phenyl-methanone	1-chloro-2-fluoro-4-isothiocyanatobenzene; 2-bromo-1-phenylethanone	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 7.28 (br dt, *J*=8.87, 1.27 Hz, 1 H), 7.45 - 7.57 (m, 4 H), 7.68 (dd, *J*=7.60, 1.77 Hz, 2 H), 7.99 (dd, *J*=11.91, 2.03 Hz, 1 H), 8.27 (br s, 2 H), 11.07 (br s, 1 H). LC-MS (method 2) Rt = 1.04 min; MS (ESIpos): m/z = 348.1 $[M+H]^+$ 67 % yield
40	 [4-amino-2-(4-chloroanilino)thiazol-5-yl]-(4-fluorophenyl)methanone	1-fluoro-4-isothiocyanatobenzene; 2-bromo-1-(4-chlorophenyl)ethanone	LC-MS (method 2) Rt = 1.12 min; MS (ESIpos): m/z = 348.1 $[M+H]^+$ 94 % yield

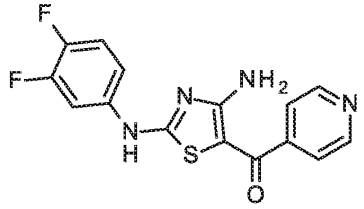
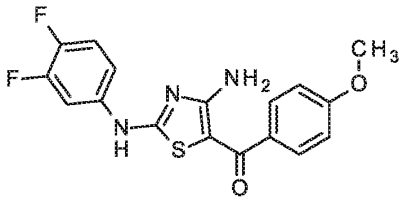
Inter-mediate number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
41	 [4-amino-2-(4-fluoroanilino)thiazol-5-yl]-(4-chlorophenyl)methanone	1-fluoro-4-isothiocyanatobenzene; 2-bromo-1-(4-chlorophenyl)ethanone	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 7.21 (t, *J*=8.87 Hz, 2 H), 7.54 (d, *J*=8.62 Hz, 2 H), 7.62 (br dd, *J*=8.87, 5.07 Hz, 2 H), 7.68 (d, *J*=8.62 Hz, 2 H), 8.28 (br s, 2 H), 10.83 (br s, 1 H). LC-MS (method 1) Rt = 1.25 min; MS (ESIneg): m/z = 346.3 $[M-H]^+$ preparative flash chromatography (method Y, 0-15%) 53 % yield
42	 ethyl 2-[4-[4-amino-2-(4-fluoroanilino)thiazole-5-carbonyl]phenoxy]-2-methyl-propanoate	1-fluoro-4-isothiocyanatobenzene; ethyl 2-[4-(bromoacetyl)phenoxy]-2-methylpropanoate	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.15 (t, *J*=7.10 Hz, 3 H), 1.56 (s, 6 H), 4.17 (q, *J*=7.10 Hz, 2 H), 6.78 (d, *J*=8.87 Hz, 2 H), 7.12 (t, *J*=8.87 Hz, 2 H), 7.34 - 7.51 (br s, 2 H), 7.58 (d, *J*=8.62 Hz, 2 H), 7.62 - 8.80 (m, 2 H), 9.78 - 10.70 (m, 1 H). LC-MS (method 2) Rt = 1.25 min; MS (ESIpos): m/z = 444.3 $[M+H]^+$ 93 % yield

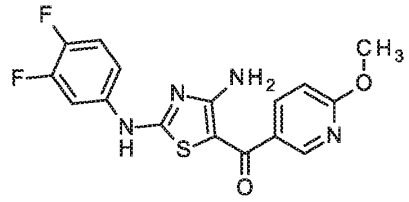
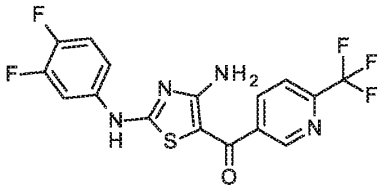
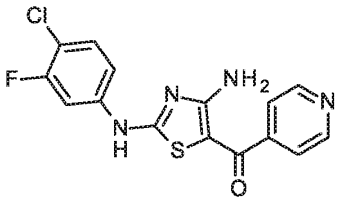
Inter-mediate number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
43	 [4-amino-2-(4-fluoroanilino)thiazol-5-yl]-[4-(trifluoromethoxy)phenyl]methanone	1-fluoro-4-isothiocyanatobenzene; 2-bromo-1-[4-(trifluoromethoxy)phenyl]ethanone	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 7.21 (t, *J*=8.87 Hz, 2 H), 7.46 (dd, *J*=8.74, 0.89 Hz, 2 H), 7.55 - 7.66 (m, 2 H), 7.79 (d, *J*=8.87 Hz, 2 H), 8.36 (br s, 2 H), 10.77 (br s, 1 H). LC-MS (method 2) Rt = 1.21 min; MS (ESIpos): m/z = 398.1 $[M+H]^+$ RP-HPLC (method D, basic) 50 % yield
44	 [4-amino-2-(4-chloroanilino)thiazol-5-yl]-(4-chlorophenyl)methanone	1-chloro-4-isothiocyanatobenzene; 2-bromo-1-(4-chlorophenyl)ethanone	LC-MS (method 2) Rt = 1.19 min; MS (ESIpos): m/z = 364.1 $[M+H]^+$ 87 % yield
45	 [4-amino-2-(4-fluoroanilino)thiazol-5-yl]-[4-(trifluoromethyl)phenyl]methanone	1-fluoro-4-isothiocyanatobenzene; 2-bromo-1-[4-(trifluoromethyl)phenyl]ethanone	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 7.22 (t, *J*=8.87 Hz, 2 H), 7.61 - 7.65 (m, 2 H), 7.85 (s, 4 H), 8.36 (br s, 2 H), 10.88 (br s, 1 H). LC-MS (method 2) Rt = 1.15 min; MS (ESIpos): m/z = 382.2 $[M+H]^+$ 66 % yield

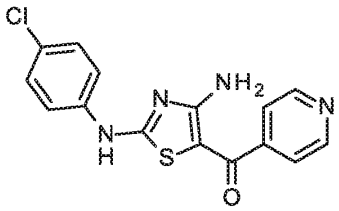
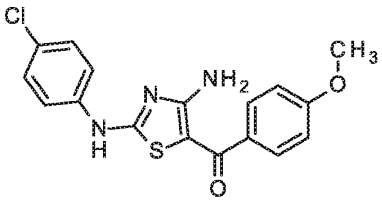
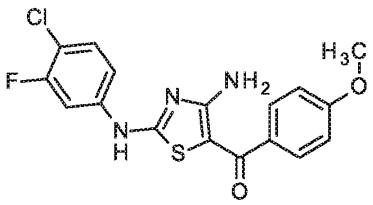
Inter-mediate number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
46	 [4-amino-2-[4-(trifluoromethyl)anilino]thiazol-5-yl]-[4-(difluoromethoxy)phenyl]methanone	1-isothiocyanato-4-(trifluoromethyl)benzene; 2-bromo-1-[4-(difluoromethoxy)phenyl]ethanone	LC-MS (method 2) Rt = 1.15 min; MS (ESIpos): m/z = 430.2 $[M+H]^+$ 87 % yield
47	 [4-amino-2-(4-fluoroanilino)thiazol-5-yl]-[4-(difluoromethoxy)phenyl]methanone	1-fluoro-4-isothiocyanatobenzene; 2-bromo-1-[4-(difluoromethoxy)phenyl]ethanone	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 7.34 (t, *J*=74.50 Hz, 1 H), 7.17 - 7.31 (m, 4 H), 7.61 (br dd, *J*=8.62, 4.82 Hz, 2 H), 7.73 (d, *J*=8.62 Hz, 2 H), 8.23 (br s, 2 H), 10.82 (br s, 1 H). LC-MS (method 2) Rt = 1.11 min; MS (ESIpos): m/z = 380.4 $[M+H]^+$ RP-HPLC (method D, basic) 94 % yield

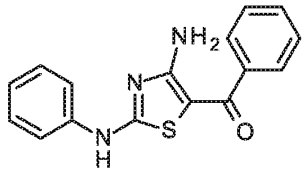
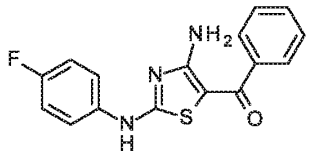
Inter-mediate number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
48	 (4-amino-2-anilino-thiazol-5-yl)-(4-hydroxyphenyl)methanone	phenyl isothiocyanate; 2-bromo-4'-hydroxyacetophenone	^{1}H-NMR (400 MHz, DMSO-d6): δ ppm = 6.78 (d, 2 H), 7.04 (t, 1 H), 7.33 (d, 2H), 7.54 (d, 2 H), 7.57 (d, 2 H), 8.06 (br s, 2 H), 9.95 (br s, 1 H), 10.68 (br s, 1 H) LC-MS (method 2) Rt = 0.61 min; MS (ESIpos): m/z = 312 $[M+H]^+$ preparative flash chromatography (ethyl acetate/heptane 4/1) 80 % yield
49	 [4-amino-2-(4-chloro-2-fluoro-anilino)thiazol-5-yl]-[4-(difluoromethoxy)phenyl]methanone	4-chloro-2-fluoro-1-isothiocyanatobenzene; 2-bromo-1-[4-(difluoromethoxy)phenyl]ethanone	LC-MS (method 2) Rt = 1.00 min; MS (ESIpos): m/z = 414.2 $[M+H]^+$ quantitave yield

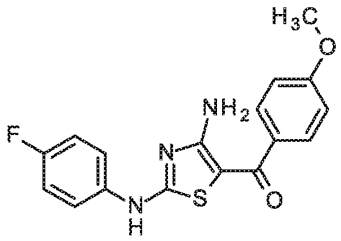
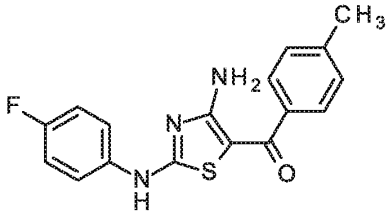
Inter-mediate number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
50	 [4-amino-2-(4-chloroanilino)thiazol-5-yl]-[4-(difluoromethoxy)phenyl]methanone	1-chloro-4-isothiocyanatobenzene; 2-bromo-1-[4-(difluoromethoxy)phenyl]ethanone	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 7.35 (t, *J*=74.77 Hz, 1 H), 7.26 (d, *J*=8.62 Hz, 2 H), 7.42 (d, *J*=8.87 Hz, 1 H), 7.66 (d, *J*=8.87 Hz, 2 H), 7.75 (d, *J*=8.62 Hz, 2 H), 8.26 (br s, 2 H), 10.92 (br s, 1 H). LC-MS (method 2) Rt = 1.19 min; MS (ESIpos): m/z = 396.2 $[M+H]^+$ RP-HPLC (method D, acidic) quantitative yield
51	 [4-amino-2-(4-chloro-3-fluoro-anilino)thiazol-5-yl]-[4-(difluoromethoxy)phenyl]methanone	1-chloro-2-fluoro-4-isothiocyanatobenzene; 2-bromo-1-[4-(difluoromethoxy)phenyl]ethanone	LC-MS (method 2) Rt = 1.08 min; MS (ESIpos): m/z = 414.2 $[M+H]^+$ 95 % yield
52	 [4-amino-2-(3,4-difluoroanilino)thiazol-5-yl]-[4-(difluoromethoxy)phenyl]methanone	1,2-difluoro-4-isothiocyanatobenzene; 2-bromo-1-[4-(difluoromethoxy)phenyl]ethanone	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 7.35 (t, *J*=76.04 Hz, 1 H), 7.27 (br d, *J*=8.62 Hz, 3 H), 7.39 - 7.48 (m, 1 H), 7.75 (d, *J*=8.87 Hz, 2 H), 7.97 (ddd, *J*=12.99, 7.29, 2.28 Hz, 1 H), 8.27 (br s, 2 H), 10.99 (br s, 1 H). LC-MS (method 2) Rt = 1.06 min; MS (ESIpos): m/z = 398.2 $[M+H]^+$ 87 % yield

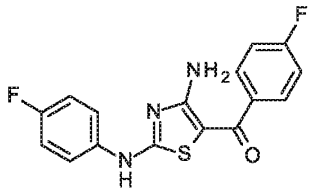
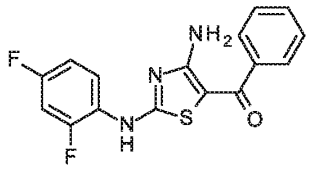
Inter-mediate number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
53	 [4-amino-2-(3,4-difluoroanilino)-1,3-thiazol-5-yl](pyridin-4-yl)methanone	2-bromo-1-(pyridin-4-yl)ethan-1-one salt with hydrogen bromide; 1,2-difluoro-4-isothiocyanatobenzene	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 7.22 - 7.28 (m, 1 H), 7.39 - 7.47 (m, 1 H), 7.56 - 7.59 (m, 2 H), 7.91 - 7.99 (m, 1 H), 8.39 (td, *J*=6.46, 2.79 Hz, 1 H), 8.36 - 8.44 (m, 1 H), 8.68 - 8.74 (m, 2 H), 10.78 - 11.25 (m, 1 H). LC-MS (method 1) Rt = 0.89 min; MS (ESIpos): m/z = 333.1 $[M+H]^+$ RP-HPLC (method C, acidic) 76 % yield
54	 [4-amino-2-(3,4-difluoroanilino)-1,3-thiazol-5-yl](4-methoxyphenyl)methanone	2-bromo-1-(4-methoxyphenyl)ethan-1-one; 1,2-difluoro-4-isothiocyanatobenzene	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 3.82 (s, 3 H), 7.02 (d, *J*=8.87 Hz, 2 H), 7.22 - 7.28 (m, 1 H), 7.38 - 7.47 (m, 1 H), 7.68 (d, *J*=8.87 Hz, 2 H), 7.91 - 8.03 (m, 1 H), 8.19 (br s, 2 H), 10.81 - 11.06 (m, 1 H). LC-MS (method 2) Rt = 1.07 min; MS (ESIpos): m/z = 362.1 $[M+H]^+$ 92 % yield

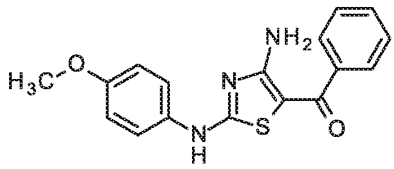
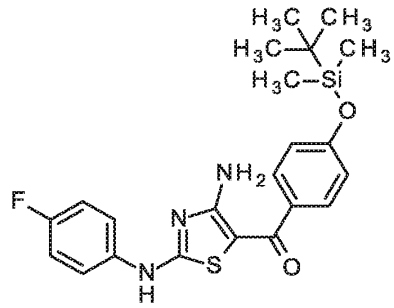
Inter-mediate number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
55	 [4-amino-2-(3,4-difluoroanilino)-1,3-thiazol-5-yl](6-methoxypyridin-3-yl)methanone	2-bromo-1-(6-methoxypyridin-3-yl)ethan-1-one; 1,2-difluoro-4-isothiocyanatobenzene	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 2.54 (s, 3 H), 6.92 (dd, *J*=8.62, 0.51 Hz, 1 H), 7.28 (br s, 1 H), 7.40 - 7.49 (m, 1 H), 7.94 - 8.03 (m, 2 H), 8.18 - 8.36 (m, 2 H), 8.53 (dd, *J*=2.53, 0.76 Hz, 1 H), 10.98 - 11.04 (m, 1 H). LC-MS (method 2) Rt = 0.92 min; MS (ESIpos): m/z = 363.2 $[M+H]^+$ 77 % yield
56	 [4-amino-2-(3,4-difluoroanilino)-1,3-thiazol-5-yl][6-(trifluoromethyl)pyridin-3-yl]methanone	2-bromo-1-[6-(trifluoromethyl)pyridin-3-yl]ethan-1-one; 1,2-difluoro-4-isothiocyanatobenzene	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 7.21 - 7.27 (m, 1 H), 7.38 - 7.47 (m, 1 H), 7.87 - 7.98 (m, 1 H), 8.03 (d, *J*=8.36 Hz, 1 H), 8.31 (dd, *J*=8.11, 2.03 Hz, 1 H), 8.33 - 8.52 (m, 2 H), 9.00 (d, *J*=1.52 Hz, 1 H), 11.04 - 11.24 (m, 1 H). LC-MS (method 2) Rt = 0.96 min; MS (ESIpos): m/z = 401.3 $[M+H]^+$ 74 % yield
57	 [4-amino-2-(4-chloro-3-fluoroanilino)-1,3-thiazol-5-yl](pyridin-4-yl)methanone	2-bromo-1-(pyridin-4-yl)ethan-1-one salt with hydrogen bromide ; 1-chloro-2-fluoro-4-isothiocyanatobenzene	LC-MS (method 2) Rt = 0.77 min; MS (ESIpos): m/z = 349.1 $[M+H]^+$ 69 % yield

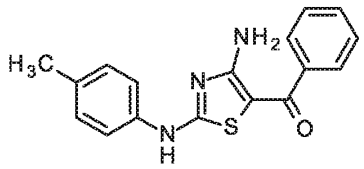
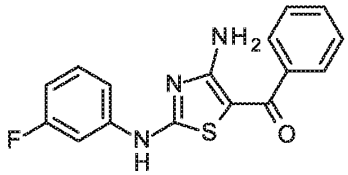
Inter-mediate number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
58	 [4-amino-2-(4-chloroanilino)-1,3-thiazol-5-yl](pyridin-4-yl)methanone	2-bromo-1-(pyridin-4-yl)ethan-1-one salt with hydrogen bromide ; 1-chloro-4-isothiocyanatobenzene	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 3.78 (d, *J*=12.42 Hz, 1 H), 4.08 (d, *J*=12.17 Hz, 1 H), 7.18 - 7.23 (m, 2 H), 7.31 - 7.36 (m, 2 H), 7.56 - 7.60 (m, 2 H), 8.39 (s, 1 H), 8.48 - 8.55 (m, 2 H). LC-MS (method 2) Rt = 0.84 min; MS (ESIpos): m/z = 331.1 $[M+H]^+$ 57 % yield
59	 [4-amino-2-(4-chloroanilino)-1,3-thiazol-5-yl](4-methoxyphenyl)methanone	2-bromo-1-(4-methoxyphenyl)ethan-1-one; 1-chloro-4-isothiocyanatobenzene	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 3.82 (s, 3 H), 7.01 (d, *J*=8.87 Hz, 2 H), 7.38 - 7.43 (m, 2 H), 7.61 - 7.70 (m, 4 H), 8.03 - 8.27 (m, 2 H), 10.78 - 10.92 (m, 1 H). LC-MS (method 2) Rt = 1.15 min; MS (ESIpos): m/z = 360.1 $[M+H]^+$ 94 % yield
60	 [4-amino-2-(4-chloro-3-fluoroanilino)-1,3-thiazol-5-yl](4-methoxyphenyl)methanone	2-bromo-1-(4-methoxyphenyl)ethan-1-one; 1-chloro-2-fluoro-4-isothiocyanatobenzene	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 3.82 (s, 3 H), 6.99 - 7.03 (m, 2 H), 7.25 (dd, *J*=8.74, 1.65 Hz, 1 H), 7.51 (t, *J*=8.74 Hz, 1 H), 7.68 (d, *J*=8.87 Hz, 2 H), 7.95 (br d, *J*=12.17 Hz, 1 H), 8.06 - 8.29 (m, 2 H), 10.92 - 11.16 (m, 1 H). LC-MS (method 2) Rt = 1.15 min; MS (ESIpos): m/z = 378.1 $[M+H]^+$ 80 % yield

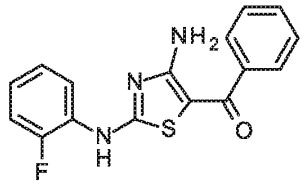
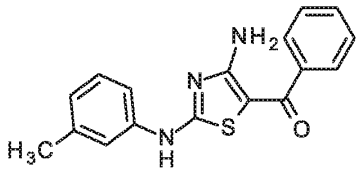
Inter-mediate number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
61	 (4-amino-2-anilino-1,3-thiazol-5-yl)(phenyl)methanone	2-bromo-1-phenylethan-1-one; isothiocyanatobenzene	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 7.08 (t, *J*=7.60 Hz, 1 H), 7.36 (t, *J*=7.86 Hz, 2 H), 7.44 - 7.51 (m, 3 H), 7.61 (d, *J*=7.86 Hz, 2 H), 7.64 - 7.69 (m, 2 H), 8.21 (br s, 2 H), 10.78 (br s, 1 H). LC-MS (method 2) Rt = 1.05 min; MS (ESIpos): m/z = 296.4 $[M+H]^+$ 14 % yield
62	 [4-amino-2-(4-fluoroanilino)-1,3-thiazol-5-yl](phenyl)methanone	2-bromo-1-phenylethan-1-one; 1-fluoro-4-isothiocyanatobenzene	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 7.21 (t, *J*=8.87 Hz, 2 H), 7.43 - 7.52 (m, 3 H), 7.59 - 7.69 (m, 4 H), 8.22 (br s, 2 H), 10.79 (br s, 1 H). LC-MS (method 2) Rt = 1.04 min; MS (ESIpos): m/z = 314.4 $[M+H]^+$ preparative flash chromatography (method Z, 0-1%) 78 % yield

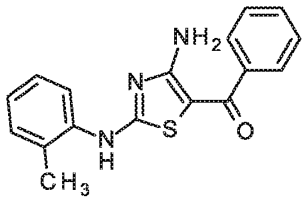
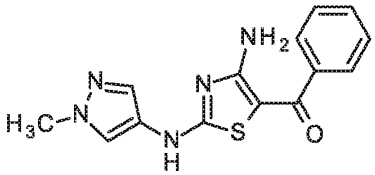
Inter-mediate number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
63	 [4-amino-2-(4-fluoroanilino)-1,3-thiazol-5-yl](4-methoxyphenyl)methanone	2-bromo-1-(4-methoxyphenyl)ethan-1-one; 1-fluoro-4-isothiocyanatobenzene	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 3.81 (s, 3 H), 7.01 (d, *J*=8.87 Hz, 2 H), 7.21 (t, *J*=8.87 Hz, 2 H), 7.66 (d, *J*=8.87 Hz, 4 H), 8.15 (br s, 2 H), 10.77 (br s, 1 H). LC-MS (method 2) Rt = 1.09 min; MS (ESIpos): m/z = 344.4 $[M+H]^+$ preparative flash chromatography (method Z, 0-3%) 57 % yield
64	 [4-amino-2-(4-fluoroanilino)-1,3-thiazol-5-yl](4-methylphenyl)methanone	2-bromo-1-(4-methylphenyl)ethan-1-one; 1-fluoro-4-isothiocyanatobenzene	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 2.35 (s, 3 H), 7.21 (t, *J*=8.87 Hz, 2 H), 7.27 (d, *J*=7.86 Hz, 2 H), 7.57 (d, *J*=8.11 Hz, 2 H), 7.63 (dd, *J*=9.13, 4.82 Hz, 2 H), 8.19 (br s, 2 H), 10.77 (s, 1 H). LC-MS (method 2) Rt = 1.14 min; MS (ESIpos): m/z = 328.4 $[M+H]^+$ preparative flash chromatography (method Z, 0-3%) 47 % yield

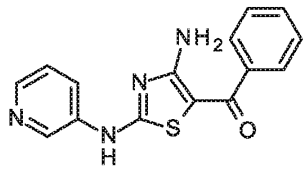
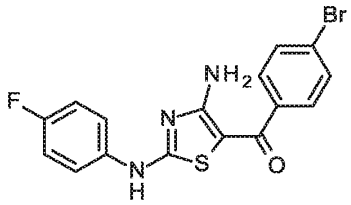
Inter-mediate number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
65	 [4-amino-2-(4-fluoroanilino)-1,3-thiazol-5-yl](4-fluorophenyl)methanone	2-bromo-1-(4-fluorophenyl)ethan-1-one; 1-fluoro-4-isothiocyanatobenzene	^{1}H NMR (400 MHz, DMSO-*d6*): δ ppm = 7.21 (t, *J*=8.87 Hz, 2 H), 7.30 (t, *J*=8.87 Hz, 2 H), 7.62 (dd, *J*=8.87, 4.82 Hz, 2 H), 7.73 (dd, *J*=8.74, 5.45 Hz, 2 H), 8.22 (br s, 2 H), 10.82 (br s, 1 H). LC-MS (method 2) Rt = 1.05 min; MS (ESIpos): m/z = 332.4 $[M+H]^+$ preparative flash chromatography (method Z, 0-2%) 66 % yield
66	 [4-amino-2-(2,4-difluoroanilino)-1,3-thiazol-5-yl](phenyl)methanone	2-bromo-1-phenylethan-1-one; 2,4-difluoro-1-isothiocyanatobenzene	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 7.09 - 7.17 (m, 1 H), 7.39 (ddd, *J*=11.15, 8.74, 2.91 Hz, 1 H), 7.43 - 7.50 (m, 3 H), 7.62 - 7.65 (m, 2 H), 8.01 (br td, *J*=9.12, 6.34 Hz, 1 H), 8.08 - 8.39 (m, 2 H), 10.50 (br s, 1 H). LC-MS (method 2) Rt = 0.88 min; MS (ESIpos): m/z = 332.4 $[M+H]^+$ preparative flash chromatography (method Z, 0-3%) 71 % yield

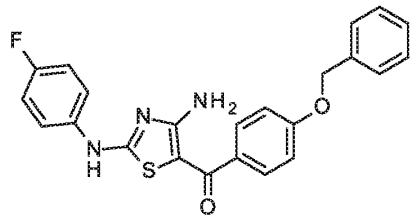
Inter-mediate number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
67	 [4-amino-2-(4-methoxyanilino)-1,3-thiazol-5-yl](phenyl)methanone	2-bromo-1-phenylethan-1-one; 1-isothiocyanato-4-methoxybenzene	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 3.70 - 3.76 (m, 3 H), 6.92 - 6.96 (m, 2 H), 7.42 - 7.50 (m, 5 H), 7.60 - 7.66 (m, 2 H), 7.93 - 8.48 (m, 2 H), 10.60 (br s, 1 H). LC-MS (method 2) Rt = 1.04 min; MS (ESIpos): m/z = 326.4 $[M+H]^+$ preparative flash chromatography (method Z, 0-1%) 76 % yield
68	 [4-amino-2-(4-fluoroanilino)-1,3-thiazol-5-yl](4-{[tert-butyl(dimethyl)silyl]oxy}phenyl)methanone	2-bromo-1-(4-{[tert-butyl(dimethyl)silyl]oxy}phenyl)ethan-1-one (Intermediate 3); 1-fluoro-4-isothiocyanatobenzene	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 0.23 (s, 6 H), 0.96 (s, 9 H), 6.92 (d, *J*=8.62 Hz, 2 H), 7.21 (t, *J*=8.87 Hz, 2 H), 7.59 - 7.66 (m, 4 H), 8.15 (br s, 2 H), 10.76 (br s, 1 H). LC-MS (method 2) Rt = 1.56 min; MS (ESIpos): m/z = 444.2 $[M+H]^+$ preparative flash chromatography (method Z, 0-3%) 27 % yield

Inter-mediate number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
69	 [4-amino-2-(4-methylanilino)-1,3-thiazol-5-yl](phenyl)methanone	2-bromo-1-phenylethan-1-one; 1-isothiocyanato-4-methylbenzene	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 2.27 (s, 3 H), 7.16 (d, *J*=8.11 Hz, 2 H), 7.44 - 7.49 (m, 5 H), 7.63 - 7.67 (m, 2 H), 7.93 - 8.63 (m, 2 H), 10.69 (br s, 1 H). LC-MS (method 2) Rt = 1.15 min; MS (ESIpos): m/z = 310.5 $[M+H]^+$ preparative flash chromatography (method Z, 0-3%) 67 % yield
70	 [4-amino-2-(3-fluoroanilino)-1,3-thiazol-5-yl](phenyl)methanone	2-bromo-1-phenylethan-1-one; 1-fluoro-3-isothiocyanatobenzene	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 6.85 - 6.93 (m, 1 H), 7.27 (ddd, *J*=8.24, 2.03, 0.89 Hz, 1 H), 7.38 (td, *J*=8.17, 6.72 Hz, 1 H), 7.45 - 7.53 (m, 3 H), 7.66 - 7.70 (m, 2 H), 7.76 (dt, *J*=11.66, 2.15 Hz, 1 H), 8.26 (br s, 2 H), 10.96 (s, 1 H). LC-MS (method 2) Rt = 1.07 min; MS (ESIpos): m/z = 314.4 $[M+H]^+$ preparative flash chromatography (method Z, 0-3%) 53 % yield

Inter-mediate number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
71	 [4-amino-2-(2-fluoroanilino)-1,3-thiazol-5-yl](phenyl)methanone	2-bromo-1-phenylethan-1-one; 1-fluoro-2-isothiocyanatobenzene	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 7.15 - 7.25 (m, 2 H), 7.27 - 7.34 (m, 1 H), 7.43 - 7.51 (m, 3 H), 7.62 - 7.68 (m, 2 H), 8.04 - 8.11 (m, 1 H), 8.10 - 8.32 (m, 2 H), 10.54 (s, 1 H). LC-MS (method 2) Rt = 0.96 min; MS (ESIpos): m/z = 314.5 $[M+H]^+$ preparative flash chromatography (method Z, 0-1%) 36 % yield
72	 [4-amino-2-(3-methylanilino)-1,3-thiazol-5-yl](phenyl)methanone	2-bromo-1-phenylethan-1-one; 1-isothiocyanato-3-methylbenzene	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 2.30 (s, 3 H), 6.91 (br d, *J*=7.35 Hz, 1 H), 7.24 (br t, *J*=7.73 Hz, 1 H), 7.38 (br s, 1 H), 7.41 - 7.54 (m, 4 H), 7.62 - 7.68 (m, 2 H), 8.20 (br s, 2 H), 10.70 (br s, 1 H). LC-MS (method 2) Rt = 1.15 min; MS (ESIpos): m/z = 310.5 $[M+H]^+$ preparative flash chromatography (method Z, 0-3%) 53 % yield

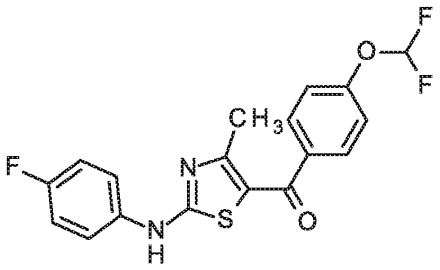
Inter-mediate number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
73	 [4-amino-2-(2-methylanilino)-1,3-thiazol-5-yl](phenyl)methanone	2-bromo-1-phenylethan-1-one; 1-isothiocyanato-2-methylbenzene	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 2.23 (s, 3 H), 7.14 - 7.26 (m, 2 H), 7.27 - 7.31 (m, 1 H), 7.38 - 7.52 (m, 4 H), 7.57 - 7.62 (m, 2 H), 8.15 (br s, 2 H), 10.18 (br s, 1 H). LC-MS (method 2) Rt = 1.10 min; MS (ESIpos): m/z = 310.5 $[M+H]^+$ preparative flash chromatography (method Z, 0-1%) 60 % yield
74	 {4-amino-2-[(1-methyl-1H-pyrazol-4-yl)amino]-1,3-thiazol-5-yl}(phenyl)methanone	2-bromo-1-phenylethan-1-one; 4-isothiocyanato-1-methyl-1H-pyrazole	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 3.81 (s, 3 H), 7.41 - 7.52 (m, 4 H), 7.58 - 7.66 (m, 2 H), 7.90 (s, 1 H), 7.94 - 8.50 (m, 2 H), 10.44 - 10.57 (m, 1 H). LC-MS (method 2) Rt = 0.78 min; MS (ESIpos): m/z = 300.5 $[M+H]^+$ preparative flash chromatography (method Z, 0-1%) 58 % yield

Inter-mediate number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
75	 {4-amino-2-[(pyridin-3-yl)amino]-1,3-thiazol-5-yl}(phenyl)methanone	2-bromo-1-phenylethan-1-one; 3-isothiocyanatopyridine	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 7.37 - 7.42 (m, 1 H), 7.45 - 7.53 (m, 3 H), 7.65 - 7.69 (m, 2 H), 8.12 (br ddd, *J*=8.36, 2.53, 1.52 Hz, 1 H), 8.16 - 8.39 (m, 2 H), 8.28 (dd, *J*=4.69, 1.39 Hz, 1 H), 8.81 (d, *J*=2.53 Hz, 1 H), 10.95 (br s, 1 H). LC-MS (method 2) Rt = 0.70 min; MS (ESIpos): m/z = 297.4 $[M+H]^+$ preparative flash chromatography (method Z, 0-3%) 23 % yield
76	 [4-amino-2-(4-fluoroanilino)-1,3-thiazol-5-yl](4-bromophenyl)methanone	2-bromo-1-(4-bromophenyl)ethan-1-one; 1-fluoro-4-isothiocyanatobenzene	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 7.21 (t, *J*=8.87 Hz, 2 H), 7.56 - 7.65 (m, 4 H), 7.66 - 7.70 (m, 2 H), 8.26 (br s, 2 H), 10.85 (br s, 1 H). LC-MS (method 2) Rt = 1.19 min; MS (ESIpos): m/z = 392.3 $[M+H]^+$ preparative flash chromatography (method Z, 0-1%) 77 % yield

Inter-mediate number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
77	 [4-amino-2-(4-fluoroanilino)-1,3-thiazol-5-yl][4-(benzyloxy)phenyl]methanone	1-[4-(benzyloxy) phenyl]-2-bromoethan-1-one; 1-fluoro-4-isothiocyanatobenzene	^{1}H-NMR (400 MHz, DMSO-*d*6): δ ppm = 5.17 (s, 2 H), 7.09 (d, *J*=8.87 Hz, 2 H), 7.21 (t, *J*=8.87 Hz, 2 H), 7.31 - 7.37 (m, 1 H), 7.41 (t, *J*=7.35 Hz, 2 H), 7.45 - 7.49 (m, 2 H), 7.60 - 7.69 (m, 4 H), 7.96 - 8.34 (m, 2 H), 10.71 - 10.79 (m, 1 H). LC-MS (method 2) Rt = 1.30 min; MS (ESIpos): m/z = 420.2 $[M+H]^+$ 87 % yield

Intermediate 78

[4-(difluoromethoxy)phenyl][2-(4-fluoroanilino)-4-methyl-1,3-thiazol-5-yl]methanone

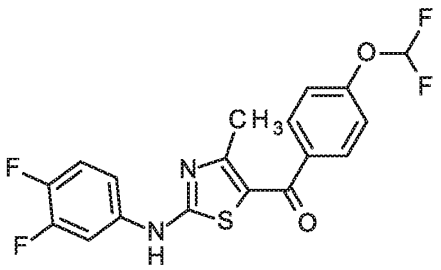


1-Fluoro-4-isothiocyanatobenzene (116 mg, 0.755 mmol) was dissolved in acetonitrile (7.5 mL) followed by the addition of 1,8-diazabicyclo(5.4.0)undec-7-ene (100 mg, 0.66 mmol) and ethanimidamide (salt withhydrogen chloride) (86 mg, 0.91 mmol). After stirring for 45 min at rt, further 1,8-diazabicyclo(5.4.0)undec-7-ene (70 mg, 0.47 mmol) and 2-bromo-1-[4-(difluoromethoxy)phenyl]ethan-1-one (200 mg, 0.755 mmol) were added. The reaction mixture was stirred at rt overnight. The reaction mixture was concentrated under vacuum and the residue was purified by preparative HPLC (method D, basic) to give 72 mg (25 % yield) of the title compound.

LC-MS (method 2) Rt = 1.30 min; MS (ESIpos): m/z = 379.4 $[M+H]^+$

Intermediate 79

[2-(3,4-difluoroanilino)-4-methyl-1,3-thiazol-5-yl][4-(difluoromethoxy)phenyl]methanone

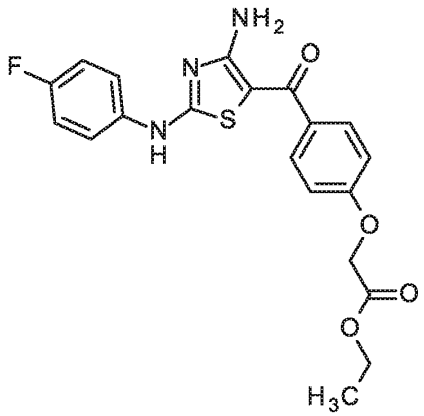


1,2-difluoro-4-isothiocyanatobenzene (129 mg, 0.755 mmol) was dissolved in acetonitrile (7.5 mL) followed by the addition of 1,8-diazabicyclo(5.4.0)undec-7-ene (100 mg, 0.66 mmol) and ethanimidamide (salt with hydrogen chloride) (86 mg, 0.91 mmol). After stirring for 45 min at rt, further 1,8-diazabicyclo(5.4.0)undec-7-ene (70 mg, 0.47 mmol) and 2-bromo-1-[4-(difluoromethoxy)phenyl]ethan-1-one (200 mg, 0.755 mmol) were added. The reaction mixture was stirred at rt overnight. The reaction mixture was concentrated under vacuum and the residue was purified by preparative HPLC (method E, basic) to give 31 mg (10 % yield) of the title compound.

LC-MS (method 2) Rt = 1.36 min; MS (ESIpos): m/z = 397.3 $[M+H]^+$

Intermediate 80

ethyl 2-[4-[4-amino-2-(4-fluoroanilino)thiazole-5-carbonyl]phenoxy]acetate



1-fluoro-4-isothiocyanatobenzene (8.91 g, 58.20 mmol) was dissolved in acetonitrile (450 mL) followed by the addition of 1,8-diazabicyclo(5.4.0)undec-7-ene (8.86 g, 58.20 mmol) and cyanamide (2.94 g, 69.82 mmol). After stirring for 45 min at rt, further 1,8-diazabicyclo(5.4.0)undec-7-ene (4.43 g, 29.07 mmol) and ethyl [4-(bromoacetyl)phenoxy]acetate (17.52 g, 58.20 mmol) were added. The reaction mixture was stirred at rt overnight. The suspension was treated with water and the precipitate was isolated

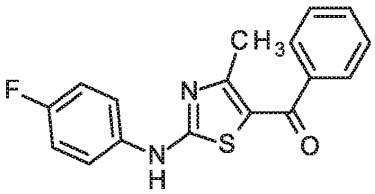
by filtration, washed with water and dried by lyophilization to give 18.54 g (77 % yield) of the title compound.

^{1}H-NMR (500 MHz, DMSO-*d*6): δ ppm = 1.22 (t, *J*=7.09 Hz, 3 H), 4.18 (q, *J*=7.25 Hz, 2 H), 4.86 (s, 2 H), 7.00 (d, *J*=9.14 Hz, 2 H), 7.21 (t, *J*=9.14 Hz, 2 H), 7.61 - 7.67 (m, 4 H), 8.21 (br s, 2 H), 10.77 (s, 1 H).

LC-MS (method 2) Rt = 1.09 min; MS (ESIpos): m/z = 416.3 $[M+H]^+$

Intermediate 81

[2-(4-fluoroanilino)-4-methyl-thiazol-5-yl]-phenyl-methanone



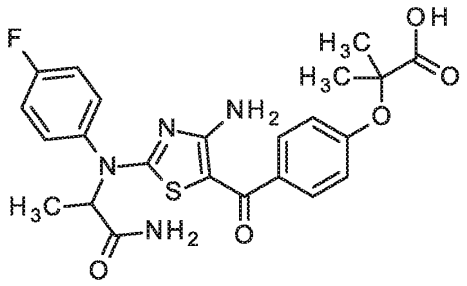
1-fluoro-4-isothiocyanatobenzene (77 mg, 0.50 mmol) was solved in acetonitrile (5 mL) followed by the addition of 1,8-diazabicyclo(5.4.0)undec-7-ene (77 mg, 0.50 mmol) and ethanimidamide (salt with hydrogen chloride) (57 mg, 0.60 mmol) . After stirring for 45 min at rt, further 1,8-diazabicyclo(5.4.0)undec-7-ene (38 mg, 0.25 mmol) and 2-bromo-1-phenylethanone (100 mg, 0.50 mmol) were added. The reaction mixture was stirred at rt overnight. The solution was filtrated and purified by RP-HPLC (method D, basic). The title compound was isolated by lyophilization (53 mg, 33 % yield).

^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 2.28 (s, 3 H), 7.18 (t, *J*=8.87 Hz, 2 H), 7.51 (d, *J*=7.86 Hz, 2 H), 7.53 - 7.58 (m, 3 H), 7.63 - 7.67 (m, 2 H), 10.67 (br s, 1 H).

LC-MS (method 2) Rt = 1.22 min; MS (ESIpos): m/z = 313.1 $[M+H]^+$

Intermediate 82

rac-2-[4-[4-amino-2-(N-(2-amino-1-methyl-2-oxo-ethyl)-4-fluoro-anilino)thiazole-5-carbonyl]phenoxy]-2-methyl-propanoic acid



Rac-ethyl 2-[4-[4-amino-2-(N-[2-amino-1-methyl-2-oxo-ethyl]-4-fluoro-anilino)thiazole-5-carbonyl]phenoxy]-2-methyl-propanoate (180 mg, 349 µmol, example 39) was dissolved in THF (1.8 ml), cooled to 0°C, and an aqueous solution of sodium hydroxide (350 µl, 1.0 M, 350 µmol) was added. The reaction mixture was stirred overnight at rt. Additional aqueous solution of sodium hydroxide (1.04 mmol) was added and the mixture was stirred for 3 days at rt. The reaction mixture was treated with water, and aqueous solution of hydrochloric acid (1 M) was added to adjust the pH to 5 and afterwards it was extracted three times with dichloromethane. The organic layer was concentrated under reduced pressure to give 36 mg (21 % yield) of the title compound.

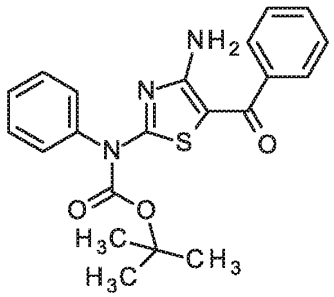
The aqueous layer was adjusted to pH 3 by addition of aqueous hydrochloric acid (1 M), the formed precipitate was isolated by filtration, washed with water and dried by lyophilization to give 90 mg (53 % yield) of the title compound.

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm = 1.15 (d, *J*=7.35 Hz, 3 H), 1.51 (s, 6 H), 4.94 - 5.14 (m, 1 H), 6.73 - 6.79 (m, 2 H), 7.22 - 7.26 (m, 1 H), 7.30 - 7.37 (m, 2 H), 7.42 - 7.47 (m, 2 H), 7.58 (br s, 1 H), 7.64 (dd, *J*=8.87, 5.07 Hz, 2 H), 7.77 - 8.44 (m, 2 H), 12.81 - 13.47 (m, 1 H)

LC-MS (method 1) Rt = 1.00 min; MS (ESIpos): m/z = 487.5 $[M+H]^+$

Intermediate 83

tert-butyl N-(4-amino-5-benzoyl-thiazol-2-yl)-N-phenyl-carbamate



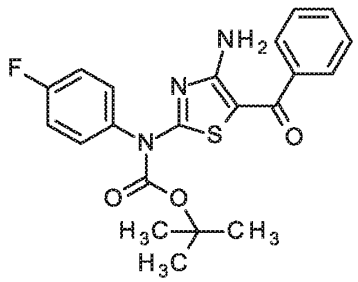
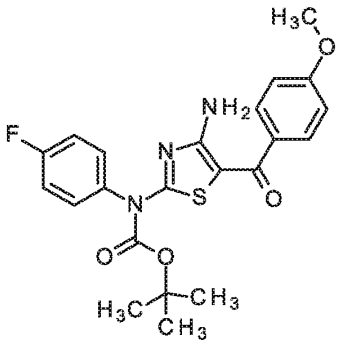
(4-amino-2-anilino-1,3-thiazol-5-yl)(phenyl)methanone (100 mg, 339 µmol, Intermediate 61) was provided in dichloromethane at rt. N,N-diisopropylethylamine (180 µl, 1.0 mmol; CAS-RN 7087-68-5), 4-(dimethylamino)pyridine (8 mg, 67.7 µmol; CAS-RN 1122-58-3) and di-tert-butyl dicarbonate (81 mg, 372 µmol; CAS-RN 24424-99-5) was added. The reaction mixture was stirred for 3 h at rt. The mixture was diluted with dichloromethane, washed with brine, dried and evaporated to give 120 mg (95 % purity, 85 % yield) of the title compound.

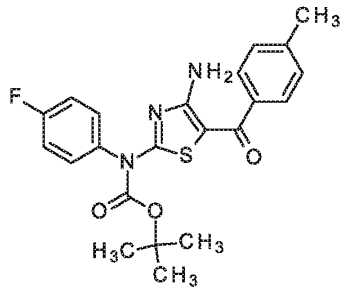
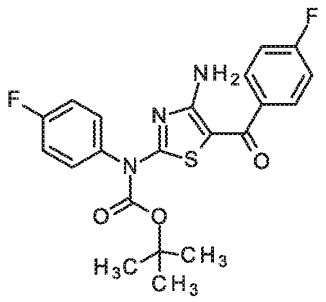
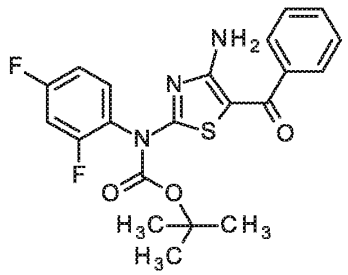
^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.32 (s, 9 H), 7.35 - 7.44 (m, 3 H), 7.45 - 7.51 (m, 2 H), 7.52 - 7.58 (m, 3 H), 7.69 - 7.73 (m, 2 H), 7.94 (s, 2 H).

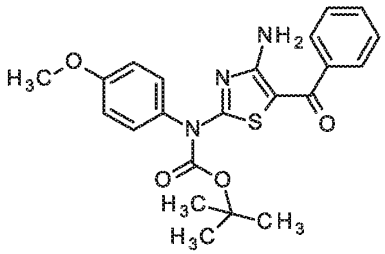
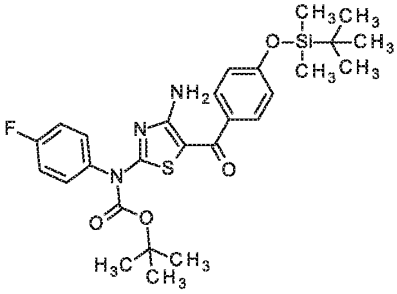
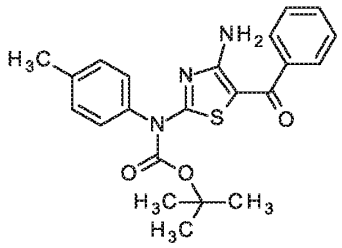
The following intermediates were prepared from the starting materials stated in Table 3, below, using the procedure as for Intermediate 83.

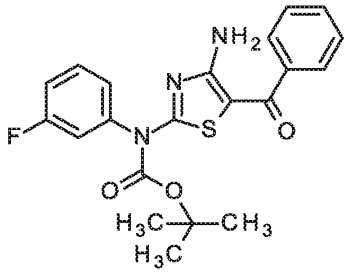
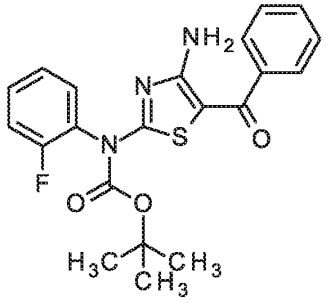
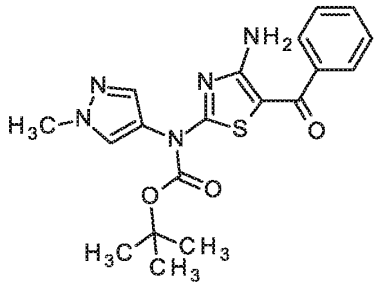
The crude product was either purified by RP-HPLC (methods A-D depending on polarity) or by preparative flash chromatography (methods X, Yor Z depending on polarity) after precipitation, extraction or filtration of the reaction mixture if necessary.

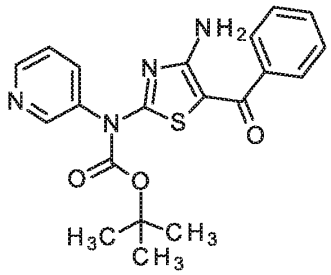
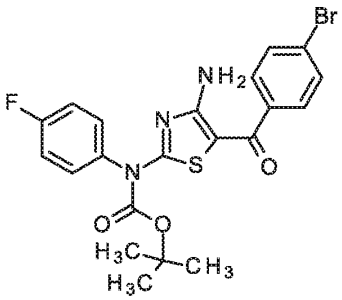
Table 3: Intermediates 84 – 96

Intermediate number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
84	 tert-butyl N-(4-amino-5-benzoyl-thiazol-2-yl)-N-(4-fluorophenyl)carbamate	Intermediate 62; di-tert-butyl dicarbonate	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.34 (s, 9 H), 7.31 (t, *J*=8.87 Hz, 2 H), 7.44 - 7.48 (m, 2 H), 7.50 - 7.59 (m, 3 H), 7.68 - 7.74 (m, 2 H), 7.93 (s, 2 H). 91 % yield
85	 tert-butyl N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-N-(4-fluorophenyl)carbamate	Intermediate 63; di-tert-butyl dicarbonate	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.35 (s, 9 H), 3.84 (s, 3 H), 7.05 - 7.10 (m, 2 H), 7.31 (t, *J*=8.74 Hz, 2 H), 7.46 (dd, *J*=8.87, 5.07 Hz, 2 H), 7.73 (d, *J*=8.87 Hz, 2 H), 7.86 (s, 2 H). 94 % yield

Intermediate number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
86	 tert-butyl N-[4-amino-5-(4-methylbenzoyl)thiazol-2-yl]-N-(4-fluorophenyl)carbamate	Intermediate 64; di-tert-butyl dicarbonate	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.34 (s, 9 H), 2.39 (s, 3 H), 7.31 (s, 4 H), 7.44 - 7.48 (m, 2 H), 7.61 (s, 2 H), 7.89 (s, 2 H). 79 % yield
87	 tert-butyl N-[4-amino-5-(4-fluorobenzoyl)thiazol-2-yl]-N-(4-fluorophenyl)carbamate	Intermediate 65; di-tert-butyl dicarbonate	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.34 (s, 9 H), 7.31 (t, *J*=8.87 Hz, 2 H), 7.37 (t, *J*=9.00 Hz, 2 H), 7.46 (dd, *J*=9.12, 5.07 Hz, 2 H), 7.79 (dd, *J*=8.87, 5.58 Hz, 2 H), 7.95 (s, 2 H). quantitative yield
88	 tert-butyl N-(4-amino-5-benzoyl-thiazol-2-yl)-N-(2,4-difluorophenyl)carbamate	Intermediate 66; di-tert-butyl dicarbonate	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.35 (s, 9 H), 7.22 - 7.27 (m, 1 H), 7.49 - 7.57 (m, 4 H), 7.67 - 7.74 (m, 3 H), 7.95 (s, 2 H). 69 % yield

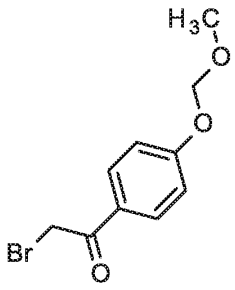
Intermediate number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
89	 tert-butyl N-(4-amino-5-benzoyl-thiazol-2-yl)-N-(4-methoxyphenyl)carbamate	Intermediate 67; di-tert-butyl dicarbonate	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.34 (s, 9 H), 3.80 (s, 3 H), 6.98 - 7.02 (m, 2 H), 7.25 - 7.30 (m, 2 H), 7.50 - 7.58 (m, 3 H), 7.68 - 7.74 (m, 2 H), 7.93 (s, 2 H). 91 % yield
90	 tert-butyl N-[4-amino-5-[4-[tert-butyl(dimethyl)silyl]oxybenzoyl]thiazol-2-yl]-N-(4-fluorophenyl)carbamate	Intermediate 68; di-tert-butyl dicarbonate	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 0.25 (s, 6 H), 0.96 - 0.99 (m, 9 H), 1.35 (s, 9 H), 6.99 (d, *J*=8.62 Hz, 2 H), 7.28 - 7.34 (m, 2 H), 7.46 (dd, *J*=8.87, 5.07 Hz, 2 H), 7.69 (d, *J*=8.87 Hz, 2 H), 7.88 (s, 2 H). 92 % yield
91	 tert-butyl N-(4-amino-5-benzoyl-thiazol-2-yl)-N-(p-tolyl)carbamate	Intermediate 69; di-tert-butyl dicarbonate	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.33 (s, 9 H), 2.36 (s, 3 H), 7.25 (d, *J*=9.38 Hz, 4 H), 7.54 (s, 3 H), 7.69 - 7.74 (m, 2 H), 7.93 (s, 2 H). 85 % yield

Intermediate number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
92	 tert-butyl N-(4-amino-5-benzoyl-thiazol-2-yl)-N-(3-fluorophenyl)carbamate	Intermediate 70; di-tert-butyl dicarbonate	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.34 (s, 9 H), 7.22 - 7.32 (m, 2 H), 7.43 (br dt, *J*=9.76, 2.22 Hz, 1 H), 7.48 - 7.60 (m, 4 H), 7.69 - 7.74 (m, 2 H), 7.95 (s, 2 H). 99 % yield
93	 tert-butyl N-(4-amino-5-benzoyl-thiazol-2-yl)-N-(2-fluorophenyl)carbamate	Intermediate 71; di-tert-butyl dicarbonate	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.34 (s, 9 H), 7.33 (td, *J*=7.67, 1.39 Hz, 1 H), 7.41 (ddd, *J*=10.01, 8.49, 1.27 Hz, 1 H), 7.47 - 7.60 (m, 5 H), 7.70 - 7.75 (m, 2 H), 7.95 (s, 2 H). 88 % yield
94	 tert-butyl N-(4-amino-5-benzoyl-thiazol-2-yl)-N-(1-methylpyrazol-4-yl)carbamate	Intermediate 74; di-tert-butyl dicarbonate	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.39 (s, 9 H), 3.85 (s, 3 H), 7.49 - 7.57 (m, 4 H), 7.68 - 7.73 (m, 2 H), 7.92 (s, 1 H), 7.98 (s, 2 H). 89 % yield

Intermediate number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
95	 tert-butyl N-(4-amino-5-benzoyl-thiazol-2-yl)-N-(3-pyridyl)carbamate	Intermediate 75; di-tert-butyl dicarbonate	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.34 (s, 9 H), 7.49 - 7.61 (m, 4 H), 7.68 - 7.75 (m, 2 H), 7.90 - 7.97 (m, 3 H), 8.60 (dd, *J*=4.56, 1.52 Hz, 1 H), 8.63 (dd, *J*=2.54, 0.51 Hz, 1 H). LC-MS (method 2) Rt = 1.24 min; MS (ESIpos): m/z = 397.5 $[M+H]^+$ 85 % yield
96	 tert-butyl N-[4-amino-5-(4-bromobenzoyl)thiazol-2-yl]-N-(4-fluorophenyl)carbamate	Intermediate 76; di-tert-butyl dicarbonate	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.34 (s, 9 H), 7.31 (t, *J*=8.74 Hz, 2 H), 7.44 - 7.48 (m, 2 H), 7.64 - 7.68 (m, 2 H), 7.73 - 7.77 (m, 2 H), 7.98 (s, 2 H). LC-MS (method 2) Rt = 1.53 min; MS (ESIpos): m/z = 492.5 $[M+H]^+$ preparative flash chromatography (method Z, 0-3%) 92 % yield

Intermediate 97

2-bromo-1-[4-(methoxymethoxy)phenyl]ethan-1-one



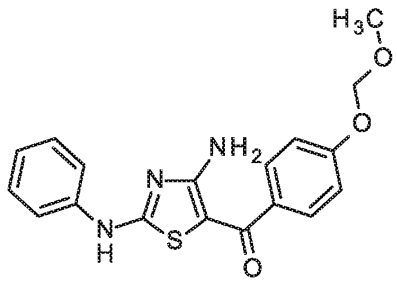
4-Hydroxyphenacyl bromide (2.50 g, 11.6 mmol) was provided in THF (50 mL). To this was added sodium hydride (511 mg, 60% in mineral oil, 12.8 mmol), and the suspension was stirred at rt for 1 h, after which time chloromethyl methyl ether (1.1 mL, 13.9 mmol) was added dropwise. The suspension was stirred at rt for 72 h. The reaction was stopped by the addition of a saturated aqueous solution of ammonium chloride and extracted with dichloromethane. The organics were washed with brine, dried over magnesium sulfate, filtered and concentrated under vacuum to give a brown oil. The residue was purified by normal phase column chromatography (10-80% EtOAc in heptane) to give 1.161 g (39 % yield) of the title compound as a light yellow oil.

^{1}H-NMR (CDCl3, 400 MHz): δ ppm = 3.48 (s, 3H); 4.40 (s, 2H); 5.23 (s, 2H); 7.09 (d, 2H); 7.96 (d, 2H)

LC-MS (method 2): Rt = 0.79 min; MS(ESIpos) m/z = 260 [M+H]$^+$

Intermediate 98

(4-amino-2-anilino-1,3-thiazol-5-yl)[4-(methoxymethoxy)phenyl]methanone



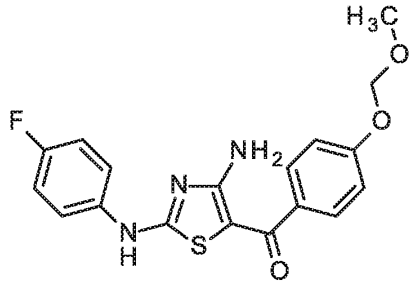
Dry acetonitrile (65 mL) was provided and phenyl isothiocyanate (350 µl, 2.9 mmol; CAS-RN 103-72-0), cyanamide (146 mg, 3.47 mmol; CAS-RN 420-04-2) and 1,8-diazabicyclo[5.4.0]undec-7-en (0.75 mL, 5.1 mmol; CAS-RN 6674-22-2) were added and the solution was stirred at rt for 45 min, after which time more 1,8-diazabicyclo(5.4.0)undec-7-ene (0.75 mL, 5.1 mmol) was added, followed by 2-bromo-1-[4-(methoxymethoxy)phenyl]ethan-1-one (750 mg, 2.89 mmol in 10 mL acetonitrile; Intermediate 97). The solution was stirred at rt for 1.5 h. The mixture was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate solution. The organics were washed with brine, and silica was added. The suspension was concentrated under vacuum. The residue was purified by normal phase column chromatography (10-80% EtOAc in heptane) to give 669 mg (65 % yield) of the title compound as a yellow solid.

LC-MS (method 2): Rt = 0.81 min; MS(ESIpos) m/z = 356 [M+H]$^+$

^{1}H-NMR (CDCl3, 400 MHz): δ ppm = 3.49 (s, 3H); 5.20 (s, 2H); 7.05 (d, 2H); 7.19 (t, 1H); 7.33-7.43 (m, 4H); 7.73 (d, 2H); 8.46 (br s, 1H); NH2 not observed.

Intermediate 99

[4-amino-2-(4-fluoroanilino)-1,3-thiazol-5-yl][4-(methoxymethoxy)phenyl]methanone



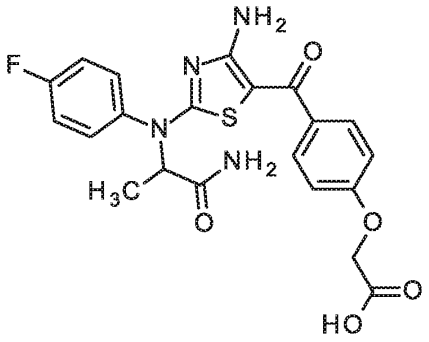
Dry acetonitrile (25 mL) was provided and 4-fluorophenyl isothiocyanate (296 mg, 1.93 mmol), cyanamide (97.4 mg, 2.32 mmol; CAS-RN 420-04-2) and 1,8-diazabicyclo(5.4.0)undec-7-ene (0.5 mL, 3.4 mmol; CAS-RN 6674-22-2) were added and the solution was stirred at rt for 45 min, after which time more 1,8-diazabicyclo(5.4.0)undec-7-ene (0.5 mL, 3.4 mmol)) was added, followed by 2-bromo-1-[4-(methoxymethoxy)phenyl]ethan-1-one (500 mg, 1.93 mmol in 10 mL acetonitrile; Intermediate 98). The solution was stirred at rt for 18 h. The mixture was evaporated to dryness under vacuum, partitioned between water and ethyl acetate and extracted into ethyl acetate. The organic layerss were combined and washed with saturated aqueous sodium hydrogen carbonate solution and brine, then dried over magnesium sulfate before being filtered. Silica was added and the suspension was evaporated. This was purified by normal phase column chromatography (15-100% EtOAc in heptane) to give 620 mg (72% yield) of the title compound.

^{1}H-NMR (DMSO-d6, 400 MHz): δ ppm = 3.43 (s, 3H); 5.29 (s, 2H); 7.12 (d, 2H); 7.25 (2H, t); 7.64-7.72 (m, 4H); 8.20 (br s, 2H); 10.79 (s, 1H).

LC-MS (method 2): Rt = 0.81 min; MS(ESIpos) m/z = 374 $[M+H]^+$

Intermediate 100

rac-2-[4-[4-amino-2-(N-[2-amino-1-methyl-2-oxo-ethyl]-4-fluoro-anilino)thiazole-5-carbonyl]phenoxy]acetic acid



To a solution of rac-ethyl 2-[4-[4-amino-2-(4-fluoro-N-[2-amino-1-methyl-2-oxo-ethyl]anilino)thiazole-5-carbonyl]phenoxy]acetate (24 mg, 0.05 mmol; Example 81) in tetrahydrofurane (2 mL) was added aqueous sodium hydroxide solution (0.1 mL, 1 M). The reaction mixture was stirred overnight at rt.

The reaction mixture was diluted with water, aqueous hydrochloride acid (1 M) was added dropwise to adjust the pH to 3 and afterwards the mixture was extracted with dichloromethane. The organic layer was washed with brine, filtered through a water repellent filter circle (MN 617 WA) and evaporated to dryness. The residue was dissolved in acetonitrile/water (1:1) and dried by lyophilization to give 15 mg (63 % yield) of the title compound.

^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.16 (d, *J*=7.35 Hz, 3 H), 4.68 (s, 2 H), 5.05 (br q, *J*=7.44 Hz, 1 H), 6.89 (d, *J*=8.87 Hz, 2 H), 7.24 (s, 1 H), 7.33 (t, *J*=8.74 Hz, 2 H), 7.47 (d, *J*=8.87 Hz, 2 H), 7.58 (s, 1 H), 7.64 (dd, *J*=8.87, 5.07 Hz, 2 H), 8.08 (br s, 2 H), 13.02 (br s, 1 H).

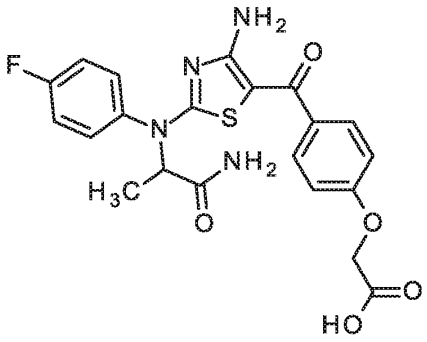
LC-MS (method 1) Rt = 0.87 min; MS (ESIpos): m/z = 459.5 $[M+H]^+$

Intermediates 100.1 and **100.2**:

(R)-2-[4-[4-amino-2-(N-[2-amino-1-methyl-2-oxo-ethyl]-4-fluoro-anilino)thiazole-5-carbonyl]phenoxy]acetic acid and (S)-2-[4-[4-amino-2-(N-[2-amino-1-methyl-2-oxo-ethyl]-4-fluoro-anilino)thiazole-5-carbonyl]phenoxy]acetic acid

Intermediate 100.1

2-[4-[4-amino-2-(N-[2-amino-1-methyl-2-oxo-ethyl]-4-fluoro-anilino)thiazole-5-carbonyl]phenoxy]acetic acid (enantiomer 1)

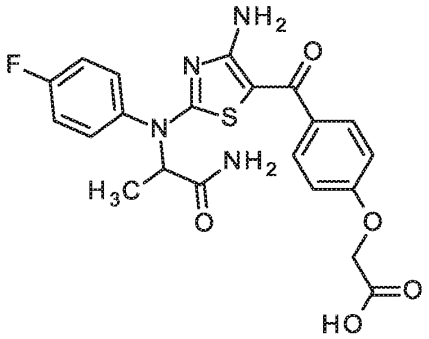


To an ice cooled solution of ethyl 2-[4-[4-amino-2-(4-fluoro-N-[2-amino-1-methyl-2-oxo-ethyl]anilino)thiazole-5-carbonyl]phenoxy]acetate (enantiomer 1) (2.50 g, 5.14 mmol, Example 81.1) in tetrahydrofurane (26.3 mL) was added aqueous sodium hydroxide solution (5.1 mL, 1 M). The mixture was stirred overnight at rt.

The reaction mixture was diluted with water, aqueous hydrochloride acid (1 M) was added dropwise to adjust the pH to 3 and afterwards the mixture was treated with dichloromethane. The resulting precipitate was isolated by filtration, washed with water and some dichloromethane and dried by lyophilization to give 1.48 g (62 % yield) of the title compound.

Intermediate 100.2

2-[4-[4-amino-2-(N-[2-amino-1-methyl-2-oxo-ethyl]-4-fluoro-anilino)thiazole-5-carbonyl]phenoxy]acetic acid (enantiomer 2)



To an ice cooled solution of ethyl 2-[4-[4-amino-2-(4-fluoro-N-[2-amino-1-methyl-2-oxo-ethyl]anilino)thiazole-5-carbonyl]phenoxy]acetate (enantiomer 2) (2.60 g, 5.34 mmol; Example 81.2) in tetrahydrofurane (27.3 mL) was added aqueous sodium hydroxide solution (5.3 mL, 1 M). The mixture was stirred overnight at rt.

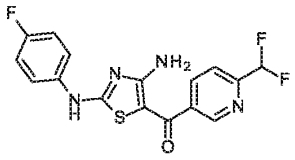
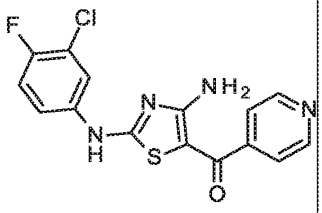
The reaction mixture was diluted with water, aqueous hydrochloride acid (1 M) was added dropwise to adjust the pH to 3 and afterwards the mixture was treated with dichloromethane. The resulting precipitate was isolated by filtration, washed with water and some dichloromethane and dried by lyophilization to give 0.95 g (37 % yield) of the title compound.

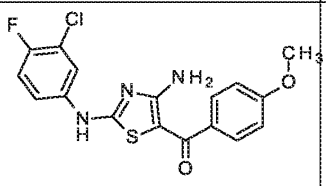
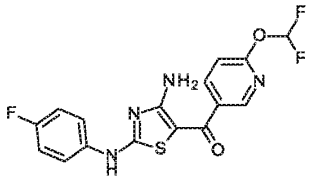
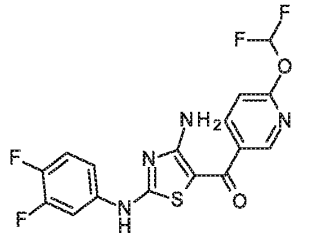
The organic layer of the filtrate was separated, washed with brine, filtered through a water repellent filter circle (MN 617 WA) and evaporated to dryness to give further 695 mg (28 % yield) of the title compound.

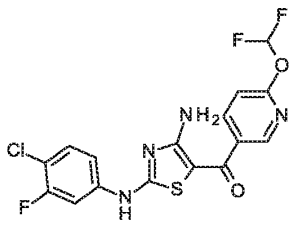
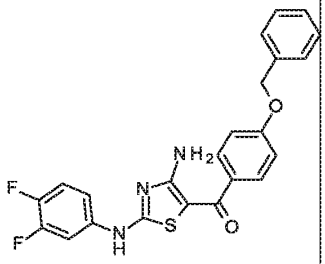
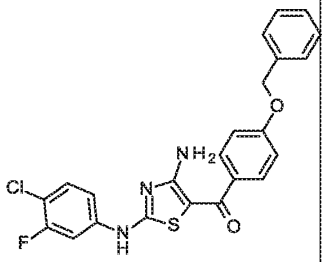
The following Intermediates were prepared from commercial starting materials stated in Table 4, below, using the procedure as for Intermediate 4, followed by purification by chromatography if needed. If no purification is specified, the respective title compound was isolated as crude product.

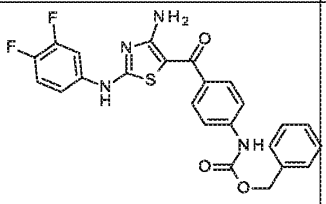
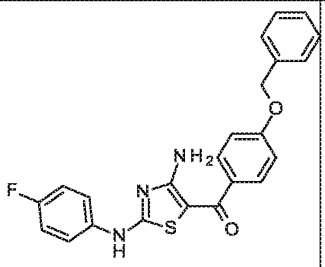
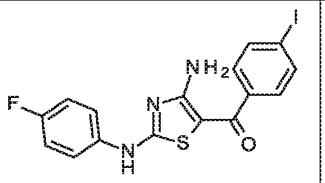
The crude product was either purified by RP-HPLC (methods A-D depending on polarity) or by preparative flash chromatography (methods X, Y or Z depending on polarity) if necessary. In case of a missing precipitation, the reaction mixture was extracted three times with ethyl acetate. The combined organic phases were dried over sodium sulfate, filtrated and evaporated to dryness. The crude product was purified by chromatography as stated in Table 4.

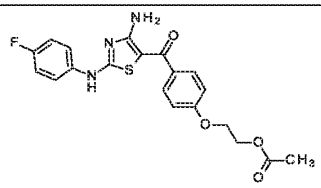
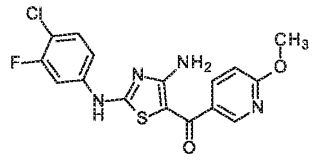
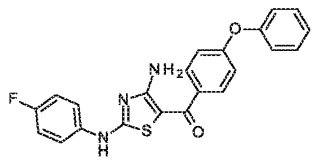
Table 4: Intermediates 101-197

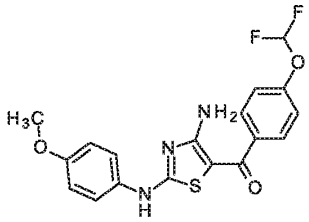
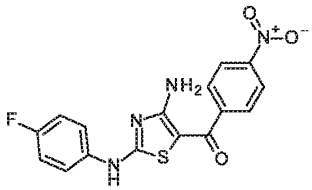
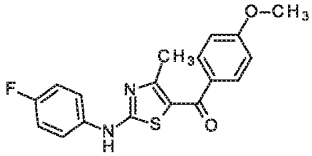
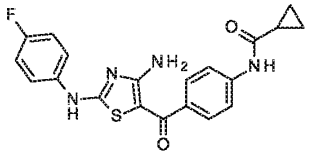
Inter-mediate number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
101	 [4-amino-2-(4-fluoroanilino)thiazol-5-yl]-[6-(difluoromethyl)-3-pyridyl]methanone	1-fluoro-4-isothiocyanato-benzene; 2-bromo-1-[6-(difluoromethyl)-3-pyridyl]ethanone	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 7.03 (t, J=60 Hz, 1 H), 7.23 (t, *J*=8.87 Hz, 2 H), 7.64 (dd, *J*=9.12, 4.82 Hz, 2 H), 7.81 (d, *J*=8.11 Hz, 1 H), 8.22 (dd, *J*=7.98, 2.15 Hz, 1 H), 8.35 – 8.40 (m, 2 H), 8.92 (d, *J*=1.52 Hz, 1 H), 10.94 (s, 1 H). LC-MS (method 1) Rt = 1.08 min; MS (ESIpos): m/z = 365.2 [M+H]$^+$ 71 % yield
102	 [4-amino-2-(3-chloro-4-fluoro-anilino)thiazol-5-yl]-(4-pyridyl)methanone	2-chloro-1-fluoro-4-isothiocyanato-benzene; 2-bromo-1-(4-pyridyl)ethanone; hydrobromide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 7.22 (ddd, *J*=8.87, 4.56, 2.53 Hz, 1 H), 7.33 – 7.37 (m, 1 H), 7.47 (dd, *J*=6.84, 2.53 Hz, 1 H), 7.57 – 7.62 (m, 2 H), 8.41 (s, 1 H), 8.50 – 8.55 (m, 2 H). LC-MS (method 2) Rt = 0.81 min; MS (ESIpos): m/z = 349.2 [M+H]$^+$ 65 % yield

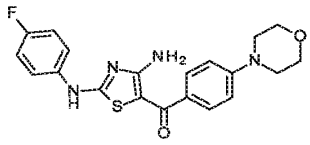
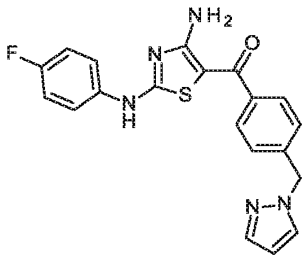
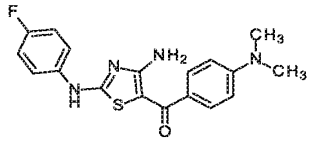
Inter-mediate number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
103	 [4-amino-2-(3-chloro-4-fluoro-anilino)thiazol-5-yl]-4-methoxyphenyl)methanone	2-chloro-1-fluoro-4-isothiocyanato-benzene; 2-bromo-1-(4-methoxyphenyl)ethanone	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 3.79 - 3.84 (m, 3 H), 7.00 (d, 2 H), 7.32 - 7.43 (m, 2 H), 7.66 (d, 2 H), 7.88 - 7.98 (m, 1 H), 8.05 - 8.34 (m, 1 H). LC-MS (method 2) Rt = 1.14 min; MS (ESIpos): m/z = 378.3 $[M+H]^+$ 96 % yield
104	 [4-amino-2-(4-fluoroanilino)thiazol-5-yl]-[6-(difluoromethoxy)-3-pyridyl]methanone	1-fluoro-4-isothiocyanatobenzene; 2-bromo-1-[6-(difluoromethoxy)pyridin-3-yl]ethanone	^{1}H-NMR (400 MHz, DMSO-d_6): δ ppm = 7.15 - 7.26 (m, 3 H), 7.61 - 7.68 (m, 2 H), 7.77 (t, 1H), 8.12 - 8.19 (m, 1 H), 8.21 - 8.40 (m, 2 H), 8.53 - 8.57 (m, 1 H), 10.90 (br s, 1 H). LC-MS (method 2) Rt = 1.03 min; MS (ESIpos): m/z = 381.2 $[M+H]^+$ 73 % yield
105	 [4-amino-2-(3,4-difluoroanilino)thiazol-5-yl]-[6-(difluoromethoxy)-3-pyridyl]methanone	1,2-difluoro-4-isothiocyanato-benzene; 2-bromo-1-[6-(difluoromethoxy)pyridin-3-yl]ethanone	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 7.16 – 7.20 (m, 1 H), 7.24 (br d, *J*=8.87 Hz, 1 H), 7.43 (d, *J*=10.39 Hz, 1 H), 7.78 (t, *J*=72 Hz, 1 H), 7.90 – 7.94 (m, 1 H), 8.17 (dd, *J*=8.36, 2.53 Hz, 1 H), 8.28 – 8.33 (m, 2 H), 8.56 (d, *J*=1.77 Hz, 1 H), 11.05 (br s, 1 H). LC-MS (method 2) Rt = 1.02 min; MS (ESIpos): m/z = 399.2 $[M+H]^+$ 63 % yield

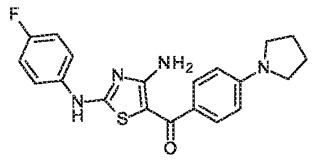
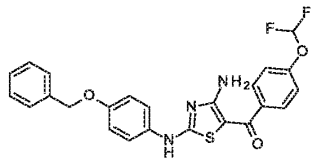
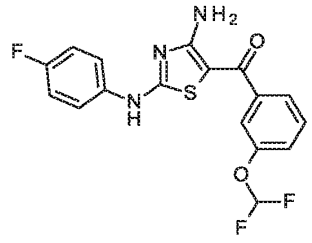
Inter-mediate number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
106	 [4-amino-2-(4-chloro-3-fluoro-anilino)thiazol-5-yl]-[6-(difluoromethoxy)-3-pyridyl]methanone	1-chloro-2-fluoro-4-isothiocyanatobenzene; 2-bromo-1-[6-(difluoromethoxy)pyridin-3-yl]ethanone	LC-MS (method 2) Rt = 1.03 min; MS (ESIpos): m/z = 415.2 $[M+H]^+$ 57 % yield
107	 [4-amino-2-(3,4-difluoroanilino)-1,3-thiazol-5-yl][4-(benzyloxy)phenyl]methanone	1,2-difluoro-4-isothiocyanato-benzene; 1-[4-(benzyloxy)phenyl]-2-bromoethanone	LC-MS (method 2) Rt = 1.29 min; MS (ESIpos): m/z = 438.3 $[M+H]^+$ 71 % yield
108	 [4-amino-2-(4-chloro-3-fluoro-anilino)thiazol-5-yl]-(4-benzyloxyphenyl)methanone	1-chloro-2-fluoro-4-isothiocyanatobenzene; 1-[4-(benzyloxy)phenyl]-2-bromoethanone	LC-MS (method 2) Rt = 1.35 min; MS (ESIpos): m/z = 454.3 $[M+H]^+$ 94 % yield

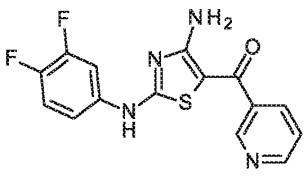
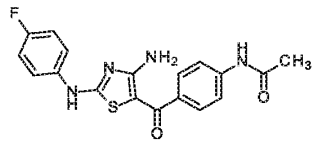
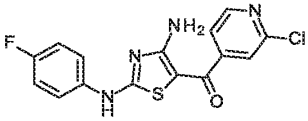
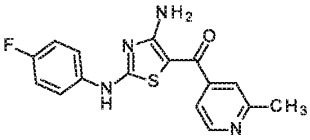
Inter-mediate number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
109	 Benzyl (4-{[4-amino-2-(3,4-difluoroanilino)-1,3-thiazol-5-yl]carbonyl}phenyl)carbamate	1,2-difluoro-4-isothiocyanato-benzene; benzyl N-[4-(2-bromoacetyl)phenyl]carbamate	LC-MS (method 2) Rt = 1.18 min; MS (ESIpos): m/z = 481.3 $[M+H]^+$ 78 % yield
110	 [4-amino-2-(4-fluoroanilino)thiazol-5-yl]-(4-benzyloxyphenyl)methanone	1-fluoro-4-isothiocyanatobenzene; 1-[4-(benzyloxy)phenyl]-2-bromoethanone	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 5.17 (s, 2 H), 7.06 – 7.10 (m, 2 H), 7.19 – 7.23 (m, 2 H), 7.39 – 7.43 (m, 5 H), 7.62 – 7.67 (m, 4 H), 8.11 – 8.15 (m, 2 H), 10.75 (br s, 1 H) LC-MS (method 2) Rt = 1.30 min; MS (ESIpos): m/z = 420.2 $[M+H]^+$ 86 % yield
111	 [4-amino-2-(4-fluoroanilino)thiazol-5-yl]-(4-iodophenyl)methanone	1-fluoro-4-isothiocyanatobenzene; 2-bromo-1-(4-iodophenyl)ethanone	LC-MS (method 2) Rt = 1.21 min; MS (ESIpos): m/z = 440.1 $[M+H]^+$ 82 % yield

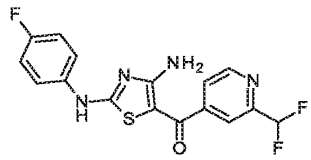
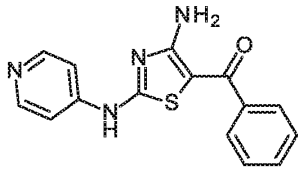
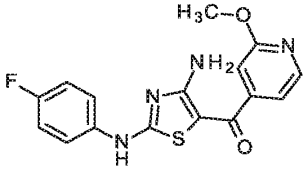
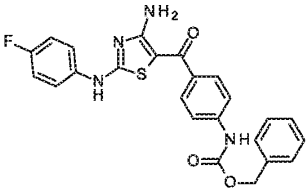
Inter-mediate number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
112	 2-[4-[4-amino-2-(4-fluoroanilino)thiazole-5-carbonyl]phenoxy]ethyl acetate	1-fluoro-4-isothiocyanatobenzene; 2-[4-(bromoacetyl)phenoxy]ethyl acetate (Intermediate 198)	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 3.73 (q, *J*=5.15 Hz, 2 H), 4.03 – 4.07 (m, 2 H), 4.91 (t, *J*=5.45 Hz, 1 H), 7.00 – 7.05 (m, 3 H), 7.19 – 7.23 (m, 2 H), 7.60 – 7.65 (m, 5 H), 8.15 – 8.19 (m, 2 H), 10.74 – 10.76 (m, 1 H). LC-MS (method 2) Rt = 1.06 min; MS (ESIpos): m/z = 416.3 $[M+H]^+$ 11 % yield
113	 [4-amino-2-(4-chloro-3-fluoroanilino)-1,3-thiazol-5-yl](6-methoxypyridin-3-yl)methanone	1-chloro-2-fluoro-4-isothiocyanatobenzene; 2-bromo-1-(6-methoxy-3-pyridyl)ethanone	LC-MS (method 2) Rt = 1.05 min; MS (ESIpos): m/z = 379.2 $[M+H]^+$ 100 % yield
114	 [4-amino-2-(4-fluoroanilino)thiazol-5-yl]-(4-phenoxyphenyl)methanone	1-fluoro-4-isothiocyanatobenzene; 2-bromo-1-(4-phenoxyphenyl)ethanone	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 7.02 – 7.06 (m, 2 H), 7.09 – 7.13 (m, 2 H), 7.19 – 7.23 (m, 3 H), 7.43 – 7.47 (m, 2 H), 7.61 – 7.65 (m, 2 H), 7.69 – 7.71 (m, 2 H), 8.19 – 8.21 (m, 2 H), 10.77 (br s, 1 H) LC-MS (method 2) Rt = 1.27 min; MS (ESIpos): m/z = 406.2 $[M+H]^+$ 84 % yield

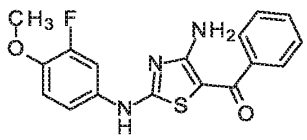
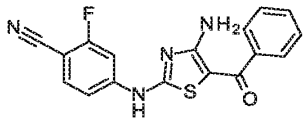
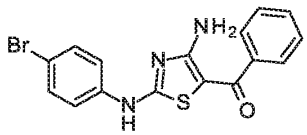
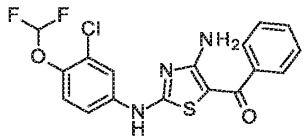
Inter-mediate number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
115	 4-amino-2-(4-methoxyanilino)thiazol-5-yl]-[4-(difluoromethoxy)phenyl]methanone	1-isothiocyanato-4-methoxybenzene; 2-bromo-1-[4-(difluoromethoxy)phenyl]ethanone	^{1}H NMR (500 MHz, DMSO-d_6) δ ppm = 3.73 – 3.76 (m, 3 H), 6.93 – 6.96 (m, 2 H), 7.22 – 7.26 (m, 2 H), 7.33 (t, 1 H), 7.45 – 7.48 (m, 2 H), 7.70 – 7.73 (m, 2 H), 8.19 – 8.21 (m, 2 H), 10.63 (m, 1 H) LC-MS (method 2) Rt = 1.27 min; MS (ESIpos): m/z = 406.2 [M+H]$^+$ 57 % yield
116	 [4-amino-2-(4-fluoroanilino)thiazol-5-yl]-(4-nitrophenyl)methanone	1-fluoro-4-isothiocyanatobenzene; 2-bromo-1-(4-nitrophenyl)ethanone	LC-MS (method 2) Rt = 0.95 min; MS (ESIpos): m/z = 359.1 [M+H]$^+$ 81 % yield
117	 [2-(4-fluoroanilino)-4-methyl-1,3-thiazol-5-yl](4-methoxyphenyl)methanone	1-fluoro-4-isothiocyanatobenzene; ethanimidamide acetate (1:1); 2-bromo-1-(4-methoxyphenyl)ethanone	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 2.34 (s, 3 H), 3.84 (s, 3 H), 7.05 (m, 2 H), 7.21 (m, 2 H), 7.64 (m, 2 H), 7.71 (m, 2 H), 10.76 (s, 1 H) LC-MS (method 2) Rt = 1.24 min; MS (ESIpos): m/z = 343.2 [M+H]$^+$ 8 % yield
118	 N-[4-[4-amino-2-(4-fluoroanilino)thiazole-5-carbonyl]phenyl]cyclopropanecarboxamide	1-fluoro-4-isothiocyanatobenzene; N-[4-(bromoacetyl)phenyl]cyclopropanecarboxamide	LC-MS (method 2) Rt = 0.77 min; MS (ESIpos): m/z = 397.3 [M+H]$^+$ 69 % yield

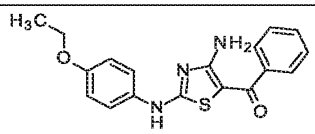
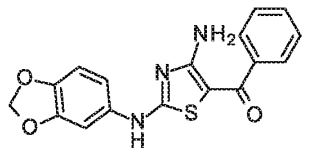
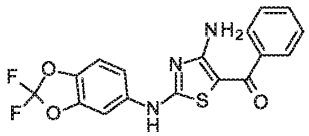
Inter-mediate number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
119	 [4-amino-2-(4-fluoroanilino)thiazol-5-yl]-(4-morpholinophenyl)methanone	1-fluoro-4-isothiocyanatobenzene; 2-bromo-1-[4-(morpholin-4-yl)phenyl]ethanone	LC-MS (method 2) Rt = 1.04 min; MS (ESIpos): m/z = 399.2 $[M+H]^+$ 66 % yield
120	 [4-amino-2-(4-fluoroanilino)-1,3-thiazol-5-yl][4-(1H-pyrazol-1-ylmethyl)phenyl]methanone	1-fluoro-4-isothiocyanatobenzene; 2-bromo-1-{4-[(1H-pyrazol-1-yl)methyl]phenyl}ethan-1-one, hydrogen bromide	LC-MS (method 2) Rt = 1.01 min; MS (ESIpos): m/z = 394.3 $[M+H]^+$ 64 % yield
121	 [4-amino-2-(4-fluoroanilino)-1,3-thiazol-5-yl][4-(dimethylamino)phenyl]methanone	1-fluoro-4-isothiocyanatobenzene; 4-(dimethylamino)phenacyl bromide	LC-MS (method 2) Rt = 1.16 min; MS (ESIpos): m/z = 357.3 $[M+H]^+$ 86 % yield

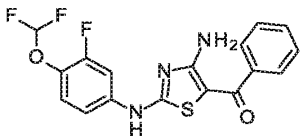
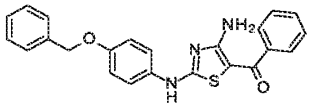
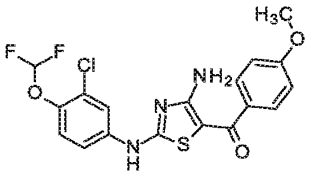
Inter-mediate number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
122	 [4-amino-2-(4-fluoroanilino)thiazol-5-yl]-(4-pyrrolidin-1-ylphenyl)methanone	1-fluoro-4-isothiocyanatobenzene; 2-bromo-1-[4-(pyrrolidin-1-yl)phenyl]ethanone	LC-MS (method 2) Rt = 1.26 min; MS (ESIpos): m/z = 383.2 $[M+H]^+$ 84 % yield
123	 [4-amino-2-(4-benzyloxyanilino)thiazol-5-yl]-[4-(difluoromethoxy)phenyl]methanone	1-(benzyloxy)-4-isothiocyanatobenzene; 2-bromo-1-[4-(difluoromethoxy)phenyl]ethanone	LC-MS (method 2) Rt = 1.32 min; MS (ESIpos): m/z = 468.3 $[M+H]^+$ 89 % yield
124	 [4-amino-2-(4-fluoroanilino)-1,3-thiazol-5-yl][3-(difluoromethoxy)phenyl]methanone	1-fluoro-4-isothiocyanatobenzene; 2-bromo-1-[3-(difluoromethoxy)phenyl]ethanone (Intermediate 199)	LC-MS (method 2) Rt = 1.10 min; MS (ESIpos): m/z = 380.2 $[M+H]^+$ 91 % yield

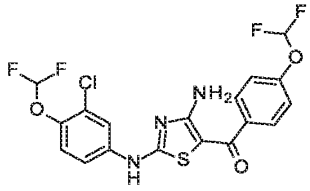
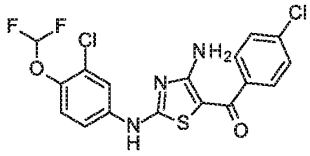
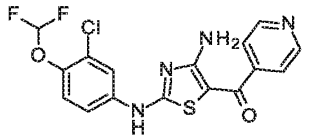
Inter-mediate number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
125	 [4-amino-2-(3,4-difluoroanilino)-1,3-thiazol-5-yl](pyridin-3-yl)methanone	1,2-difluoro-4-isothiocyanatobenzene; 2-bromo-1-(pyridin-3-yl)ethanone hydrobromide (1:1)	LC-MS (method 2) Rt = 0.77 min; MS (ESIpos): m/z = 333.2 $[M+H]^+$ 88 % yield
126	 N-(4-{[4-amino-2-(4-fluoroanilino)-1,3-thiazol-5-yl]carbonyl}phenyl)acetamide	1-fluoro-4-isothiocyanatobenzene; 4-acetamidophenacyl bromide	LC-MS (method 2) Rt = 0.87 min; MS (ESIpos): m/z = 371.3 $[M+H]^+$ 58 % yield
127	 [4-amino-2-(4-fluoroanilino)-1,3-thiazol-5-yl](2-chloropyridin-4-yl)methanone	1-fluoro-4-isothiocyanatobenzene; 2-bromo-1-(2-chloropyridin-4-yl)ethanone	LC-MS (method 2) Rt = 0.86 min; MS (ESIpos): m/z = 349.2 $[M+H]^+$ 88 % yield
128	 [4-amino-2-(4-fluoroanilino)thiazol-5-yl]-(2-methyl-4-pyridyl)methanone	1-fluoro-4-isothiocyanatobenzene; 2-bromo-1-(2-methylpyridin-4-yl)ethanone hydrobromide (1:1)	LC-MS (method 2) Rt = 0.80 min; MS (ESIpos): m/z = 329.2 $[M+H]^+$ 80 % yield

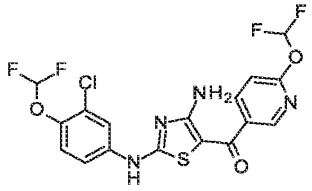
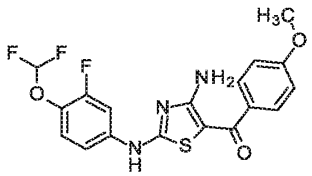
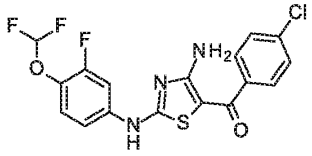
Inter-mediate number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
129	 [4-amino-2-(4-fluoroanilino)-1,3-thiazol-5-yl][2-(difluoromethyl)pyridin-4-yl]methanone	1-fluoro-4-isothiocyanatobenzene; 2-bromo-1-[2-(difluoromethyl)-4-pyridyl]ethanone	LC-MS (method 2) Rt = 0.87 min; MS (ESIpos): m/z = 365.2 $[M+H]^+$ 78 % yield
130	 [4-amino-2-(pyridin-4-ylamino)-1,3-thiazol-5-yl](phenyl)methanone	4-isothiocyanatopyridine; 2-bromo-1-phenylethanone	LC-MS (method 2) Rt = 0.69 min; MS (ESIpos): m/z = 297.2 $[M+H]^+$ 17 % yield
131	 [4-amino-2-(4-fluoroanilino)thiazol-5-yl]-(2-methoxy-4-pyridyl)methanone	1-fluoro-4-isothiocyanatobenzene; 2-bromo-1-(2-methoxypyridin-4-yl)ethanone	LC-MS (method 2) Rt = 0.91 min; MS (ESIpos): m/z = 345.2 $[M+H]^+$ 80 % yield
132	 Benzyl (4-{[4-amino-2-(4-fluoroanilino)-1,3-thiazol-5-yl]carbonyl}phenyl)carbamate	1-fluoro-4-isothiocyanatobenzene; benzyl N-[4-(2-bromoacetyl)phenyl]carbamate	LC-MS (method 2) Rt = 1.20 min; MS (ESIpos): m/z = 463.3 $[M+H]^+$ 72 % yield

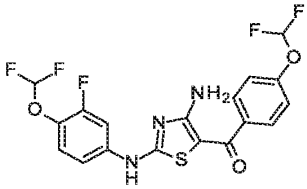
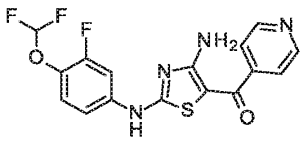
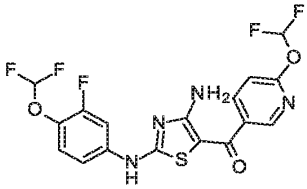
Inter-mediate number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
133	 [4-amino-2-(3-fluoro-4-methoxyanilino)-1,3-thiazol-5-yl](phenyl)methanone	2-fluoro-4-isothiocyanato-1-methoxybenzene; 2-bromo-1-phenylethanone	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 10.75 (s, 1H), 8.23 (br s, 2H), 7.68-7.75 (m, 1H), 7.64-7.68 (m, 2H), 7.44-7.52 (m, 3H), 7.13-7.22 (m, 2H), 3.82 (s, 3H). LC-MS (method 2) Rt = 1.08 min MS (ESIpos): m/z = 344.6 $[M+H]^+$ 96 % yield
134	 4-[(4-amino-5-benzoyl-1,3-thiazol-2-yl)amino]-2-fluorobenzonitrile	2-fluoro-4-isothiocyanatobenzonitrile; 2-bromo-1-phenylethanone	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 11.42 (br s, 1H), 8.28 (br s, 2H), 8.10 (dd, J = 12.5, 1.9 Hz, 1H), 7.86 (dd, J = 8.6, 7.9 Hz, 1H), 7.67-7.72 (m, 2H), 7.46-7.56 (m, 3H), 7.39 (dd, J = 8.6, 2.0 Hz, 1H). LC-MS (method 2) Rt = 0.9 min MS (ESIpos): m/z = 339.5 $[M+H]^+$ 87 % yield
135	 [4-amino-2-(4-bromoanilino)-1,3-thiazol-5-yl](phenyl)methanone	1-bromo-4-isothiocyanatobenzene; 2-bromo-1-phenylethanone	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 10.89 (br s, 1H), 8.22 (br s, 2H), 7.64-7.70 (m, 2H), 7.57-7.64 (m, 2H), 7.44-7.57 (m, 5H). LC-MS (method 2) Rt = 1.18 min MS (ESIpos): m/z = 375.2 $[M+H]^+$ 100 % yield
136	 {4-amino-2-[3-chloro-4-(difluoromethoxy)anilino]-1,3-thiazol-5-yl}(phenyl)methanone	2-chloro-1-(difluoromethoxy)-4-isothiocyanatobenzene; 2-bromo-1-phenylethanone	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 10.97 (br s, 1H), 8.26 (br s, 2H), 8.05 (d, J = 2.5 Hz, 1H), 7.64-7.70 (m, 2H), 7.45-7.54 (m, 4H), 7.36 (d, J = 8.9 Hz, 1H), 7.20 (t, J = 73.3 Hz, 1H). LC-MS (method 2) Rt = 1.14 min MS (ESIpos): m/z = 396.3 $[M+H]^+$ 92 % yield

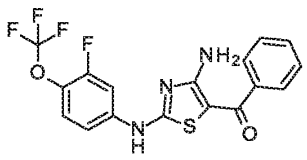
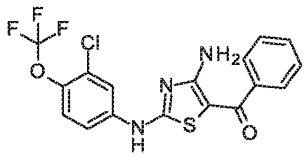
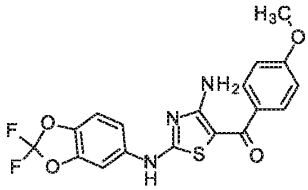
Inter-mediate number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
137	 [4-amino-2-(4-ethoxyanilino)-1,3-thiazol-5-yl](phenyl)methanone	1-ethoxy-4-isothiocyanatobenzene; 2-bromo-1-phenylethanone	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 10.58 (br s, 1H), 7.69-8.55 (m, 2H), 7.60-7.66 (m, 2H), 7.40-7.51 (m, 5H), 6.88-6.95 (m, 2H), 4.00 (q, J = 7.1 Hz, 2H), 1.31 (t, J = 7.0 Hz, 3H). LC-MS (method 2) Rt = 1.14 min MS (ESIpos): m/z = 340.4 [M+H]$^+$ 100 % yield
138	 [4-amino-2-(1,3-benzodioxol-5-ylamino)-1,3-thiazol-5-yl](phenyl)methanone	5-isothiocyanato-1,3-benzodioxole; 2-bromo-1-phenylethanone	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 10.64 (s, 1H), 8.20 (br s, 2H), 7.62-7.67 (m, 2H), 7.43-7.52 (m, 3H), 7.32-7.37 (m, 1H), 6.88-6.95 (m, 2H), 6.02 (s, 2H). LC-MS (method 2) Rt = 0.99 min MS (ESIpos): m/z = 340.2 [M+H]$^+$ 57 % yield
139	 {4-amino-2-[(2,2-difluoro-1,3-benzodioxol-5-yl)amino]-1,3-thiazol-5-yl}(phenyl)methanone	2,2-difluoro-5-isothiocyanato-1,3-benzodioxole; 2-bromo-1-phenylethanone	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 10.95 (br s, 1H), 8.24 (br s, 2H), 7.94 (d, J = 2.0 Hz, 1H), 7.64-7.69 (m, 2H), 7.45-7.53 (m, 3H), 7.40 (d, J = 8.6 Hz, 1H), 7.24 (dd, J = 8.7, 2.2 Hz, 1H). LC-MS (method 2) Rt = 1.17 min MS (ESIpos): m/z = 376.4 [M+H]$^+$ 78 % yield

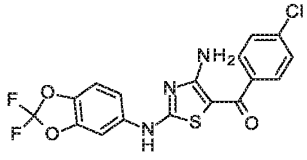
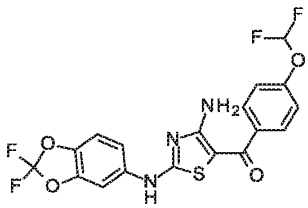
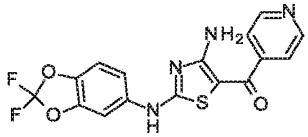
Inter-mediate number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
140	 {4-amino-2-[4-(difluoromethoxy)-3-fluoroanilino]-1,3-thiazol-5-yl}(phenyl)methanone	1-(difluoromethoxy)-2-fluoro-4-isothiocyanatobenzene; 2-bromo-1-phenylethanone	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 11.00 (s, 1H), 8.26 (br s, 2H), 7.97 (dd, J = 12.9, 2.5 Hz, 1H), 7.65-7.70 (m, 2H), 7.45-7.54 (m, 3H), 7.33-7.39 (m, 1H), 7.24-7.29 (m, 1H), 7.18 (t, J = 73.3 Hz, 1H). LC-MS (method 2) Rt = 1.08 min MS (ESIpos): m/z = 380.2 $[M+H]^+$ 92 % yield
141	 {4-amino-2-[4-(benzyloxy)anilino]-1,3-thiazol-5-yl}(phenyl)methanone	1-(benzyloxy)-4-isothiocyanatobenzene; 2-bromo-1-phenylethanone	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 10.61 (br s, 1H), 8.17 (br s, 2H), 7.64 (dd, J = 7.6, 1.8 Hz, 2H), 7.42-7.50 (m, 7H), 7.36-7.42 (m, 2H), 7.30-7.36 (m, 1H), 6.99-7.04 (m, 2H), 5.09 (s, 2H). LC-MS (method 2) Rt = 1.3 min MS (ESIpos): m/z = 402.4 $[M+H]^+$ 98 % yield
142	 {4-amino-2-[3-chloro-4-(difluoromethoxy)anilino]-1,3-thiazol-5-yl}(4-methoxyphenyl)methanone	2-chloro-1-(difluoromethoxy)-4-isothiocyanatobenzene; 2-bromo-1-(4-methoxyphenyl)ethanone	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 10.94 (br s, 1H), 8.21 (br s, 2H), 8.06 (d, J = 2.5 Hz, 1H), 7.66-7.71 (m, 2H), 7.48 (dd, J = 8.9, 2.5 Hz, 1H), 7.36 (d, J = 8.9 Hz, 1H), 7.20 (t, J = 73.8 Hz, 1H), 7.02-7.05 (m, 1H), 7.00-7.02 (m, 1H), 3.82 (s, 3H). LC-MS (method 2) Rt = 1.17 min MS (ESIpos): m/z = 426.2 $[M+H]^+$ 99 % yield

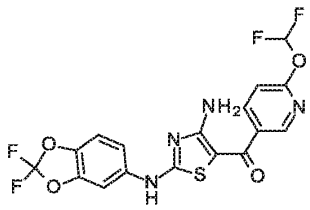
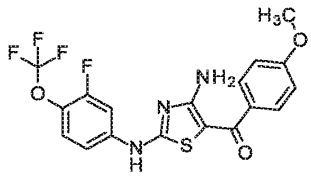
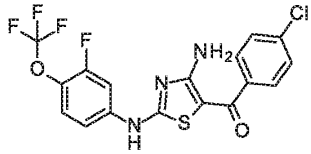
Inter-mediate number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
143	 {4-amino-2-[3-chloro-4-(difluoromethoxy)anilino]-1,3-thiazol-5-yl}[4-(difluoromethoxy)phenyl]methanone	2-chloro-1-(difluoromethoxy)-4-isothiocyanatobenzene; 2-bromo-1-[4-(difluoromethoxy)phenyl]ethanone	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 11.00 (br s, 1H), 8.14-8.42 (m, 2H), 8.05 (d, J = 2.5 Hz, 1H), 7.73-7.78 (m, 2H), 7.48 (dd, J = 9.0, 2.7 Hz, 1H), 7.38 (d, J = 6.1 Hz, 1H), 7.35 (t, J = 73.8 Hz, 1H), 7.24-7.29 (m, 2H), 7.20 (t, J = 73.3 Hz, 1H). LC-MS (method 2) Rt = 1.15 min MS (ESIpos): m/z = 462.2 [M+H]$^+$ 87 % yield
144	 {4-amino-2-[3-chloro-4-(difluoromethoxy)anilino]-1,3-thiazol-5-yl}(4-chlorophenyl)methanone	2-chloro-1-(difluoromethoxy)-4-isothiocyanatobenzene; 2-bromo-1-(4-chlorophenyl)ethanone	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 11.02 (br s, 1H), 8.31 (br s, 2H), 8.05 (d, J = 2.3 Hz, 1H), 7.67-7.72 (m, 2H), 7.53-7.58 (m, 2H), 7.47 (dd, J = 9.0, 2.7 Hz, 1H), 7.36 (d, J = 8.9 Hz, 1H), 7.20 (t, J = 73.5 Hz, 1H). LC-MS (method 2) Rt = 1.20 min MS (ESIpos): m/z = 430.2 [M+H]$^+$ 100 % yield
145	 {4-amino-2-[3-chloro-4-(difluoromethoxy)anilino]-1,3-thiazol-5-yl}(pyridin-4-yl)methanone	2-chloro-1-(difluoromethoxy)-4-isothiocyanatobenzene; 2-bromo-1-(pyridin-4-yl)ethanone hydrobromide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 11.08 (br s, 1H), 8.70-8.74 (m, 2H), 8.42 (br s, 2H), 8.06 (d, J = 2.5 Hz, 1H), 7.56-7.60 (m, 2H), 7.46-7.51 (m, 1H), 7.37 (d, J = 9.1 Hz, 1H), 7.21 (t, J = 73.3 Hz, 1H). LC-MS (method 2) Rt = 0.82 min MS (ESIpos): m/z = 397.2 [M+H]$^+$ 45 % yield

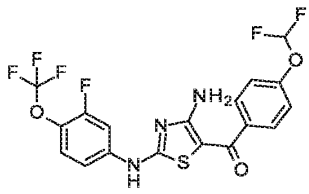
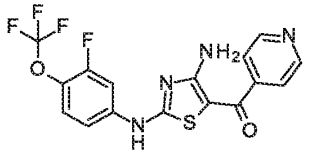
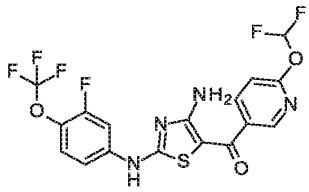
Inter-mediate number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
146	 {4-amino-2-[3-chloro-4-(difluoromethoxy)anilino]-1,3-thiazol-5-yl}[6-(difluoromethoxy)pyridin-3-yl]methanone	2-chloro-1-(difluoromethoxy)-4-isothiocyanatobenzene; 2-bromo-1-[6-(difluoromethoxy)pyridin-3-yl]ethanone	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 11.07 (br s, 1H), 8.55-8.58 (m, 1H), 8.34 (br s, 2H), 8.18 (dd, J = 8.6, 2.5 Hz, 1H), 8.04 (d, J = 2.0 Hz, 1H), 7.78 (t, J = 72.5 Hz, 1H), 7.47 (dd, J = 9.0, 2.7 Hz, 1H), 7.37 (d, J = 8.9 Hz, 1H), 7.21 (t, J = 73.5 Hz, 1H), 7.18-7.21 (m, 1H). LC-MS (method 2) Rt = 1.06 min MS (ESIpos): m/z = 463.2 $[M+H]^+$ 92 % yield
147	 {4-amino-2-[4-(difluoromethoxy)-3-fluoroanilino]-1,3-thiazol-5-yl}(4-methoxyphenyl)methanone	1-(difluoromethoxy)-2-fluoro-4-isothiocyanatobenzene; 2-bromo-1-(4-methoxyphenyl)ethanone	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 10.99 (br s, 1H), 8.20 (br s, 2H), 7.97 (dd, J = 13.1, 2.4 Hz, 1H), 7.66-7.71 (m, 2H), 7.33-7.39 (m, 1H), 7.24-7.30 (m, 1H), 7.17 (t, J = 73.3 Hz, 1H), 7.00-7.05 (m, 2H), 3.82 (s, 3H). LC-MS (method 2) Rt = 1.13 min MS (ESIpos): m/z = 410.2 $[M+H]^+$ 96 % yield
148	 {4-amino-2-[4-(difluoromethoxy)-3-fluoroanilino]-1,3-thiazol-5-yl}(4-chlorophenyl)methanone	1-(difluoromethoxy)-2-fluoro-4-isothiocyanatobenzene; 2-bromo-1-(4-chlorophenyl)ethanone	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 11.06 (br s, 1H), 8.30 (br s, 2H), 7.96 (dd, J = 12.9, 2.5 Hz, 1H), 7.68-7.72 (m, 2H), 7.53-7.58 (m, 2H), 7.33-7.39 (m, 1H), 7.24-7.29 (m, 1H), 7.18 (t, J = 73.3 Hz, 1H). LC-MS (method 2) Rt = 1.18 min MS (ESIpos): m/z = 414.2 $[M+H]^+$ 95 % yield

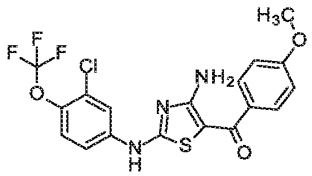
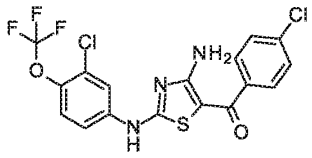
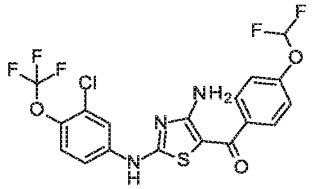
Inter-mediate number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
149	 {4-amino-2-[4-(difluoromethoxy)-3-fluoroanilino]-1,3-thiazol-5-yl}[4-(difluoromethoxy)phenyl]methanone	1-(difluoromethoxy)-2-fluoro-4-isothiocyanatobenzene; 2-bromo-1-[4-(difluoromethoxy)phenyl]ethanone	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 11.03 (br s, 1H), 8.28 (br s, 2H), 7.96 (dd, J = 12.9, 2.3 Hz, 1H), 7.73-7.78 (m, 2H), 7.32-7.55 (m, 2H), 6.99-7.30 (m, 4H). LC-MS (method 2) Rt = 1.14 min MS (ESIpos): m/z = 446.2 $[M+H]^+$ 88 % yield
150	 {4-amino-2-[4-(difluoromethoxy)-3-fluoroanilino]-1,3-thiazol-5-yl}(pyridin-4-yl)methanone	1-(difluoromethoxy)-2-fluoro-4-isothiocyanatobenzene; 2-bromo-1-(pyridin-4-yl)ethanone hydrobromide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 11.12 (s, 1H), 8.70-8.74 (m, 2H), 8.41 (br s, 2H), 7.97 (dd, J = 12.9, 2.5 Hz, 1H), 7.57-7.60 (m, 2H), 7.34-7.38 (m, 1H), 7.25-7.30 (m, 1H), 7.18 (t, J = 73.3 Hz, 1H). LC-MS (method 2) Rt = 0.8 min MS (ESIpos): m/z = 381.2 $[M+H]^+$ 15 % yield
151	 {4-amino-2-[4-(difluoromethoxy)-3-fluoroanilino]-1,3-thiazol-5-yl}[6-(difluoromethoxy)pyridin-3-yl]methanone	1-(difluoromethoxy)-2-fluoro-4-isothiocyanatobenzene; 2-bromo-1-[6-(difluoromethoxy)pyridin-3-yl]ethanone	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 11.02-11.23 (m, 1H), 8.57 (d, J = 2.3 Hz, 1H), 8.25-8.41 (m, 2H), 8.18 (dd, J = 8.5, 2.4 Hz, 1H), 7.92-7.98 (m, 1H), 7.78 (t, J = 72.2 Hz, 1H), 7.33-7.40 (m, 1H), 7.24-7.30 (m, 1H), 7.20 (d, J = 9.1 Hz, 1H), 7.18 (t, J = 73.5 Hz, 1H). LC-MS (method 2) Rt = 1.06 min MS (ESIpos): m/z = 447.2 $[M+H]^+$ 86 % yield

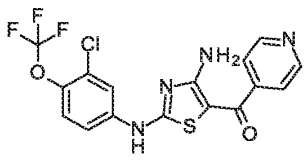
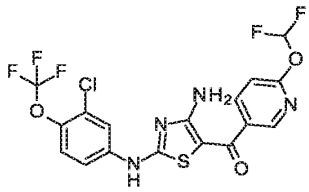
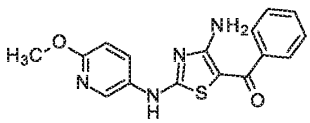
Inter-mediate number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
152	 {4-amino-2-[3-fluoro-4-(trifluoromethoxy)anilino]-1,3-thiazol-5-yl}(phenyl)methanone	2-fluoro-4-isothiocyanato-1-(trifluoromethoxy)benzene (Intermediate 200); 2-bromo-1-phenylethanone	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 11.12 (br s, 1H), 8.26 (br s, 2H), 8.08 (dd, J = 12.9, 2.5 Hz, 1H), 7.66-7.70 (m, 2H), 7.45-7.59 (m, 4H), 7.29-7.34 (m, 1H). LC-MS (method 2) Rt = 1.21 min MS (ESIpos): m/z = 398.2 $[M+H]^+$ 96 % yield
153	 {4-amino-2-[3-chloro-4-(trifluoromethoxy)anilino]-1,3-thiazol-5-yl}(phenyl)methanone	2-chloro-4-isothiocyanato-1-(trifluoromethoxy)benzene; 2-bromo-1-phenylethanone	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 11.08 (br s, 1H), 8.28 (br s, 2H), 8.16 (d, J = 2.3 Hz, 1H), 7.65-7.72 (m, 2H), 7.45-7.59 (m, 5H). LC-MS (method 2) Rt = 1.22 min MS (ESIpos): m/z = 414.2 $[M+H]^+$ 91 % yield
154	 {4-amino-2-[(2,2-difluoro-1,3-benzodioxol-5-yl)amino]-1,3-thiazol-5-yl}(4-methoxyphenyl)methanone	2,2-difluoro-5-isothiocyanato-1,3-benzodioxole; 2-bromo-1-(4-methoxyphenyl)ethanone	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 10.92 (br s, 1H), 8.17 (br s, 2H), 7.95 (d, J = 2.0 Hz, 1H), 7.65-7.70 (m, 2H), 7.40 (d, J = 8.6 Hz, 1H), 7.24 (dd, J = 8.7, 2.2 Hz, 1H), 6.99-7.05 (m, 2H), 3.82 (s, 3H). LC-MS (method 2) Rt = 1.21 min MS (ESIpos): m/z = 406.2 $[M+H]^+$ 89 % yield

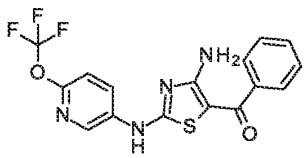
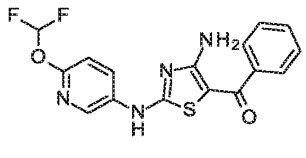
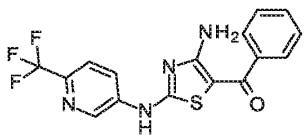
Inter-mediate number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
155	 {4-amino-2-[(2,2-difluoro-1,3-benzodioxol-5-yl)amino]-1,3-thiazol-5-yl}(4-chlorophenyl)methanone	2,2-difluoro-5-isothiocyanato-1,3-benzodioxole; 2-bromo-1-(4-chlorophenyl)ethanone	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 11.00 (br d, J = 1.3 Hz, 1H), 8.28 (br s, 2H), 7.94 (d, J = 2.0 Hz, 1H), 7.66-7.73 (m, 2H), 7.51-7.58 (m, 2H), 7.40 (d, J = 8.6 Hz, 1H), 7.24 (dd, J = 8.9, 2.3 Hz, 1H). LC-MS (method 2) Rt = 1.25 min MS (ESIpos): m/z = 410.2 $[M+H]^+$ 93 % yield
156	 {4-amino-2-[(2,2-difluoro-1,3-benzodioxol-5-yl)amino]-1,3-thiazol-5-yl}[4-(difluoromethoxy)phenyl]methanone	2,2-difluoro-5-isothiocyanato-1,3-benzodioxole; 2-bromo-1-[4-(difluoromethoxy)phenyl]ethanone	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 10.98 (br s, 1H), 8.24 (br s, 2H), 7.93 (d, J = 1.5 Hz, 1H), 7.71-7.78 (m, 2H), 7.40 (d, J = 8.6 Hz, 1H), 7.35 (t, J = 73.8 Hz, 1H), 7.21-7.29 (m, 3H). LC-MS (method 2) Rt = 1.23 min MS (ESIpos): m/z = 442.2 $[M+H]^+$ 61 % yield
157	 {4-amino-2-[(2,2-difluoro-1,3-benzodioxol-5-yl)amino]-1,3-thiazol-5-yl}(pyridin-4-yl)methanone	2,2-difluoro-5-isothiocyanato-1,3-benzodioxole; 2-bromo-1-(pyridin-4-yl)ethanone hydrobromide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 11.06 (s, 1H), 8.69-8.74 (m, 2H), 8.38 (br s, 2H), 7.94 (d, J = 1.8 Hz, 1H), 7.56-7.60 (m, 2H), 7.41 (d, J = 8.9 Hz, 1H), 7.25 (dd, J = 8.7, 2.2 Hz, 1H). LC-MS (method 2) Rt = 0.85 min MS (ESIpos): m/z = 377.2 $[M+H]^+$ 13 % yield

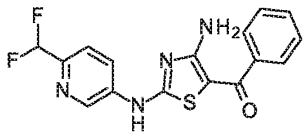
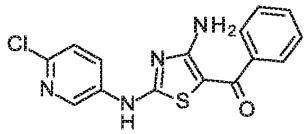
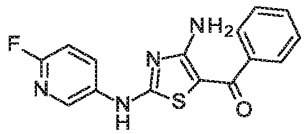
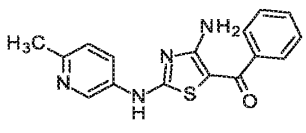
Inter-mediate number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
158	 {4-amino-2-[(2,2-difluoro-1,3-benzodioxol-5-yl)amino]-1,3-thiazol-5-yl}[6-(difluoromethoxy)pyridin-3-yl]methanone	2,2-difluoro-5-isothiocyanato-1,3-benzodioxole; 2-bromo-1-[6-(difluoromethoxy)pyridin-3-yl]ethanone	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 11.05 (br s, 1H), 8.54-8.58 (m, 1H), 8.31 (br s, 2H), 8.17 (dd, J = 8.6, 2.5 Hz, 1H), 7.94 (d, J = 1.8 Hz, 1H), 7.78 (t, J = 72.5 Hz, 1H), 7.41 (d, J = 8.9 Hz, 1H), 7.25 (dd, J = 8.9, 2.3 Hz, 1H), 7.17-7.22 (m, 1H). LC-MS (method 2) Rt = 1.15 min MS (ESIpos): m/z = 443.2 $[M+H]^+$ 85 % yield
159	 {4-amino-2-[3-fluoro-4-(trifluoromethoxy)anilino]-1,3-thiazol-5-yl}(4-methoxyphenyl)methanone	2-fluoro-4-isothiocyanato-1-(trifluoromethoxy)benzene (Intermediate 200); 2-bromo-1-(4-methoxyphenyl)ethanone	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 11.10 (br s, 1H), 8.20 (br s, 2H), 8.08 (dd, J = 12.9, 2.5 Hz, 1H), 7.66-7.72 (m, 2H), 7.55 (td, J = 8.9, 1.0 Hz, 1H), 7.30-7.35 (m, 1H), 7.00-7.05 (m, 2H), 3.82 (s, 3H). LC-MS (method 2) Rt = 1.24 min MS (ESIpos): m/z = 428.2 $[M+H]^+$ 90 % yield
160	 {4-amino-2-[3-fluoro-4-(trifluoromethoxy)anilino]-1,3-thiazol-5-yl}(4-chlorophenyl)methanone	2-fluoro-4-isothiocyanato-1-(trifluoromethoxy)benzene (Intermediate 200); 2-bromo-1-(4-chlorophenyl)ethanone	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 11.10 (br s, 1H), 8.20 (br s, 2H), 8.08 (dd, J = 12.9, 2.5 Hz, 1H), 7.66-7.72 (m, 2H), 7.55 (td, J = 9.0, 1.0 Hz, 1H), 7.30-7.35 (m, 1H), 7.00-7.06 (m, 2H), 3.82 (s, 3H). LC-MS (method 2) Rt = 1.23 min MS (ESIpos): m/z = 432.2 $[M+H]^+$ 91 % yield

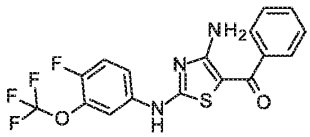
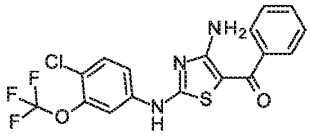
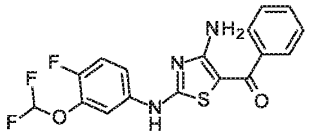
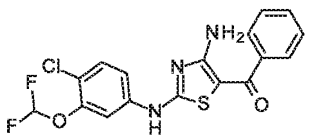
Inter-mediate number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
161	 {4-amino-2-[3-fluoro-4-(trifluoromethoxy)anilino]-1,3-thiazol-5-yl}[4-(difluoromethoxy)phenyl]methanone	2-fluoro-4-isothiocyanato-1-(trifluoromethoxy)benzene (Intermediate 200); 2-bromo-1-[4-(difluoromethoxy)phenyl]ethanone	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 11.15 (br s, 1H), 8.28 (br s, 2H), 8.07 (dd, J = 12.9, 2.5 Hz, 1H), 7.73-7.80 (m, 2H), 7.51-7.62 (m, 1H), 7.36 (t, J = 73.8 Hz, 1H), 7.30-7.34 (m, 1H), 7.25-7.30 (m, 2H). LC-MS (method 2) Rt = 1.24 min MS (ESIpos): m/z = 464.2 $[M+H]^+$ 86 % yield
162	 {4-amino-2-[3-fluoro-4-(trifluoromethoxy)anilino]-1,3-thiazol-5-yl}(pyridin-4-yl)methanone	2-fluoro-4-isothiocyanato-1-(trifluoromethoxy)benzene (Intermediate 200); 2-bromo-1-(pyridin-4-yl)ethanone hydrobromide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 11.23 (s, 1H), 8.70-8.75 (m, 2H), 8.42 (br s, 2H), 8.08 (dd, J = 12.9, 2.5 Hz, 1H), 7.53-7.62 (m, 3H), 7.30-7.35 (m, 1H). LC-MS (method 2) Rt = 0.89 min MS (ESIpos): m/z = 399.2 $[M+H]^+$ 21 % yield
163	 {4-amino-2-[3-fluoro-4-(trifluoromethoxy)anilino]-1,3-thiazol-5-yl}[6-(difluoromethoxy)pyridin-3-yl]methanone	2-fluoro-4-isothiocyanato-1-(trifluoromethoxy)benzene (Intermediate 200); 2-bromo-1-[6-(difluoromethoxy)pyridin-3-yl]ethanone	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 11.22 (br s, 1H), 8.55-8.61 (m, 1H), 8.34 (br s, 2H), 8.19 (dd, J = 8.5, 2.4 Hz, 1H), 8.07 (dd, J = 12.9, 2.5 Hz, 1H), 7.78 (t, J = 72.5 Hz, 1H), 7.56 (td, J = 8.9, 1.0 Hz, 1H), 7.30-7.36 (m, 1H), 7.18-7.22 (m, 1H). LC-MS (method 2) Rt = 1.15 min MS (ESIpos): m/z = 465.2 $[M+H]^+$ 84 % yield

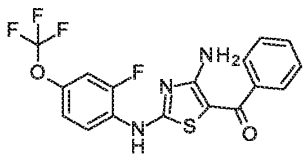
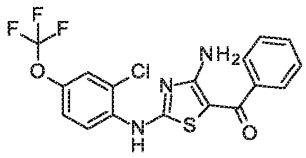
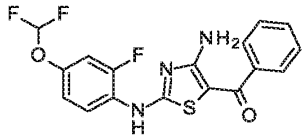
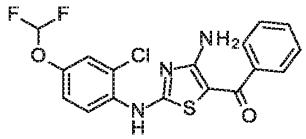
Inter-mediate number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
164	 {4-amino-2-[3-chloro-4-(trifluoromethoxy)anilino]-1,3-thiazol-5-yl}(4-methoxyphenyl)methanone	2-chloro-4-isothiocyanato-1-(trifluoromethoxy)benzene; 2-bromo-1-(4-methoxyphenyl)ethanone	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 11.06 (br s, 1H), 8.05-8.37 (m, 3H), 7.66-7.72 (m, 2H), 7.50-7.58 (m, 2H), 7.00-7.05 (m, 2H), 3.82 (s, 3H). LC-MS (method 2) Rt = 1.22 min MS (ESIpos): m/z = 444.2 $[M+H]^+$ 79 % yield
165	 {4-amino-2-[3-chloro-4-(trifluoromethoxy)anilino]-1,3-thiazol-5-yl}(4-chlorophenyl)methanone	2-chloro-4-isothiocyanato-1-(trifluoromethoxy)benzene; 2-bromo-1-(4-chlorophenyl)ethanone	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 7.87-7.99 (m, 1H), 7.64-7.71 (m, 2H), 7.48-7.54 (m, 2H), 7.43 (s, 1H), 7.37 (br d, J = 0.8 Hz, 1H). LC-MS (method 2) Rt = 1.3 min MS (ESIpos): m/z = 448.2 $[M+H]^+$ 53 % yield
166	 {4-amino-2-[3-chloro-4-(trifluoromethoxy)anilino]-1,3-thiazol-5-yl}[4-(difluoromethoxy)phenyl]methanone	2-chloro-4-isothiocyanato-1-(trifluoromethoxy)benzene; 2-bromo-1-[4-(difluoromethoxy)phenyl]ethanone	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 11.11 (br s, 1H), 8.29 (br s, 2H), 8.15 (d, J = 2.5 Hz, 1H), 7.73-7.79 (m, 2H), 7.50-7.58 (m, 2H), 7.36 (t, J = 73.2 Hz, 1H), 7.25-7.30 (m, 2H). LC-MS (method 2) Rt = 1.24 min MS (ESIpos): m/z = 480.2 $[M+H]^+$ 71 % yield

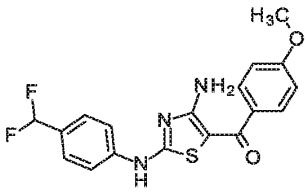
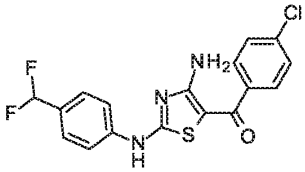
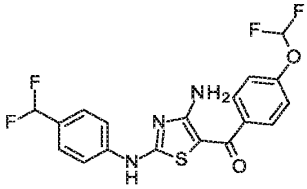
Inter-mediate number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
167	 {4-amino-2-[3-chloro-4-(trifluoromethoxy)anilino]-1,3-thiazol-5-yl}(pyridin-4-yl)methanone	2-chloro-4-isothiocyanato-1-(trifluoromethoxy)benzene; 2-bromo-1-(pyridin-4-yl)ethanone hydrobromide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 11.19 (s, 1H), 8.70-8.75 (m, 2H), 8.43 (br s, 2H), 8.17 (d, J = 2.3 Hz, 1H), 7.51-7.61 (m, 4H). LC-MS (method 2) Rt = 0.93 min MS (ESIpos): m/z = 415.2 [M+H]$^+$ 47 % yield
168	 {4-amino-2-[3-chloro-4-(trifluoromethoxy)anilino]-1,3-thiazol-5-yl}[6-(difluoromethoxy)pyridin-3-yl]methanone	2-chloro-4-isothiocyanato-1-(trifluoromethoxy)benzene; 2-bromo-1-[6-(difluoromethoxy)pyridin-3-yl]ethanone	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 11.20 (br s, 1H), 8.54-8.59 (m, 1H), 8.21-8.52 (m, 2H), 8.18 (dd, J = 8.4, 2.5 Hz, 1H), 8.11 (br s, 1H), 7.78 (t, J = 72.5 Hz, 1H), 7.46-7.58 (m, 2H), 7.17-7.21 (m, 1H). LC-MS (method 2) Rt = 1.19 min MS (ESIpos): m/z = 481.2 [M+H]$^+$ 34 % yield
169	 {4-amino-2-[(6-methoxypyridin-3-yl)amino]-1,3-thiazol-5-yl}(phenyl)methanone	5-isothiocyanato-2-methoxypyridine; 2-bromo-1-phenylethanone	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 10.69 (br s, 1H), 8.40 (d, J = 2.5 Hz, 1H), 7.96-8.38 (m, 2H), 7.93 (dd, J = 8.9, 2.8 Hz, 1H), 7.62-7.67 (m, 2H), 7.43-7.52 (m, 3H), 6.84-6.88 (m, 1H), 3.83 (s, 3H). LC-MS (method 2) Rt = 0.91 min MS (ESIpos): m/z = 327.2 [M+H]$^+$ 87 % yield

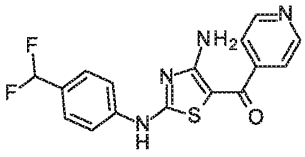
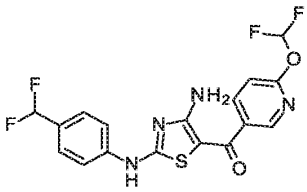
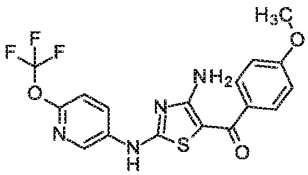
Inter-mediate number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
170	 (4-amino-2-{[6-(trifluoromethoxy)pyridin-3-yl]amino}-1,3-thiazol-5-yl)(phenyl)methanone	5-isothiocyanato-2-(trifluoromethoxy)pyridine (Intermediate 201); 2-bromo-1-phenylethanone	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 11.10 (br s, 1H), 8.67 (d, J = 2.8 Hz, 1H), 8.27 (dd, J = 8.9, 2.8 Hz, 3H), 7.66-7.70 (m, 2H), 7.46-7.53 (m, 3H), 7.34 (d, J = 8.9 Hz, 1H). LC-MS (method 2) Rt = 0.96 min MS (ESIpos): m/z = 381.2 [M+H]$^+$ 82 % yield
171	 (4-amino-2-{[6-(difluoromethoxy)pyridin-3-yl]amino}-1,3-thiazol-5-yl)(phenyl)methanone	2-(difluoromethoxy)-5-isothiocyanatopyridine (Intermediate 202); 2-bromo-1-phenylethanone	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 10.94 (br s, 1H), 8.56 (d, J = 2.8 Hz, 1H), 8.16 (dd, J = 8.9, 2.8 Hz, 3H), 7.67 (dd, J = 7.6, 1.8 Hz, 2H), 7.65 (t, J = 73.0 Hz, 1H), 7.45-7.53 (m, 3H), 7.14 (d, J = 8.9 Hz, 1H). LC-MS (method 2) Rt = 0.93 min MS (ESIpos): m/z = 363.2 [M+H]$^+$ 90 % yield
172	 (4-amino-2-{[6-(trifluoromethyl)pyridin-3-yl]amino}-1,3-thiazol-5-yl)(phenyl)methanone	5-isothiocyanato-2-(trifluoromethyl)pyridine; 2-bromo-1-phenylethanone	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 11.26-11.46 (m, 1H), 8.93 (d, J = 2.5 Hz, 1H), 8.40 (dd, J = 8.5, 2.2 Hz, 1H), 8.25 (br s, 2H), 7.89 (d, J = 8.6 Hz, 1H), 7.67-7.72 (m, 2H), 7.46-7.56 (m, 3H). LC-MS (method 2) Rt = 0.88 min MS (ESIpos): m/z = 365.2 [M+H]$^+$ 69 % yield

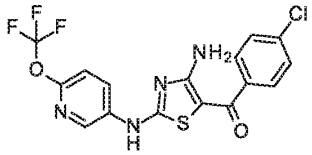
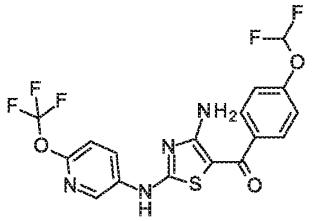
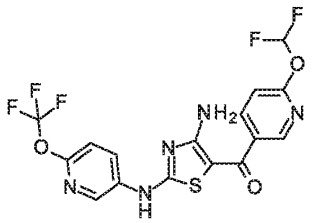
Inter-mediate number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
173	 (4-amino-2-{[6-(difluoromethyl)pyridin-3-yl]amino}-1,3-thiazol-5-yl)(phenyl)methanone	2-(difluoromethyl)-5-isothiocyanatopyridine (Intermediate 203); 2-bromo-1-phenylethanone	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 11.21 (br s, 1H), 8.88 (d, J = 2.3 Hz, 1H), 8.15-8.37 (m, 3H), 7.66-7.72 (m, 3H), 7.46-7.55 (m, 3H), 6.92 (t, J = 55.3 Hz, 1H). LC-MS (method 2) Rt = 0.79 min MS (ESIpos): m/z = 347.2 $[M+H]^+$ 66 % yield
174	 {4-amino-2-[(6-chloropyridin-3-yl)amino]-1,3-thiazol-5-yl}(phenyl)methanone	2-chloro-5-isothiocyanatopyridine; 2-bromo-1-phenylethanone	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 11.09 (br s, 1H), 8.68 (d, J = 2.5 Hz, 1H), 8.12-8.37 (m, 3H), 7.65-7.71 (m, 2H), 7.45-7.55 (m, 4H). LC-MS (method 2) Rt = 0.79 min MS (ESIpos): m/z = 331.2 $[M+H]^+$ 60 % yield
175	 {4-amino-2-[(6-fluoropyridin-3-yl)amino]-1,3-thiazol-5-yl}(phenyl)methanone	2-fluoro-5-isothiocyanatopyridine; 2-bromo-1-phenylethanone	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 10.99 (br s, 1H), 8.52 (dd, J = 2.5, 1.3 Hz, 1H), 7.96-8.46 (m, 3H), 7.65-7.70 (m, 2H), 7.44-7.54 (m, 3H), 7.22 (dd, J = 8.9, 3.0 Hz, 1H). LC-MS (method 2) Rt = 0.79 min MS (ESIpos): m/z = 315.2 $[M+H]^+$ 70 % yield
176	 {4-amino-2-[(6-methylpyridin-3-yl)amino]-1,3-thiazol-5-yl}(phenyl)methanone	5-isothiocyanato-2-methylpyridine; 2-bromo-1-phenylethanone	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 10.83 (br s, 1H), 8.63 (d, J = 2.5 Hz, 1H), 8.03-8.52 (m, 2H), 8.00 (dd, J = 8.4, 2.5 Hz, 1H), 7.63-7.70 (m, 2H), 7.44-7.53 (m, 3H), 7.25 (d, J = 8.4 Hz, 1H), 2.43 (s, 3H). LC-MS (method 2) Rt = 0.81 min MS (ESIpos): m/z = 311.2 $[M+H]^+$ 88 % yield

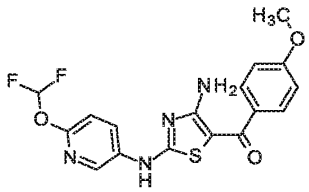
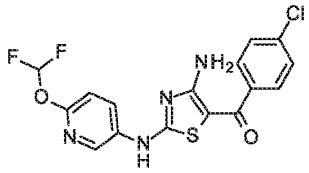
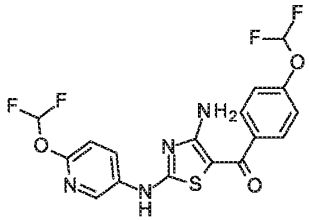
Inter-mediate number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
177	 {4-amino-2-[4-fluoro-3-(trifluoromethoxy)anilino]-1,3-thiazol-5-yl}(phenyl)methanone	1-fluoro-4-isothiocyanato-2-(trifluoromethoxy)benzene (Intermediate 204); 2-bromo-1-phenylethanone	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 11.01 (br s, 1H), 8.09-8.42 (m, 2H), 7.99 (dd, J = 7.1, 1.3 Hz, 1H), 7.66-7.70 (m, 2H), 7.56-7.61 (m, 1H), 7.45-7.55 (m, 4H). LC-MS (method 2) Rt = 1.21 min MS (ESIpos): m/z = 398.2 $[M+H]^+$ 94 % yield
178	 {4-amino-2-[4-chloro-3-(trifluoromethoxy)anilino]-1,3-thiazol-5-yl}(phenyl)methanone	1-chloro-4-isothiocyanato-2-(trifluoromethoxy)benzene; 2-bromo-1-phenylethanone	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 11.12 (br s, 1H), 8.25 (br s, 2H), 8.01 (d, J = 0.8 Hz, 1H), 7.60-7.71 (m, 4H), 7.45-7.55 (m, 3H). LC-MS (method 2) Rt = 1.28 min MS (ESIpos): m/z = 414.2 $[M+H]^+$ 90 % yield
179	 {4-amino-2-[3-(difluoromethoxy)-4-fluoroanilino]-1,3-thiazol-5-yl}(phenyl)methanone	2-(difluoromethoxy)-1-fluoro-4-isothiocyanatobenzene (Intermediate 205); 2-bromo-1-phenylethanone	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 10.91 (br s, 1H), 8.06-8.43 (m, 2H), 7.74 (dd, J = 6.7, 2.2 Hz, 1H), 7.64-7.70 (m, 2H), 7.45-7.53 (m, 4H), 7.37-7.42 (m, 1H), 7.25 (t, J = 73.0 Hz, 1H). LC-MS (method 2) Rt = 1.1 min MS (ESIpos): m/z = 380.2 $[M+H]^+$ 95 % yield
180	 {4-amino-2-[4-chloro-3-(difluoromethoxy)anilino]-1,3-thiazol-5-yl}(phenyl)methanone	1-chloro-2-(difluoromethoxy)-4-isothiocyanatobenzene; 2-bromo-1-phenylethanone	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 11.03 (br s, 1H), 8.23 (br s, 2H), 7.75 (d, J = 2.0 Hz, 1H), 7.65-7.70 (m, 2H), 7.46-7.58 (m, 5H), 7.27 (t, J = 73.0 Hz, 1H). LC-MS (method 2) Rt = 1.12 min MS (ESIpos): m/z = 396.2 $[M+H]^+$ 98 % yield

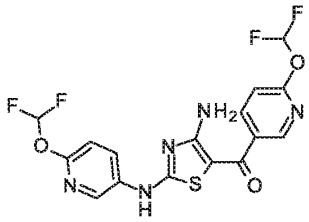
Inter-mediate number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
181	 {4-amino-2-[2-fluoro-4-(trifluoromethoxy)anilino]-1,3-thiazol-5-yl}(phenyl)methanone	2-fluoro-1-isothiocyanato-4-(trifluoromethoxy)benzene (Intermediate 206); 2-bromo-1-phenylethanone	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 10.69 (br s, 1H), 8.25 (br t, J = 9.0 Hz, 3H), 7.63-7.69 (m, 2H), 7.43-7.56 (m, 4H), 7.28 (dd, J = 9.1, 1.0 Hz, 1H). LC-MS (method 2) Rt = 1.02 min MS (ESIpos): m/z = 398.2 $[M+H]^+$ 100 % yield
182	 {4-amino-2-[2-chloro-4-(trifluoromethoxy)anilino]-1,3-thiazol-5-yl}(phenyl)methanone	2-chloro-1-isothiocyanato-4-(trifluoromethoxy)benzene; 2-bromo-1-phenylethanone	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 9.25-9.70 (m, 1H), 8.46 (s, 1H), 7.55-7.68 (m, 3H), 7.32-7.46 (m, 4H), 7.16-7.25 (m, 1H). LC-MS (method 2) Rt = 1.05 min MS (ESIpos): m/z = 414.2 $[M+H]^+$ 45 % yield
183	 {4-amino-2-[4-(difluoromethoxy)-2-fluoroanilino]-1,3-thiazol-5-yl}(phenyl)methanone	4-(difluoromethoxy)-2-fluoro-1-isothiocyanatobenzene (Intermediate 207); 2-bromo-1-phenylethanone	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 10.25-10.79 (m, 1H), 7.90-8.47 (m, 3H), 7.61-7.66 (m, 2H), 7.40-7.50 (m, 4H), 7.24-7.29 (m, 2H), 7.02-7.09 (m, 1H). LC-MS (method 2) Rt = 0.98 min MS (ESIpos): m/z = 380.2 $[M+H]^+$ 100 % yield
184	 {4-amino-2-[2-chloro-4-(difluoromethoxy)anilino]-1,3-thiazol-5-yl}(phenyl)methanone	2-chloro-4-(difluoromethoxy)-1-isothiocyanatobenzene (Intermediate 208); 2-bromo-1-phenylethanone	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 10.43 (br s, 1H), 7.88-8.41 (m, 2H), 7.84 (d, J = 8.6 Hz, 1H), 7.62 (dd, J = 7.6, 1.8 Hz, 2H), 7.41-7.48 (m, 4H), 7.30 (t, J = 73.8 Hz, 1H), 7.21 (dd, J = 8.7, 2.7 Hz, 1H). LC-MS (method 2) Rt = 1.02 min MS (ESIpos): m/z = 396.2 $[M+H]^+$ 99 % yield

Inter-mediate number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
185	 {4-amino-2-[4-(difluoromethyl)anilino]-1,3-thiazol-5-yl}(4-methoxyphenyl)methanone	1-(difluoromethyl)-4-isothiocyanatobenzene; 2-bromo-1-(4-methoxyphenyl)ethanone	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 10.97 (br s, 1H), 8.17 (br s, 2H), 7.77 (d, J = 8.6 Hz, 2H), 7.66-7.71 (m, 2H), 7.56 (d, J = 8.6 Hz, 2H), 7.00-7.05 (m, 2H), 6.98 (t, J = 56.0 Hz, 1H), 3.82 (s, 3H). LC-MS (method 2) Rt = 1.07 min MS (ESIpos): m/z = 376.1 [M+H]$^+$ 88 % yield
186	 {4-amino-2-[4-(difluoromethyl)anilino]-1,3-thiazol-5-yl}(4-chlorophenyl)methanone	1-(difluoromethyl)-4-isothiocyanatobenzene; 2-bromo-1-(4-chlorophenyl)ethanone	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 11.06 (br s, 1H), 8.28 (br s, 2H), 7.75 (br d, J = 8.4 Hz, 2H), 7.68-7.72 (m, 2H), 7.52-7.58 (m, 4H), 6.98 (t, J = 56.0 Hz, 1H). LC-MS (method 2) Rt = 1.11 min MS (ESIpos): m/z = 380.1 [M+H]$^+$ 94 % yield
187	 {4-amino-2-[4-(difluoromethyl)anilino]-1,3-thiazol-5-yl}[4-(difluoromethoxy)phenyl]methanone	1-(difluoromethyl)-4-isothiocyanatobenzene; 2-bromo-1-[4-(difluoromethoxy)phenyl]ethanone	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 11.03 (br s, 1H), 8.24 (br s, 2H), 7.73-7.78 (m, 4H), 7.56 (d, J = 8.6 Hz, 2H), 7.35 (t, J = 73.8 Hz, 1H), 7.24-7.29 (m, 2H), 6.99 (t, J = 56.0 Hz, 1H). LC-MS (method 2) Rt = 1.09 min MS (ESIpos): m/z = 412.1 [M+H]$^+$ 91 % yield

Inter-mediate number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
188	 {4-amino-2-[4-(difluoromethyl)anilino]-1,3-thiazol-5-yl}(pyridin-4-yl)methanone	1-(difluoromethyl)-4-isothiocyanatobenzene; 2-bromo-1-(pyridin-4-yl)ethanone hydrobromide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 10.83-11.29 (m, 1H), 8.67-8.76 (m, 2H), 8.39 (br s, 2H), 7.77 (d, J = 8.6 Hz, 2H), 7.53-7.63 (m, 4H), 6.99 (t, J = 55.8 Hz, 1H). LC-MS (method 2) Rt = 0.72 min MS (ESIpos): m/z = 347.1 $[M+H]^+$ 39 % yield
189	 {4-amino-2-[4-(difluoromethyl)anilino]-1,3-thiazol-5-yl}[6-(difluoromethoxy)pyridin-3-yl]methanone	1-(difluoromethyl)-4-isothiocyanatobenzene; 2-bromo-1-[6-(difluoromethoxy)pyridin-3-yl]ethanone	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 11.10 (br s, 1H), 8.56-8.60 (m, 1H), 8.32 (br s, 2H), 8.18 (dd, J = 8.4, 2.5 Hz, 1H), 7.78 (t, J = 72.5 Hz, 1H), 7.77 (d, J = 8.4 Hz, 2H), 7.57 (d, J = 8.6 Hz, 2H), 7.18-7.22 (m, 1H), 6.99 (t, J = 55.8 Hz, 1H). LC-MS (method 2) Rt = 1.04 min MS (ESIpos): m/z = 413 $[M+H]^+$ 89 % yield
190	 (4-amino-2-{[6-(trifluoromethoxy)pyridin-3-yl]amino}-1,3-thiazol-5-yl)(4-methoxyphenyl)methanone	5-isothiocyanato-2-(trifluoromethoxy)pyridine (Intermediate 201); 2-bromo-1-(4-methoxyphenyl)ethanone	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 11.07 (br s, 1H), 8.67 (d, J = 2.8 Hz, 1H), 8.27 (dd, J = 8.9, 2.8 Hz, 1H), 8.17 (br s, 2H), 7.65-7.71 (m, 2H), 7.34 (d, J = 8.9 Hz, 1H), 7.00-7.05 (m, 2H), 3.82 (s, 3H). LC-MS (method 2) Rt = 0.95 min MS (ESIpos): m/z = 411.2 $[M+H]^+$ 63 % yield

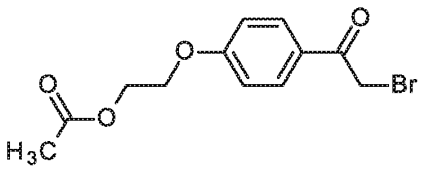
Inter-mediate number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
191	 (4-amino-2-{[6-(trifluoromethoxy)pyridin-3-yl]amino}-1,3-thiazol-5-yl)(4-chlorophenyl)methanone	5-isothiocyanato-2-(trifluoromethoxy)pyridine (Intermediate 201); 2-bromo-1-(4-chlorophenyl)ethanone	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 11.18 (br s, 1H), 8.64 (d, J = 2.5 Hz, 1H), 8.25 (br dd, J = 8.9, 3.0 Hz, 3H), 7.67-7.73 (m, 2H), 7.53-7.58 (m, 2H), 7.33 (d, J = 8.9 Hz, 1H). LC-MS (method 2) Rt = 0.98 min MS (ESIpos): m/z = 415.2 [M+H]$^+$ 68 % yield
192	 (4-amino-2-{[6-(trifluoromethoxy)pyridin-3-yl]amino}-1,3-thiazol-5-yl)[4-(difluoromethoxy)phenyl]methanone	5-isothiocyanato-2-(trifluoromethoxy)pyridine (Intermediate 201); 2-bromo-1-[4-(difluoromethoxy)phenyl]ethanone	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 11.13 (br s, 1H), 8.67 (d, J = 2.8 Hz, 1H), 8.27 (dd, J = 8.9, 2.8 Hz, 3H), 7.72-7.79 (m, 2H), 7.16-7.55 (m, 4H). LC-MS (method 2) Rt = 0.97 min MS (ESIpos): m/z = 447.4 [M+H]$^+$ 90 % yield
193	 (4-amino-2-{[6-(trifluoromethoxy)pyridin-3-yl]amino}-1,3-thiazol-5-yl)[6-(difluoromethoxy)pyridin-3-yl]methanone	5-isothiocyanato-2-(trifluoromethoxy)pyridine (Intermediate 201); 2-bromo-1-[6-(difluoromethoxy)pyridin-3-yl]ethanone	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 11.23 (br s, 1H), 8.65 (d, J = 2.5 Hz, 1H), 8.55-8.59 (m, 1H), 8.21-8.48 (m, 3H), 8.18 (dd, J = 8.6, 2.5 Hz, 1H), 7.78 (t, J = 72.9 Hz, 1H), 7.34 (d, J = 8.9 Hz, 1H), 7.17-7.22 (m, 1H). LC-MS (method 2) Rt = 0.85 min MS (ESIpos): m/z = 448.2 [M+H]$^+$ 70 % yield

Inter-mediate number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
194	 (4-amino-2-{[6-(difluoromethoxy)pyridin-3-yl]amino}-1,3-thiazol-5-yl)(4-methoxyphenyl)methanone	2-(difluoromethoxy)-5-isothiocyanatopyridine (Intermediate 202); 2-bromo-1-(4-methoxyphenyl)ethanone	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 10.91 (s, 1H), 8.57 (d, J = 2.5 Hz, 1H), 8.17 (dd, J = 8.9, 2.8 Hz, 3H), 7.65-7.70 (m, 2H), 7.65 (t, J = 73.0 Hz, 1H), 7.13 (d, J = 8.9 Hz, 1H), 6.99-7.05 (m, 2H), 3.82 (s, 3H). LC-MS (method 2) Rt = 0.94 min MS (ESIpos): m/z = 393.2 [M+H]$^+$ 86 % yield
195	 (4-amino-2-{[6-(difluoromethoxy)pyridin-3-yl]amino}-1,3-thiazol-5-yl)(4-chlorophenyl)methanone	2-(difluoromethoxy)-5-isothiocyanatopyridine (Intermediate 202); 2-bromo-1-(4-chlorophenyl)ethanone	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 11.00 (br s, 1H), 8.52 (d, J = 2.5 Hz, 1H), 8.14 (dd, J = 8.9, 2.8 Hz, 3H), 7.66-7.71 (m, 2H), 7.65 (t, J = 73.3 Hz, 1H), 7.54 (d, J = 8.6 Hz, 2H), 7.12 (d, J = 8.9 Hz, 1H). LC-MS (method 2) Rt = 0.94 min MS (ESIpos): m/z = 397.1 [M+H]$^+$ 82 % yield
196	 (4-amino-2-{[6-(difluoromethoxy)pyridin-3-yl]amino}-1,3-thiazol-5-yl)[4-(difluoromethoxy)phenyl]methanone	2-(difluoromethoxy)-5-isothiocyanatopyridine (Intermediate 202); 2-bromo-1-[4-(difluoromethoxy)phenyl]ethanone	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 8.56-10.12 (m, 1H), 7.70-8.09 (m, 2H), 7.65 (d, J = 8.6 Hz, 2H), 7.57 (t, J = 73.8 Hz, 1H), 7.27 (t, J = 74.1 Hz, 1H), 7.14 (d, J = 8.6 Hz, 2H), 6.88 (d, J = 8.9 Hz, 1H). LC-MS (method 2) Rt = 1.04 min MS (ESIpos): m/z = 429.1 [M+H]$^+$ 87 % yield

Inter-mediate number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
197	 (4-amino-2-{[6-(difluoromethoxy)pyridin-3-yl]amino}-1,3-thiazol-5-yl)[6-(difluoromethoxy)pyridin-3-yl]methanone	2-(difluoromethoxy)-5-isothiocyanatopyridine (Intermediate 202); 2-bromo-1-[6-(difluoromethoxy)pyridin-3-yl]ethanone	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1H NMR (400 MHz, DMSO-d6, 22°C): Shift = 11.04 (br s, 1H), 8.53-8.59 (m, 2H), 8.31 (br s, 2H), 8.14-8.19 (m, 2H), 7.78 (t, J = 72.5 Hz, 1H), 7.65 (t, J = 73.0 Hz, 1H), 7.20 (dd, J = 8.6, 0.8 Hz, 1H), 7.14 (d, J = 8.9 Hz, 1H). LC-MS (method 2) Rt = 0.92 min MS (ESIpos): m/z = 430.4 $[M+H]^+$ 86 % yield

Intermediate 198

2-[4-(2-bromoacetyl)phenoxy]ethyl acetate

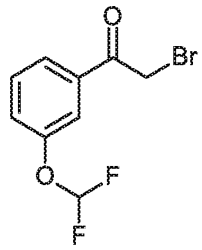


2-(4-acetylphenoxy)ethyl acetate (940 mg, 4.23 mmol) in THF (12.5 mL) at 0°C was treated with phenyl trimethyl ammonium tribromide (1.59 g, 4.23 mmol). The reaction mixture was stirred at rt overnight, diluted with water and extracted three times with dichloromethane. The combined organic phases were washed with brine, filtered through a water repellent filter circle (MN 617 WA) and evaporated to dryness. The crude product was purified by Biotage (method X) to give 237 mg (0.79 mmol, 18 % yield) of the title compound.

LC-MS (method 1): Rt = 1.05 min; MS(ESIpos) m/z = 300.0 $[M+H]^+$

Intermediate 199

2-bromo-1-[3-(difluoromethoxy)phenyl]ethanone

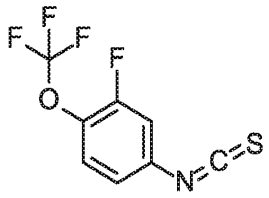


3'-(difluoromethoxy)acetophenone (1 g, 5.37 mmol) in THF (15 mL) at 0°C was treated with phenyl trimethyl ammonium tribromide (2.02 g, 5.37 mmol). The reaction mixture was stirred at rt overnight, diluted with water and extracted three times with ethyl acetate. The combined organic phases were washed with brine, filtered through a water repellent filter circle (MN 617 WA) and evaporated to dryness. The crude product (quant.) was used without further purification.

LC-MS (method 1): Rt = 1.14 min; MS(ESIpos) m/z = 264.9 $[M+H]^+$

Intermediate 200

2-Fluoro-4-isothiocyanato-1-(trifluoromethoxy)benzene

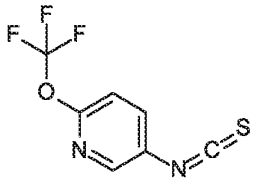
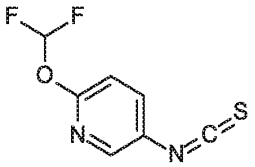
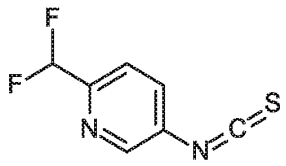


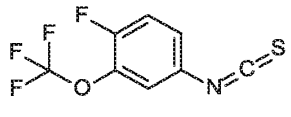
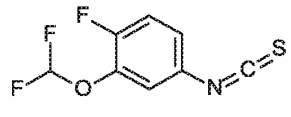
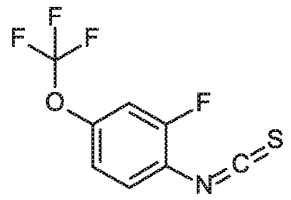
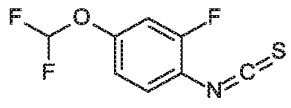
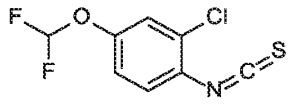
3-fluoro-4-(trifluoromethoxy)aniline (560 mg, 2.81 mmol) was suspended in dichloromethane (12 mL) followed by the addition of triethylamine (1.76 mL, 12.65 mmol). The mixture was cooled to 0 °C and carbonothioyl dichloride (356 mg, 3.09 mmol) diluted in dichloromethane (1.5 mL) was added slowly. After removal of the ice bath the batch was stirred at room temperature for one hour. Water (12 mL) and dichloromethane (7.5 mL) were added, the organic layer was separated, and the aqueous phase was extracted with dichloromethane. The combined organic phases were filtered through a water repellent filter circle (MN 617 WA) and evaporated to dryness. The crude material was purified via Biotage (hexanes/ethyl acetate) to yield 350 mg (1.36 mmol, 48 %) of the title compound.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 7.79 (dd, J = 11.0, 2.4 Hz, 1H), 7.65-7.71 (m, 1H), 7.43 (ddd, J = 8.9, 2.5, 1.5 Hz, 1H).

The following Intermediates were prepared from the starting materials stated in Table 5, below, using the procedure as for 2-fluoro-4-isothiocyanato-1-(trifluoromethoxy)benzene / Intermediate 200.

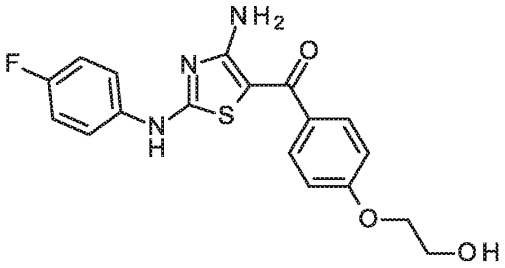
Table 5: Intermediates 201-208

Intermediate number	Chemical structure Compound name	Starting materials	Analytics/yield
201	 5-isothiocyanato-2-(trifluoromethoxy)pyridine	6-(trifluoromethoxy)pyridin-3-amine dihydrochloride; carbonothioyl dichloride	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 8.52 (d, J = 2.8 Hz, 1H), 8.13 (dd, J = 8.7, 2.7 Hz, 1H), 7.39-7.43 (m, 1H). 79 % yield
202	 2-(difluoromethoxy)-5-isothiocyanato-pyridine	6-(difluoromethoxy)pyridin-3-amine; carbonothioyl dichloride	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 8.43 (d, J = 2.8 Hz, 1H), 8.05 (dd, J = 8.7, 2.7 Hz, 1H), 7.69 (t, J = 72.5 Hz, 1H), 7.20 (d, J = 8.9 Hz, 1H). 86 % yield
203	 2-(difluoromethyl)-5-isothiocyanato-pyridine	6-(difluoromethyl)pyridin-3-amine dihydrochloride; carbonothioyl dichloride	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1H NMR (400 MHz, DMSO-d6, 22°C): Shift = 8.78 (d, J = 2.0 Hz, 1H), 8.06 (dd, J = 8.4, 2.3 Hz, 1H), 7.78 (d, J = 8.4 Hz, 1H), 7.00 (t, J = 54.8 Hz, 1H). 77 % yield

Intermediate number	Chemical structure Compound name	Starting materials	Analytics/yield
204	 1-fluoro-4-isothiocyanato-2-(trifluoromethoxy)-benzene	4-fluoro-3-(trifluoromethoxy)aniline; carbonothioyl dichloride	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 7.83-7.88 (m, 1H), 7.59-7.65 (m, 2H). 53 % yield
205	 2-(difluoromethoxy)-1-fluoro-4-isothiocyanato-benzene	3-(difluoromethoxy)-4-fluoroaniline hydrochloride; carbonothioyl dichloride	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 7.60 (dd, J = 7.0, 2.4 Hz, 1H), 7.51 (dd, J = 10.4, 8.9 Hz, 1H), 7.39-7.44 (m, 1H), 7.30 (t, J = 72.8 Hz, 1H). 73 % yield
206	 2-fluoro-1-isothiocyanato-4-(trifluoromethoxy)-benzene	2-fluoro-4-(trifluoromethoxy)aniline; carbonothioyl dichloride	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 7.70 (dd, J = 10.0, 2.4 Hz, 1H), 7.64 (t, J = 8.7 Hz, 1H), 7.33 (ddt, J = 8.9, 2.4, 1.3 Hz, 1H). 35 % yield
207	 4-(difluoromethoxy)-2-fluoro-1-isothiocyanato-benzene	4-(difluoromethoxy)-2-fluoroaniline; carbonothioyl dichloride	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 7.58 (t, J = 8.9 Hz, 1H), 7.43 (dd, J = 11.0, 2.7 Hz, 1H), 7.34 (t, J = 73.3 Hz, 1H), 7.07-7.13 (m, 1H). 70 % yield
208	 2-chloro-4-(difluoromethoxy)-1-isothiocyanato-benzene	2-chloro-4-(difluoromethoxy)aniline; carbonothioyl dichloride	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 7.64 (d, J = 8.9 Hz, 1H), 7.57 (d, J = 2.8 Hz, 1H), 7.34 (t, J = 73.3 Hz, 1H), 7.25 (dd, J = 8.9, 2.8 Hz, 1H). 48 % yield

Intermediate 209

[4-amino-2-(4-fluoroanilino)thiazol-5-yl]-[4-(2-hydroxyethoxy)phenyl]methanone

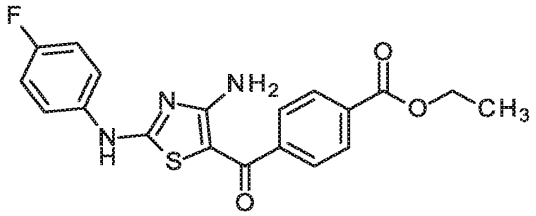


The title compound (36 mg, 0.09 mmol, 11 % yield) was isolated as a byproduct in the formation of 2-(4-{[4-amino-2-(4-fluoroanilino)-1,3-thiazol-5-yl]carbonyl}phenoxy)ethyl acetate (Intermediate 112).

LC-MS (method 2): Rt = 0.90 min; MS(ESIpos) m/z = 374.3 $[M+H]^+$

Intermediate 210

Ethyl 4-[4-amino-2-(4-fluoroanilino)thiazole-5-carbonyl]benzoate



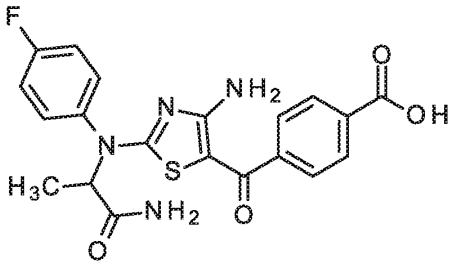
1-fluoro-4-isothiocyanatobenzene (5.65 g, 36.9 mmol) was dissolved in acetonitrile (200 mL) followed by the addition of 1,8-diazabicyclo(5.4.0)undec-7-ene (5.61 g, 36.9 mmol) and cyanamide (1.86 g, 44.3 mmol). After stirring for 45 min at rt, further 1,8-diazabicyclo(5.4.0)undec-7-ene (2.8 g, 18.5 mmol) and ethyl 4-(bromoacetyl)benzoate (10 g, 36.9 mmol) dissolved in acetonitrile (80 mL) were added. The reaction mixture was stirred at rt for 2.5 h and treated with water. The precipitate was filtered off, washed with water and dried in vacuo to give 14.2 g (quant.) of the title compound.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.34 (t, *J*=7.1 Hz, 3 H), 4.34 (d, *J*=7.1 Hz, 3 H), 7.22 (m, 2 H), 7.61 (m, 1 H), 7.78 (d, *J*=8.62 Hz, 2 H), 8.04 (d, *J*=8.62 Hz, 2 H), 8.32 (m, 2 H), 10.87 (br s, 1 H).

LC-MS (method 2): Rt = 1.10 min; MS(ESIpos) m/z = 386.3 $[M+H]^+$

Intermediate 211

rac-4-[(4-amino-2-{[(2RS)-1-amino-1-oxopropan-2-yl](4-fluorophenyl)amino}-1,3-thiazol-5-yl)carbonyl]benzoic acid

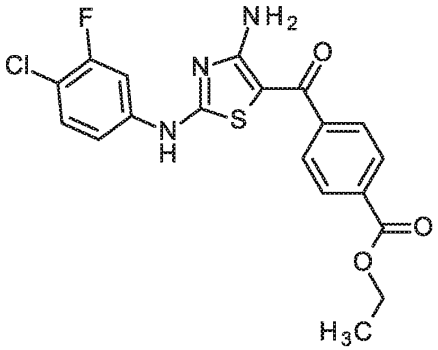


rac-Ethyl 4-[4-amino-2-(N-(2-amino-1-methyl-2-oxo-ethyl)-4-fluoro-anilino)thiazole-5-carbonyl]benzoate (15.47 g, 33 mmol, Example 257) was suspended in THF (150 mL) and treated with 1M aqueous sodium hydroxide (43 mL, 43 mmol). The reaction mixture was stirred overnight followed by the addition of 1M aqueous hydrochloric acid up to pH 3. The solution was extracted three times with ethyl acetate. The combined organic phases were washed with brine, filtered through a water repellent filter circle (MN 617 WA) and evaporated to dryness to give 11.63 g (25 mmol, 87 % yield) of the title compound.

LC-MS (method 2): Rt = 0.53 min; MS(ESIpos) m/z = 429.4 $[M+H]^+$

Intermediate 212

Ethyl 4-[4-amino-2-(4-chloro-3-fluoro-anilino)thiazole-5-carbonyl]benzoate



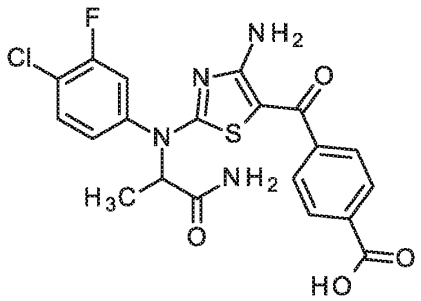
1-chloro-2-fluoro-4-isothiocyanatobenzene (692 mg, 3.7 mmol) was dissolved in acetonitrile (20 mL) followed by the addition of 1,8-diazabicyclo(5.4.0)undec-7-ene (561.5 mg, 3.68 mmol) and cyanamide (186 mg, 4.43 mmol). After stirring for 45 min at rt, further 1,8-

diazabicyclo(5.4.0)undec-7-ene (280.75 mg, 1.84 mmol) and ethyl 4-(bromoacetyl)benzoate (1 g, 3.7 mmol) dissolved in acetonitrile (14 mL) were added. The reaction mixture was stirred 2 h at rt. The suspension was treated with water and the precipitate was isolated by filtration, washed with water and some ethyl acetate and dried in vacuo to give 1.24 g (2.52 mmol, 68 %, purity 85 %) of the title compound.

LC-MS (method 2): Rt = 1.12 min; MS(ESIpos) m/z = 420.2 $[M+H]^+$

Intermediate 213

rac-4-[4-amino-2-(N-(2-amino-1-methyl-2-oxo-ethyl)-4-chloro-3-fluoro-anilino)thiazole-5-carbonyl]benzoic acid

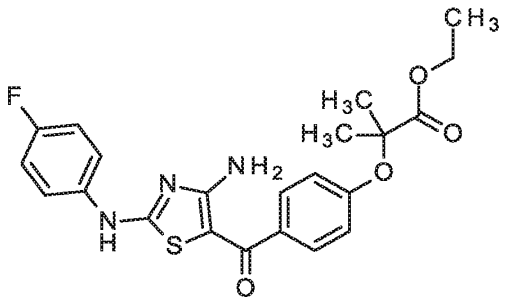


rac-Ethyl 4-[4-amino-2-(N-(2-amino-1-methyl-2-oxo-ethyl)-4-chloro-3-fluoro-anilino)thiazole-5-carbonyl]benzoate (830 mg, 1.7 mmol, Example 258) was suspended in THF (10 mL) and treated with 2M aqueous sodium hydroxide (8.5 mL, 17 mmol). The reaction mixture was stirred at room temperature overnight followed by the addition of 2M aqueous hydrochloric acid up to pH 3. The precipitate was filtered off, washed with water and dried in vacuo to yield 680 mg (1.47 mmol, 88 %) of the title compound.

LC-MS (method 1): Rt = 1.07 min; MS(ESIpos) m/z = 463.1 $[M+H]^+$

Intermediate 214

Ethyl 2-[4-[4-amino-2-(4-fluoroanilino)thiazole-5-carbonyl]phenoxy]-2-methyl-propanoate



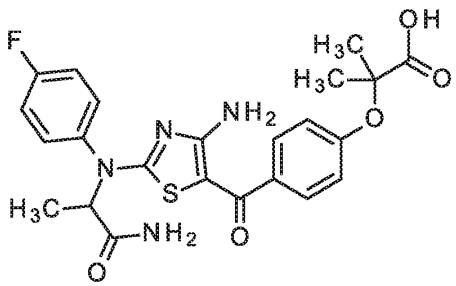
1-fluoro-4-isothiocyanatobenzene (349 mg, 2.28 mmol) was dissolved in acetonitrile (8 mL) followed by the addition of 1,8-diazabicyclo(5.4.0)undec-7-ene (346 mg, 2.28 mmol) and cyanamide (115 mg, 2.7 mmol). After stirring for 45 min at rt, further 1,8-diazabicyclo(5.4.0)undec-7-ene (173 mg, 1.14 mmol) and ethyl 2-[4-(2-bromoacetyl)phenoxy]-2-methyl-propanoate (750 mg, 2.28 mmol) dissolved in acetonitrile (4 mL) were added. The reaction mixture was stirred overnight at rt. The suspension was treated with water and the precipitate was isolated by filtration, washed with water and dried in vacuo to give 1.01 g (2.28 mmol, 70 %) of the title compound.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.15 (t, *J*=7.1 Hz, 3 H), 1.57 (s, 6 H), 4.17 (q, *J*=7.1 Hz, 2 H), 6.80 (m, 2 H), 7.15 (m, 2 H), 7.50 (m, 2 H), 7.59 (m, 2 H), 8.12 (m, 2 H), 10.51 (m, 1 H).

LC-MS (method 2): Rt = 1.24 min; MS(ESIpos) m/z = 444.3 $[M+H]^+$

Intermediate 215

rac-2-[4-[4-amino-2-(N-(2-amino-1-methyl-2-oxo-ethyl)-4-fluoro-anilino)thiazole-5-carbonyl]phenoxy]-2-methyl-propanoic acid



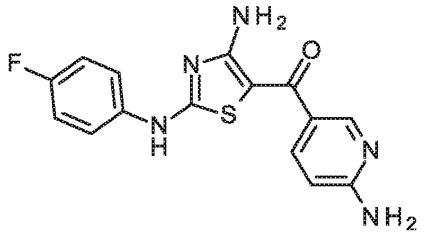
Rac-Ethyl 2-[4-[4-amino-2-(N-(2-amino-1-methyl-2-oxo-ethyl)-4-fluoro-anilino)thiazole-5-carbonyl]phenoxy]-2-methyl-propanoate (925 mg, 1.79 mmol, Example 259) was suspended in THF (10 mL) and treated with 1M aqueous sodium hydroxide (2.7 mL, 2.7 mmol). The reaction mixture was stirred at room temperature overnight followed by the addition of 1M aqueous hydrochloric acid up to pH 3. The reaction mixture was extracted three times with ethyl acetate. The combined organic phases were washed with brine, filtered through a water repellent filter circle (MN 617 WA) and evaporated to dryness to yield 861 mg (1.6 mmol, 91 %) of the title compound.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.16 (d, J=7.35 Hz, 3 H), 1.52 (s, 6 H), 5.06 (m, 1 H), 6.76 (m, 2 H), 7.24 (s, 1 H), 7.33 (t, J=8.74 Hz, 2 H), 7.45 (m, 2 H), 7.57 (s, 1 H), 7.64 (m, 2 H), 8.10 (m, 2 H), 13.15 (m, 1 H).

LC-MS (method 2): Rt = 0.63 min; MS(ESIpos) m/z = 487.4 $[M+H]^+$

Intermediate 216

[4-amino-2-(4-fluoroanilino)thiazol-5-yl]-(6-amino-3-pyridyl)methanone



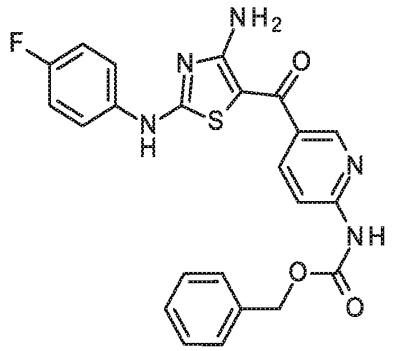
1-fluoro-4-isothiocyanatobenzene (250 mg, 1.63 mmol) was dissolved in acetonitrile (8 mL) followed by the addition of 1,8-diazabicyclo(5.4.0)undec-7-ene (248.5 mg, 1.63 mmol) and cyanamide (82 mg, 1.96 mmol). After stirring for 45 min at rt, further 1,8-diazabicyclo(5.4.0)undec-7-ene (124.2 mg, 0.82 mmol) and 1-(6-amino-3-pyridyl)-2-bromo-ethanone (351 mg, 1.63 mmol) dissolved in acetonitrile (7 mL) were added. The reaction mixture was stirred 2.5 h at rt. The suspension was treated with water and the precipitate was isolated by filtration, washed with water and dried in vacuo to give 350 mg (1.05 mmol, 64 %) of the title compound.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 4.65 (s, 2 H), 6.96 (d, J=9.63 Hz, 1 H), 7.03 (d, J=9.38 Hz, 2 H), 8.24 (m, 3 H), 8.62 (d, J=2.28 Hz, 2 H), 8.82 (d, J=2.28 Hz, 1 H).

LC-MS (method 2): Rt = 0.82 min; MS(ESIpos) m/z = 330.2 $[M+H]^+$

Intermediate 217

Benzyl N-[5-[4-amino-2-(4-fluoroanilino)thiazole-5-carbonyl]-2-pyridyl]carbamate

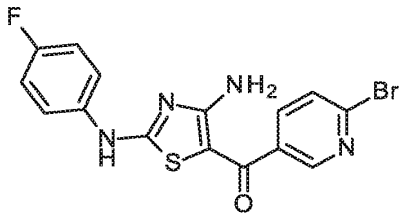


[4-amino-2-(4-fluoroanilino)thiazol-5-yl]-(6-amino-3-pyridyl)methanone (205 mg, 0.62 mmol, Intermediate 216) was suspended in THF (5 mL) and treated with benzyl carbonochloridate (106 mg, 0.62 mmol) and triethylamine (94 mg, 0.93 mmol). The reaction mixture was stirred overnight at rt followed by the addition of further benzyl carbonochloridate (106 mg, 0.62 mmol), triethylamine (94 mg, 0.93 mmol) and DMAP (1 mg). After 4.5 h water was added and the reaction mixture was extracted three times with ethyl acetate. The combined organic phases were washed with brine, filtered through a water repellent filter circle (MN 617 WA) and evaporated to dryness. The residue was purified via Biotage chromatography (method Y) to yield 25 mg (0.05 mmol, 9 %) of the title compound.

LC-MS (method 2): Rt = 1.11 min; MS(ESIpos) m/z = 464.3 $[M+H]^+$

Intermediate 218

[4-amino-2-(4-fluoroanilino)-1,3-thiazol-5-yl](6-bromopyridin-3-yl)methanone



1-fluoro-4-isothiocyanatobenzene (1.29 g, 8.43 mmol) was dissolved in acetonitrile (65 mL) followed by the addition of 1,8-diazabicyclo(5.4.0)undec-7-ene (1.28 g, 8.43 mmol) and cyanamide (0.43 g, 10.1 mmol). After stirring for 45 min at rt, further 1,8-

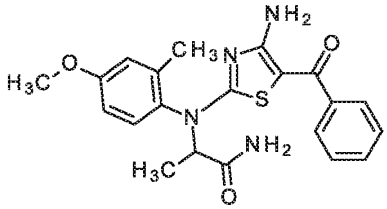
diazabicyclo(5.4.0)undec-7-ene (0.64 g, 4.2 mmol) and 2-bromo-1-(6-bromo-3-pyridyl)ethanone (2.35 g, 8.43 mmol) dissolved in acetonitrile (15 mL) were added. The reaction mixture was stirred at rt overnight and treated with water. The precipitate was filtered off, washed with water and dried in vacuo to give 2.52 g (6.4 mmol, 76 %) of the title compound.

LC-MS (method 2): Rt = 0.95 min; MS(ESIpos) m/z = 395.1 $[M+H]^+$

EXPERIMENTAL SECTION – PREPARATION OF EXAMPLE COMPOUNDS

Example 1

rac-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-4-methoxy-2-methyl-anilino)propanamide



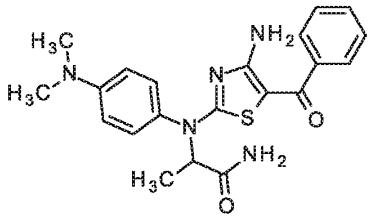
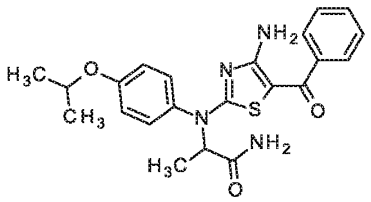
[4-amino-2-(4-methoxy-2-methyl-anilino)thiazol-5-yl]-phenyl-methanone (100 mg, 0.295 mmol; Intermediate 4) were dissolved in N,N-dimethylformamide (3 mL) followed by the addition of potassium carbonate (407 mg, 2.95 mmol) and rac-2-bromopropanamide (224 mg, 1.47 mmol). The reaction mixture was stirred at 90°C for 2 h. The reaction mixture was filtrated and purified by RP-HPLC (method D, basic) to give 57 mg (47 % yield) of the title compound.

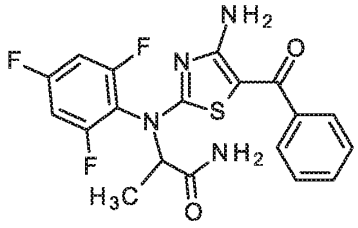
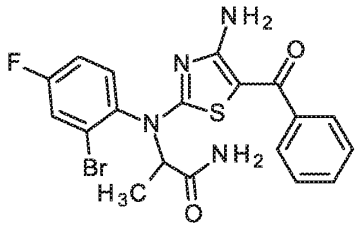
^{1}H-NMR: (400 MHz, DMSO-*d6*): δ ppm = 1.03 (d, *J*=7.35 Hz, 3 H), 2.13 (s, 3 H), 3.75 - 3.78 (m, 3 H), 4.93 - 5.13 (m, 1 H), 6.85 - 6.93 (m, 2 H), 7.17 - 7.24 (m, 1 H), 7.34 - 7.42 (m, 3 H), 7.42 - 7.50 (m, 2 H), 7.54 (br s, 1 H), 7.64 (d, *J*=8.62 Hz, 1 H), 7.73 - 8.60 (m, 2 H).

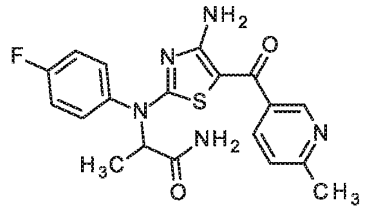
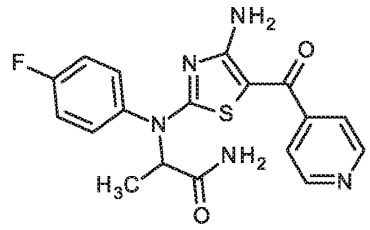
LC-MS (method 2) Rt = 1.08 min; MS (ESIpos): m/z = 411.5 $[M+H]^+$

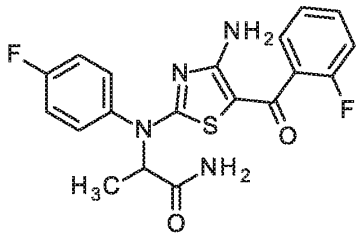
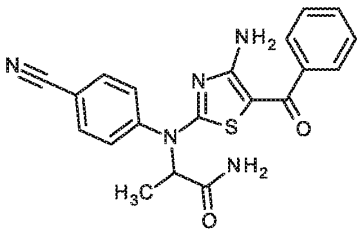
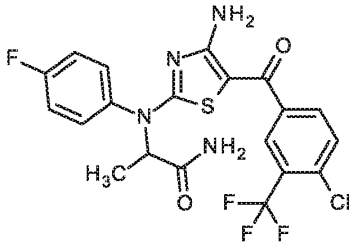
The following examples were prepared from the starting materials stated in Table 6, below, using the procedure as for Example 1.
The crude product was either purified by RP-HPLC (methods A-D depending on polarity) or by preparative flash chromatography (methods X, Y or Z depending on polarity) after precipitation, extraction or filtration of the reaction mixture if necessary.
Enantiomers were separated from their racemate by chiral HPLC using the column and solvent conditions stated.

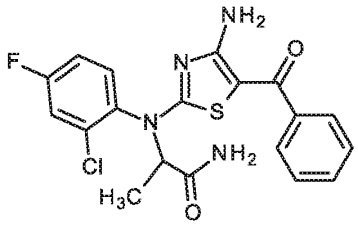
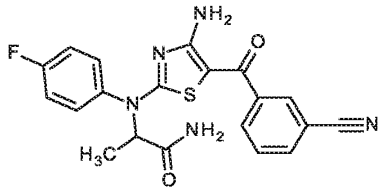
Table 6: Examples 2 - 80

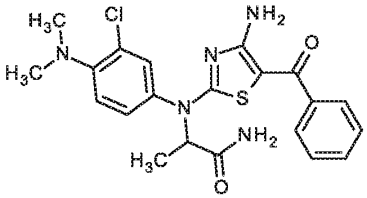
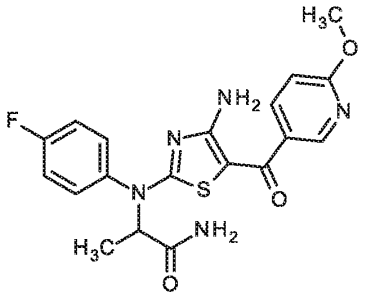
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
2	 rac-2-[N-(4-amino-5-benzoyl-thiazol-2-yl)-4-(dimethylamino)anilino]propanamide	Intermediate 5; rac-2-bromopropanamide	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.14 (d, *J*=7.35 Hz, 3 H), 2.93 (s, 6 H), 5.06 (br d, *J*=6.08 Hz, 1 H), 6.70 (d, *J*=9.38 Hz, 2 H), 7.15 - 7.20 (m, 1 H), 7.28 (d, *J*=8.87 Hz, 2 H), 7.34 - 7.41 (m, 3 H), 7.43 - 7.50 (m, 3 H), 7.74 - 8.53 (m, 2 H). LC-MS (method 2) Rt = 1.11 min; MS (ESIpos): m/z = 410.6 $[M+H]^+$ RP-HPLC (method D, basic) 51 % yield
3	 rac-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-4-isopropoxy-anilino)propanamide	Intermediate 6; rac-2-bromopropanamide	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.15 (d, *J*=7.35 Hz, 3 H), 1.27 (d, *J*=6.08 Hz, 6 H), 4.62 (spt, *J*=6.04 Hz, 1 H), 5.01 - 5.11 (m, 1 H), 6.96 (d, *J*=9.12 Hz, 2 H), 7.21 (s, 1 H), 7.35 - 7.49 (m, 7 H), 7.52 (s, 1 H), 7.75 - 8.51 (m, 2 H). LC-MS (method 1) Rt = 1.18 min; MS (ESIpos): m/z = 425.7 $[M+H]^+$ RP-HPLC (method D, basic) 42 % yield

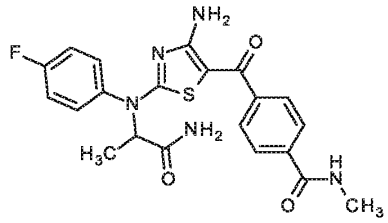
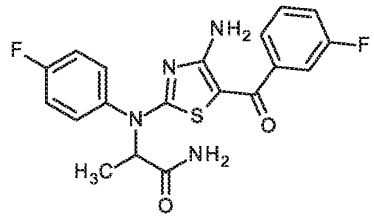
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
4	 rac-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-2,4,6-trifluoro-anilino)propanamide	Intermediate 7; rac-2-bromopropanamide	^{1}H-NMR (500 MHz, DMSO-*d6*): δ ppm = 1.32 (d, *J*=6.99 Hz, 3 H), 4.95 (q, *J*=6.57 Hz, 1 H), 7.04 - 7.11 (m, 1 H), 7.33 (br s, 2 H), 7.39 - 7.48 (m, 4 H), 7.56 (dd, *J*=7.79, 1.75 Hz, 2 H), 7.96 (br s, 2 H) LC-MS (method 2) Rt = 1.08 min; MS (ESIpos): m/z = 421.5 $[M+H]^+$ RP-HPLC (method D, basic) preparative flash chromatography (method X, 40-100%) 33 % yield
5	 rac-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-2-bromo-4-fluoro-anilino)propanamide	Intermediate 8; rac-2-bromopropanamide	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.03 - 1.15 (m, 3 H), 4.98 - 5.13 (m, 1 H), 7.21 - 7.34 (m, 1 H), 7.34 - 7.55 (m, 6 H), 7.57 - 7.87 (m, 2 H), 7.90 - 8.49 (m, 3 H). LC-MS (method 2) Rt = 1.11 min; MS (ESIpos): m/z = 463.2 $[M+H]^+$ RP-HPLC (method D, basic) 83 % yield

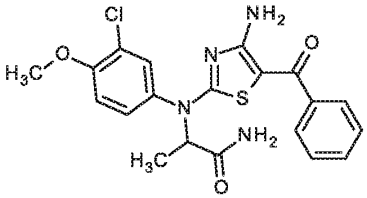
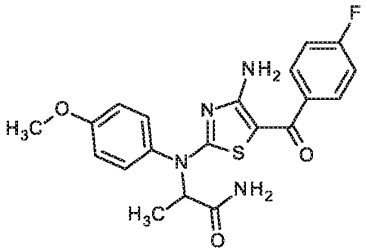
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
6	 rac-2-(N-[4-amino-5-(6-methylpyridine-3-carbonyl)thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 9; rac-2-bromopropanamide	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.16 (d, *J*=7.60 Hz, 3 H), 2.45 (s, 3 H), 5.00 - 5.11 (m, 1 H), 7.24 - 7.28 (m, 2 H), 7.33 (t, *J*=8.87 Hz, 2 H), 7.59 (s, 1 H), 7.62 - 7.67 (m, 2 H), 7.74 (dd, *J*=8.11, 2.28 Hz, 1 H), 7.97 - 8.46 (m, 2 H), 8.54 (d, *J*=2.03 Hz, 1 H). LC-MS (method 2) Rt = 0.93 min; MS (ESIpos): m/z = 400.4 $[M+H]^+$ RP-HPLC (method C, basic) 59 % yield
7	 rac-2-(N-[4-amino-5-(pyridine-4-carbonyl)thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 10; rac-2-bromopropanamide	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.16 (d, *J*=7.60 Hz, 3 H), 5.06 (br d, *J*=7.10 Hz, 1 H), 7.26 (s, 1 H), 7.33 (t, *J*=8.74 Hz, 2 H), 7.38 - 7.42 (m, 2 H), 7.59 (s, 1 H), 7.61 - 7.67 (m, 2 H), 8.10 - 8.50 (m, 2 H), 8.59 - 8.64 (m, 2 H). LC-MS (method 2) Rt = 0.85 min; MS (ESIpos): m/z = 386.3 $[M+H]^+$ RP-HPLC (method C, acidic) 17 % yield

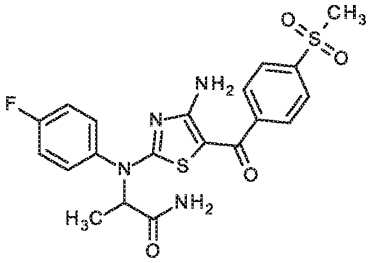
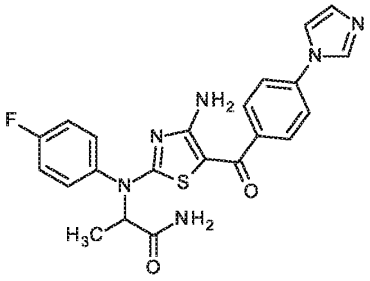
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
8	 rac-2-(N-[4-amino-5-(2-fluorobenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 11; rac-2-bromopropanamide	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.14 (d, *J*=7.35 Hz, 3 H), 4.89 - 5.13 (m, 1 H), 7.15 - 7.34 (m, 7 H), 7.40 (tdd, *J*=7.73, 7.73, 5.58, 1.77 Hz, 1 H), 7.53 - 7.66 (m, 3 H), 8.09 (br s, 2 H). LC-MS (method 1) Rt = 1.05 min; MS (ESIpos): m/z = 403.4 $[M+H]^+$ RP-HPLC (method D, basic) 71 % yield
9	 rac-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-4-cyano-anilino)propanamide	Intermediate 12; rac-2-bromopropanamide	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.18 (d, *J*=7.35 Hz, 3 H), 5.05 (q, *J*=7.69 Hz, 1 H), 7.31 (s, 1 H), 7.36 - 7.43 (m, 3 H), 7.48 - 7.52 (m, 2 H), 7.64 (s, 1 H), 7.81 (d, *J*=8.62 Hz, 2 H), 8.16 (br s, 2 H), 7.99 (d, *J*=8.36 Hz, 2 H). LC-MS (method 1) Rt = 0.99 min; MS (ESIpos): m/z = 392.3 $[M+H]^+$ RP-HPLC (method C, basic) 8 % yield
10	 rac-2-(N-[4-amino-5-[4-chloro-3-(trifluoromethyl)benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 13; rac-2-bromopropanamide	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.16 (d, *J*=7.35 Hz, 3 H), 5.01 - 5.14 (m, 1 H), 7.27 (s, 1 H), 7.34 (t, *J*=8.87 Hz, 2 H), 7.59 (s, 1 H), 7.62 - 7.67 (m, 2 H), 7.77 (s, 2 H), 7.89 - 7.91 (m, 1 H), 8.08 - 8.64 (m, 2 H). LC-MS (method 2) Rt = 1.30 min; MS (ESIpos): m/z = 487.2 $[M+H]^+$ RP-HPLC (method D, basic) 22 % yield

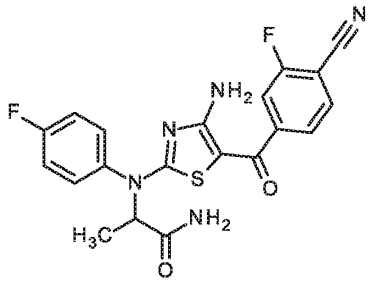
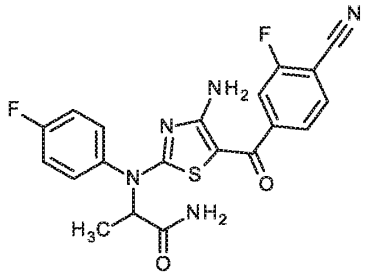
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
11	 rac-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-2-chloro-4-fluoro-anilino)propanamide	Intermediate 14; rac-2-bromopropanamide	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.09 (d, *J*=7.35 Hz, 3 H), 4.98 - 5.21 (m, 1 H), 7.26 - 7.34 (m, 1 H), 7.36 - 7.55 (m, 6 H), 7.59 - 7.76 (m, 2 H), 7.89 - 8.45 (m, 2 H), 8.03 (dd, *J*=8.87, 5.83 Hz, 1 H). LC-MS (method 2) Rt = 1.13 min; MS (ESIpos): m/z = 419.4 $[M+H]^+$ RP-HPLC (method D, basic) 48 % yield
12	 rac-2-(N-[4-amino-5-(3-cyanobenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 15; rac-2-bromopropanamide	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.16 (d, *J*=7.35 Hz, 3 H), 5.01 - 5.10 (m, 1 H), 7.24 - 7.28 (m, 1 H), 7.33 (t, *J*=8.87 Hz, 2 H), 7.57 - 7.66 (m, 4 H), 7.78 (dt, *J*=7.79, 1.30 Hz, 1 H), 7.86 - 7.89 (m, 2 H), 8.25 (br s, 2 H). LC-MS (method 2) Rt = 1.02 min; MS (ESIpos): m/z = 410.3 $[M+H]^+$ RP-HPLC (method C, basic) 31 % yield

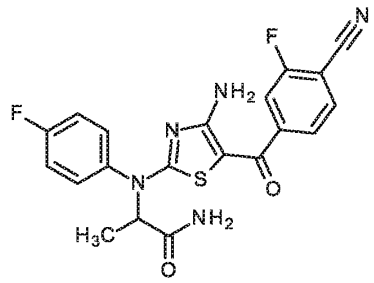
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
13	 rac-2-[N-(4-amino-5-benzoyl-thiazol-2-yl)-3-chloro-4-(dimethylamino)anilino]propanamide	Intermediate 16; rac-2-bromopropanamide	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.16 (d, *J*=7.35 Hz, 3 H), 2.77 (s, 6 H), 4.99 - 5.09 (m, 1 H), 7.18 (d, *J*=8.62 Hz, 1 H), 7.22 - 7.27 (m, 1 H), 7.35 - 7.46 (m, 4 H), 7.47 - 7.52 (m, 2 H), 7.57 (s, 1 H), 7.63 (d, *J*=2.28 Hz, 1 H), 8.16 (br s, 2 H). LC-MS (method 2) Rt = 0.91 min; MS (ESIpos): m/z = 444.5 $[M+H]^+$ RP-HPLC (method C, basic) 51 % yield
14	 rac-2-(N-[4-amino-5-(6-methoxypyridine-3-carbonyl)thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 17; rac-2-bromopropanamide	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.16 (d, *J*=7.60 Hz, 3 H), 3.85 (s, 3 H), 5.01 - 5.11 (m, 1 H), 6.83 (dd, *J*=8.62, 0.51 Hz, 1 H), 7.24 - 7.28 (m, 1 H), 7.34 (t, *J*=8.87 Hz, 2 H), 7.59 (s, 1 H), 7.62 - 7.68 (m, 2 H), 7.82 (dd, *J*=8.62, 2.53 Hz, 1 H), 8.17 (br s, 2 H), 8.33 (d, *J*=2.03 Hz, 1 H). LC-MS (method 2) Rt = 1.02 min; MS (ESIpos): m/z = 416.4 $[M+H]^+$ RP-HPLC (method C, basic) 43 % yield

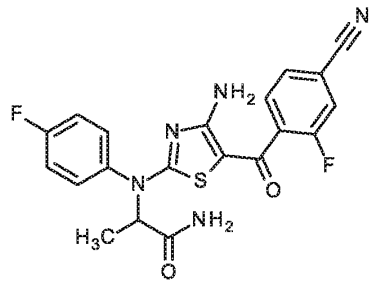
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
15	 rac-4-[4-amino-2-(N-[2-amino-1-methyl-2-oxo-ethyl]-4-fluoro-anilino)thiazole-5-carbonyl]-N-methyl-benzamide	Intermediate 18; rac-2-bromopropanamide	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.16 (d, *J*=7.35 Hz, 3 H), 2.75 (d, *J*=4.56 Hz, 3 H), 4.99 - 5.12 (m, 1 H), 7.25 (s, 1 H), 7.32 (t, *J*=8.87 Hz, 2 H), 7.53 (d, *J*=8.36 Hz, 2 H), 7.58 (br s, 1 H), 7.60 - 7.66 (m, 2 H), 7.78 (d, *J*=8.36 Hz, 2 H), 8.17 (br s, 2 H), 8.46 (q, *J*=4.48 Hz, 1 H). LC-MS (method 2) Rt = 0.85 min; MS (ESIpos): m/z = 442.5 $[M+H]^+$ RP-HPLC (method C, basic) 10 % yield
16	 rac-2-(N-[4-amino-5-(3-fluorobenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 19; rac-2-bromopropanamide	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.16 (d, *J*=7.35 Hz, 3 H), 4.98 - 5.17 (m, 1 H), 7.22 - 7.29 (m, 3 H), 7.29 - 7.36 (m, 3 H), 7.39 - 7.48 (m, 1 H), 7.58 (s, 1 H), 7.64 (dd, *J*=8.62, 5.07 Hz, 2 H), 7.97 - 8.59 (m, 2 H). LC-MS (method 1) Rt = 1.10 min; MS (ESIpos): m/z = 403.3 $[M+H]^+$ RP-HPLC (method D, basic) 68 % yield

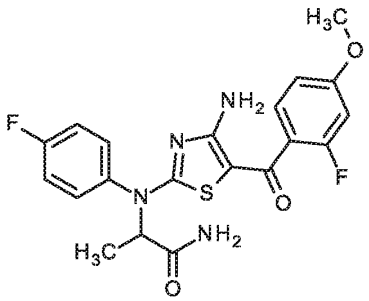
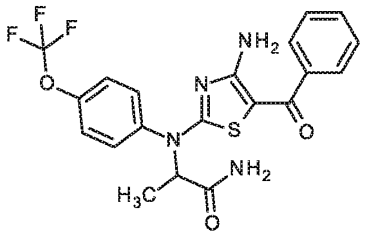
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
17	 rac-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-3-chloro-4-methoxy-anilino)propanamide	Intermediate 20; rac-2-bromopropanamide	^{1}H-NMR (400 MHz, DMSO-d_6): δ ppm = 1.16 (d, *J*=7.35 Hz, 3 H), 3.89 (s, 3 H), 4.96 - 5.10 (m, 1 H), 7.22 (d, *J*=8.87 Hz, 1 H), 7.25 (s, 1 H), 7.35 - 7.43 (m, 3 H), 7.46 - 7.54 (m, 3 H), 7.59 (s, 1 H), 7.71 (d, *J*=2.53 Hz, 1 H), 7.87 - 8.37 (m, 2 H). LC-MS (method 2) Rt = 1.10 min; MS (ESIpos): m/z = 431.3 $[M+H]^+$ RP-HPLC (method D, basic) 60 % yield
18	 rac-2-(N-[4-amino-5-(4-fluorobenzoyl)thiazol-2-yl]-4-methoxy-anilino)propanamide	Intermediate 21; rac-2-bromopropanamide	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.14 (d, *J*=7.35 Hz, 3 H), 3.78 (s, 3 H), 5.01 - 5.10 (m, 1 H), 7.01 (d, *J*=9.13 Hz, 2 H), 7.17 - 7.24 (m, 3 H), 7.46 (d, *J*=8.62 Hz, 2 H), 7.51 - 7.58 (m, 3 H), 8.09 (br s, 2 H). LC-MS (method 1) Rt = 1.08 min; MS (ESIpos): m/z = 415.6 $[M+H]^+$ RP-HPLC (method C, acidic) 36 % yield

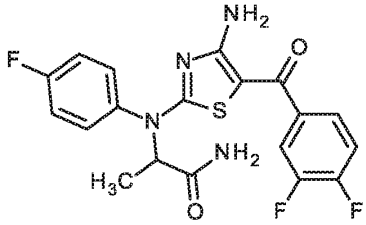
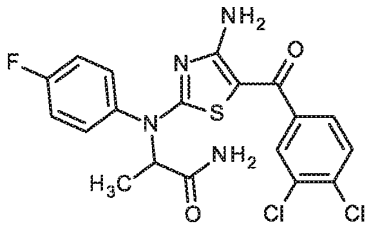
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
19	 rac-2-(N-[4-amino-5-(4-methylsulfonylbenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 22; rac-2-bromopropanamide	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.16 (d, *J*=7.35 Hz, 3 H), 3.23 (s, 3 H), 4.96 - 5.15 (m, 1 H), 7.26 (s, 1 H), 7.33 (t, *J*=8.74 Hz, 2 H), 7.59 (s, 1 H), 7.64 (dd, *J*=8.87, 5.07 Hz, 2 H), 7.70 (d, *J*=8.36 Hz, 2 H), 7.93 (d, *J*=8.62 Hz, 2 H), 8.04 - 8.56 (m, 2 H). LC-MS (method 1) Rt = 0.91 min; MS (ESIpos): m/z = 463.4 $[M+H]^+$ RP-HPLC (method C, basic) 31 % yield
20	 rac-2-(N-[4-amino-5-(4-imidazol-1-ylbenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 23; rac-2-bromopropanamide	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.16 (d, *J*=7.35 Hz, 3 H), 5.00 - 5.13 (m, 1 H), 7.10 (s, 1 H), 7.26 (s, 1 H), 7.34 (t, *J*=8.74 Hz, 2 H), 7.56 - 7.73 (m, 7 H), 7.78 (t, *J*=1.27 Hz, 1 H), 7.88 - 8.62 (m, 2 H), 8.30 (s, 1 H). LC-MS (method 1) Rt = 0.70 min; MS (ESIpos): m/z = 451.5 $[M+H]^+$ RP-HPLC (method C, basic) 68 % yield

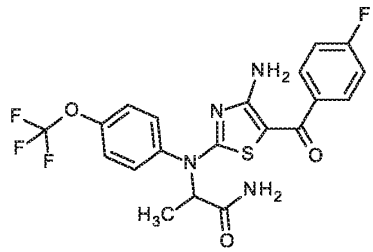
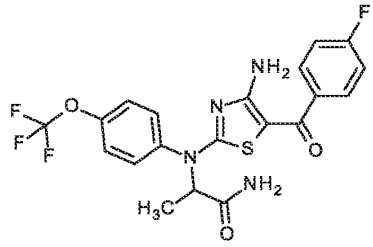
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
21	 rac-2-(N-[4-amino-5-(4-cyano-3-fluoro-benzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 24; rac-2-bromopropanamide	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.15 (d, *J*=7.35 Hz, 3 H), 5.01 - 5.11 (m, 1 H), 7.25 (s, 1 H), 7.33 (t, *J*=8.87 Hz, 2 H), 7.45 (dd, *J*=7.86, 1.27 Hz, 1 H), 7.55 (dd, *J*=9.89, 1.27 Hz, 1 H), 7.58 - 7.66 (m, 3 H), 7.93 (dd, *J*=7.86, 6.59 Hz, 1 H), 8.11 - 8.52 (m, 2 H). LC-MS (method 1) Rt = 1.08 min; MS (ESIpos): m/z = 428.3 $[M+H]^+$ RP-HPLC (method C, basic) 5 % yield
21.1 and **21.2**	(R)-2-(N-[4-amino-5-(4-cyano-3-fluoro-benzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide and (S)-2-(N-[4-amino-5-(4-cyano-3-fluoro-benzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide		
21.1	 2-(N-[4-amino-5-(4-cyano-3-fluoro-benzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide (enantiomer 1)	Example 21	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.15 (d, *J*=7.35 Hz, 3 H), 5.01 - 5.11 (m, 1 H), 7.25 (s, 1 H), 7.33 (t, *J*=8.87 Hz, 2 H), 7.45 (dd, *J*=7.86, 1.27 Hz, 1 H), 7.55 (dd, *J*=9.89, 1.27 Hz, 1 H), 7.58 - 7.66 (m, 3 H), 7.93 (dd, *J*=7.86, 6.59 Hz, 1 H), 8.11 - 8.52 (m, 2 H). LC-MS (method 1) Rt = 1.07 min; MS (ESIpos): m/z = 428.3 $[M+H]^+$ RP-HPLC (method C, basic) 8 % yield

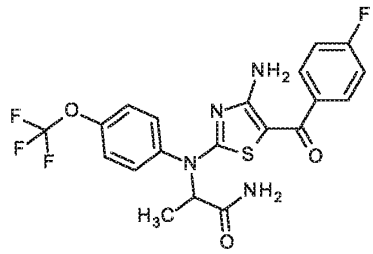
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
Chiral HPLC Example 21.1 HPLC separation of rac-2-(N-[4-amino-5-(4-cyano-3-fluoro-benzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide (Example 21, 106 mg. 0.25 mmol) on a chiral column followed by another preparative HPLC gave 9.2 mg (8 % yield) of 2-(N-[4-amino-5-(4-cyano-3-fluoro-benzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, enantiomer 1. Preparative chiral HPLC Instrument: PrepCon Labomatic HPLC; Column: YMC Cellulose SB 5µ, 250x30; eluent A: hexane + 0.1 vol % diethylamine; eluent B: ethanol + 0.1 vol % diethylamine; isocratic: 80%A+20%B; flow: 50 mL/min; temperature: 25°C; UV: 254 nm Analytical chiral HPLC: Rt = 5.46 min Instrument: Waters Alliance 2695; Column: YMC Cellulose SB 3µ, 100x4.6; eluent A: hexane + 0.1 vol % diethylamine; eluent B: ethanol; isocratic: 80%A+20%B; flow: 1.4 mL/min; temperature: 25°C; UV: 254 nm			
21.2	 2-(N-[4-amino-5-(4-cyano-3-fluoro-benzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide (enantiomer 2)	Example 21	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.15 (d, *J*=7.35 Hz, 3 H), 5.01 - 5.11 (m, 1 H), 7.25 (s, 1 H), 7.33 (t, *J*=8.87 Hz, 2 H), 7.45 (dd, *J*=7.86, 1.27 Hz, 1 H), 7.55 (dd, *J*=9.89, 1.27 Hz, 1 H), 7.58 - 7.66 (m, 3 H), 7.93 (dd, *J*=7.86, 6.59 Hz, 1 H), 8.11 - 8.52 (m, 2 H). LC-MS (method 1) Rt = 1.07 min; MS (ESIpos): m/z = 428.3 $[M+H]^+$ RP-HPLC (method C, basic) 7 % yield

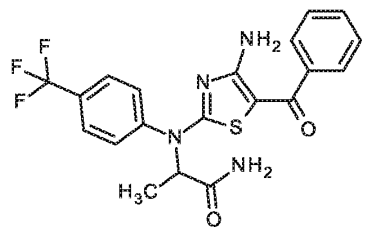
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
Chiral HPLC Example 21.2 HPLC separation of rac-2-(N-[4-amino-5-(4-cyano-3-fluoro-benzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide (Example 21, 106 mg. 0.25 mmol) on a chiral column followed by another preparative HPLC gave 7 mg (6 % yield) of 2-(N-[4-amino-5-(4-cyano-3-fluoro-benzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, enantiomer 2. Preparative chiral HPLC Instrument: PrepCon Labomatic HPLC; Column: YMC Cellulose SB 5µ, 250x30; eluent A: hexane + 0.1 vol % diethylamine; eluent B: ethanol + 0.1 vol % diethylamine; isocratic: 80%A+20%B; flow: 50 mL/min; temperature: 25°C; UV: 254 nm Analytical chiral HPLC: Rt = 7.71 min Instrument: Waters Alliance 2695; Column: YMC Cellulose SB 3µ, 100x4.6; eluent A: hexane + 0.1 vol % diethylamine; eluent B: ethanol; isocratic: 80%A+20%B; flow: 1.4 mL/min; temperature: 25°C; UV: 254 nm			
22	 rac-2-(N-[4-amino-5-(4-cyano-2-fluoro-benzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 25; rac-2-bromopropanamide	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.16 (d, *J*=7.35 Hz, 3 H), 5.01 - 5.11 (m, 1 H), 7.27 (s, 1 H), 7.34 (t, *J*=8.87 Hz, 2 H), 7.45 (dd, *J*=8.11, 1.27 Hz, 1 H), 7.56 (dd, *J*=9.76, 1.14 Hz, 1 H), 7.59 (s, 1 H), 7.64 (dd, *J*=8.74, 4.94 Hz, 2 H), 7.92 - 7.97 (m, 1 H), 8.18 - 8.50 (m, 2 H). LC-MS (method 1) Rt = 1.07 min; MS (ESIpos): m/z = 428.3 $[M+H]^+$ RP-HPLC (method D, basic) 40 % yield

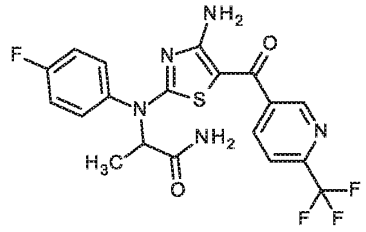
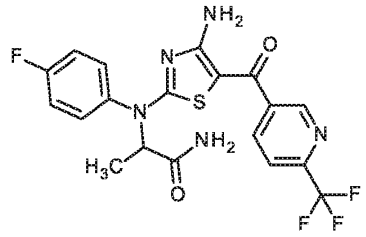
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
23	 rac-2-(N-[4-amino-5-(2-fluoro-4-methoxy-benzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 26; rac-2-bromopropanamide	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.14 (d, *J*=7.60 Hz, 3 H), 3.75 (s, 3 H), 4.98 - 5.09 (m, 1 H), 6.76 (d, *J*=20.28 Hz, 1 H), 6.78 (br d, *J*=23.32 Hz, 1 H), 7.22 - 7.27 (m, 2 H), 7.31 (t, *J*=8.87 Hz, 2 H), 7.57 (s, 1 H), 7.59 - 7.64 (m, 2 H), 8.03 (br s, 2 H). LC-MS (method 2) Rt = 1.06 min; MS (ESIpos): m/z = 433.4 $[M+H]^+$ RP-HPLC (method D, basic) 47 % yield
24	 rac-2-[N-(4-amino-5-benzoyl-thiazol-2-yl)-4-(trifluoromethoxy)anilino]propanamide	Intermediate 27; rac-2-bromopropanamide	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.17 (d, *J*=7.35 Hz, 3 H), 5.05 (q, *J*=7.18 Hz, 1 H), 7.28 (s, 1 H), 7.36 - 7.42 (m, 3 H), 7.45 - 7.52 (m, 4 H), 7.61 (s, 1 H), 7.69 - 7.75 (m, 2 H), 8.16 (br s, 2 H). LC-MS (method 2) Rt = 1.20 min; MS (ESIpos): m/z = 451.5 $[M+H]^+$ RP-HPLC (method D, basic) 49 % yield

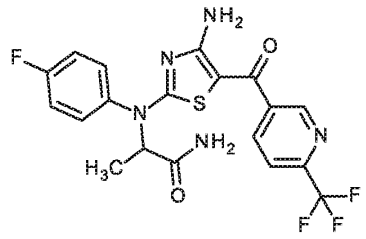
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
25	 rac-2-(N-[4-amino-5-(3,4-difluorobenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 28; rac-2-bromopropanamide	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.16 (d, *J*=7.35 Hz, 3 H), 5.02 - 5.10 (m, 1 H), 7.26 (s, 1 H), 7.34 (t, *J*=8.62 Hz, 3 H), 7.41 - 7.49 (m, 1 H), 7.52 (ddd, *J*=11.15, 7.98, 2.15 Hz, 1 H), 7.58 (s, 1 H), 7.62 - 7.66 (m, 2 H), 7.98 - 8.50 (m, 2 H). LC-MS (method 2) Rt = 1.14 min; MS (ESIpos): m/z = 419.3 $[M+H]^+$ RP-HPLC (method D, basic) 30 % yield
26	 rac-2-(N-[4-amino-5-(3,4-dichlorobenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 29, rac-2-bromopropanamide	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.16 (d, *J*=7.35 Hz, 3 H), 5.00 - 5.11 (m, 1 H), 7.26 (s, 1 H), 7.34 (t, *J*=8.74 Hz, 2 H), 7.44 (dd, *J*=8.36, 2.03 Hz, 1 H), 7.57 - 7.61 (m, 1 H), 7.62 - 7.66 (m, 2 H), 7.67 (d, *J*=11.66 Hz, 1 H), 7.67 (d, *J*=1.27 Hz, 1 H), 8.03 - 8.48 (m, 2 H). LC-MS (method 2) Rt = 1.24 min; MS (ESIpos): m/z = 453.1 [M+H]+ RP-HPLC (method D, basic) 38 % yield

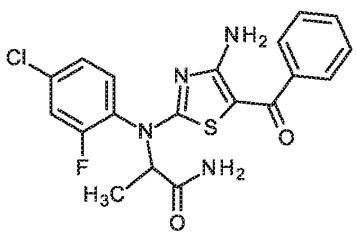
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
27	 rac-2-[N-[4-amino-5-(4-fluorobenzoyl)thiazol-2-yl]-4-(trifluoromethoxy)anilino]propanamide	Intermediate 30; rac-2-bromopropanamide	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.15 - 1.19 (m, 3 H), 5.02 - 5.09 (m, 1 H), 7.22 (t, *J*=8.87 Hz, 2 H), 7.28 (s, 1 H), 7.50 (d, *J*=8.11 Hz, 2 H), 7.56 (dd, *J*=8.62, 5.58 Hz, 2 H), 7.61 (s, 1 H), 7.73 (d, *J*=9.13 Hz, 2 H), 7.90 - 8.49 (m, 2 H). LC-MS (method 2) Rt = 1.23 min; MS (ESIpos): m/z = 469.3 $[M+H]^+$ 59 % yield
27.1 and **27.2**	(R)-2-[N-[4-amino-5-(4-fluorobenzoyl)thiazol-2-yl]-4-(trifluoromethoxy)anilino]propanamide and (S)-2-[N-[4-amino-5-(4-fluorobenzoyl)thiazol-2-yl]-4-(trifluoromethoxy)anilino]propanamide		
27.1	 2-[N-[4-amino-5-(4-fluorobenzoyl)thiazol-2-yl]-4-(trifluoromethoxy)anilino]propanamide (enantiomer 1)	Example 27	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.17 (d, *J*=7.35 Hz, 3 H), 5.05 (q, *J*=7.27 Hz, 1 H), 7.22 (t, *J*=9.00 Hz, 2 H), 7.28 (s, 1 H), 7.48 - 7.53 (m, 2 H), 7.53 - 7.59 (m, 2 H), 7.61 (s, 1 H), 7.70 - 7.75 (m, 2 H), 7.95 - 8.42 (m, 2 H). LC-MS (method 1) Rt = 1.23 min; MS (ESIpos): m/z = 469.3 $[M+H]^+$ 39 % yield

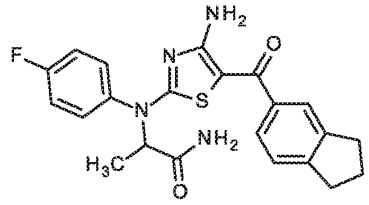
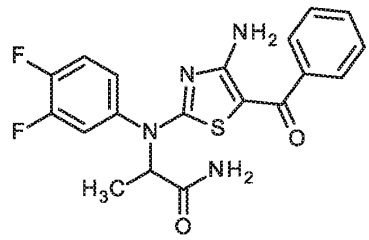
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
Chiral HPLC Example 27.1 HPLC separation of rac-2-[N-[4-amino-5-(4-fluorobenzoyl)thiazol-2-yl]-4-(trifluoromethoxy)anilino]propanamide (1130 mg, 2.4 mmol; Example 27) on a chiral column gave 448 mg (39 % yield) of 2-[N-[4-amino-5-(4-fluorobenzoyl)thiazol-2-yl]-4-(trifluoromethoxy)anilino]propanamide, enantiomer 1. Preparative chiral HPLC Instrument: PrepCon Labomatic HPLC; Column: YMC Cellulose SB 5µ, 250x30; eluent A: hexane + 0.1 vol % diethylamine; eluent B: ethanol + 0.1 vol % diethylamine; isocratic: 80%A+20%B; flow: 60 mL/min; temperature: 25°C; UV: 254 nm Analytical chiral HPLC: Rt = 2.99 min Instrument: Waters Alliance 2695; Column: YMC Cellulose SB 3µ, 100x4.6; eluent A: hexane + 0.1 vol % diethylamine; eluent B: ethanol; isocratic: 80%A+20%B; flow: 1.4 mL/min; temperature: 25°C; UV: 254 nm			
27.2	 2-[N-[4-amino-5-(4-fluorobenzoyl)thiazol-2-yl]-4-(trifluoromethoxy)anilino]propanamide (enantiomer 2)	Example 27	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.17 (d, *J*=7.60 Hz, 3 H), 5.05 (br d, *J*=7.10 Hz, 1 H), 7.19 - 7.25 (m, 2 H), 7.28 (s, 1 H), 7.47 - 7.53 (m, 2 H), 7.53 - 7.59 (m, 2 H), 7.59 - 7.63 (m, 1 H), 7.70 - 7.76 (m, 2 H), 7.96 - 8.40 (m, 2 H). LC-MS (method 1) Rt = 1.23 min; MS (ESIpos): m/z = 469.2 $[M+H]^+$ 37 % yield

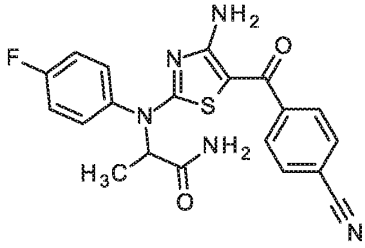
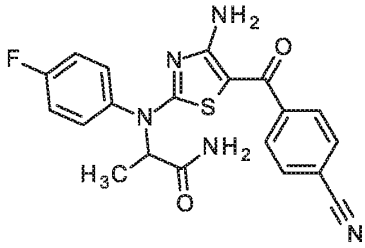
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
Chiral HPLC Example 27.2 HPLC separation of rac-2-[N-[4-amino-5-(4-fluorobenzoyl)thiazol-2-yl]-4-(trifluoromethoxy)anilino]propanamide (1130 mg, 2.4 mmol; Example 27) on a chiral column gave 430 mg (37 % yield) of 2-[N-[4-amino-5-(4-fluorobenzoyl)thiazol-2-yl]-4-(trifluoromethoxy)anilino]propanamide, enantiomer 2. Preparative chiral HPLC Instrument: PrepCon Labomatic HPLC; Column: YMC Cellulose SB 5µ, 250x30; eluent A: hexane + 0.1 vol % diethylamine; eluent B: ethanol + 0.1 vol % diethylamine; isocratic: 80%A+20%B; flow: 60 mL/min; temperature: 25°C; UV: 254 nm Analytical chiral HPLC: Rt = 3.81 min Instrument: Waters Alliance 2695; Column: YMC Cellulose SB 3µ, 100x4.6; eluent A: hexane + 0.1 vol % diethylamine; eluent B: ethanol; isocratic: 80%A+20%B; flow: 1.4 mL/min; temperature: 25°C; UV: 254 nm			
28	 rac-2-[N-(4-amino-5-benzoyl-thiazol-2-yl)-4-(trifluoromethyl)anilino]propanamide	Intermediate 31; rac-2-bromopropanamide	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.18 (d, *J*=7.35 Hz, 3 H), 5.06 (q, *J*=7.52 Hz, 1 H), 7.30 (s, 1 H), 7.36 - 7.44 (m, 3 H), 7.47 - 7.52 (m, 2 H), 7.63 (s, 1 H), 7.80 - 7.91 (m, 4 H), 8.18 (br s, 2 H). LC-MS (method 1) Rt = 1.18 min; MS (ESIpos): m/z = 435.3 $[M+H]^+$ RP-HPLC (method D, basic) 29 % yield

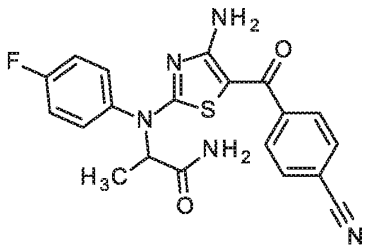
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
29	 rac-2-(N-[4-amino-5-[6-(trifluoromethyl)pyridine-3-carbonyl]thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 32; rac-2-bromopropanamide	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.16 (d, *J*=7.60 Hz, 3 H), 5.02 - 5.13 (m, 1 H), 7.25 (s, 1 H), 7.30 - 7.38 (m, 2 H), 7.60 (s, 1 H), 7.64 (dd, *J*=8.87, 5.07 Hz, 2 H), 7.94 (d, *J*=7.86 Hz, 1 H), 8.12 (dd, *J*=8.11, 1.77 Hz, 1 H), 8.23 - 8.46 (m, 2 H), 8.84 (br d, *J*=1.80 Hz, 1 H). LC-MS (method 1) Rt = 1.13 min; MS (ESIpos): m/z = 454.5 $[M+H]^+$ RP-HPLC (method C, basic) 42 % yield
29.1 and **29.2**	(R)-2-(N-[4-amino-5-[6-(trifluoromethyl)pyridine-3-carbonyl]thiazol-2-yl]-4-fluoro-anilino)propanamide and (S)-2-(N-[4-amino-5-[6-(trifluoromethyl)pyridine-3-carbonyl]thiazol-2-yl]-4-fluoro-anilino)propanamide		
29.1	 2-(N-[4-amino-5-[6-(trifluoromethyl)pyridine-3-carbonyl]thiazol-2-yl]-4-fluoro-anilino)propanamide (enantiomer 1)	Example 29	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.16 (d, *J*=7.35 Hz, 3 H), 5.00 - 5.16 (m, 1 H), 7.27 (s, 1 H), 7.33 (t, *J*=8.74 Hz, 2 H), 7.58 - 7.69 (m, 3 H), 7.93 (d, *J*=8.11 Hz, 1 H), 8.11 (br d, *J*=1.77 Hz, 1 H), 8.17 - 8.50 (m, 2 H), 8.84 (d, *J*=1.27 Hz, 1 H). LC-MS (method 1) Rt = 1.13 min; MS (ESIpos): m/z = 454.5 $[M+H]^+$ $[\alpha]_D^{20}$ = +53.2° (c = 1.00, dimethylsulfoxide) 13 % yield

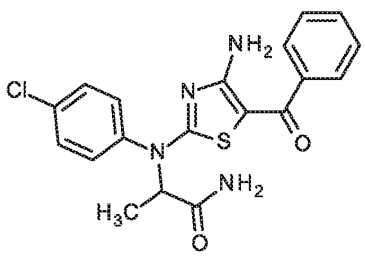
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
Chiral HPLC Example 29.1 HPLC separation of rac-2-(N-[4-amino-5-[6-(trifluoromethyl)pyridine-3-carbonyl]thiazol-2-yl]-4-fluoro-anilino)propanamide (394 mg, 1.0 mmol; Example 29) on a chiral column gave 163 mg (33 % yield) of 2-(N-[4-amino-5-[6-(trifluoromethyl)pyridine-3-carbonyl]thiazol-2-yl]-4-fluoro-anilino)propanamide, enantiomer 1. Preparative chiral HPLC Instrument: PrepCon Labomatic HPLC; Column: YMC Cellulose SB 10µ, 250x50; eluent A: hexane + 0.1 vol % diethylamine; eluent B: 2-propanol + 0.1 vol % diethylamine; isocratic: 60%A+40%B; flow: 140 mL/min; temperature: 25°C; UV: 254 nm Analytical chiral HPLC: Rt = 2.24 min Instrument: Waters Alliance 2695; Column: YMC Cellulose SB 3µ, 100x4.6; eluent A: hexane + 0.1 vol % diethylamine; eluent B: 2-propanol; isocratic: 60%A+40%B; flow: 1.4 mL/min; temperature: 25°C; UV: 254 nm			
29.2	 2-(N-[4-amino-5-[6-(trifluoromethyl)pyridine-3-carbonyl]thiazol-2-yl]-4-fluoro-anilino)propanamide (enantiomer 2)	Example 29	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.17 (d, *J*=7.35 Hz, 3 H), 5.01 - 5.17 (m, 1 H), 7.28 (s, 1 H), 7.33 (t, *J*=8.74 Hz, 2 H), 7.54 - 7.72 (m, 3 H), 7.93 (d, *J*=8.11 Hz, 1 H), 8.12 (dd, *J*=8.11, 1.77 Hz, 1 H), 8.21 - 8.54 (m, 2 H), 8.84 (d, *J*=1.27 Hz, 1 H). LC-MS (method 1) Rt = 1.12 min; MS (ESIpos): m/z = 454.5 $[M+H]^+$ $[\alpha]_D^{20}$ = -44.3° (c = 1.00, dimethylsulfoxide) 13 % yield

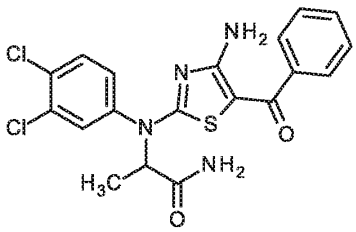
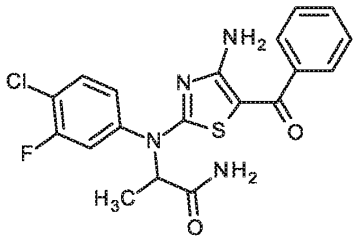
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
Chiral HPLC Example 29.2 HPLC separation of rac-2-(N-[4-amino-5-[6-(trifluoromethyl)pyridine-3-carbonyl]thiazol-2-yl]-4-fluoro-anilino)propanamide (394 mg, 1.0 mmol; Example 29) on a chiral column gave 164 mg (33 % yield) of 2-(N-[4-amino-5-[6-(trifluoromethyl)pyridine-3-carbonyl]thiazol-2-yl]-4-fluoro-anilino)propanamide, enantiomer 2. Preparative chiral HPLC Instrument: PrepCon Labomatic HPLC; Column: YMC Cellulose SB 10µ, 250x50; eluent A: hexane + 0.1 vol % diethylamine; eluent B: 2-propanol + 0.1 vol % diethylamine; isocratic: 60%A+40%B; flow: 140 mL/min; temperature: 25°C; UV: 254 nm Analytical chiral HPLC: Rt = 3.26 min Instrument: Waters Alliance 2695; Column: YMC Cellulose SB 3µ, 100x4.6; eluent A: hexane + 0.1 vol % diethylamine; eluent B: 2-propanol; isocratic: 60%A+40%B; flow: 1.4 mL/min; temperature: 25°C; UV: 254 nm			
30	 rac-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-4-chloro-2-fluoro-anilino)propanamide	Intermediate 33; rac-2-bromopropanamide	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.11 - 1.22 (m, 3 H), 4.92 - 5.22 (m, 1 H), 7.28 - 7.36 (m, 1 H), 7.39 - 7.54 (m, 6 H), 7.59 - 7.76 (m, 2 H), 7.79 - 7.93 (m, 1 H), 7.97 - 8.32 (m, 2 H). LC-MS (method 1) Rt = 1.16 min; MS (ESIpos): m/z = 417.2 $[M+H]^+$ RP-HPLC (method D, basic) 37 % yield

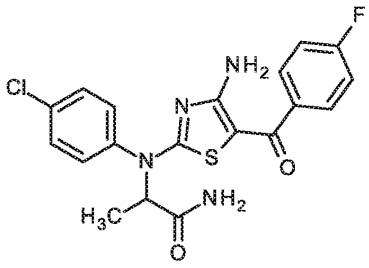
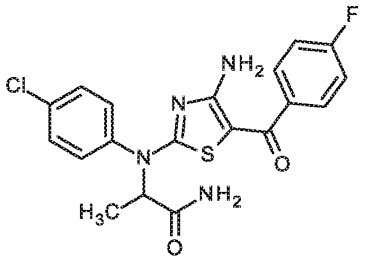
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
31	 rac-2-(N-[4-amino-5-(indane-5-carbonyl)thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 34; rac-2-bromopropanamide	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.15 (d, *J*=7.35 Hz, 3 H), 1.98 (quin, *J*=7.41 Hz, 2 H), 2.82 (td, *J*=7.29, 4.18 Hz, 4 H), 5.04 (br q, *J*=6.67 Hz, 1 H), 7.18 - 7.23 (m, 2 H), 7.24 (s, 1 H), 7.29 - 7.35 (m, 3 H), 7.56 - 7.59 (m, 1 H), 7.60 - 7.65 (m, 2 H), 7.80 - 8.40 (m, 2 H). LC-MS (method 2) Rt = 1.23 min; MS (ESIpos): m/z = 425.6 $[M+H]^+$ RP-HPLC (method D, basic) 24 % yield
32	 rac-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-3,4-difluoro-anilino)propanamide	Intermediate 35; rac-2-bromopropanamide	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.18 (d, *J*=7.35 Hz, 3 H), 5.02 (q, *J*=7.69 Hz, 1 H), 7.29 (s, 1 H), 7.36 - 7.44 (m, 3 H), 7.47 - 7.53 (m, 3 H), 7.54 - 7.60 (m, 1 H), 7.61 - 7.65 (m, 1 H), 7.77 (ddd, *J*=11.47, 7.54, 2.28 Hz, 1 H), 8.15 (br s, 2 H). LC-MS (method 1) Rt = 1.11 min; MS (ESIpos): m/z = 403.3 $[M+H]^+$ RP-HPLC (method C, basic) 48 % yield

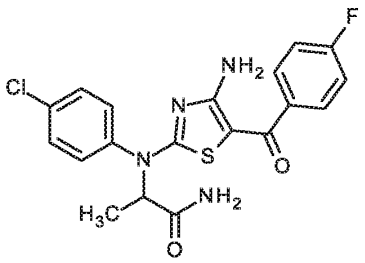
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
33	 rac-2-(N-[4-amino-5-(4-cyanobenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 36; rac-2-bromopropanamide	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.16 (d, *J*=7.35 Hz, 3 H), 4.90 - 5.24 (m, 1 H), 7.23 - 7.29 (m, 1 H), 7.33 (t, *J*=8.74 Hz, 2 H), 7.59 (s, 1 H), 7.60 - 7.66 (m, 4 H), 7.86 (d, *J*=8.36 Hz, 2 H), 8.05 - 8.57 (m, 2 H). LC-MS (method 2) Rt = 1.02 min; MS (ESIpos): m/z = 410.3 $[M+H]^+$ RP-HPLC (method C, basic) 78 % yield
33.1 and **33.2**	(R)-2-(N-[4-amino-5-(4-cyanobenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide and (S)-2-(N-[4-amino-5-(4-cyanobenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide		
33.1	 2-(N-[4-amino-5-(4-cyanobenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide (enantiomer 1)	Example 33	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.16 (d, *J*=7.35 Hz, 3 H), 5.02 - 5.11 (m, 1 H), 7.24 - 7.28 (m, 1 H), 7.33 (t, *J*=8.74 Hz, 2 H), 7.58 (s, 1 H), 7.61 - 7.66 (m, 4 H), 7.86 (d, *J*=8.62 Hz, 2 H), 8.05 - 8.50 (m, 2 H). LC-MS (method 2) Rt = 1.02 min; MS (ESIpos): m/z = 410.3 $[M+H]^+$ $[\alpha]_D^{20}$ = +93.9° (c = 1.00, dimethylsulfoxide) 31 % yield

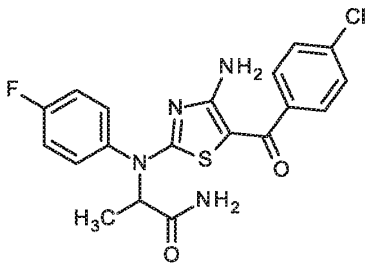
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
Chiral HPLC Example 33.1 HPLC separation of rac-2-(N-[4-amino-5-(4-cyanobenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide (96 mg, 0.23 mmol; Example 33) on a chiral column gave 30 mg (30 % yield) of 2-(N-[4-amino-5-(4-cyanobenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, enantiomer 1. Preparative chiral HPLC Instrument: PrepCon Labomatic HPLC; Column: YMC Cellulose SB 10µ, 250x50; eluent A: hexane + 0.1 vol % diethylamine; eluent B: ethanol; isocratic: 60%A+40%B; flow: 150 mL/min; temperature: 25°C; UV: 254 nm Analytical chiral HPLC: Rt = 2.26 min Instrument: Waters Alliance 2695; Column: YMC Cellulose SB 3µ, 100x4.6; eluent A: hexane + 0.1 vol % diethylamine; eluent B: ethanol; isocratic: 60%A+40%B; flow: 1.4 mL/min; temperature: 25°C; UV: 254 nm			
33.2	 2-(N-[4-amino-5-(4-cyanobenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide (enantiomer 2)	Example 33	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.16 (d, *J*=7.60 Hz, 3 H), 5.01 - 5.12 (m, 1 H), 7.26 (s, 1 H), 7.33 (t, *J*=8.87 Hz, 2 H), 7.58 (s, 1 H), 7.63 (d, *J*=8.36 Hz, 4 H), 7.86 (d, *J*=8.36 Hz, 2 H), 8.05 - 8.53 (m, 2 H). LC-MS (method 2) Rt = 1.02 min; MS (ESIpos): m/z = 410.3 $[M+H]^+$ $[\alpha]_D^{20}$ = -89.9° (c = 1.00, dimethylsulfoxide) 30 % yield

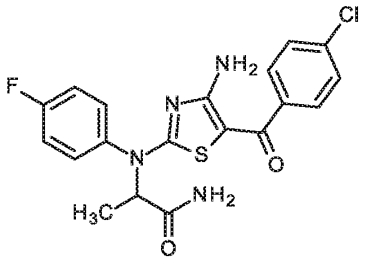
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
Chiral HPLC Example 33.2 HPLC separation of rac-2-(N-[4-amino-5-(4-cyanobenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide (96 mg, 0.23 mmol; Example 33) on a chiral column gave 32 mg (31 % yield) of 2-(N-[4-amino-5-(4-cyanobenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, enantiomer 2. Preparative chiral HPLC Instrument: PrepCon Labomatic HPLC; Column: YMC Cellulose SB 10µ, 250x50; eluent A: hexane + 0.1 vol % diethylamine; eluent B: ethanol; isocratic: 60%A+40%B; flow: 150 mL/min; temperature: 25°C; UV: 254 nm Analytical chiral HPLC: Rt = 3.05 min Instrument: Waters Alliance 2695; Column: YMC Cellulose SB 3µ, 100x4.6; eluent A: hexane + 0.1 vol % diethylamine; eluent B: ethanol; isocratic: 60%A+40%B; flow: 1.4 mL/min; temperature: 25°C; UV: 254 nm			
34	 rac-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-4-chloro-anilino)propanamide	Intermediate 37; rac-2-bromopropanamide	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.16 (d, *J*=7.35 Hz, 3 H), 5.05 (q, *J*=7.18 Hz, 1 H), 7.26 (s, 1 H), 7.35 - 7.42 (m, 3 H), 7.47 - 7.50 (m, 2 H), 7.54 - 7.63 (m, 5 H), 8.16 (br s, 2 H). LC-MS (method 2) Rt = 1.15 min; MS (ESIpos): m/z = 402.2 $[M+H]^+$ RP-HPLC (method D, basic) 9 % yield

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
35	 rac-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-3,4-dichloro-anilino)propanamide	Intermediate 38; rac-2-bromopropanamide	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.19 (d, *J*=7.35 Hz, 3 H), 5.01 (q, *J*=7.18 Hz, 1 H), 7.31 (s, 1 H), 7.37 - 7.45 (m, 3 H), 7.49 - 7.54 (m, 2 H), 7.62 (dd, *J*=8.90, 2.53 Hz, 1 H), 7.64 (s, 1 H), 7.79 (d, *J*=8.36 Hz, 1 H), 7.95 (d, *J*=2.28 Hz, 1 H), 8.24 (br s, 2 H). LC-MS (method 1) Rt = 1.23 min; MS (ESIneg): m/z = 433.4 $[M-H]^+$ RP-HPLC (method D, basic) 27 % yield
36	 rac-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-4-chloro-3-fluoro-anilino)propanamide	Intermediate 39; rac-2-bromopropanamide	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.19 (d, *J*=7.35 Hz, 3 H), 5.02 (q, *J*=7.35 Hz, 1 H), 7.30 (s, 1 H), 7.38 - 7.45 (m, 3 H), 7.49 - 7.53 (m, 3 H), 7.63 (s, 1 H), 7.72 - 7.77 (m, 2 H), 8.15 (br s, 2 H). LC-MS (method 1) Rt = 1.17 min; MS (ESIpos): m/z = 419.3 $[M+H]^+$ RP-HPLC (method D, basic) 39 % yield

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
37	 rac-2-(N-[4-amino-5-(4-fluorobenzoyl)thiazol-2-yl]-4-chloro-anilino)propanamide	Intermediate 40; rac-2-bromopropanamide	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.16 (d, *J*=7.60 Hz, 3 H), 5.02 - 5.11 (m, 1 H), 7.25 (s, 1 H), 7.33 (t, *J*=8.87 Hz, 2 H), 7.43 - 7.52 (m, 4 H), 7.58 (s, 1 H), 7.64 (dd, *J*=8.87, 5.07 Hz, 2 H), 7.98 - 8.43 (m, 2 H). LC-MS (method 2) Rt = 1.18 min; MS (ESIpos): m/z = 419.2 $[M+H]^+$ 55 % yield
37.1 and **37.2**	(R)-2-(N-[4-amino-5-(4-fluorobenzoyl)thiazol-2-yl]-4-chloro-anilino)propanamide and (S)-2-(N-[4-amino-5-(4-fluorobenzoyl)thiazol-2-yl]-4-chloro-anilino)propanamide		
37.1	 2-(N-[4-amino-5-(4-fluorobenzoyl)thiazol-2-yl]-4-chloro-anilino)propanamide (enantiomer 1)	Example 37	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.13 - 1.19 (m, 3 H), 5.01 - 5.11 (m, 1 H), 7.25 (s, 1 H), 7.33 (t, *J*=8.87 Hz, 2 H), 7.43 - 7.53 (m, 4 H), 7.58 (s, 1 H), 7.64 (dd, *J*=8.87, 5.07 Hz, 2 H), 7.88 - 8.52 (m, 2 H). LC-MS (method 1) Rt = 1.19 min; MS (ESIpos): m/z = 419.2 $[M+H]^+$ 31 % yield

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
Chiral HPLC Example 37.1 HPLC separation of rac-2-(N-[4-amino-5-(4-fluorobenzoyl)thiazol-2-yl]-4-chloro-anilino)propanamide (170 mg, 0.41 mmol, Example 37) on a chiral column gave 54 mg (31 % yield) of 2-(N-[4-amino-5-(4-fluorobenzoyl)thiazol-2-yl]-4-chloro-anilino)propanamide, enantiomer 1. Preparative chiral HPLC Instrument: PrepCon Labomatic HPLC; Column: YMC Cellulose SB 5µ, 250x30; eluent A: hexane + 0.1 vol % diethylamine; eluent B: ethanol + 0.1 vol % diethylamine; isocratic: 60%A+40%B; flow: 50 mL/min; temperature: 25°C; UV: 254 nm Analytical chiral HPLC: Rt = 1.66 min Instrument: Waters Alliance 2695; Column: YMC Cellulose SB 3µ, 100x4.6; eluent A: hexane + 0.1 vol % diethylamine; eluent B: ethanol; isocratic: 60%A+40%B; flow: 1.4 mL/min; temperature: 25°C; UV: 254 nm			
37.2	 2-(N-[4-amino-5-(4-fluorobenzoyl)thiazol-2-yl]-4-chloro-anilino)propanamide (enantiomer 2)	Example 37	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.16 (d, *J*=7.35 Hz, 3 H), 5.01 - 5.11 (m, 1 H), 7.23 - 7.27 (m, 1 H), 7.33 (t, *J*=8.87 Hz, 2 H), 7.43 - 7.53 (m, 4 H), 7.58 (s, 1 H), 7.64 (dd, *J*=8.87, 5.07 Hz, 2 H), 7.92 - 8.37 (m, 2 H). LC-MS (method 1) Rt = 1.19 min; MS (ESIpos): m/z = 419.2 $[M+H]^+$ 32 % yield

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
Chiral HPLC Example 37.2 HPLC separation of rac-2-(N-[4-amino-5-(4-fluorobenzoyl)thiazol-2-yl]-4-chloro-anilino)propanamide (170 mg, 0.41 mmol, Example 37) on a chiral column gave 57 mg (32 % yield) 2-(N-[4-amino-5-(4-fluorobenzoyl)thiazol-2-yl]-4-chloro-anilino)propanamide, enantiomer 2. Preparative chiral HPLC Instrument: PrepCon Labomatic HPLC; Column: YMC Cellulose SB 5µ, 250x30; eluent A: hexane + 0.1 vol % diethylamine; eluent B: ethanol + 0.1 vol % diethylamine; isocratic: 60%A+40%B; flow: 50 mL/min; temperature: 25°C; UV: 254 nm Analytical chiral HPLC: Rt = 2.20 min Instrument: Waters Alliance 2695; Column: YMC Cellulose SB 3µ, 100x4.6; eluent A: hexane + 0.1 vol % diethylamine; eluent B: ethanol; isocratic: 60%A+40%B; flow: 1.4 mL/min; temperature: 25°C; UV: 254 nm			
38	 rac-2-(N-[4-amino-5-(4-chlorobenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 41; rac-2-bromopropanamide	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.16 (d, *J*=7.60 Hz, 3 H), 5.01 - 5.12 (m, 1 H), 7.25 (s, 1 H), 7.29 - 7.37 (m, 2 H), 7.43 - 7.53 (m, 4 H), 7.58 (s, 1 H), 7.63 (dd, *J*=8.87, 5.07 Hz; 2 H), 7.92 - 8.44 (m, 2 H). LC-MS (method 1) Rt = 1.19 min; MS (ESIpos): m/z = 419.2 $[M+H]^+$ RP-HPLC (method C, basic) 42 % yield
38.1 and **38.2**	(R)-2-(N-[4-amino-5-(4-chlorobenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide and (S)-2-(N-[4-amino-5-(4-chlorobenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide		

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
38.1	 2-(N-[4-amino-5-(4-chlorobenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide (enantiomer 1)	Example 38	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.16 (d, *J*=7.35 Hz, 3 H), 4.98 - 5.16 (m, 1 H), 7.25 (s, 1 H), 7.33 (t, *J*=8.87 Hz, 2 H), 7.43 - 7.52 (m, 4 H), 7.58 (s, 1 H), 7.63 (dd, *J*=8.87, 5.07 Hz, 2 H), 7.92 - 8.50 (m, 2 H). LC-MS (method 1) Rt = 1.19 min; MS (ESIpos): m/z = 419.2 $[M+H]^+$ RP-HPLC (method D, basic) 16 % yield

Chiral HPLC Example 38.1

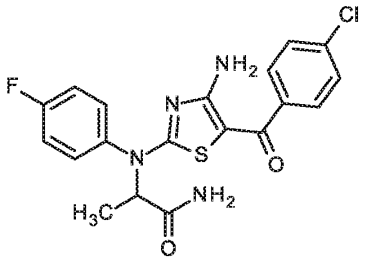
HPLC separation of rac-2-(N-[4-amino-5-(4-chlorobenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide (115 mg, 0.27 mmol; Example 38) on a chiral column, followed by an additional RP-HPLC gave 19 mg (16 % yield) of 2-(N-[4-amino-5-(4-chlorobenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, enantiomer 1.

Preparative chiral HPLC

Instrument: PrepCon Labomatic HPLC; Column: YMC Cellulose SB 10µ, 250x50; eluent A: hexane + 0.1 vol % diethylamine; eluent B: 2-propanol + 0.1 vol % diethylamine; isocratic: 60%A+40%B; flow: 140 mL/min; temperature: 25°C; UV: 254 nm

Analytical chiral HPLC: Rt = 2.23 min

Instrument: Waters Alliance 2695; Column: YMC Cellulose SB 3µ, 100x4.6;
eluent A: hexane + 0.1 vol % diethylamine; eluent B: 2-propanol; isocratic: 60%A+40%B; flow: 1.4 mL/min; temperature: 25°C; UV: 254 nm

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
38.2	 2-(N-[4-amino-5-(4-chlorobenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide (enantiomer 2)	Example 38	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.16 (d, *J*=7.35 Hz, 3 H), 5.02 - 5.10 (m, 1 H), 7.25 (s, 1 H), 7.33 (t, *J*=8.87 Hz, 2 H), 7.43 - 7.52 (m, 4 H), 7.57 - 7.60 (m, 1 H), 7.63 (dd, *J*=8.87, 5.07 Hz, 2 H), 7.95 - 8.47 (m, 2 H). LC-MS (method 1) Rt = 1.19 min; MS (ESIpos): m/z = 419.2 $[M+H]^+$ RP-HPLC (method D, basic) 38 % yield

Chiral HPLC Example 38.2

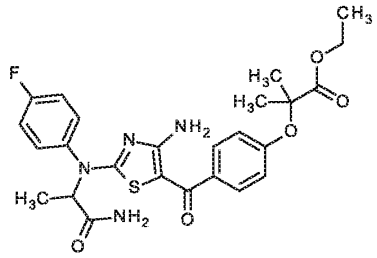
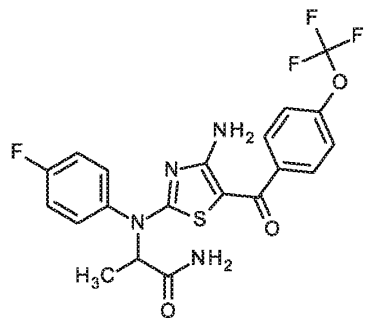
HPLC separation of rac-2-(N-[4-amino-5-(4-chlorobenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide (115 mg, 0.27 mmol; Example 38) on a chiral column, followed by an additional RP-HPLC gave 20 mg (17 % yield) of 2-(N-[4-amino-5-(4-chlorobenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, enantiomer 2.

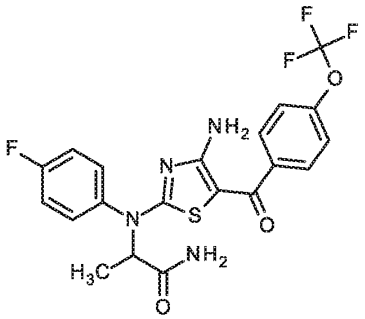
Preparative chiral HPLC

Instrument: PrepCon Labomatic HPLC; Column: YMC Cellulose SB 10µ, 250x50; eluent A: hexane + 0.1 vol % diethylamine; eluent B: 2-propanol + 0.1 vol % diethylamine; isocratic: 60%A+40%B; flow: 140 mL/min; temperature: 25°C; UV: 254 nm

Analytical chiral HPLC: Rt = 3.79 min

Instrument: Waters Alliance 2695; Column: YMC Cellulose SB 3µ, 100x4.6;
eluent A: hexane + 0.1 vol % diethylamine; eluent B: 2-propanol; isocratic: 60%A+40%B; flow: 1.4 mL/min; temperature: 25°C; UV: 254 nm

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
39	 rac-ethyl 2-[4-[4-amino-2-(N-[2-amino-1-methyl-2-oxo-ethyl]-4-fluoro-anilino)thiazole-5-carbonyl]phenoxy]-2-methyl-propanoate	Intermediate 42; rac-2-bromopropanamide	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.07 (t, *J*=7.10 Hz, 3 H), 1.15 (d, *J*=7.35 Hz, 3 H), 1.53 (s, 6 H), 4.12 (q, *J*=7.01 Hz, 2 H), 5.02 - 5.09 (m, 1 H), 6.72 - 6.76 (m, 2 H), 7.24 (s, 1 H), 7.33 (t, *J*=8.87 Hz, 2 H), 7.44 (d, *J*=8.87 Hz, 2 H), 7.58 (s, 1 H), 7.63 (dd, *J*=9.00, 5.20 Hz, 2 H), 7.88 (br s, 2 H). LC-MS (method 1) Rt = 1.21 min; MS (ESIpos): m/z = 515.4 $[M+H]^+$ RP-HPLC (method D, basic) 50 % yield
40	 rac-2-(N-[4-amino-5-[4-(trifluoromethoxy)benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 43; rac-2-bromopropanamide	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.16 (d, *J*=7.35 Hz, 3 H), 5.06 (br d, *J*=6.84 Hz, 1 H), 7.26 (s, 1 H), 7.33 (t, *J*=8.74 Hz, 2 H), 7.38 (d, *J*=7.86 Hz, 2 H), 7.58 (s, 1 H), 7.60 - 7.67 (m, 4 H), 7.95 - 8.56 (m, 2 H). LC-MS (method 1) Rt = 1.25 min; MS (ESIpos): m/z = 469.5 $[M+H]^+$ RP-HPLC (method D, basic) 83 % yield
40.1 and **40.2**	(R)-2-(N-[4-amino-5-[4-(trifluoromethoxy)benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide and (S)-2-(N-[4-amino-5-[4-(trifluoromethoxy)benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide		

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
40.1	 2-(N-[4-amino-5-[4-(trifluoromethoxy)benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide (enantiomer 1)	Example 40	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.16 (d, *J*=7.35 Hz, 3 H), 5.02 - 5.11 (m, 1 H), 7.26 (s, 1 H), 7.33 (t, *J*=8.74 Hz, 2 H), 7.38 (d, *J*=8.11 Hz, 2 H), 7.58 (s, 1 H), 7.60 - 7.67 (m, 4 H), 7.95 - 8.46 (m, 2 H). LC-MS (method 2) Rt = 1.24 min; MS (ESIpos): m/z = 469.4 [M+H]+ 20 % yield

Chiral HPLC Example 40.1

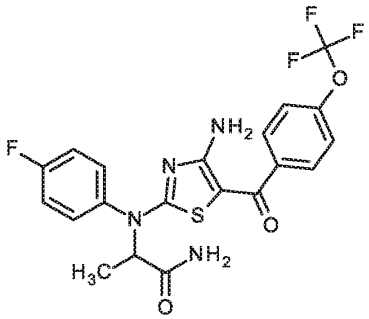
HPLC separation of rac-2-(N-[4-amino-5-[4-(trifluoromethoxy)benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide (69 mg, 0.15 mmol; Example 40) on a chiral column gave 20 mg (20 % yield) of 2-(N-[4-amino-5-[4-(trifluoromethoxy)benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide, enantiomer 1.

Preparative chiral HPLC

Instrument: Sepiatec: Prep SFC100; Column: Chiralpak IC 5µ 250x30mm; eluent A: CO_2; eluent B: ethanol + 0.2 vol % aqueous ammonia (32%); isocratic: 15%B; flow: 100 mL/min; temperature: 40°C; BPR: 150bar; UV: 254 nm

Analytical chiral HPLC: Rt = 2.73 min

Instrument: Agilent: 1260, Aurora SFC-Modul; Column: Chiralpak IC 5µ 100x4.6mm; eluent A: CO_2; eluent B: ethanol + 0.2 vol % aqueous ammonia (32%); isocratic: 15%B; flow: 4 mL/min; temperature: 37.5°C; BPR: 100bar; UV: 254 nm

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
40.2	 2-(N-[4-amino-5-[4-(trifluoromethoxy)benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide (enantiomer 2)	Example 40	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.16 (d, *J*=7.35 Hz, 3 H), 5.02 - 5.11 (m, 1 H), 7.26 (s, 1 H), 7.33 (t, *J*=8.87 Hz, 2 H), 7.38 (d, *J*=8.11 Hz, 2 H), 7.58 (s, 1 H), 7.60 - 7.67 (m, 4 H), 7.95 - 8.48 (m, 2 H). LC-MS (method 2) Rt = 1.25 min; MS (ESIpos): m/z = 469.3 [M+H]+ 21 % yield

Chiral HPLC Example 40.2

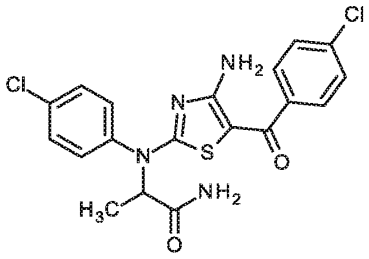
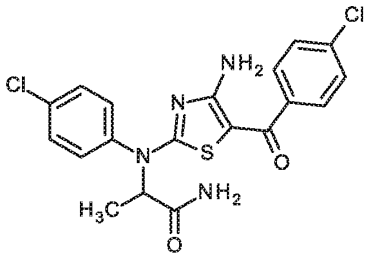
HPLC separation of rac-2-(N-[4-amino-5-[4-(trifluoromethoxy)benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide (69 mg, 0.15 mmol; Example 40) on a chiral column gave 20 mg (21 % yield) of 2-(N-[4-amino-5-[4-(trifluoromethoxy)benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide, enantiomer 2.

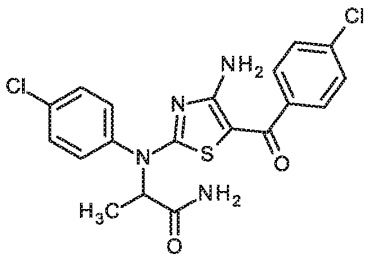
Preparative chiral HPLC

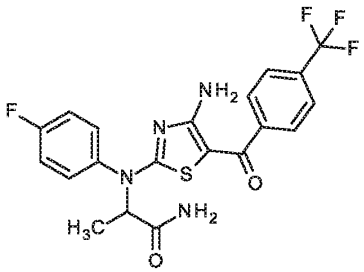
Instrument: Sepiatec: Prep SFC100; Column: Chiralpak IC 5µ 250x30mm; eluent A: CO_2; eluent B: ethanol + 0.2 vol % aqueous ammonia (32%); isocratic: 15%B; flow: 100 mL/min; temperature: 40°C; BPR: 150bar; UV: 254 nm

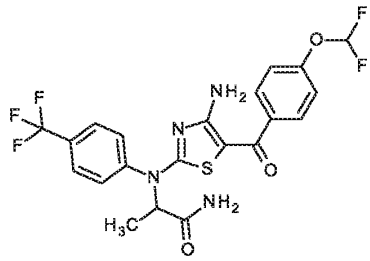
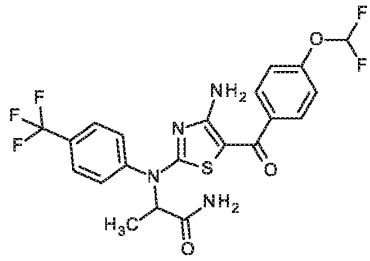
Analytical chiral HPLC: Rt = 3.48 min

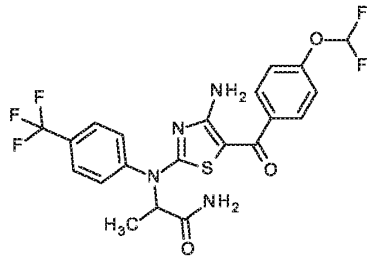
Instrument: Agilent: 1260, Aurora SFC-Modul; Column: Chiralpak IC 5µ 100x4.6mm; eluent A: CO_2; eluent B: ethanol + 0.2 vol % aqueous ammonia (32%); isocratic: 15%B; flow: 4 mL/min; temperature: 37.5°C; BPR: 100bar; UV: 254 nm

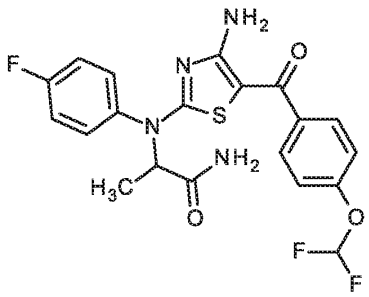
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
41	 rac-2-(N-[4-amino-5-(4-chlorobenzoyl)thiazol-2-yl]-4-chloro-anilino)propanamide	Intermediate 44; rac-2-bromopropanamide	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.16 (d, *J*=7.35 Hz, 3 H), 5.06 (q, *J*=7.27 Hz, 1 H), 7.23 - 7.28 (m, 1 H), 7.44 - 7.53 (m, 4 H), 7.55 - 7.63 (m, 5 H), 7.96 - 8.44 (m, 2 H). LC-MS (method 2) Rt = 1.27 min; MS (ESIpos): m/z = 435.2 $[M+H]^+$ 47 % yield
41.1 and **41.2**	(R)-2-(N-[4-amino-5-(4-chlorobenzoyl)thiazol-2-yl]-4-chloro-anilino)propanamide and (S)-2-(N-[4-amino-5-(4-chlorobenzoyl)thiazol-2-yl]-4-chloro-anilino)propanamide		
41.1	 2-(N-[4-amino-5-(4-chlorobenzoyl)thiazol-2-yl]-4-chloro-anilino)propanamide (enantiomer 1)	Example 41	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.14 - 1.19 (m, 3 H), 5.06 (q, *J*=7.10 Hz, 1 H), 7.27 (s, 1 H), 7.44 - 7.53 (m, 4 H), 7.55 - 7.64 (m, 5 H), 7.99 - 8.41 (m, 2 H). LC-MS (method 1) Rt = 1.27 min; MS (ESIpos): m/z = 435.2 $[M+H]^+$ $[\alpha]_D^{20}$ = +83.8° (c = 1.00, dimethylsulfoxide) 25 % yield

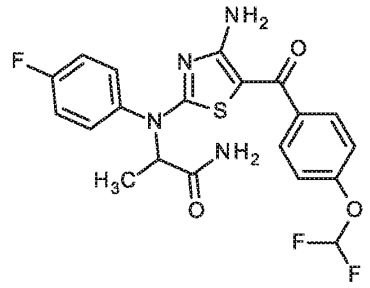
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
Chiral HPLC Example 41.1 HPLC separation of rac-2-(N-[4-amino-5-(4-chlorobenzoyl)thiazol-2-yl]-4-chloro-anilino)propanamide (144 mg, 0.33 mmol; Example 41) on a chiral column gave 36 mg (25 % yield) of 2-(N-[4-amino-5-(4-chlorobenzoyl)thiazol-2-yl]-4-chloro-anilino)propanamide, enantiomer 1. Preparative chiral HPLC Instrument: PrepCon Labomatic HPLC; Column: YMC Cellulose SB 10µ, 250x50; eluent A: hexane; eluent B: ethanol; isocratic: 60%A+40%B; flow: 150 mL/min; temperature: 25°C; UV: 254 nm Analytical chiral HPLC: Rt = 1.84 min Instrument: Waters Alliance 2695; Column: YMC Cellulose SB 3µ, 100x4.6; eluent A: hexane + 0.1 vol % diethylamine; eluent B: ethanol; isocratic: 60%A+40%B; flow: 1.4 mL/min; temperature: 25°C; UV: 254 nm			
41.2	 2-(N-[4-amino-5-(4-chlorobenzoyl)thiazol-2-yl]-4-chloro-anilino)propanamide (enantiomer 2)	Example 41	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.16 (d, *J*=7.35 Hz, 3 H), 5.06 (q, *J*=7.10 Hz, 1 H), 7.26 - 7.29 (m, 1 H), 7.44 - 7.52 (m, 4 H), 7.55 - 7.63 (m, 5 H), 7.94 - 8.68 (m, 2 H). LC-MS (method 1) Rt = 1.27 min; MS (ESIpos): m/z = 435.2 $[M+H]^+$ $[\alpha]_D^{20}$ = -78.4° (c = 1.00, dimethylsulfoxide) 18 % yield

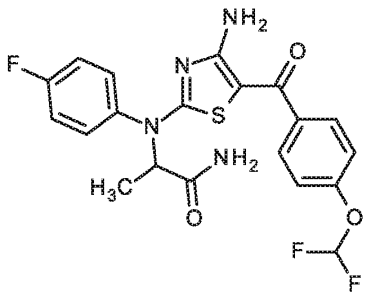
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
Chiral HPLC Example 41.2 HPLC separation of rac-2-(N-[4-amino-5-(4-chlorobenzoyl)thiazol-2-yl]-4-chloro-anilino)propanamide (144 mg, 0.33 mmol; Example 41) on a chiral column gave 26 mg (18 % yield) of 2-(N-[4-amino-5-(4-chlorobenzoyl)thiazol-2-yl]-4-chloro-anilino)propanamide, enantiomer 2. Preparative chiral HPLC Instrument: PrepCon Labomatic HPLC; Column: YMC Cellulose SB 10µ, 250x50; eluent A: hexane; eluent B: ethanol; isocratic: 60%A+40%B; flow: 150 mL/min; temperature: 25°C; UV: 254 nm Analytical chiral HPLC: Rt = 2.34 min Instrument: Waters Alliance 2695; Column: YMC Cellulose SB 3µ, 100x4.6; eluent A: hexane + 0.1 vol % diethylamine; eluent B: ethanol; isocratic: 60%A+40%B; flow: 1.4 mL/min; temperature: 25°C; UV: 254 nm			
42	 rac-2-(N-[4-amino-5-[4-(trifluoromethyl)benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 45; rac-2-bromopropanamide	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.16 (d, *J*=7.35 Hz, 3 H), 5.00 - 5.13 (m, 1 H), 7.26 (s, 1 H), 7.33 (t, *J*=8.87 Hz, 2 H), 7.59 (s, 1 H), 7.64 (dd, *J*=8.87, 5.07 Hz, 2 H), 7.72 (dd, *J*=37.13, 8.24 Hz, 4 H), 7.98 - 8.51 (m, 2 H). LC-MS (method 1) Rt = 1.22 min; MS (ESIpos): m/z = 453.4 $[M+H]^+$ RP-HPLC (method D, basic) 71 % yield

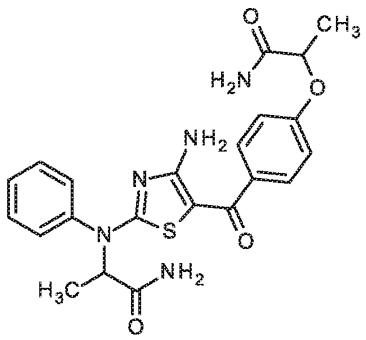
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
43	 rac-2-[N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-(trifluoromethyl)anilino]propanamide	Intermediate 46; rac-2-bromopropanamide	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.18 (d, *J*=7.35 Hz, 3 H), 5.07 (q, *J*=7.27 Hz, 1 H), 7.28 (t, *J*=72.24 Hz, 1 H), 7.18 (d, *J*=9.38 Hz, 2 H), 7.30 (s, 1 H), 7.57 (d, *J*=8.87 Hz, 2 H), 7.64 (s, 1 H), 7.86 (dd, *J*=27.88, 8.36 Hz, 4 H), 8.18 (br s, 2 H). LC-MS (method 1) Rt = 1.22 min; MS (ESIpos): m/z = 501.4 $[M+H]^+$ RP-HPLC (method D, basic) 54 % yield
43.1 and **43.2**	(R)-2-[N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-(trifluoromethyl)anilino]propanamide and (S)-2-[N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-(trifluoromethyl)anilino]propanamide		
43.1	 2-[N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-(trifluoromethyl)anilino]propanamide (enantiomer 1)	Example 43	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.18 (d, *J*=7.35 Hz, 3 H), 5.07 (q, *J*=7.35 Hz, 1 H), 7.28 (t, *J*=74.01 Hz, 1 H), 7.18 (d, *J*=8.62 Hz, 2 H), 7.31 (s, 1 H), 7.57 (d, *J*=8.87 Hz, 2 H), 7.63 (s, 1 H), 7.86 (dd, *J*=27.88, 8.62 Hz, 4 H), 7.99 - 8.36 (m, 2 H). LC-MS (method 1) Rt = 1.22 min; MS (ESIpos): m/z = 501.4 $[M+H]^+$ 34 % yield

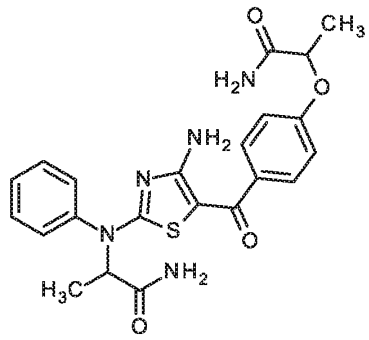
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
Chiral HPLC Example 43.1 HPLC separation of rac-2-[N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-(trifluoromethyl)anilino]propanamide (280 mg, 0.56 mmol; Example 43) on a chiral column gave 99 mg (35 % yield) of 2-[N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-(trifluoromethyl)anilino]propanamide, enantiomer 1. Preparative chiral HPLC Instrument: PrepCon Labomatic HPLC; Column: YMC Cellulose SB 5µ, 250x30; eluent A: hexane + 0.1 vol % diethylamine; eluent B: ethanol + 0.1 vol % diethylamine; isocratic: 80%A+20%B; flow: 50 mL/min; temperature: 25°C; UV: 254 nm Analytical chiral HPLC: Rt = 4.50 min Instrument: Waters Alliance 2695; Column: YMC Cellulose SB 3µ, 100x4.6; eluent A: hexane + 0.1 vol % diethylamine; eluent B: ethanol; isocratic: 80%A+20%B; flow: 1.4 mL/min; temperature: 25°C; UV: 254 nm			
43.2	 2-[N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-(trifluoromethyl)anilino]propanamide (enantiomer 2)	Example 43	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.18 (d, *J*=7.35 Hz, 3 H), 5.07 (q, *J*=7.35 Hz, 1 H), 7.28 (t, *J*=73.76 Hz, 1 H), 7.18 (d, *J*=8.62 Hz, 2 H), 7.31 (s, 1 H), 7.57 (d, *J*=8.87 Hz, 2 H), 7.63 (s, 1 H), 7.86 (dd, *J*=27.88, 8.62 Hz, 4 H), 8.18 (br s, 2 H). LC-MS (method 1) Rt = 1.22 min; MS (ESIpos): m/z = 501.3 $[M+H]^+$ 27 % yield

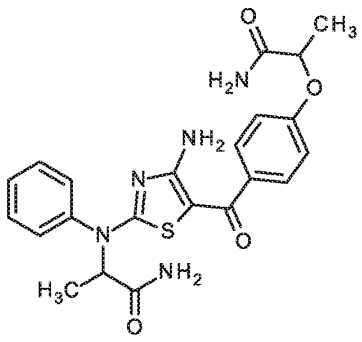
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
Chiral HPLC Example 43.2 HPLC separation of rac-2-[N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-(trifluoromethyl)anilino]propanamide (280 mg, 0.56 mmol; Example 43) on a chiral column gave 79 mg (27 % yield) of 2-[N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-(trifluoromethyl)anilino]propanamide, enantiomer 2. Preparative chiral HPLC Instrument: PrepCon Labomatic HPLC; Column: YMC Cellulose SB 5µ, 250x30; eluent A: hexane + 0.1 vol % diethylamine; eluent B: ethanol + 0.1 vol % diethylamine; isocratic: 80%A+20%B; flow: 50 mL/min; temperature: 25°C; UV: 254 nm Analytical chiral HPLC: Rt = 5.44 min Instrument: Waters Alliance 2695; Column: YMC Cellulose SB 3µ, 100x4.6; eluent A: hexane + 0.1 vol % diethylamine; eluent B: ethanol; isocratic: 80%A+20%B; flow: 1.4 mL/min; temperature: 25°C; UV: 254 nm			
44	 rac-2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 47: rac-2-bromopropanamide	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.16 (d, *J*=7.35 Hz, 3 H), 5.06 (q, *J*=7.10 Hz, 1 H), 7.28 (t, *J*=73.76 Hz, 1 H), 7.17 (d, *J*=8.62 Hz, 2 H), 7.25 (br s, 1 H), 7.33 (t, *J*=8.87 Hz, 2 H), 7.55 (d, *J*=8.87 Hz, 2 H), 7.58 (br s, 1 H), 7.64 (dd, *J*=8.87, 5.07 Hz, 2 H), 8.21 (br s, 2 H). LC-MS (method 2) Rt = 1.13 min; MS (ESIpos): m/z = 451.6 $[M+H]^+$ RP-HPLC (method D, basic) 87 % yield

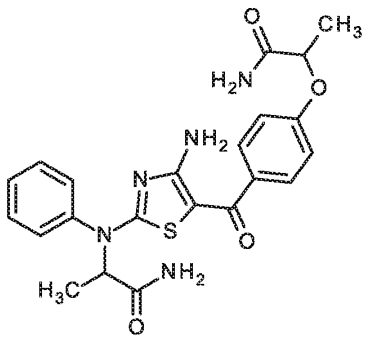
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
44.1 and **44.2**	(R)-2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide and (S)-2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide		
44.1	 2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide (enantiomer 1)	Example 44	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.16 (d, *J*=7.35 Hz, 3 H), 5.02 - 5.10 (m, 1 H), 7.26 (t, *J*=74.01 Hz, 1 H), 7.17 (d, *J*=9.38 Hz, 2 H), 7.25 (s, 1 H), 7.33 (t, *J*=8.74 Hz, 2 H), 7.55 (d, *J*=8.87 Hz, 2 H), 7.58 (br s, 1 H), 7.64 (dd, *J*=8.87, 5.07 Hz, 2 H), 7.86 - 8.45 (m, 2 H). LC-MS (method 2) Rt = 1.12 min; MS (ESIpos): m/z = 451.3 $[M+H]^+$ $[\alpha]_D^{20}$ = +77.2° (c = 1.00, dimethylsulfoxide) 38 % yield

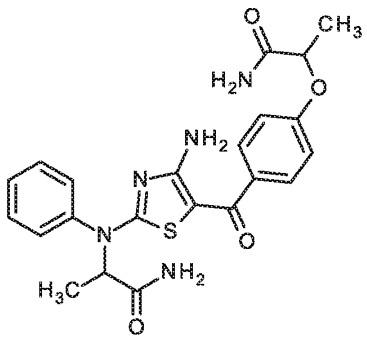
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
Chiral HPLC Example 44.1 HPLC separation of rac-2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide (2552 mg, 5.61 mmol; Example 44) on a chiral column gave 1096 mg (35 % yield) of 2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide, enantiomer 1. Preparative chiral HPLC Instrument: PrepCon Labomatic HPLC; Column: YMC Cellulose SB 10µ, 250x50; eluent A: hexane + 0.1 vol % diethylamine; eluent B: 2-propanol + 0.1 vol % diethylamine; isocratic: 60%A+40%B; flow: 140 mL/min; temperature: 25°C; UV: 254 nm Analytical chiral HPLC: Rt = 2.81 min Instrument: Waters Alliance 2695; Column: YMC Cellulose SB 3µ, 100x4.6; eluent A: hexane + 0.1 vol % diethylamine; eluent B: 2-propanol; isocratic: 80%A+20%B; flow: 1.4 mL/min; temperature: 25°C; UV: 254 nm			
44.2	 2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide (enantiomer 2)	Example 44	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.16 (d, *J*=7.35 Hz, 3 H), 5.01 - 5.12 (m, 1 H), 7.28 (t, *J*=73.76 Hz, 1 H), 7.17 (d, *J*=8.62 Hz, 2 H), 7.25 (s, 1 H), 7.33 (t, *J*=8.87 Hz, 2 H), 7.55 (d, *J*=8.87 Hz, 2 H), 7.58 (br s, 1 H), 7.64 (dd, *J*=8.87, 5.07 Hz, 2 H), 8.15 (br s, 2 H). LC-MS (method 2) Rt = 1.12 min; MS (ESIpos): m/z = 451.4 $[M+H]^+$ $[\alpha]_D^{20}$ = -79.7° (c = 1.00, dimethylsulfoxide) 38 % yield

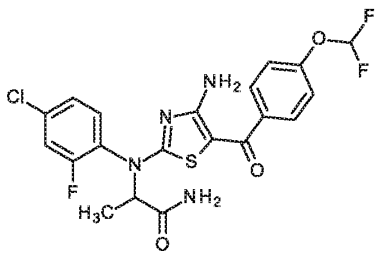
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
Chiral HPLC Example 44.2 HPLC separation of rac-2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide (2552 mg, 5.61 mmol; Example 44) on a chiral column gave 1139 mg (37 % yield) of 2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide, enantiomer 2. Preparative chiral HPLC Instrument: PrepCon Labomatic HPLC; Column: YMC Cellulose SB 10µ, 250x50; eluent A: hexane + 0.1 vol % diethylamine; eluent B: 2-propanol + 0.1 vol % diethylamine; isocratic: 60%A+40%B; flow: 140 mL/min; temperature: 25°C; UV: 254 nm Analytical chiral HPLC: Rt = 4.61 min Instrument: Waters Alliance 2695; Column: YMC Cellulose SB 3µ, 100x4.6; eluent A: hexane + 0.1 vol % diethylamine; eluent B: 2-propanol; isocratic: 80%A+20%B; flow: 1.4 mL/min; temperature: 25°C; UV: 254 nm			
45	 2-(N-[4-amino-5-[4-[2-amino-1-methyl-2-oxo-ethoxy]benzoyl]thiazol-2-yl]anilino)propanamide (mixture of stereoisomers)	Intermediate 48; rac-2-bromopropanamide	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.16 (d, *J*=7.35 Hz, 3 H), 1.41 (d, *J*=6.59 Hz, 3 H), 4.63 (q, *J*=6.59 Hz, 1 H), 5.04 - 5.12 (m, 1 H), 6.86 (d, *J*=8.87 Hz, 2 H), 7.24 (br d, *J*=3.80 Hz, 2 H), 7.42 - 7.52 (m, 6 H), 7.53 - 7.58 (m, 3 H), 8.08 (br s, 2 H). LC-MS (method 2) Rt = 0.85 min; MS (ESIpos): m/z = 454.4 $[M+H]^+$ RP-HPLC (method C, basic) 70 % yield

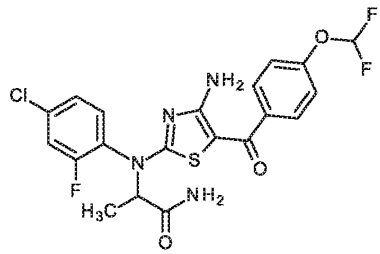
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
45.1, **45.2**, **45.3** and **45.4**	(2R)-(N-[4-amino-5-[4-[2-amino-(1R)-methyl-2-oxo-ethoxy]benzoyl]thiazol-2-yl]anilino)propanamide, (2R)-(N-[4-amino-5-[4-[2-amino-(1S)-methyl-2-oxo-ethoxy]benzoyl]thiazol-2-yl]anilino)propanamide, (2S)-(N-[4-amino-5-[4-[2-amino-(1R)-methyl-2-oxo-ethoxy]benzoyl]thiazol-2-yl]anilino)propanamide, and (2S)-(N-[4-amino-5-[4-[2-amino-(1S)-methyl-2-oxo-ethoxy]benzoyl]thiazol-2-yl]anilino)propanamide		
45.1	 2-(N-[4-amino-5-[4-[2-amino-1-methyl-2-oxo-ethoxy]benzoyl]thiazol-2-yl]anilino)propanamide (stereoisomer 1)	Example 45	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.16 (d, *J*=7.35 Hz, 3 H), 1.41 (d, *J*=6.59 Hz, 3 H), 4.63 (q, *J*=6.76 Hz, 1 H), 5.08 (q, *J*=7.35 Hz, 1 H), 6.86 (d, *J*=8.87 Hz, 2 H), 7.23 (br d, *J*=3.30 Hz, 2 H), 7.43 - 7.52 (m, 6 H), 7.53 - 7.60 (m, 3 H), 7.75 - 8.37 (m, 2 H). LC-MS (method 1) Rt = 0.86 min; MS (ESIpos): m/z = 454.3 $[M+H]^+$ 4 % yield

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
Chiral HPLC Example 45.1 HPLC separation of 2-(N-[4-amino-5-[4-[2-amino-1-methyl-2-oxo-ethoxy]benzoyl]thiazol-2-yl]anilino)propanamide (mixture of stereoisomers; 449 mg, 0.99 mmol; Example 45) on a chiral column gave 29 mg (6 % yield) of 2-(N-[4-amino-5-[4-[2-amino-1-methyl-2-oxo-ethoxy]benzoyl]thiazol-2-yl]anilino)propanamide, stereoisomer 1. Preparative chiral HPLC Instrument: PrepCon Labomatic HPLC; Column: YMC Amylose SA 10µ, 250x50; eluent A: methyl tert-butyl ether; eluent B: acetonitrile; isocratic: 80%A+20%B; flow: 100 mL/min; temperature: 25°C; UV: 254 nm Analytical chiral HPLC: Rt = 6.48 min Instrument: Waters Alliance 2695; Column: YMC Amylose SA 3µ, 100x4.6; eluent A: methyl tert-butyl ether; eluent B: acetonitrile; isocratic: 80%A+20%B; flow: 1.4 ml/min; temperature: 25°C; UV: 254 nm			
45.2	 2-(N-[4-amino-5-[4-[2-amino-1-methyl-2-oxo-ethoxy]benzoyl]thiazol-2-yl]anilino)propanamide (stereoisomer 2)	Example 45	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.16 (d, *J*=7.35 Hz, 3 H), 1.41 (d, *J*=6.59 Hz, 3 H), 4.63 (q, *J*=6.59 Hz, 1 H), 5.08 (q, *J*=7.27 Hz, 1 H), 6.86 (d, *J*=8.87 Hz, 2 H), 7.23 (br d, *J*=4.82 Hz, 2 H), 7.42 - 7.52 (m, 6 H), 7.55 (br d, *J*=1.27 Hz, 3 H), 8.14 (br s, 2 H). LC-MS (method 1) Rt = 0.85 min; MS (ESIpos): m/z = 454.3 $[M+H]^+$ 5 % yield

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
Chiral HPLC Example 45.2 HPLC separation of 2-(N-[4-amino-5-[4-[2-amino-1-methyl-2-oxo-ethoxy]benzoyl]thiazol-2-yl]anilino)propanamide (mixture of stereoisomers; 449 mg, 0.99 mmol; Example 45) on a chiral column gave 36 mg (7 % yield) of 2-(N-[4-amino-5-[4-[2-amino-1-methyl-2-oxo-ethoxy]benzoyl]thiazol-2-yl]anilino)propanamide, stereoisomer 2. Preparative chiral HPLC Instrument: PrepCon Labomatic HPLC; Column: YMC Amylose SA 10µ, 250x50; eluent A: methyl tert-butyl ether; eluent B: acetonitrile; isocratic: 80%A+20%B; flow: 100 mL/min; temperature: 25°C; UV: 254 nm Analytical chiral HPLC: Rt = 6.48 min Instrument: Waters Alliance 2695; Column: YMC Amylose SA 3µ, 100x4.6; eluent A: methyl tert-butyl ether; eluent B: acetonitrile; isocratic: 80%A+20%B; flow: 1.4 ml/min; temperature: 25°C; UV: 254 nm			
45.3	 2-(N-[4-amino-5-[4-[2-amino-1-methyl-2-oxo-ethoxy]benzoyl]thiazol-2-yl]anilino)propanamide (stereoisomer 3)	Example 45	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.16 (d, *J*=7.35 Hz, 3 H), 1.41 (d, *J*=6.59 Hz, 3 H), 4.59 - 4.66 (m, 1 H), 5.08 (q, *J*=7.77 Hz, 1 H), 6.86 (d, *J*=8.87 Hz, 2 H), 7.23 (br d, *J*=4.06 Hz, 2 H), 7.42 - 7.52 (m, 6 H), 7.53 - 7.59 (m, 3 H), 8.05 (br s, 2 H). LC-MS (method 1) Rt = 0.85 min; MS (ESIpos): m/z = 454.3 $[M+H]^+$ 5 % yield

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
Chiral HPLC Example 45.3 HPLC separation of 2-(N-[4-amino-5-[4-[2-amino-1-methyl-2-oxo-ethoxy]benzoyl]thiazol-2-yl]anilino)propanamide (mixture of stereoisomers; 449 mg, 0.99 mmol; Example 45) on a chiral column gave 36 mg (8 % yield) of 2-(N-[4-amino-5-[4-[2-amino-1-methyl-2-oxo-ethoxy]benzoyl]thiazol-2-yl]anilino)propanamide, stereoisomer 3. Preparative chiral HPLC Instrument: PrepCon Labomatic HPLC; Column: YMC Amylose SA 10µ, 250x50; eluent A: methyl tert-butyl ether; eluent B: acetonitrile; isocratic: 80%A+20%B; flow: 100 mL/min; temperature: 25°C; UV: 254 nm Analytical chiral HPLC: Rt = 6.48 min Instrument: Waters Alliance 2695; Column: YMC Amylose SA 3µ, 100x4.6; eluent A: methyl tert-butyl ether; eluent B: acetonitrile; isocratic: 80%A+20%B; flow: 1.4 ml/min; temperature: 25°C; UV: 254 nm			
45.4	 2-(N-[4-amino-5-[4-[2-amino-1-methyl-2-oxo-ethoxy]benzoyl]thiazol-2-yl]anilino)propanamide (stereoisomer 4)	Example 45	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.16 (d, *J*=7.35 Hz, 3 H), 1.41 (d, *J*=6.59 Hz, 3 H), 4.63 (q, *J*=6.59 Hz, 1 H), 5.08 (q, *J*=6.93 Hz, 1 H), 6.86 (d, *J*=8.87 Hz, 2 H), 7.23 (br d, *J*=3.04 Hz, 2 H), 7.43 - 7.52 (m, 6 H), 7.53 - 7.58 (m, 3 H), 8.04 (br s, 2 H). LC-MS (method 2) Rt = 0.86 min; MS (ESIpos): m/z = 454.3 $[M+H]^+$ 5 % yield

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
Chiral HPLC Example 45.4 HPLC-separation of 2-(N-[4-amino-5-[4-[2-amino-1-methyl-2-oxo-ethoxy]benzoyl]thiazol-2-yl]anilino)propanamide (mixture of stereoisomers; 449 mg, 0.99 mmol; Example 45) on a chiral column gave 36 mg (8 % yield) of 2-(N-[4-amino-5-[4-[2-amino-1-methyl-2-oxo-ethoxy]benzoyl]thiazol-2-yl]anilino)propanamide, stereoisomer 4. Preparative chiral HPLC Instrument: PrepCon Labomatic HPLC; Column: YMC Amylose SA 10µ, 250x50; eluent A: methyl tert-butyl ether; eluent B: acetonitrile; isocratic: 80%A+20%B; flow: 100 mL/min; temperature: 25°C; UV: 254 nm Analytical chiral HPLC: Rt = 6.48 min Instrument: Waters Alliance 2695; Column: YMC Amylose SA 3µ, 100x4.6; eluent A: methyl tert-butyl ether; eluent B: acetonitrile; isocratic: 80%A+20%B; flow: 1.4 ml/min; temperature: 25°C; UV: 254 nm			
46	 rac-2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-chloro-2-fluoro-anilino)propanamide	Intermediate 49: rac-2-bromopropanamide	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.17 (s, 3 H), 4.98 - 5.23 (m, 1 H), 7.30 (br t, *J*=73.76 Hz, 1 H), 7.19 (br d, *J*=8.36 Hz, 2 H), 7.32 (br s, 1 H), 7.48 (br d, *J*=8.90 Hz, 1 H), 7.59 (br d, *J*=7.35 Hz, 2 H), 7.65 (br s, 1 H), 7.71 (br d, *J*=9.12 Hz, 1 H), 7.80 - 7.91 (m, 1 H), 8.18 (br s, 2 H). LC-MS (method 1) Rt = 1.21 min; MS (ESIpos): m/z = 485.3 $[M+H]^+$ RP-HPLC (method D, basic) 40 % yield

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
46.1 and **46.2**	(R)-2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-chloro-2-fluoro-anilino)propanamide and (S)-2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-chloro-2-fluoro-anilino)propanamide		
46.1	 2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-chloro-2-fluoro-anilino)propanamide (enantiomer 1)	Example 46	^{1}H-NMR (400 MHz, DMSO-*d6*) δ ppm = 1.13 - 1.22 (m, 3 H), 5.02 - 5.22 (m, 1 H), 7.19 (br d, *J*=8.36 Hz, 2 H), 7.30 (t, 1 H), 7.32 (br s, 1 H), 7.47 - 7.50 (m, 1 H), 7.56 - 7.63 (m, 2 H), 7.63 - 7.67 (m, 1 H), 7.68 - 7.75 (m, 1 H), 7.81 - 7.94 (m, 1 H), 8.02 - 8.36 (m, 2 H). LC-MS (method 1) Rt = 1.21 min; MS (ESIpos): m/z = 485.3 $[M+H]^+$ 35 % yield

Chiral HPLC Example 46.1

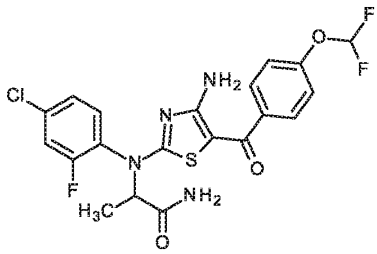
HPLC separation of rac-2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-chloro-2-fluoro-anilino)propanamide (253 mg, 0.52 mmol; Example 46) on a chiral column gave 90 mg (35 % yield) of 2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-chloro-2-fluoro-anilino)propanamide, enantiomer 1.

Preparative chiral HPLC

Instrument: PrepCon Labomatic HPLC; Column: YMC Cellulose SB 5µ, 250x30; eluent A: hexane + 0.1 vol % diethylamine; eluent B: ethanol + 0.1 vol % diethylamine; isocratic: 70%A+30%B; flow: 40 mL/min; temperature: 25°C; UV: 254 nm

Analytical chiral HPLC: Rt = 2.42 min

Instrument: Waters Alliance 2695; Column: YMC Cellulose SB 3µ, 100x4.6; eluent A: hexane + 0.1 vol % diethylamine; eluent B: ethanol; isocratic: 70%A+30%B; flow: 1.4 mL/min; temperature: 25°C; UV: 254 nm

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
46.2	 2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-chloro-2-fluoro-anilino)propanamide (enantiomer 2)	Example 46	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.12 - 1.22 (m, 3 H), 4.97 - 5.23 (m, 1 H), 7.19 (br d, *J*=8.36 Hz, 2 H), 7.30 (s, 1 H), 7.32 (br s, 1 H), 7.47 - 7.51 (m, 1 H), 7.59 (br d, *J*=7.60 Hz, 2 H), 7.65 (br s, 1 H), 7.69 - 7.76 (m, 1 H), 7.82 - 7.92 (m, 1 H), 7.99 - 8.31 (m, 2 H). LC-MS (method 1) Rt = 1.21 min; MS (ESIpos): m/z = 485.2 $[M+H]^+$ 52 % yield

Chiral HPLC Example 46.2

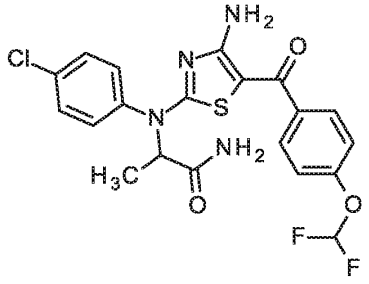
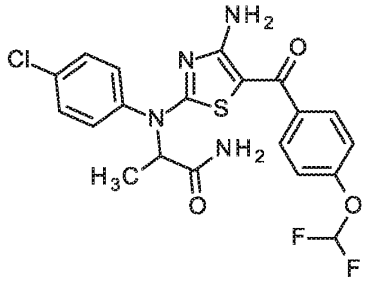
HPLC separation of rac-2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-chloro-2-fluoro-anilino)propanamide (253 mg, 0.52 mmol; Example 46) on a chiral column gave 135 mg (52 % yield) of 2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-chloro-2-fluoro-anilino)propanamide, enantiomer 2.

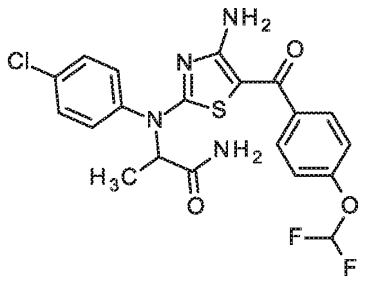
Preparative chiral HPLC

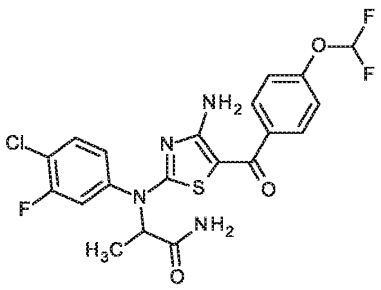
Instrument: PrepCon Labomatic HPLC; Column: YMC Cellulose SB 5µ, 250x30;
eluent A: hexane + 0.1 vol % diethylamine; eluent B: ethanol + 0.1 vol % diethylamine;
isocratic: 70%A+30%B; flow: 40 mL/min; temperature: 25°C; UV: 254 nm

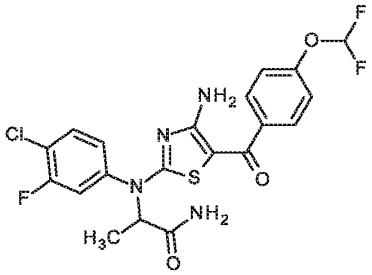
Analytical chiral HPLC: Rt = 3.13 min

Instrument: Waters Alliance 2695; Column: YMC Cellulose SB 3µ, 100x4.6; eluent A: hexane + 0.1 vol % diethylamine; eluent B: ethanol; isocratic: 70%A+30%B; flow: 1.4 mL/min; temperature: 25°C; UV: 254 nm

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
47	 rac-2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-chloro-anilino)propanamide	Intermediate 50; rac-2-bromopropanamide	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.16 (d, *J*=7.35 Hz, 3 H), 5.06 (br q, *J*=7.27 Hz, 1 H), 7.28 (t, *J*=73.51 Hz, 1 H), 7.17 (d, *J*=8.62 Hz, 2 H), 7.26 (s, 1 H), 7.54 - 7.64 (m, 7 H), 8.14 (br s, 2 H). LC-MS (method 2) Rt = 1.19 min; MS (ESIpos): m/z = 467.3 $[M+H]^+$ 40 % yield
47.1 and **47.2**	(R)-2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-chloro-anilino)propanamide and (S)-2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-chloro-anilino)propanamide		
47.1	 2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-chloro-anilino)propanamide (enantiomer 1)	Example 47	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.17 (d, *J*=7.35 Hz, 3 H), 5.06 (q, *J*=7.18 Hz, 1 H), 7.28 (t, *J*=73.76 Hz, 1 H), 7.18 (d, *J*=8.62 Hz, 2 H), 7.27 (s, 1 H), 7.54 - 7.64 (m, 7 H), 8.14 (br s, 2 H). LC-MS (method 2) Rt = 1.19 min; MS (ESIpos): m/z = 467.2 $[M+H]^+$ $[\alpha]_D^{20}$ = +73.5° (c = 1.00, dimethylsulfoxide). RP-HPLC (method D, basic) 11 % yield

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
Chiral HPLC Example 47.1 HPLC separation of rac-2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-chloro-anilino)propanamide (524 mg, 1.12 mmol; Example 47) on a chiral column gave 147 mg (29 % yield) of 2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-chloro-anilino)propanamide, enantiomer 1. Preparative chiral HPLC Instrument: PrepCon Labomatic HPLC; Column: YMC Cellulose SB 5µ, 250x30; eluent A: hexane + 0.1 vol % diethylamine; eluent B: 2-propanol; isocratic: 60%A+40%B; flow: 40 mL/min; temperature: 25°C; UV: 254 nm Analytical chiral HPLC: Rt = 2.99 min Instrument: Waters Alliance 2695; Column: YMC Cellulose SB 3µ, 100x4.6; eluent A: hexane + 0.1 vol % diethylamine; eluent B: 2-propanol; isocratic: 60%A+40%B; flow: 1.4 mL/min; temperature: 25°C; UV: 254 nm			
47.2	 2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-chloro-anilino)propanamide (enantiomer 2)	Example 47	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.17 (d, *J*=7.35 Hz, 3 H), 5.06 (q, *J*=7.18 Hz, 1 H), 7.28 (t, *J*=73.76 Hz, 1 H), 7.18 (d, *J*=8.62 Hz, 2 H), 7.27 (s, 1 H), 7.54 - 7.64 (m, 7 H), 8.14 (br s, 2 H). LC-MS (method 2) Rt = 1.19 min; MS (ESIpos): m/z = 467.2 [M+H]+ $[\alpha]_D^{20}$ = -67.1° (c = 1.00, dimethylsulfoxide). RP-HPLC (method D, basic) 13 % yield

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
Chiral HPLC Example 47.2 HPLC separation of rac-2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-chloro-anilino)propanamide (524 mg, 1.12 mmol; Example 47) on a chiral column gave 178 mg (34 % yield) of 2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-chloro-anilino)propanamide, enantiomer 2. Preparative chiral HPLC Instrument: PrepCon Labomatic HPLC; Column: YMC Cellulose SB 5µ, 250x30; eluent A: hexane + 0.1 vol % diethylamine; eluent B: 2-propanol; isocratic: 60%A+40%B; flow: 40 mL/min; temperature: 25°C; UV: 254 nm Analytical chiral HPLC: Rt =4.37 min Instrument: Waters Alliance 2695; Column: YMC Cellulose SB 3µ, 100x4.6; eluent A: hexane + 0.1 vol % diethylamine; eluent B: 2-propanol; isocratic: 60%A+40%B; flow: 1.4 mL/min; temperature: 25°C; UV: 254 nm			
48	 rac-2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-chloro-3-fluoro-anilino)propanamide	Intermediate 51; rac-2-bromopropanamide	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.19 (d, *J*=7.35 Hz, 3 H), 5.00 - 5.07 (m, 1 H), 7.29 (t, *J*=73.76 Hz, 1 H), 7.19 (d, *J*=8.62 Hz, 2 H), 7.30 (s, 1 H), 7.49 - 7.54 (m, 1 H), 7.58 (d, *J*=8.87 Hz, 2 H), 7.63 (s, 1 H), 7.73 - 7.79 (m, 2 H), 8.19 (br s, 2 H). LC-MS (method 1) Rt = 1.22 min; MS (ESIpos): m/z = 485.4 $[M+H]^+$ RP-HPLC (method D, basic) 25 % yield

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
48.1 and **48.2**	(R)-2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-chloro-3-fluoro-anilino)propanamide and (S)-2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-chloro-3-fluoro-anilino)propanamide		
48.1	 2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-chloro-3-fluoro-anilino)propanamide (enantiomer 1)	Example 48	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.19 (d, *J*=7.60 Hz, 3 H), 5.03 (q, *J*=7.44 Hz, 1 H), 7.29 (t, *J*=73.76 Hz, 1 H), 7.19 (d, *J*=8.62 Hz, 2 H), 7.30 (s, 1 H), 7.49 - 7.54 (m, 1 H), 7.58 (d, *J*=8.87 Hz, 2 H), 7.63 (s, 1 H), 7.73 - 7.78 (m, 2 H), 8.17 (br s, 2 H). LC-MS (method 1) Rt = 1.22 min; MS (ESIpos): m/z = 485.2 $[M+H]^+$ 19 % yield

Chiral HPLC Example 48.1

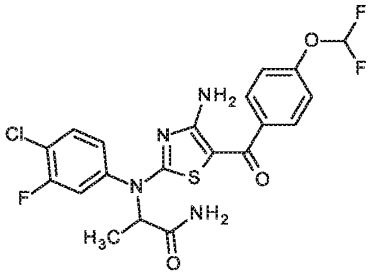
HPLC separation of rac-2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-chloro-3-fluoro-anilino)propanamide (144 mg, 0.3 mmol; Example 48) on a chiral column gave 29 mg (20 % yield) of 2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-chloro-3-fluoro-anilino)propanamide, enantiomer 1.

Preparative chiral HPLC

Instrument: PrepCon Labomatic HPLC; Column: YMC Amylose SA 5µ, 250x30; eluent A: methyl tert-butyl ether + 0.1 vol % diethylamine; eluent B: acetonitrile; isocratic: 85%A+15%B; flow: 50 mL/min; temperature: 25°C; UV: 254 nm

Analytical chiral HPLC: Rt =1.54 min

Instrument: Waters Alliance 2695; Column: YMC Amylose SA 3µ, 100x4.6; eluent A: methyl tert-butyl ether + 0.1 vol % diethylamine; eluent B: acetonitrile; isocratic: 85%A+15%B; flow: 1.4 mL/min; temperature: 25°C; UV: 254 nm

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
48.2	 2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-chloro-3-fluoro-anilino)propanamide (enantiomer 2)	Example 48	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.19 (d, *J*=7.35 Hz, 3 H), 5.03 (q, *J*=7.10 Hz, 1 H), 7.29 (t, *J*=73.76 Hz, 1 H), 7.19 (d, *J*=8.87 Hz, 2 H), 7.30 (s, 1 H), 7.51 (dt, *J*=8.62, 1.27 Hz, 1 H), 7.58 (d, *J*=8.62 Hz, 2 H), 7.63 (s, 1 H), 7.73 - 7.79 (m, 2 H), 8.18 (br s, 2 H). LC-MS (method 1) Rt = 1.22 min; MS (ESIpos): m/z = 485.3 $[M+H]^+$ 24 % yield

Chiral HPLC Example 48.2

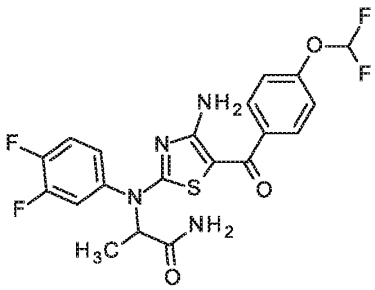
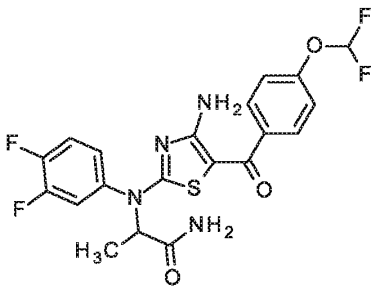
HPLC separation of rac-2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-chloro-3-fluoro-anilino)propanamide (144 mg, 0.3 mmol; Example 48) on a chiral column gave 36 mg (24 % yield) of 2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-chloro-3-fluoro-anilino)propanamide, enantiomer 2.

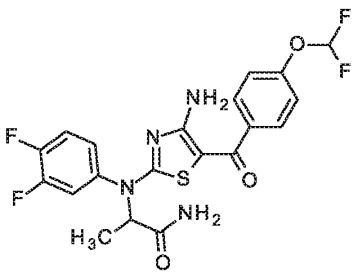
Preparative chiral HPLC

Instrument: PrepCon Labomatic HPLC; Column: YMC Amylose SA 5µ, 250x30; eluent A: methyl tert-butyl ether + 0.1 vol % diethylamine; eluent B: acetonitrile; isocratic: 85%A+15%B; flow: 50 mL/min; temperature: 25°C; UV: 254 nm

Analytical chiral HPLC: Rt =2.09 min

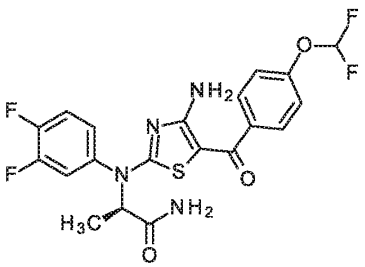
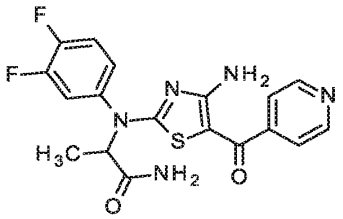
Instrument: Waters Alliance 2695; Column: YMC Amylose SA 3µ, 100x4.6; eluent A: methyl tert-butyl ether + 0.1 vol % diethylamine; eluent B: acetonitrile; isocratic: 85%A+15%B; flow: 1.4 mL/min; temperature: 25°C; UV: 254 nm

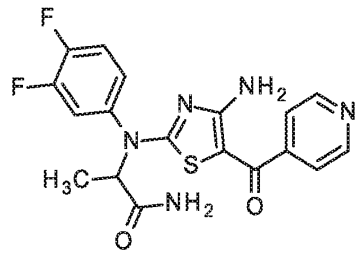
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
49	 rac-2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-3,4-difluoro-anilino)propanamide	Intermediate 52; rac-2-bromopropanamide	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.18 (d, *J*=7.35 Hz, 3 H), 5.03 (q, *J*=6.76 Hz, 1 H), 7.28 (t, *J*=73.76 Hz, 1 H), 7.18 (d, *J*=8.62 Hz, 2 H), 7.30 (s, 1 H), 7.48 - 7.53 (m, 1 H), 7.58 (d, *J*=8.62 Hz, 4 H), 7.78 (ddd, *J*=11.34, 7.41, 2.53 Hz, 1 H), 8.13 (br s, 2 H). LC-MS (method 1) Rt = 1.16 min; MS (ESIpos): m/z = 469.3 $[M+H]^+$ RP-HPLC (method D, basic) 65 % yield
49.1 and **49.2**	(R)-2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-3,4-difluoro-anilino)propanamide and (S)-2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-3,4-difluoro-anilino)propanamide		
49.1	 2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-3,4-difluoro-anilino)propanamide (enantiomer 1)	Example 49	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.18 (d, *J*=7.35 Hz, 3 H), 5.03 (br q, *J*=7.18 Hz, 1 H), 7.29 (t, *J*=73.51 Hz, 3 H), 7.18 (d, *J*=8.36 Hz, 1 H), 7.30 (s, 1 H), 7.48 - 7.53 (m, 1 H), 7.56 - 7.64 (m, 4 H), 7.78 (ddd, *J*=11.34, 7.54, 2.41 Hz, 1 H), 8.17 (br s, 2 H). LC-MS (method 1) Rt = 1.16 min; MS (ESIpos): m/z = 469.3 $[M+H]^+$ 39 % yield

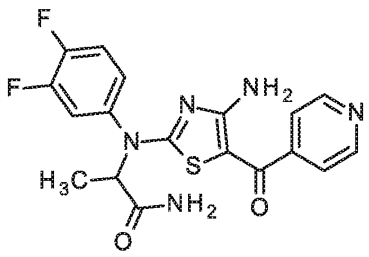
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
Chiral HPLC Example 49.1 HPLC separation of rac-2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-3,4-difluoro-anilino)propanamide (381 mg, 0.81 mmol; Example 49) on a chiral column gave 155 mg (39 % yield) of 2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-3,4-difluoro-anilino)propanamide, enantiomer 1. Preparative chiral HPLC Instrument: PrepCon Labomatic HPLC; Column: YMC Cellulose SB 5µ, 250x30; eluent A: hexane + 0.1 vol % diethylamine; eluent B: ethanol + 0.1 vol % diethylamine; isocratic: 80%A+20%B; flow: 50 mL/min; temperature: 25°C; UV: 254 nm Analytical chiral HPLC: Rt = 4.31 min Instrument: Waters Alliance 2695; Column: YMC Cellulose SB 3µ, 100x4.6; eluent A: hexane + 0.1 vol % diethylamine; eluent B: ethanol; isocratic: 80%A+20%B; flow: 1.4 mL/min; temperature: 25°C; UV: 254 nm			
49.2	 2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-3,4-difluoro-anilino)propanamide (enantiomer 2)	Example 49	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.18 (d, *J*=7.35 Hz, 3 H), 5.03 (q, *J*=7.35 Hz, 1 H), 7.28 (t, *J*=74.01 Hz, 1 H), 7.18 (d, *J*=8.62 Hz, 2 H), 7.30 (s, 1 H), 7.48 - 7.53 (m, 1 H), 7.55 - 7.65 (m, 4 H), 7.78 (ddd, *J*=11.34, 7.54, 2.41 Hz, 1 H), 8.19 (br s, 2 H). LC-MS (method 1) Rt = 1.16 min; MS (ESIpos): m/z = 469.3 $[M+H]^+$ 34 % yield

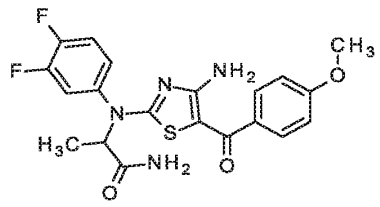
<table>
<tr><th>Example number</th><th>Chemical structure
Compound name</th><th>Starting materials</th><th colspan="2">Analytics/purification/yield</th></tr>
<tr><td colspan="5">Chiral HPLC Example 49.2
HPLC separation of rac-2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-3,4-difluoro-anilino)propanamide (381 mg, 0.81 mmol; Example 49) on a chiral column gave 136 mg (34 % yield) of 2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-3,4-difluoro-anilino)propanamide, enantiomer 2.

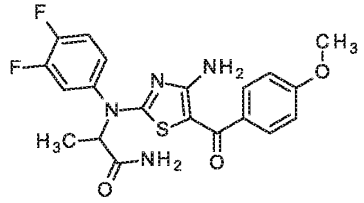
Preparative chiral HPLC
Instrument: PrepCon Labomatic HPLC; Column: YMC Cellulose SB 5µ, 250x30; eluent A: hexane + 0.1 vol % diethylamine; eluent B: ethanol + 0.1 vol % diethylamine; isocratic: 80%A+20%B; flow: 50 mL/min; temperature: 25°C; UV: 254 nm

Analytical chiral HPLC: Rt = 5.54 min
Instrument: Waters Alliance 2695; Column: YMC Cellulose SB 3µ, 100x4.6; eluent A: hexane + 0.1 vol % diethylamine; eluent B: ethanol; isocratic: 80%A+20%B; flow: 1.4 mL/min; temperature: 25°C; UV: 254 nm</td></tr>
<tr><td>49.2</td><td>  </td><td colspan="2">Example 49.2 was determined to be (R)-2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-3,4-difluoro-anilino)propanamide, by means of X-ray crystal structure analysis.</td></tr>
<tr><td>50</td><td> 
rac-2-(N-[4-amino-5-(pyridine-4-carbonyl)thiazol-2-yl]-3,4-difluoro-anilino)propanamide</td><td>Intermediate 53;
rac-2-bromopropanamide</td><td>^{1}H-NMR (400MHz, DMSO-d6): δ ppm = 1.18 (d, J=7.60 Hz, 3 H), 5.03 (q, J=7.35 Hz, 1 H), 7.30 (s, 1 H), 7.40 - 7.44 (m, 2 H), 7.47 - 7.53 (m, 1 H), 7.55 - 7.66 (m, 2 H), 7.77 (ddd, J=11.34, 7.54, 2.41 Hz, 1 H), 8.13 - 8.49 (m, 2 H), 8.60 - 8.66 (m, 2 H).
LC-MS (method 2) Rt = 0.90 min; MS (ESIpos): m/z = 404.3 [M+H]$^+$
97 % yield</td></tr>
</table>

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
50.1 and **50.2**	(R)-2-(N-[4-amino-5-(pyridine-4-carbonyl)thiazol-2-yl]-3,4-difluoro-anilino)propanamide and (S)-2-(N-[4-amino-5-(pyridine-4-carbonyl)thiazol-2-yl]-3,4-difluoro-anilino)propanamide		
50.1	 2-(N-[4-amino-5-(pyridine-4-carbonyl)thiazol-2-yl]-3,4-difluoro-anilino)propanamide (enantiomer 1)	Example 50	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.18 (d, *J*=7.35 Hz, 3 H), 5.03 (br q, *J*=7.27 Hz, 1 H), 7.30 (s, 1 H), 7.40 - 7.45 (m, 2 H), 7.47 - 7.53 (m, 1 H), 7.55 - 7.65 (m, 2 H), 7.78 (br ddd, *J*=11.34, 7.54, 2.41 Hz, 1 H), 8.17 - 8.47 (m, 2 H), 8.60 - 8.66 (m, 2 H). LC-MS (method 2) Rt = 0.87 min; MS (ESIpos): m/z = 404.2 $[M+H]^+$ $[\alpha]_D^{20}$ = -79.8° (c = 1.00, dimethylsulfoxide) 21 % yield

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
Chiral HPLC Example 50.1 HPLC separation of rac-2-(N-[4-amino-5-(pyridine-4-carbonyl)thiazol-2-yl]-3,4-difluoro-anilino)propanamide (974 mg, 2.35 mmol; Example 50) on a chiral column gave 205 mg (21 % yield) of 2-(N-[4-amino-5-(pyridine-4-carbonyl)thiazol-2-yl]-3,4-difluoro-anilino)propanamide, enantiomer 1. Preparative chiral HPLC Instrument: PrepCon Labomatic HPLC; Column: YMC Cellulose SC 10µ, 250x50; eluent A: methyl tert-butyl ether; eluent B: acetonitrile; isocratic: 20%A+80%B; flow: 140 mL/min; temperature: 25°C; UV: 254 nm Analytical chiral HPLC: Rt = 2.71 min Instrument: Thermo Fisher UltiMate 3000; Column: YMC Cellulose SC 3µ, 100x4.6; eluent A: methyl tert-butyl ether + 0.1 vol % diethylamine; eluent B: acetonitrile; isocratic: 20%A+80%B; flow: 1.4 mL/min; temperature: 25°C; UV: 254 nm			
50.2	 2-(N-[4-amino-5-(pyridine-4-carbonyl)thiazol-2-yl]-3,4-difluoro-anilino)propanamide (enantiomer 2)	Example 50	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.18 (d, *J*=7.60 Hz, 3 H), 5.03 (q, *J*=6.67 Hz, 1 H), 7.30 (s, 1 H), 7.40 - 7.44 (m, 2 H), 7.47 - 7.53 (m, 1 H), 7.55 - 7.65 (m, 2 H), 7.77 (ddd, *J*=11.34, 7.54, 2.41 Hz, 1 H), 8.14 - 8.46 (m, 2 H), 8.60 - 8.66 (m, 2 H). LC-MS (method 2) Rt = 0.87 min; MS (ESIpos): m/z = 404.2 $[M+H]^+$ $[\alpha]_D^{20}$ = +84.9° (c = 1.00, dimethylsulfoxide) 21 % yield

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
Chiral HPLC Example 50.2 HPLC separation of rac-2-(N-[4-amino-5-(pyridine-4-carbonyl)thiazol-2-yl]-3,4-difluoro-anilino)propanamide (974 mg, 2.35 mmol; Example 50) on a chiral column gave 204 mg (21 % yield) of 2-(N-[4-amino-5-(pyridine-4-carbonyl)thiazol-2-yl]-3,4-difluoro-anilino)propanamide, enantiomer 2. Preparative chiral HPLC Instrument: PrepCon Labomatic HPLC; Column: YMC Cellulose SC 10µ, 250x50; eluent A: methyl tert-butyl ether; eluent B: acetonitrile; isocratic: 20%A+80%B; flow: 140 mL/min; temperature: 25°C; UV: 254 nm Analytical chiral HPLC: Rt = 3.06 min Instrument: Thermo Fisher UltiMate 3000; Column: YMC Cellulose SC 3µ, 100x4.6; eluent A: methyl tert-butyl ether + 0.1 vol % diethylamine; eluent B: acetonitrile; isocratic: 20%A+80%B; flow: 1.4 mL/min; temperature: 25°C; UV: 254 nm			
51	 rac-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-3,4-difluoro-anilino)propanamide	Intermediate 54; rac-2-bromopropanamide	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.18 (d, *J*=7.60 Hz, 3 H), 3.76 (s, 3 H), 5.02 (q, *J*=7.27 Hz, 1 H), 6.94 (d, *J*=8.87 Hz, 2 H), 7.29 (s, 1 H), 7.50 (d, *J*=8.62 Hz, 3 H), 7.56 - 7.65 (m, 2 H), 7.78 (ddd, *J*=11.41, 7.48, 2.41 Hz, 1 H), 7.89 - 8.45 (m, 2 H) LC-MS (method 2) Rt = 1.09 min; MS (ESIpos): m/z = 433.2 $[M+H]^+$ 85 % yield
51.1 and **51.2**	(R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-3,4-difluoro-anilino)propanamide and (S)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-3,4-difluoro-anilino)propanamide		

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
51.1	 2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-3,4-difluoro-anilino)propanamide (enantiomer 1)	Example 51	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.19 (d, *J*=7.35 Hz, 3 H), 3.76 (s, 3 H), 5.03 (q, *J*=7.18 Hz, 1 H), 6.94 (d, *J*=8.87 Hz, 2 H), 7.29 (s, 1 H), 7.48 - 7.53 (m, 3 H), 7.55 - 7.64 (m, 2 H), 7.78 (ddd, *J*=11.47, 7.41, 2.41 Hz, 1 H), 7.87 - 8.36 (m, 2 H). LC-MS (method 1) Rt = 1.10 min; MS (ESIpos): m/z = 433.5 $[M+H]^+$ 33 % yield

Chiral HPLC Example 51.1

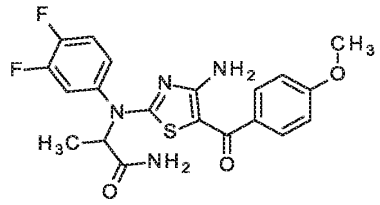
HPLC separation of rac-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-3,4-difluoro-anilino)propanamide (88 mg, 0.20 mmol; Example 51) on a chiral column gave 19 mg (21 % yield) of 2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-3,4-difluoro-anilino)propanamide, enantiomer 1.

Preparative chiral HPLC

Instrument: PrepCon Labomatic HPLC; Column: YMC Cellulose SC 10µ, 250x50; eluent A: methyl tert-butyl ether + 0.1 vol % diethylamine; eluent B: acetonitrile; isocratic: 50%A+50%B; flow: 100 mL/min; temperature: 25°C; UV: 254 nm

Analytical chiral HPLC: Rt =1.57 min

Instrument: Waters Alliance 2695; Column: YMC Cellulose SC 3µ, 100x4.6; eluent A: methyl tert-butyl ether + 0.1 vol % diethylamine; eluent B: acetonitrile; isocratic: 50%A+50%B; flow: 1.4 mL/min; temperature: 25°C; UV: 254 nm

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
51.2	 2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-3,4-difluoro-anilino)propanamide (enantiomer 2)	Example 51	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.19 (d, *J*=7.35 Hz, 3 H), 3.76 (s, 3 H), 5.03 (q, *J*=7.10 Hz, 1 H), 6.94 (d, *J*=8.87 Hz, 2 H), 7.29 (s, 1 H), 7.48 - 7.53 (m, 3 H), 7.56 - 7.65 (m, 2 H), 7.75 - 7.82 (m, 1 H), 7.89 - 8.38 (m, 2 H). LC-MS (method 1) Rt = 1.10 min; MS (ESIpos): m/z = 433.5 $[M+H]^+$ 36 % yield

Chiral HPLC Example 51.2

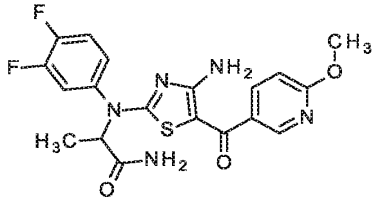
HPLC separation of rac-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-3,4-difluoro-anilino)propanamide (88 mg, 0.20 mmol; Example 51) on a chiral column gave 22 mg (24 % yield) of 2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-3,4-difluoro-anilino)propanamide, enantiomer 2.

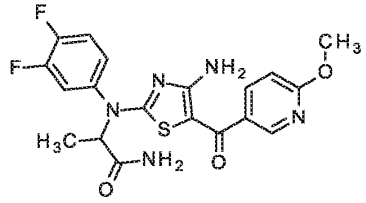
Preparative chiral HPLC

Instrument: PrepCon Labomatic HPLC; Column: YMC Cellulose SC 10µ, 250x50; eluent A: methyl tert-butyl ether + 0.1 vol % diethylamine; eluent B: acetonitrile; isocratic: 50%A+50%B; flow: 100 mL/min; temperature: 25°C; UV: 254 nm

Analytical chiral HPLC: Rt = 1.84 min

Instrument: Waters Alliance 2695; Column: YMC Cellulose SC 3µ, 100x4.6; eluent A: methyl tert-butyl ether + 0.1 vol % diethylamine; eluent B: acetonitrile; isocratic: 50%A+50%B; flow: 1.4 mL/min; temperature: 25°C; UV: 254 nm

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
52	 rac-2-(N-[4-amino-5-(6-methoxypyridine-3-carbonyl)thiazol-2-yl]-3,4-difluoro-anilino)propanamide	Intermediate 55; rac-2-bromopropanamide	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.19 (d, *J*=7.35 Hz, 3 H), 3.86 (s, 3 H), 5.03 (q, *J*=7.69 Hz, 1 H), 6.84 (dd, *J*=8.62, 0.76 Hz, 1 H), 7.30 (s, 1 H), 7.49 - 7.54 (m, 1 H), 7.56 - 7.65 (m, 2 H), 7.79 (ddd, *J*=11.41, 7.35, 2.53 Hz, 1 H), 7.84 (dd, *J*=8.62, 2.28 Hz, 1 H), 8.16 (br s, 2 H), 8.36 (dd, *J*=2.41, 0.63 Hz, 1 H). LC-MS (method 1) Rt = 1.07 min; MS (ESIpos): m/z = 434.3 $[M+H]^+$ RP-HPLC (method C, basic) 48 % yield
52.1 and **52.2**	(R)-2-(N-[4-amino-5-(6-methoxypyridine-3-carbonyl)thiazol-2-yl]-3,4-difluoro-anilino)propanamide and (S)-2-(N-[4-amino-5-(6-methoxypyridine-3-carbonyl)thiazol-2-yl]-3,4-difluoro-anilino)propanamide		

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
52.1	 2-(N-[4-amino-5-(6-methoxypyridine-3-carbonyl)thiazol-2-yl]-3,4-difluoro-anilino)propanamide (enantiomer 1)	Example 52	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.19 (d, *J*=7.35 Hz, 3 H), 3.86 (s, 3 H), 5.03 (q, *J*=6.84 Hz, 1 H), 6.84 (dd, *J*=8.49, 0.63 Hz, 1 H), 7.30 (s, 1 H), 7.49 - 7.54 (m, 1 H), 7.56 - 7.65 (m, 2 H), 7.79 (ddd, *J*=11.34, 7.54, 2.41 Hz, 1 H), 7.84 (dd, *J*=8.62, 2.28 Hz, 1 H), 7.97 - 8.32 (m, 2 H), 8.35 - 8.37 (m, 1 H). LC-MS (method 1) Rt = 1.07 min; MS (ESIpos): m/z = 434.3 $[M+H]^+$ 31 % yield

Chiral HPLC Example 52.1

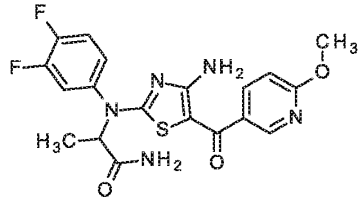
HPLC separation of rac-2-(N-[4-amino-5-(6-methoxypyridine-3-carbonyl)thiazol-2-yl]-3,4-difluoro-anilino)propanamide (31 mg, 0.07 mmol; Example 52) on a chiral column gave 9 mg (27 % yield) of 2-(N-[4-amino-5-(6-methoxypyridine-3-carbonyl)thiazol-2-yl]-3,4-difluoro-anilino)propanamide, enantiomer 1.

Preparative chiral HPLC

Instrument: PrepCon Labomatic HPLC; Column: YMC Amylose SA 5µ, 250x30; eluent A: methyl tert-butyl ether + 0.1 vol % diethylamine; eluent B: acetonitrile + 0.1 vol % diethylamine; isocratic: 50%A+50%B; flow: 40 mL/min; temperature: 25°C; UV: 254 nm

Analytical chiral HPLC: Rt = 1.25 min

Instrument: Waters Alliance 2695; Column: YMC Amylose SA 3µ, 100x4.6; eluent A: methyl tert-butyl ether + 0.1 vol % diethylamine; eluent B: acetonitrile; isocratic: 50%A+50%B; flow: 1.4 mL/min; temperature: 25°C; UV: 254 nm

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
52.2	 2-(N-[4-amino-5-(6-methoxypyridine-3-carbonyl)thiazol-2-yl]-3,4-difluoro-anilino)propanamide (enantiomer 2)	Example 52	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.19 (d, *J*=7.35 Hz, 3 H), 3.86 (s, 3 H), 5.03 (q, *J*=6.93 Hz, 1 H), 6.82 - 6.86 (m, 1 H), 7.30 (s, 1 H), 7.49 - 7.54 (m, 1 H), 7.56 - 7.64 (m, 2 H), 7.79 (ddd, *J*=11.28, 7.48, 2.28 Hz, 1 H), 7.84 (dd, *J*=8.62, 2.53 Hz, 1 H), 7.96 - 8.31 (m, 2 H), 8.36 (d, *J*=2.03 Hz, 1 H). LC-MS (method 1) Rt = 1.07 min; MS (ESIpos): m/z = 434.3 $[M+H]^+$ 31 % yield

Chiral HPLC Example 52.2

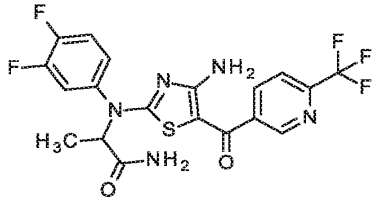
HPLC separation of rac-2-(N-[4-amino-5-(6-methoxypyridine-3-carbonyl)thiazol-2-yl]-3,4-difluoro-anilino)propanamide (31 mg, 0.07 mmol; Example 52) on a chiral column gave 7 mg (20 % yield) of 2-(N-[4-amino-5-(6-methoxypyridine-3-carbonyl)thiazol-2-yl]-3,4-difluoro-anilino)propanamide, enantiomer 2.

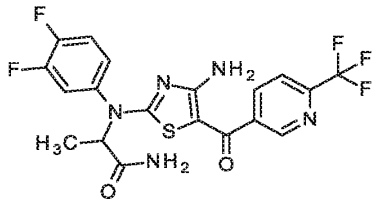
Preparative chiral HPLC

Instrument: PrepCon Labomatic HPLC; Column: YMC Amylose SA 5µ, 250x30; eluent A: methyl tert-butyl ether + 0.1 vol % diethylamine; eluent B: acetonitrile + 0.1 vol % diethylamine; isocratic: 50%A+50%B; flow: 40 mL/min; temperature: 25°C; UV: 254 nm

Analytical chiral HPLC: Rt = 1.74 min

Instrument: Waters Alliance 2695; Column: YMC Amylose SA 3µ, 100x4.6; eluent A: methyl tert-butyl ether + 0.1 vol % diethylamine; eluent B: acetonitrile; isocratic: 50%A+50%B; flow: 1.4 mL/min; temperature: 25°C; UV: 254 nm

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
53	 rac-2-(N-[4-amino-5-[6-(trifluoromethyl)pyridine-3-carbonyl]thiazol-2-yl]-3,4-difluoro-anilino)propanamide	Intermediate 56; rac-2-bromopropanamide	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.19 (d, *J*=7.60 Hz, 3 H), 4.99 - 5.09 (m, 1 H), 7.31 (s, 1 H), 7.47 - 7.54 (m, 1 H), 7.55 - 7.67 (m, 2 H), 7.78 (ddd, *J*=11.22, 7.54, 2.53 Hz, 1 H), 7.95 (d, *J*=7.60 Hz, 1 H), 8.15 (dd, *J*=7.98, 1.90 Hz, 1 H), 8.24 - 8.49 (m, 2 H), 8.86 (d, *J*=1.77 Hz, 1 H). LC-MS (method 1) Rt = 1.16 min; MS (ESIpos): m/z = 472.3 $[M+H]^+$ RP-HPLC (method C, basic) 55 % yield
53.1 and **53.2**	(R)-2-(N-[4-amino-5-[6-(trifluoromethyl)pyridine-3-carbonyl]thiazol-2-yl]-3,4-difluoro-anilino)propanamide and (S)-2-(N-[4-amino-5-[6-(trifluoromethyl)pyridine-3-carbonyl]thiazol-2-yl]-3,4-difluoro-anilino)propanamide		

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
53.1	 2-(N-[4-amino-5-[6-(trifluoromethyl)pyridine-3-carbonyl]thiazol-2-yl]-3,4-difluoro-anilino)propanamide (enantiomer 1)	Example 53	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.19 (d, *J*=7.60 Hz, 3 H), 5.04 (br q, *J*=6.84 Hz, 1 H), 7.31 (s, 1 H), 7.48 - 7.53 (m, 1 H), 7.55 - 7.66 (m, 2 H), 7.78 (ddd, *J*=11.28, 7.48, 2.28 Hz, 1 H), 7.95 (dd, *J*=8.24, 0.63 Hz, 1 H), 8.15 (dd, *J*=7.98, 1.90 Hz, 1 H), 8.23 - 8.51 (m, 2 H), 8.86 (d, *J*=1.77 Hz, 1 H). LC-MS (method 1) Rt = 1.13 min; MS (ESIpos): m/z = 472.2 $[M+H]^+$ 30 % yield

Chiral HPLC Example 53.1

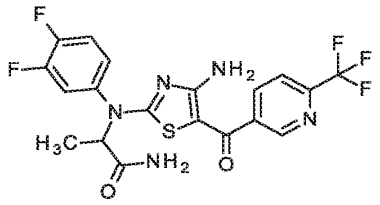
HPLC separation of rac-2-(N-[4-amino-5-[6-(trifluoromethyl)pyridine-3-carbonyl]thiazol-2-yl]-3,4-difluoro-anilino)propanamide (164 mg, 0.35 mmol; Example 53) on a chiral column gave 51 mg (30 % yield) of 2-(N-[4-amino-5-[6-(trifluoromethyl)pyridine-3-carbonyl]thiazol-2-yl]-3,4-difluoro-anilino)propanamide, enantiomer 1.

Preparative chiral HPLC

Instrument: PrepCon Labomatic HPLC; Column: YMC Amylose SA 5µ, 250x30; eluent A: methyl tert-butyl ether + 0.1 vol % diethylamine; eluent B: acetonitrile; isocratic: 50%A+50%B; flow: 50 mL/min; temperature: 25°C; UV: 254 nm

Analytical chiral HPLC: Rt = 1.05 min

Instrument: Waters Alliance 2695; Column: YMC Amylose SA 3µ, 100x4.6; eluent A: methyl tert-butyl ether + 0.1 vol % diethylamine; eluent B: acetonitrile; isocratic: 50%A+50%B; flow: 1.4 mL/min; temperature: 25°C; UV: 254 nm

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
53.2	 2-(N-[4-amino-5-[6-(trifluoromethyl)pyridine-3-carbonyl]thiazol-2-yl]-3,4-difluoro-anilino)propanamide (enantiomer 2)	Example 53	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.19 (d, *J*=7.35 Hz, 3 H), 5.04 (br q, *J*=7.10 Hz, 1 H), 7.31 (s, 1 H), 7.46 - 7.53 (m, 1 H), 7.55 - 7.66 (m, 2 H), 7.78 (ddd, *J*=11.34, 7.54, 2.41 Hz, 1 H), 7.95 (dd, *J*=8.24, 0.63 Hz, 1 H), 8.15 (dd, *J*=7.98, 1.90 Hz, 1 H), 8.23 - 8.56 (m, 2 H), 8.86 (d, *J*=1.77 Hz, 1 H). LC-MS (method 1) Rt = 1.13 min; MS (ESIpos): m/z = 472.2 $[M+H]^+$ 27 % yield

Chiral HPLC Example 53.2

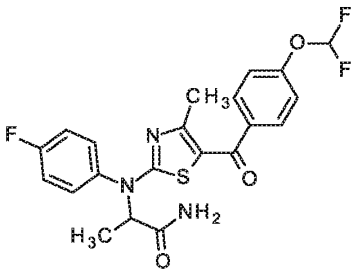
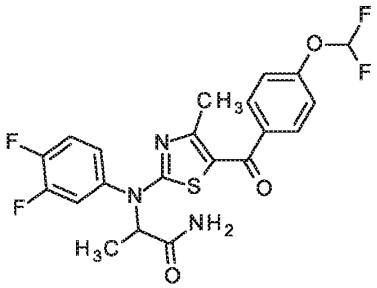
HPLC separation of rac-2-(N-[4-amino-5-[6-(trifluoromethyl)pyridine-3-carbonyl]thiazol-2-yl]-3,4-difluoro-anilino)propanamide (164 mg, 0.35 mmol; Example 53) on a chiral column gave 47 mg (27 % yield) of 2-(N-[4-amino-5-[6-(trifluoromethyl)pyridine-3-carbonyl]thiazol-2-yl]-3,4-difluoro-anilino)propanamide, enantiomer 2.

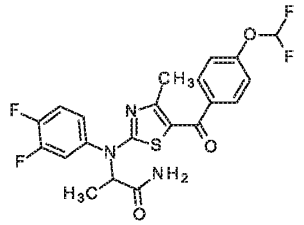
Preparative chiral HPLC

Instrument: PrepCon Labomatic HPLC; Column: YMC Amylose SA 5µ, 250x30; eluent A: methyl tert-butyl ether + 0.1 vol % diethylamine; eluent B: acetonitrile; isocratic: 50%A+50%B; flow: 50 mL/min; temperature: 25°C; UV: 254 nm

Analytical chiral HPLC: Rt = 1.36 min

Instrument: Waters Alliance 2695; Column: YMC Amylose SA 3µ, 100x4.6; eluent A: methyl tert-butyl ether + 0.1 vol % diethylamine; eluent B: acetonitrile; isocratic: 50%A+50%B; flow: 1.4 mL/min; temperature: 25°C; UV: 254 nm

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
54	 rac-2-(N-[5-[4-(difluoromethoxy)benzoyl]-4-methyl-thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 78; rac-2-bromopropanamide	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.16 (d, *J*=7.60 Hz, 3 H), 2.28 (s, 3 H), 5.11 (q, *J*=7.10 Hz, 1 H), 7.15 - 7.25 (m, 3 H), 7.33 - 7.39 (m, 3 H), 7.61 - 7.71 (m, 5 H). LC-MS (method 1) Rt = 1.20 min; MS (ESIpos): m/z = 449.1 $[M+H]^+$ RP-HPLC (method D, basic) 52 % yield
55	 rac-2-(N-[5-[4-(difluoromethoxy)benzoyl]-4-methyl-thiazol-2-yl]-3,4-difluoro-anilino)propanamide	Intermediate 79; rac-2-bromopropanamide	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.19 (d, *J*=7.35 Hz, 3 H), 2.27 (s, 3 H), 5.09 (q, *J*=7.27 Hz, 1 H), 7.16 - 7.38 (m, 4 H), 7.51 - 7.56 (m, 1 H), 7.58 - 7.69 (m, 4 H), 7.82 (ddd, *J*=11.34, 7.54, 2.41 Hz, 1 H). LC-MS (method 1) Rt = 1.23 min; MS (ESIpos): m/z = 466.3 $[M+H]^+$ RP-HPLC (method D, basic) 7 % yield
55.1 and **55.2**	(R)-2-(N-[5-[4-(difluoromethoxy)benzoyl]-4-methyl-thiazol-2-yl]-3,4-difluoro-anilino)propanamide and (S)-2-(N-[5-[4-(difluoromethoxy)benzoyl]-4-methyl-thiazol-2-yl]-3,4-difluoro-anilino)propanamide		

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
55.1	 2-(N-[5-[4-(difluoromethoxy)benzoyl]-4-methyl-thiazol-2-yl]-3,4-difluoro-anilino)propanamide (enantiomer 1)	Example 55	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.19 (d, *J*=7.35 Hz, 3 H), 2.27 (s, 3 H), 5.08 – 5.10 (m, 1 H), 7.20 – 7.24 (m, 3 H), 7.35 (t, J=72 Hz, 1 H), 7.52 – 7.54 (m, 1 H), 7.60 – 7.66 (m, 4 H), 7.81 – 7.83 (m, 1 H) LC-MS (method 1) Rt = 1.23 min MS (ESIpos): m/z = 468.5 $[M+H]^+$ 35 % yield

Chiral HPLC Example 55.1

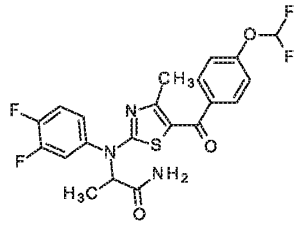
HPLC separation of rac-2-(N-[5-[4-(difluoromethoxy)benzoyl]-4-methyl-thiazol-2-yl]-3,4-difluoro-anilino)propanamide (59 mg, 0.13 mmol, Example 55) on a chiral column gave 21 mg (35 % yield) of 2-(N-[5-[4-(difluoromethoxy)benzoyl]-4-methyl-thiazol-2-yl]-3,4-difluoro-anilino)propanamide, enantiomer 1.

Preparative chiral HPLC

Instrument: PrepCon Labomatic HPLC-2; Column: Chiralpak AS 5µ, 250x20; eluent A: hexane + 0.1 vol % diethylamine; eluent B: 2-propanol; isocratic: 80%A+20%B; flow: 20 mL/min; temperature: 25°C; UV: 254 nm

Analytical chiral HPLC: Rt = 5.43 min

Instrument: Thermo Fisher UltiMate 3000; Column: Chiralpak AS 3µ, 100x4.6; eluent A: hexane + 0.1 vol % diethylamine; eluent B: 2-propanol; isocratic: 80%A+20%B; flow: 1.4 mL/min; temperature: 25°C; UV: 254 nm

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
55.2	 2-(N-[5-[4-(difluoromethoxy)benzoyl]-4-methyl-thiazol-2-yl]-3,4-difluoro-anilino)propanamidepropanamide (enantiomer 2)	Example 55	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.19 (d, *J*=7.35 Hz, 3 H), 2.27 (s, 3 H), 5.08 – 5.10 (m, 1 H), 7.20 – 7.24 (m, 3 H), 7.35 (t, J=72 Hz, 1 H), 7.52 – 7.54 (m, 1 H), 7.60 – 7.66 (m, 4 H), 7.81 – 7.83 (m, 1 H) LC-MS (method 1) Rt = 1.23 min MS (ESIpos): m/z = 468.5 $[M+H]^+$ 17 % yield

Chiral HPLC Example 55.2

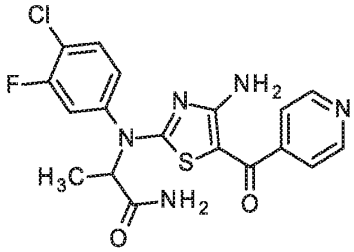
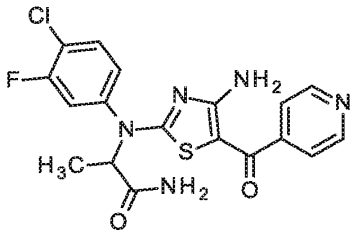
HPLC separation of rac-2-(N-[5-[4-(difluoromethoxy)benzoyl]-4-methyl-thiazol-2-yl]-3,4-difluoro-anilino)propanamide (59 mg, 0.13 mmol, Example 55) on a chiral column gave 10 mg (17 % yield) of 2-(N-[5-[4-(difluoromethoxy)benzoyl]-4-methyl-thiazol-2-yl]-3,4-difluoro-anilino)propanamide, enantiomer 2.

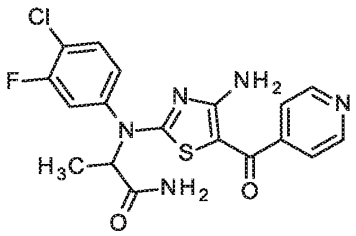
Preparative chiral HPLC

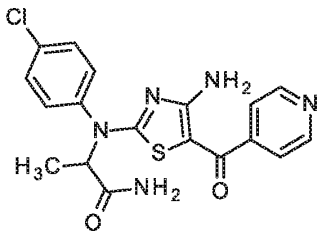
Instrument: PrepCon Labomatic HPLC-2; Column: Chiralpak AS 5µ, 250x20; eluent A: hexane + 0.1 vol % diethylamine; eluent B: 2-propanol; isocratic: 80%A+20%B; flow: 20 mL/min; temperature: 25°C; UV: 254 nm

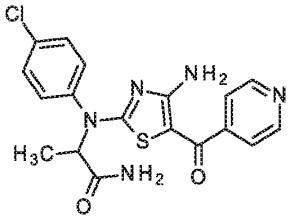
Analytical chiral HPLC: Rt = 9.88 min

Instrument: Thermo Fisher UltiMate 3000; Column: Chiralpak AS 3µ, 100x4.6; eluent A: hexane + 0.1 vol % diethylamine; eluent B: 2-propanol; isocratic: 80%A+20%B; flow: 1.4 mL/min; temperature: 25°C; UV: 254 nm

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
56	 rac-2-(N-[4-amino-5-(pyridine-4-carbonyl)thiazol-2-yl]-4-chloro-3-fluoro-anilino)propanamide	Intermediate 57; rac-2-bromopropanamide	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.19 (d, *J*=7.35 Hz, 3 H), 5.03 (q, *J*=7.35 Hz, 1 H), 7.31 (s, 1 H), 7.43 (br d, *J*=4.31 Hz, 2 H), 7.49 - 7.53 (m, 1 H), 7.64 (s, 1 H), 7.71 - 7.78 (m, 2 H), 8.13 - 8.48 (m, 2 H), 8.63 (br s, 2 H). LC-MS (method 2) Rt = 0.96 min; MS (ESIpos): m/z = 420.3 $[M+H]^+$ RP-HPLC (method C, basic) 33 % yield
56.1 and **56.2**	(R)-2-(N-[4-amino-5-(pyridine-4-carbonyl)thiazol-2-yl]-4-chloro-3-fluoro-anilino)propanamide and (S)-2-(N-[4-amino-5-(pyridine-4-carbonyl)thiazol-2-yl]-4-chloro-3-fluoro-anilino)propanamide		
56.1	 2-(N-[4-amino-5-(pyridine-4-carbonyl)thiazol-2-yl]-4-chloro-3-fluoro-anilino)propanamide (enantiomer 1)	Example 56	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.19 (d, *J*=7.60 Hz, 3 H), 4.98 - 5.08 (m, 1 H), 7.31 (s, 1 H), 7.41 - 7.45 (m, 2 H), 7.48 - 7.53 (m, 1 H), 7.64 (s, 1 H), 7.72 - 7.77 (m, 2 H), 8.07 - 8.45 (m, 2 H), 8.62 - 8.65 (m, 2 H). LC-MS (method 2) Rt = 0.94 min; MS (ESIpos): m/z = 420.2 $[M+H]^+$ 19 % yield

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
Chiral HPLC Example 56.1 HPLC separation of rac-2-(N-[4-amino-5-(pyridine-4-carbonyl)thiazol-2-yl]-4-chloro-3-fluoro-anilino)propanamide (133 mg, 0.32 mmol; Example 56) on a chiral column gave 26 mg (20 % yield) of 2-(N-[4-amino-5-(pyridine-4-carbonyl)thiazol-2-yl]-4-chloro-3-fluoro-anilino)propanamide, enantiomer 1. Preparative chiral HPLC Instrument: PrepCon Labomatic HPLC; Column: YMC Cellulose SC 10µ, 250x50; eluent A: methyl tert-butyl ether; eluent B: acetonitrile; isocratic: 60%A+40%B; flow: 140 mL/min; temperature: 25°C; UV: 254 nm Analytical chiral HPLC: Rt = 3.10 min Instrument: Thermo Fisher UltiMate 3000; Column: YMC Cellulose SC 3µ, 100x4.6; eluent A: methyl tert-butyl ether + 0.1 vol % diethylamine; eluent B: acetonitrile; isocratic: 60%A+40%B; flow: 1.4 mL/min; temperature: 25°C; UV: 254 nm			
56.2	 2-(N-[4-amino-5-(pyridine-4-carbonyl)thiazol-2-yl]-4-chloro-3-fluoro-anilino)propanamide (enantiomer 2)	Example 56	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.19 (d, *J*=7.60 Hz, 3 H), 5.03 (q, *J*=7.35 Hz, 1 H), 7.31 (s, 1 H), 7.40 - 7.46 (m, 2 H), 7.49 - 7.53 (m, 1 H), 7.64 (s, 1 H), 7.72 - 7.79 (m, 2 H), 8.12 - 8.47 (m, 2 H), 8.61 - 8.66 (m, 2 H) LC-MS (method 2) Rt = 0.94 min; MS (ESIpos): m/z = 420.2 $[M+H]^+$ 20 % yield

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
Chiral HPLC Example 56.2 HPLC separation of rac-2-(N-[4-amino-5-(pyridine-4-carbonyl)thiazol-2-yl]-4-chloro-3-fluoro-anilino)propanamide (133 mg, 0.32 mmol; Example 56) on a chiral column gave 27 mg (20 % yield) of 2-(N-[4-amino-5-(pyridine-4-carbonyl)thiazol-2-yl]-4-chloro-3-fluoro-anilino)propanamide, enantiomer 2. Preparative chiral HPLC Instrument: PrepCon Labomatic HPLC; Column: YMC Cellulose SC 10µ, 250x50; eluent A: methyl tert-butyl ether; eluent B: acetonitrile; isocratic: 60%A+40%B; flow: 140 mL/min; temperature: 25°C; UV: 254 nm Analytical chiral HPLC: Rt =3.34 min Instrument: Thermo Fisher UltiMate 3000; Column: YMC Cellulose SC 3µ, 100x4.6; eluent A: methyl tert-butyl ether + 0.1 vol % diethylamine; eluent B: acetonitrile; isocratic: 60%A+40%B; flow: 1.4 mL/min; temperature: 25°C; UV: 254 nm			
57	 rac-2-(N-[4-amino-5-(pyridine-4-carbonyl)thiazol-2-yl]-4-chloro-anilino)propanamide	Intermediate 58; rac-2-bromopropanamide	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.16 (d, *J*=7.35 Hz, 3 H), 5.06 (q, *J*=7.27 Hz, 1 H), 7.27 (s, 1 H), 7.41 (d, *J*=6.08 Hz, 2 H), 7.59 (d, *J*=10.90 Hz, 5 H), 8.08 - 8.48 (m, 2 H), 8.62 (d, *J*=6.08 Hz, 2 H). LC-MS (method 2) Rt = 0.91 min; MS (ESIpos): m/z = 402.2 $[M+H]^+$ 50 % yield
57.1 and **57.2**	(R)-2-(N-[4-amino-5-(pyridine-4-carbonyl)thiazol-2-yl]-4-chloro-anilino)propanamide and (S)-2-(N-[4-amino-5-(pyridine-4-carbonyl)thiazol-2-yl]-4-chloro-anilino)propanamide		

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
57.1	 2-(N-[4-amino-5-(pyridine-4-carbonyl)thiazol-2-yl]-4-chloro-anilino)propanamide (enantiomer 1)	Example 57	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.17 (d, J=7.35 Hz, 3 H), 5.06 (m, 1 H), 7.28 (s, 1 H), 7.41 (m, 2 H), 7.59 (m, 5 H), 8.28 (m, 2 H), 8.62 (m, 2 H) LC-MS (method 1) Rt = 0.85 min MS (ESIpos): m/z = 402.4 $[M+H]^+$ $[\alpha]_D^{20}$ = -67° c = 8.2 mg/mL in DMSO 38 % yield

Chiral HPLC Example 57.1

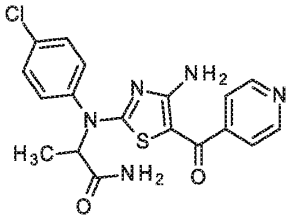
HPLC separation of rac-2-(N-[4-amino-5-(pyridine-4-carbonyl)thiazol-2-yl]-4-chloro-anilino)propanamide (590 mg, 1.47 mmol, Example 57) on a chiral column gave 234 mg (38 % yield) of 2-(N-[4-amino-5-(pyridine-4-carbonyl)thiazol-2-yl]-4-chloro-anilino)propanamide, enantiomer 1.

Preparative chiral HPLC

Instrument: Sepiatec: Prep SFC100; Column: Chiralpak IG 5µ 250x30mm; eluent A: CO_2; eluent B: ethanol + 0.2 vol % aqueous ammonia (32%); isocratic: 30%B; flow: 100 mL/min; temperature: 40°C; BPR: 150bar; UV: 254 nm

Analytical chiral HPLC: Rt = 4.76 min

Instrument: Agilent: 1260, Aurora SFC-Modul; Column: Chiralpak IG 5µ 100x4.6mm; eluent A: CO_2; eluent B: ethanol + 0.2 vol % aqueous ammonia (32%); isocratic: 30%B; flow: 4 mL/min; temperature: 37.5°C; BPR: 100bar; UV: 254 nm

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
57.2	 2-(N-[4-amino-5-(pyridine-4-carbonyl)thiazol-2-yl]-4-chloro-anilino)propanamide (enantiomer 2)	Example 57	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.17 (d, *J*=7.35 Hz, 3 H), 5.06 (m, 1 H), 7.28 (s, 1 H), 7.41 (m, 2 H), 7.59 (m, 5 H), 8.28 (m, 2 H), 8.62 (m, 2 H) LC-MS (method 1) Rt = 0.85 min MS (ESIpos): m/z = 402.4 $[M+H]^+$ $[\alpha]_D^{20}$ = 76° c = 9.6 mg/mL in DMSO 36 % yield

Chiral HPLC Example 57.2

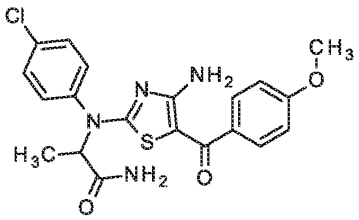
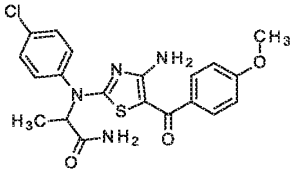
HPLC separation of rac-2-(N-[4-amino-5-(pyridine-4-carbonyl)thiazol-2-yl]-4-chloro-anilino)propanamide (590 mg, 1.47 mmol, Example 57) on a chiral column gave 225 mg (36 % yield) of 2-(N-[4-amino-5-(pyridine-4-carbonyl)thiazol-2-yl]-4-chloro-anilino)propanamide, enantiomer 2.

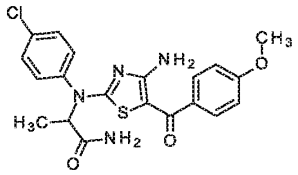
Preparative chiral HPLC

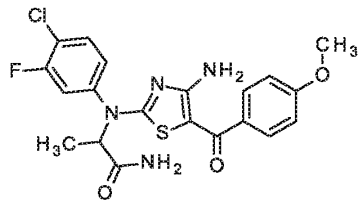
Instrument: Sepiatec: Prep SFC100; Column: Chiralpak IG 5µ 250x30mm; eluent A: CO_2; eluent B: ethanol + 0.2 vol % aqueous ammonia (32%); isocratic: 30%B; flow: 100 mL/min; temperature: 40°C; BPR: 150bar; UV: 254 nm

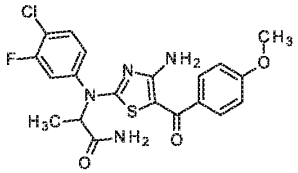
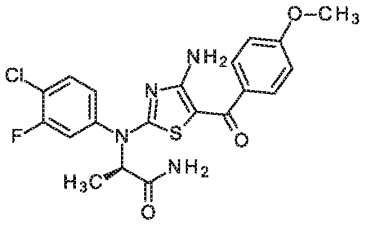
Analytical chiral HPLC: Rt = 2.59 min

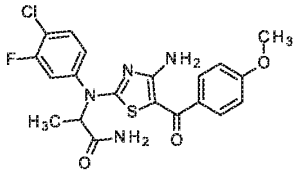
Instrument: Agilent: 1260, Aurora SFC-Modul; Column: Chiralpak IG 5µ 100x4.6mm; eluent A: CO_2; eluent B: ethanol + 0.2 vol % aqueous ammonia (32%); isocratic: 30%B; flow: 4 mL/min; temperature: 37.5°C; BPR: 100bar; UV: 254 nm

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
58	 rac-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-chloro-anilino)propanamide	Intermediate 59; rac-2-bromopropanamide	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.16 (d, *J*=7.35 Hz, 3 H), 3.76 (s, 3 H), 5.05 (q, *J*=7.18 Hz, 1 H), 6.93 (d, *J*=8.87 Hz, 2 H), 7.26 (s, 1 H), 7.49 (d, *J*=8.87 Hz, 2 H), 7.55 - 7.64 (m, 5 H), 7.82 - 8.39 (m, 2 H). LC-MS (method 2) Rt = 1.13 min; MS (ESIpos): m/z = 431.2 $[M+H]^+$ 77 % yield
58.1 and **58.2**	(R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-chloro-anilino)propanamide and (S)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-chloro-anilino)propanamide		
58.1	 2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-chloro-anilino)propanamide (enantiomer 1)	Example 58	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.16 (d, *J*=7.35 Hz, 3 H), 3.76 (s, 3 H), 5.06 (m, 1 H), 6.93 (m, 2 H), 7.25 (m, 1 H), 7.49 (m, 2 H), 7.60 (m, 5 H), 8.04 (m, 2 H) LC-MS (method 1) Rt = 1.14 min MS (ESIpos): m/z = 431.4 $[M+H]^+$ $[\alpha]_D^{20}$ = - 80° c = 11.1 mg/mL in DMSO 36 % yield

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
Chiral HPLC Example 58.1 HPLC separation of rac-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-chloro-anilino)propanamide (2.83 g, 6.57 mmol, Example 58) on a chiral column gave 1.03 g (36 % yield) of 2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-chloro-anilino)propanamide, enantiomer 1. Preparative chiral HPLC Instrument: Labomatic HD3000, Knauer Pump 100, Labcol Vario 4000 Plus, Knauer DAD 2600; Column: Cellulose SB 5µ 250x50mm Nr. 034; eluent A: hexane + 0.1 Vol-% diethylamine (99%); eluent B: ethanol + 0.1 Vol-% diethylamine (99%); isocratic: 60%A + 40%B; flow 100.0 mL/min, UV @ 254 nm Analytical chiral HPLC: Rt = 4.15 min Instrument: Agilent HPLC 1260; Column: Cellulose SB 3µ 100x4,6mm; eluent A: hexane + 0.1 Vol-% diethylamine (99%); eluent B: ethanol + 0.1 Vol-% diethylamine (99%); isocratic: 60%A + 40%B; flow 1.0 mL/min; temperature: 25 °C; DAD 254 nm			
58.2	 2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-chloro-anilino)propanamide (enantiomer 2)	Example 58	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.16 (d, *J*=7.35 Hz, 3 H), 3.76 (s, 3 H), 5.06 (m, 1 H), 6.93 (m, 2 H), 7.25 (m, 1 H), 7.49 (m, 2 H), 7.60 (m, 5 H), 8.04 (m, 2 H) LC-MS (method 1) Rt = 1.14 min MS (ESIpos): m/z = 431.4 $[M+H]^+$ $[\alpha]_D^{20}$ = 79° c = 11.1 mg/mL in DMSO 41 % yield

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
Chiral HPLC Example 58.2 HPLC separation of rac-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-chloro-anilino)propanamide (2.83 g, 6.57 mmol, Example 58) on a chiral column gave 1.18 g (41 % yield) of 2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-chloro-anilino)propanamide, enantiomer 2. Preparative chiral HPLC Instrument: Labomatic HD3000, Knauer Pump 100, Labcol Vario 4000 Plus, Knauer DAD 2600; Column: Cellulose SB 5µ 250x50mm Nr. 034; eluent A: hexane + 0.1 Vol-% diethylamine (99%); eluent B: ethanol + 0.1 Vol-% diethylamine (99%); isocratic: 60%A + 40%B; flow 100.0 mL/min, UV @ 254 nm Analytical chiral HPLC: Rt = 3.40 min Instrument: Agilent HPLC 1260; Column: Cellulose SB 3µ 100x4,6mm; eluent A: hexane + 0.1 Vol-% diethylamine (99%); eluent B: ethanol + 0.1 Vol-% diethylamine (99%); isocratic: 60%A + 40%B; flow 1.0 mL/min; temperature: 25 °C; DAD 254 nm			
59	 rac-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-chloro-3-fluoro-anilino)propanamide	Intermediate 60; rac-2-bromopropanamide	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.20 (d, *J*=7.35 Hz, 3 H), 3.77 (s, 3 H), 5.03 (q, *J*=7.35 Hz, 1 H), 6.94 (d, *J*=8.87 Hz, 2 H), 7.30 (s, 1 H), 7.49 - 7.53 (m, 3 H), 7.63 (s, 1 H), 7.73 - 7.79 (m, 2 H), 7.88 - 8.31 (m, 2 H). LC-MS (method 2) Rt = 1.17 min; MS (ESIpos): m/z = 449.3 $[M+H]^+$ 83 % yield
59.1 and **59.2**	(R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-chloro-3-fluoro-anilino)propanamide and (S)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-chloro-3-fluoro-anilino)propanamide		

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
59.1	 2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-chloro-3-fluoro-anilino)propanamide (enantiomer 1)	Example 59	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.20 (d, *J*=7.35 Hz, 3 H), 3.76 (s, 3 H), 5.03 (q, *J*=7.35 Hz, 1 H), 6.94 (m, 2 H), 7.30 (s, 1 H), 7.52 (m, 3 H), 7.63 (s, 1 H), 7.75 (m, 2 H), 8.10 (m, 2 H) LC-MS (method 1) Rt = 1.16 min MS (ESIpos): m/z = 449.4 $[M+H]^+$ $[\alpha]_D^{20}$ = -82° c = 8.2 mg/mL in DMSO 29 % yield
Chiral HPLC Example 59.1 HPLC separation of rac-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-chloro-3-fluoro-anilino)propanamide (442 mg, 0.98 mmol, Example 59) on a chiral column gave 132 mg (29 % yield) of 2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-chloro-3-fluoro-anilino)propanamide, enantiomer 1. Preparative chiral HPLC Instrument: PrepCon Labomatic HPLC-4; Column: YMC Amylose SA 5µ, 250x30; eluent A: methyl tert-butyl ether + 0.1 vol % diethylamine; eluent B: acetonitrile; isocratic: 70%A+30%B; flow: 50 mL/min; temperature: 25°C; UV: 254 nm Analytical chiral HPLC: Rt = 1.49 min Instrument: Waters Alliance 2695; Column: YMC Amylose SA 3µ, 100x4.6; eluent A: methyl tert-butyl ether + 0.1 vol % diethylamine; eluent B: acetonitrile; isocratic: 70%A+30%B; flow: 1.4 mL/min; temperature: 25°C; UV: 254 nm			
59.1		Example 59.1 was determined to be (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-chloro-3-fluoro-anilino)propanamide, by means of X-ray crystal structure analysis.	

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
59.2	 2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-chloro-3-fluoro-anilino)propanamide (enantiomer 2)	Example 59	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.20 (d, *J*=7.35 Hz, 3 H), 3.76 (s, 3 H), 5.03 (q, *J*=7.35 Hz, 1 H), 6.94 (m, 2 H), 7.30 (s, 1 H), 7.52 (m, 3 H), 7.63 (s, 1 H), 7.75 (m, 2 H), 8.10 (m, 2 H) LC-MS (method 1) Rt = 1.16 min MS (ESIpos): m/z = 449.4 $[M+H]^+$ $[\alpha]_D^{20}$ = 87° c = 7.6 mg/mL in DMSO 15 % yield

Chiral HPLC Example 59.2

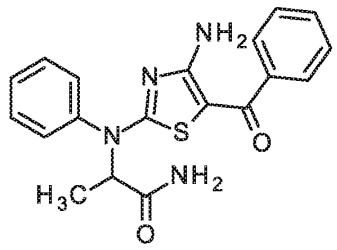
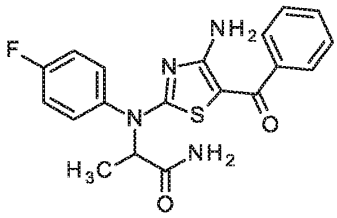
HPLC separation of rac-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-chloro-3-fluoro-anilino)propanamide (442 mg, 0.98 mmol, Example 59) on a chiral column gave 68 mg (15 % yield) of 2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-chloro-3-fluoro-anilino)propanamide, enantiomer 2.

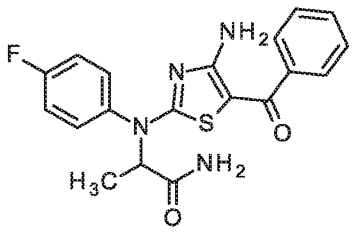
Preparative chiral HPLC

Instrument: PrepCon Labomatic HPLC-4; Column: YMC Amylose SA 5µ, 250x30;
eluent A: methyl tert-butyl ether + 0.1 vol % diethylamine; eluent B: acetonitrile; isocratic: 70%A+30%B; flow: 50 mL/min; temperature: 25°C; UV: 254 nm

Analytical chiral HPLC: Rt = 2.03 min

Instrument: Waters Alliance 2695; Column: YMC Amylose SA 3µ, 100x4.6;
eluent A: methyl tert-butyl ether + 0.1 vol % diethylamine; eluent B: acetonitrile; isocratic: 70%A+30%B; flow: 1.4 mL/min; temperature: 25°C; UV: 254 nm

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
60	 rac-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)anilino)propanamide	Intermediate 83; rac-2-bromopropanamide	^{1}H-NMR (600 MHz, DMSO-*d6*): δ ppm = 1.16 (d, *J*=7.25 Hz, 3 H), 5.09 (q, *J*=7.25 Hz, 1 H), 7.24 (s, 1 H), 7.35 - 7.40 (m, 3 H), 7.42 - 7.50 (m, 5 H), 7.54 - 7.57 (m, 3 H), 7.74 - 8.52 (m, 2 H). LC-MS (method 2) Rt = 1.02 min; MS (ESIpos): m/z = 367.1 $[M+H]^+$ preparative flash chromatography (method Z, 0-3%) 46 % yield
61	 rac-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-4-fluoro-anilino)propanamide	Intermediate 84; rac-2-bromopropanamide	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.16 (d, *J*=7.35 Hz, 3 H), 5.00 - 5.10 (m, 1 H), 7.25 (s, 1 H), 7.32 (t, *J*=8.87 Hz, 2 H), 7.35 - 7.42 (m, 3 H), 7.45 - 7.52 (m, 2 H), 7.58 (s, 1 H), 7.63 (dd, *J*=9.00, 5.20 Hz, 2 H), 7.80 - 8.46 (m, 2 H). LC-MS (method 2) Rt = 1.07 min; MS (ESIpos): m/z = 385.3 $[M+H]^+$ preparative flash chromatography (method Z, 0-3%) 87 % yield
61.1 and **61.2**	(R)-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-4-fluoro-anilino)propanamide and (S)-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-4-fluoro-anilino)propanamide		

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
61.1	 2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-4-fluoro-anilino)propanamide (enantiomer 1)	Example 61	^{1}H-NMR (400 MHz, DMSO-*d*6): δ ppm = 1.15 (d, *J*=7.60 Hz, 3 H), 5.02 - 5.09 (m, 1 H), 7.25 (s, 1 H), 7.32 (t, *J*=8.87 Hz, 2 H), 7.36 - 7.42 (m, 3 H), 7.46 - 7.50 (m, 2 H), 7.58 (s, 1 H), 7.63 (dd, *J*=8.74, 5.20 Hz, 2 H), 7.80 - 8.50 (m, 2 H). LC-MS (method 1) Rt = 1.07 min; MS (ESIpos): m/z = 385.5 $[M+H]^+$ 24 % yield

Chiral HPLC Example 61.1

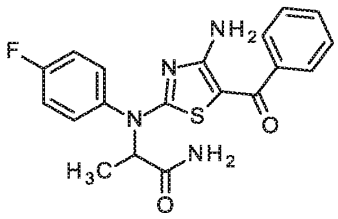
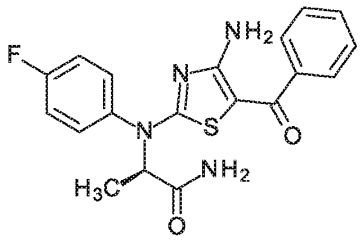
HPLC separation of rac-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-4-fluoro-anilino)propanamide (414 mg, 1.08 mmol; Example 61) on a chiral column gave 139 mg (33 % yield) of 2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-4-fluoro-anilino)propanamide, enantiomer 1.

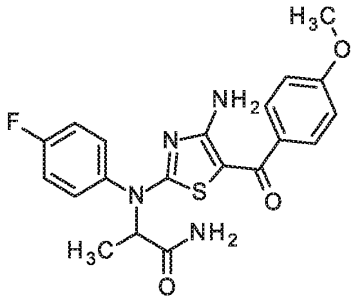
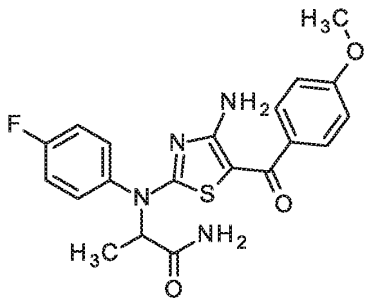
Preparative chiral HPLC

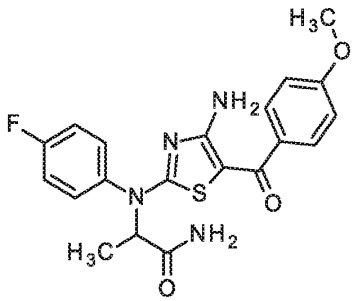
Instrument: Sepiatec: Prep SFC100; Column: Chiralpak IA 5µ 250x30mm; eluent A: CO_2; eluent B: 2-propanol + 0.4 vol % diethylamine; isocratic: 25%B; flow: 100 mL/min; temperature: 40°C; BPR: 150bar; UV: 280 nm

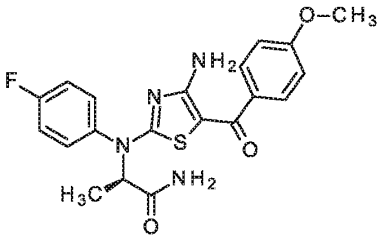
Analytical chiral HPLC: Rt = 2.10 min

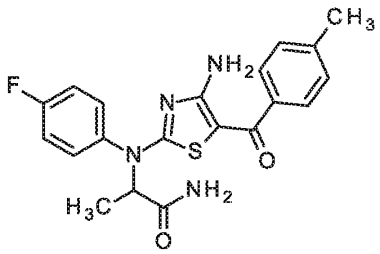
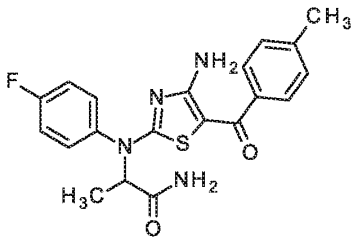
Instrument: Agilent: 1260, Aurora SFC-Modul;column Chiralpak IA 5µ 100x4.6mm; eluent A: CO_2; eluent B: 2-propanol + 0.4% diethylamine (99%); isocratic: 25%B; flow: 4 mL/min; temperature: 37.5°C; BPR: 100bar; UV: 280 nm

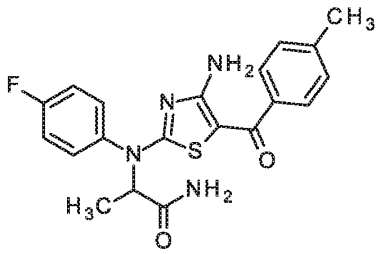
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
61.2	 2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-4-fluoro-anilino)propanamide (enantiomer 2)	Example 61	^{1}H-NMR (400 MHz, DMSO-*d*6): δ ppm = 1.15 (d, *J*=7.60 Hz, 3 H), 5.02 - 5.09 (m, 1 H), 7.25 (s, 1 H), 7.32 (t, *J*=8.87 Hz, 2 H), 7.36 - 7.42 (m, 3 H), 7.46 - 7.50 (m, 2 H), 7.58 (s, 1 H), 7.63 (dd, *J*=8.74, 5.20 Hz, 2 H), 7.80 - 8.50 (m, 2 H). LC-MS (method 1) Rt = 1.07 min; MS (ESIpos): m/z = 385.5 $[M+H]^+$ 26 % yield
Chiral HPLC Example 61.2 HPLC separation of rac-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-4-fluoro-anilino)propanamide (414 mg, 1.08 mmol; Example 61) on a chiral column gave 103 mg (24 % yield) of 2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-4-fluoro-anilino)propanamide, enantiomer 2. Preparative chiral HPLC Instrument: Sepiatec: Prep SFC100; Column: Chiralpak IA 5µ 250x30mm; eluent A: CO_2; eluent B: 2-propanol + 0.4 vol % diethylamine; isocratic: 25%B; flow: 100 mL/min; temperature: 40°C; BPR: 150bar; UV: 280 nm Analytical chiral HPLC: Rt = 3.08 min Instrument: Agilent: 1260, Aurora SFC-Modul; column: Chiralpak IA 5µ 100x4.6mm; eluent A: CO2; eluent B: 2-Propanol + 0.4% diethylamine (99%); isocratic: 25%B; flow: 4 mL/min; temperature: 37.5°C; BPR: 100bar; UV: 280 nm			
61.2		Example 61.2 was determined to be (R)-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-4-fluoro-anilino)propanamide, by means of X-ray crystal structure analysis.	

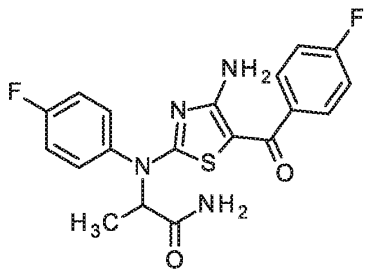
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
62	 rac-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 85; rac-2-bromopropanamide	^{1}H-NMR (400 MHz, DMSO-*d*6): δ ppm = 1.16 (d, *J*=7.60 Hz, 3 H), 3.75 (s, 3 H), 5.06 (q, *J*=6.76 Hz, 1 H), 6.93 (d, *J*=8.87 Hz, 2 H), 7.22 - 7.27 (m, 1 H), 7.34 (t, *J*=8.87 Hz, 2 H), 7.48 (d, *J*=8.87 Hz, 2 H), 7.57 (s, 1 H), 7.64 (dd, *J*=8.87, 5.07 Hz, 2 H), 7.79 - 8.38 (m, 2 H). LC-MS (method 2) Rt = 1.06 min; MS (ESIpos): m/z = 415.5 $[M+H]^+$ preparative flash chromatography (method Z, 0-3%) 49 % yield
62.1 and **62.2**	(R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide and (S)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide		
62.1	 2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide (enantiomer 1)	Example 62	^{1}H-NMR (400 MHz, DMSO-*d*6): δ ppm = 1.16 (d, *J*=7.60 Hz, 3 H), 3.75 (s, 3 H), 5.06 (q, *J*=6.76 Hz, 1 H), 6.93 (d, *J*=8.87 Hz, 2 H), 7.22 - 7.27 (m, 1 H), 7.34 (t, *J*=8.87 Hz, 2 H), 7.48 (d, *J*=8.87 Hz, 2 H), 7.57 (s, 1 H), 7.64 (dd, *J*=8.87, 5.07 Hz, 2 H), 7.79 - 8.38 (m, 2 H). $[\alpha]_D^{20}$ = -142.9° (c = 1.00, chloroform) 45 % yield

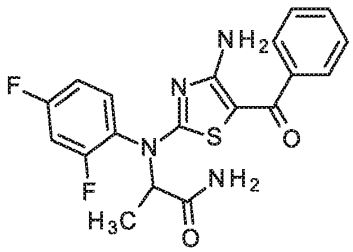
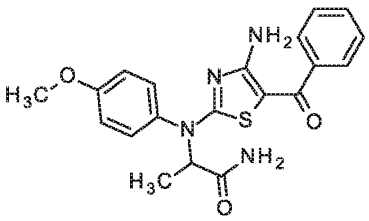
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
Chiral HPLC Example 62.1 HPLC separation of rac-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide (350 mg, 0.80 mmol; Example 62) on a chiral column gave 135 mg (45 % yield) of 2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, enantiomer 1. Preparative chiral HPLC Instrument: Sepiatec: Prep SFC100; Column: Chiralpak IA 5µ 250x30mm; eluent A: CO_2; eluent B: 2-propanol + 0.4 vol % diethylamine; isocratic: 30%B; flow: 100 mL/min; temperature: 40°C; BPR: 150bar; UV: 254 nm Analytical chiral HPLC: Rt = 1.72 min Instrument: Agilent: 1260, Aurora SFC-Modul; Column: Chiralpak IA 5µ 100x4.6mm; eluent A: CO_2; eluent B: 2-propanol + 0.4 vol % diethylamine; isocratic: 30%B; flow: 4 mL/min; temperature: 37.5°C; BPR: 100bar; UV: 254 nm			
62.2	 2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide (enantiomer 2)	Example 62	^{1}H-NMR (400 MHz, DMSO-*d*6): δ ppm = 1.16 (d, *J*=7.60 Hz, 3 H), 3.75 (s, 3 H), 5.06 (q, *J*=6.76 Hz, 1 H), 6.93 (d, *J*=8.87 Hz, 2 H), 7.22 - 7.27 (m, 1 H), 7.34 (t, *J*=8.87 Hz, 2 H), 7.48 (d, *J*=8.87 Hz, 2 H), 7.57 (s, 1 H), 7.64 (dd, *J*=8.87, 5.07 Hz, 2 H), 7.79 - 8.38 (m, 2 H). $[\alpha]_D^{20}$ = +114.5° (c = 1.00, chloroform) 49 % yield

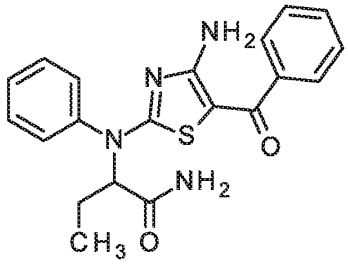
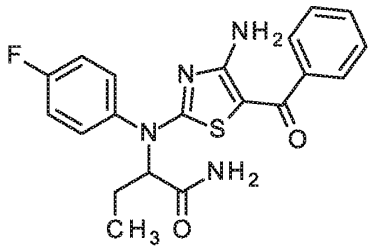
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
Chiral HPLC Example 62.2 HPLC separation of rac-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide (350 mg, 0.80 mmol; Example 62) on a chiral column gave 15 mg (49 % yield) of 2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, enantiomer 2. Preparative chiral HPLC Instrument: Sepiatec: Prep SFC100; Column: Chiralpak IA 5µ 250x30mm; eluent A: CO_2; eluent B: 2-propanol + 0.4 vol % diethylamine; isocratic: 30%B; flow: 100 mL/min; temperature: 40°C; BPR: 150bar; UV: 254 nm Analytical chiral HPLC: Rt = 2.61 min Instrument: Agilent: 1260, Aurora SFC-Modul; Column: Chiralpak IA 5µ 100x4.6mm; eluent A: CO_2; eluent B: 2-propanol + 0.4 vol % diethylamine; isocratic: 30%B; flow: 4 mL/min; temperature: 37.5°C; BPR: 100bar; UV: 254 nm			
62.2			Example 62.2 was determined to be (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, by means of X-ray crystal structure analysis.

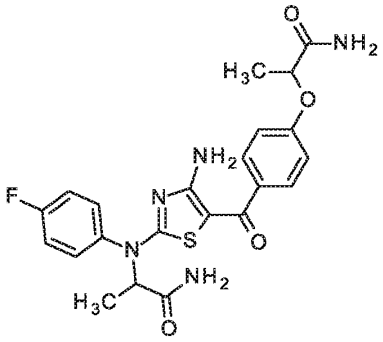
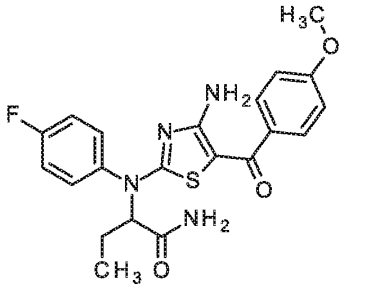
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
63	 rac-2-(N-[4-amino-5-(4-methylbenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 86; rac-2-bromopropanamide	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.16 (d, *J*=7.60 Hz, 3 H), 2.29 (s, 3 H), 5.05 (q, *J*=6.67 Hz, 1 H), 7.18 (d, *J*=8.11 Hz, 2 H), 7.24 (s, 1 H), 7.32 (t, *J*=8.87 Hz, 2 H), 7.38 (d, *J*=8.11 Hz, 2 H), 7.57 (s, 1 H), 7.63 (dd, *J*=8.62, 5.07 Hz, 2 H), 8.10 (br s, 2 H). LC-MS (method 2) Rt = 1.15 min; MS (ESIpos): m/z = 399.3 $[M+H]^+$ preparative flash chromatography (method Z, 0-3%) 18 % yield
63.1 and **63.2**	(R)-2-(N-[4-amino-5-(4-methylbenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide and (S)-2-(N-[4-amino-5-(4-methylbenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide		
63.1	 2-(N-[4-amino-5-(4-methylbenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide (enantiomer 1)	Example 63	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.16 (d, *J*=7.60 Hz, 3 H), 2.29 (s, 3 H), 5.05 (q, *J*=6.67 Hz, 1 H), 7.18 (d, *J*=8.11 Hz, 2 H), 7.24 (s, 1 H), 7.32 (t, *J*=8.87 Hz, 2 H), 7.38 (d, *J*=8.11 Hz, 2 H), 7.57 (s, 1 H), 7.63 (dd, *J*=8.62, 5.07 Hz, 2 H), 8.10 (br s, 2 H). $[\alpha]_D^{20}$ = -159.9° (c = 1.00, chloroform) 13 % yield

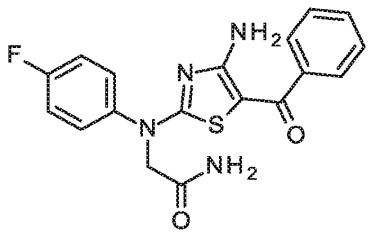
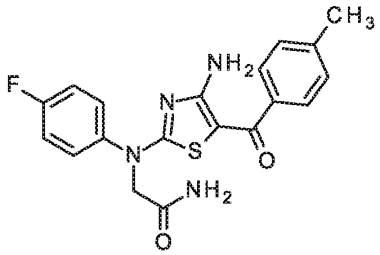
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
Chiral HPLC Example 63.1 HPLC separation of rac-2-(N-[4-amino-5-(4-methylbenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide (1.5 g, 3.58 mmol; Example 63) on a chiral column gave 660 mg (45 % yield) of 2-(N-[4-amino-5-(4-methylbenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, enantiomer 1. Preparative chiral HPLC Instrument: PrepCon Labomatic HPLC; Column: YMC Cellulose SB 10µ, 250x50; eluent A: hexane + 0.1 vol % diethylamine; eluent B: 2-propanol + 0.1 vol % diethylamine; isocratic: 60%A+40%B; flow: 140 mL/min; temperature: 25°C; UV: 254 nm Analytical chiral HPLC: Rt = 2.46 min Instrument: Waters Alliance 2695; Column: YMC Cellulose SB 3µ, 100x4.6; eluent A: hexane + 0.1 vol % diethylamine; eluent B: 2-propanol; isocratic: 60%A+40%B; flow: 1.4 mL/min; temperature: 25°C; UV: 254 nm			
63.2	 2-(N-[4-amino-5-(4-methylbenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide (enantiomer 2)	Example 63	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.16 (d, *J*=7.60 Hz, 3 H), 2.29 (s, 3 H), 5.05 (q, *J*=6.67 Hz, 1 H), 7.18 (d, *J*=8.11 Hz, 2 H), 7.24 (s, 1 H), 7.32 (t, *J*=8.87 Hz, 2 H), 7.38 (d, *J*=8.11 Hz, 2 H), 7.57 (s, 1 H), 7.63 (dd, *J*=8.62, 5.07 Hz, 2 H), 8.10 (br s, 2 H). $[\alpha]_D^{20}$ = +147.0° (c = 1.00, chloroform) 13 % yield

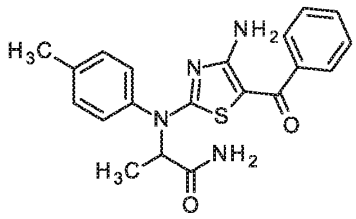
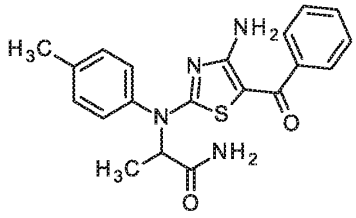
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
Chiral HPLC Example 63.2 HPLC separation of rac-2-(N-[4-amino-5-(4-methylbenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide (1.5 g, 3.58 mmol; Example 63) on a chiral column gave 680 mg (44 % yield) of 2-(N-[4-amino-5-(4-methylbenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, enantiomer 2. Preparative chiral HPLC Instrument: PrepCon Labomatic HPLC; Column: YMC Cellulose SB 10µ, 250x50; eluent A: hexane + 0.1 vol % diethylamine; eluent B: 2-propanol + 0.1 vol % diethylamine; isocratic: 60%A+40%B; flow: 140 mL/min; temperature: 25°C; UV: 254 nm Analytical chiral HPLC: Rt = 3.69 min Instrument: Waters Alliance 2695; Column: YMC Cellulose SB 3µ, 100x4.6; eluent A: hexane + 0.1 vol % diethylamine; eluent B: 2-propanol; isocratic: 60%A+40%B; flow: 1.4 mL/min; temperature: 25°C; UV: 254 nm			
64	 rac-2-(N-[4-amino-5-(4-fluorobenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 87; rac-2-bromopropanamide	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.16 (d, *J*=7.35 Hz, 3 H), 5.06 (br q, *J*=6.84 Hz, 1 H), 7.22 (t, *J*=8.87 Hz, 2 H), 7.25 (s, 1 H), 7.33 (t, *J*=8.87 Hz, 2 H), 7.55 (dd, *J*=8.74, 5.45 Hz, 2 H), 7.58 (br s, 1 H), 7.64 (dd, *J*=8.87, 5.07 Hz, 2 H), 7.86 - 8.56 (m, 2 H). LC-MS (method 2) Rt = 1.09 min; MS (ESIpos): m/z = 403.3 $[M+H]^+$ preparative flash chromatography (method Z, 0-3%) 7 % yield

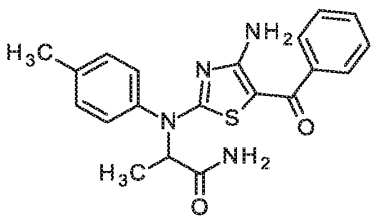
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
65	 rac-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-2,4-difluoro-anilino)propanamide	Intermediate 88; rac-2-bromopropanamide	^{1}H-NMR (400 MHz, CHLOROFORM-*d*): δ ppm = 1.27 (d, *J*=7.10 Hz, 3 H), 5.23 (q, *J*=7.18 Hz, 1 H), 5.39 - 5.48 (m, 1 H), 6.58 - 6.70 (m, 1 H), 6.94 - 7.02 (m, 2 H), 7.33 - 7.43 (m, 4 H), 7.58 - 7.64 (m, 2 H) (NH2 missing). LC-MS (method 2) Rt = 1.08 min; MS (ESIpos): m/z = 403.3 $[M+H]^+$ preparative flash chromatography (method Z, 0-3%) 29 % yield
66	 rac-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-4-methoxy-anilino)propanamide	Intermediate 89; rac-2-bromopropanamide	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.15 (d, *J*=6.84 Hz, 3 H), 3.78 (s, 3 H), 5.06 (q, *J*=6.59 Hz, 1 H), 7.00 (d, *J*=9.12 Hz, 2 H), 7.21 (s, 1 H), 7.35 - 7.42 (m, 3 H), 7.43 - 7.49 (m, 4 H), 7.52 (s, 1 H), 7.65 - 8.49 (m, 2 H). LC-MS (method 2) Rt = 1.03 min; MS (ESIpos): m/z = 397.4 $[M+H]^+$ preparative flash chromatography (method Z, 0-3%) 19 % yield

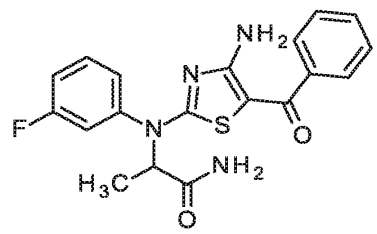
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
67	 rac-2-[(4-amino-5-benzoyl-1,3-thiazol-2-yl)(phenyl)amino]butanamide	Intermediate 83; rac-2-bromobutanamide	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 0.84 (t, *J*=7.35 Hz, 3 H), 1.47 - 1.60 (m, 1 H), 1.69 - 1.81 (m, 1 H), 4.87 - 4.95 (m, 1 H), 7.30 (s, 1 H), 7.34 - 7.51 (m, 8 H), 7.54 - 7.58 (m, 3 H), 7.78 - 8.48 (m, 2 H). LC-MS (method 2) Rt = 1.09 min; MS (ESIpos): m/z = 381.3 $[M+H]^+$ preparative flash chromatography (method Z, 0-3%) 43 % yield
68	 rac-2-[(4-amino-5-benzoyl-1,3-thiazol-2-yl)(4-fluorophenyl)amino]butanamide	Intermediate 84; rac-2-bromobutanamide	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 0.84 (t, *J*=7.35 Hz, 3 H), 1.46 - 1.58 (m, 1 H), 1.68 - 1.79 (m, 1 H), 4.85 - 4.92 (m, 1 H), 7.32 (s, 3 H), 7.37 - 7.42 (m, 3 H), 7.47 - 7.50 (m, 2 H), 7.59 (s, 1 H), 7.64 (dd, *J*=9.12, 5.07 Hz, 2 H), 7.83 - 8.36 (m, 2 H). LC-MS (method 2) Rt = 1.12 min; MS (ESIpos): m/z = 399.3 $[M+H]^+$ preparative flash chromatography (method Z, 0-3%) 29 % yield

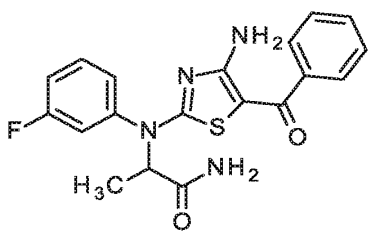
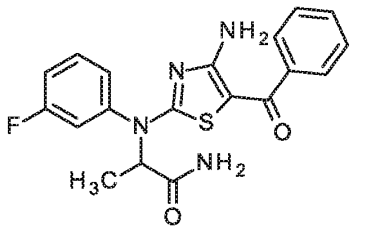
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
69	 2-(N-[4-amino-5-[4-(2-amino-1-methyl-2-oxo-ethoxy)benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide (mixture of stereoisomers)	Intermediate 90; rac-2-bromopropanamide	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.16 (d, *J*=7.35 Hz, 3 H), 1.41 (d, *J*=6.59 Hz, 3 H), 4.64 (q, *J*=6.59 Hz, 1 H), 5.05 (q, *J*=6.76 Hz, 1 H), 6.87 (d, *J*=8.87 Hz, 2 H), 7.25 (br s, 2 H), 7.33 (t, *J*=8.74 Hz, 2 H), 7.46 (d, *J*=8.62 Hz, 2 H), 7.50 (s, 1 H), 7.57 (s, 1 H), 7.64 (dd, *J*=9.00, 5.20 Hz, 2 H), 7.78 - 8.35 (m, 2 H). LC-MS (method 2) Rt = 0.87 min; MS (ESIpos): m/z = 472.2 $[M+H]^+$ preparative flash chromatography (method Z, 0-8%) 28 % yield
70	 rac-2-{[4-amino-5-(4-methoxybenzoyl)-1,3-thiazol-2-yl](4-fluorophenyl)amino}butanamide	Intermediate 85; rac-2-bromobutanamide	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 0.84 (t, *J*=7.22 Hz, 3 H), 1.46 - 1.58 (m, 1 H), 1.67 - 1.78 (m, 1 H), 3.76 (s, 3 H), 4.85 - 4.93 (m, 1 H), 6.93 (d, *J*=8.87 Hz, 2 H), 7.33 (t, *J*=8.74 Hz, 2 H), 7.32 (br s, 1 H), 7.49 (d, *J*=8.87 Hz, 2 H), 7.59 (s, 1 H), 7.65 (dd, *J*=9.00, 4.94 Hz, 2 H), 8.11 (br s, 2 H). LC-MS (method 2) Rt = 1.12 min; MS (ESIpos): m/z = 429.3 $[M+H]^+$ preparative flash chromatography (method Z, 0-3%) 28 % yield

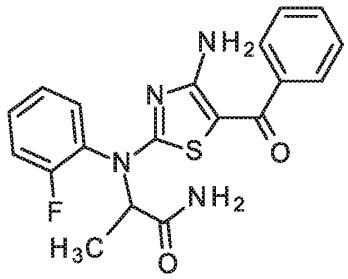
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
71	 2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-4-fluoro-anilino)acetamide	Intermediate 84; 2-bromoacetamide	^{1}H-NMR (500 MHz, DMSO-*d6*): δ ppm = 4.44 (s, 2 H), 7.23 (s, 1 H), 7.32 (t, *J*=8.67 Hz, 2 H), 7.38 - 7.43 (m, 3 H), 7.50 - 7.53 (m, 2 H), 7.56 (s, 1 H), 7.61 (dd, *J*=8.83, 5.04 Hz, 2 H), 7.94 - 8.44 (m, 2 H). LC-MS (method 2) Rt = 1.00 min; MS (ESIpos): m/z = 371.4 $[M+H]^+$ preparative flash chromatography (method Z, 0-3%) 8 % yield
72	 2-(N-[4-amino-5-(4-methylbenzoyl)thiazol-2-yl]-4-fluoro-anilino)acetamide	Intermediate 86; 2-bromoacetamide	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 2.30 (s, 3 H), 4.44 (s, 2 H), 7.18 - 7.24 (m, 3 H), 7.32 (t, *J*=8.87 Hz, 2 H), 7.42 (d, *J*=8.11 Hz, 2 H), 7.55 (s, 1 H), 7.61 (dd, *J*=9.13, 5.07 Hz, 2 H), 7.79 - 8.41 (m, 2 H). LC-MS (method 2) Rt = 1.07 min; MS (ESIpos): m/z = 385.5 $[M+H]^+$ preparative flash chromatography (method Z, 0-3%) 6 % yield

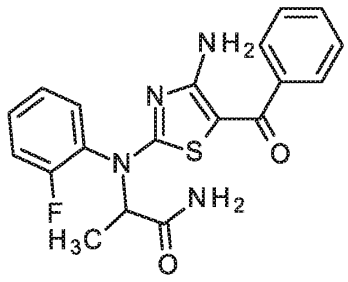
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
73	 rac-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-4-methyl-anilino)propanamide	Intermediate 91; rac-2-bromopropanamide	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.15 (d, *J*=7.35 Hz, 3 H), 2.33 (s, 3 H), 5.07 (q, *J*=7.01 Hz, 1 H), 7.21 (s, 1 H), 7.27 (d, *J*=8.11 Hz, 2 H), 7.35 - 7.43 (m, 5 H), 7.44 - 7.48 (m, 2 H), 7.52 (s, 1 H), 8.10 (br s, 2 H). LC-MS (method 2) Rt = 1.10 min; MS (ESIpos): m/z = 381.5 $[M+H]^+$ preparative flash chromatography (method Z, 0-3%) 35 % yield
73.1 and **73.2**	(R)-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-4-methyl-anilino)propanamide and (S)-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-4-methyl-anilino)propanamide		
73.1	 2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-4-methyl-anilino)propanamide (enantiomer 1)	Example 73	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.15 (d, *J*=7.35 Hz, 3 H), 2.33 (s, 3 H), 5.07 (q, *J*=7.01 Hz, 1 H), 7.21 (s, 1 H), 7.27 (d, *J*=8.11 Hz, 2 H), 7.35 - 7.43 (m, 5 H), 7.44 - 7.48 (m, 2 H), 7.52 (s, 1 H), 8.10 (br s, 2 H). $[\alpha]_D^{20}$ = -173.6° (c = 1.00, chloroform) 35 % yield

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
Chiral HPLC Example 73.1 HPLC separation of rac-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-4-methyl-anilino)propanamide (440 mg, 1.10 mmol; Example 73) on a chiral column gave 160 mg (36 % yield) of 2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-4-methyl-anilino)propanamide, enantiomer 1. Preparative chiral HPLC Instrument: Sepiatec: Prep SFC100; Column: Chiralpak IA 5µ 250x30mm; eluent A: CO_2; eluent B: 2-propanol + 0.4 vol % diethylamine; isocratic: 25%B; flow: 100 mL/min; temperature: 40°C; BPR: 150bar; UV: 280 nm Analytical chiral HPLC: Rt = 2.88 min Instrument: Agilent: 1260, Aurora SFC-module; column: Chiralpak IA 5µ 100x4.6mm; eluent A: CO_2; eluent B: 2-propanol + 0.4 vol % diethylamine, isocratic: 25%B; flow: 4 mL/min; temperature: 37.5°C; BPR: 100bar; UV: 280 nm			
73.2	 2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-4-methyl-anilino)propanamide (enantiomer 2)	Example 73	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.15 (d, *J*=7.35 Hz, 3 H), 2.33 (s, 3 H), 5.07 (q, *J*=7.01 Hz, 1 H), 7.21 (s, 1 H), 7.27 (d, *J*=8.11 Hz, 2 H), 7.35 - 7.43 (m, 5 H), 7.44 - 7.48 (m, 2 H), 7.52 (s, 1 H), 8.10 (br s, 2 H). $[\alpha]_D^{20}$ = +161.4° (c = 1.00, chloroform) 8 % yield

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
Chiral HPLC Example 73.2 HPLC separation of rac-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-4-methyl-anilino)propanamide (440 mg, 1.10 mmol; Example 73) on a chiral column gave 100 mg (23 % yield) of 2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-4-methyl-anilino)propanamide, enantiomer 2. Preparative chiral HPLC Instrument: Sepiatec: Prep SFC100; Column: Chiralpak IA 5µ 250x30mm; eluent A: CO_2; eluent B: 2-propanol + 0.4 vol % diethylamine; isocratic: 25%B; flow: 100 mL/min; temperature: 40°C; BPR: 150bar; UV: 280 nm Analytical chiral HPLC: Rt = 4.57 min Instrument: Agilent: 1260, Aurora SFC-module; column: Chiralpak IA 5µ 100x4.6mm; eluent A: CO_2; eluent B: 2-propanol + 0.4 vol % diethylamine, isocratic: 25%B; flow: 4 mL/min; temperature: 37.5°C; BPR: 100bar; UV: 280 nm			
74	 rac-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-3-fluoro-anilino)propanamide	Intermediate 92; rac-2-bromopropanamide	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.18 (d, *J*=7.35 Hz, 3 H), 5.05 (q, *J*=7.18 Hz, 1 H), 7.28 (s, 1 H), 7.32 (td, *J*=8.30, 2.15 Hz, 1 H), 7.37 - 7.46 (m, 4 H), 7.47 - 7.56 (m, 4 H), 7.60 (s, 1 H), 7.85 - 8.35 (m, 2 H). LC-MS (method 2) Rt = 1.06 min; MS (ESIpos): m/z = 385.5 $[M+H]^+$ preparative flash chromatography (method Z, 0-3%) 15 % yield
74.1 and **74.2**	(R)-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-3-fluoro-anilino)propanamide and (S)-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-3-fluoro-anilino)propanamide		

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
74.1	 2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-3-fluoro-anilino)propanamide (enantiomer 1)	Example 74	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.18 (d, *J*=7.35 Hz, 3 H), 5.05 (q, *J*=7.18 Hz, 1 H), 7.28 (s, 1 H), 7.32 (td, *J*=8.30, 2.15 Hz, 1 H), 7.37 - 7.46 (m, 4 H), 7.47 - 7.56 (m, 4 H), 7.60 (s, 1 H), 7.85 - 8.35 (m, 2 H). $[\alpha]_D^{20}$ = -143.6° (c = 1.00, chloroform) 4 % yield
Chiral HPLC Example 74.1 HPLC separation of rac-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-3-fluoro-anilino)propanamide (260 mg, 0.64 mmol; Example 74) on a chiral column gave 65 mg (25 % yield) of 2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-3-fluoro-anilino)propanamide, enantiomer 1. Preparative chiral HPLC Instrument: PrepCon Labomatic HPLC; Column: YMC Cellulose SC 10µ, 250x50; eluent A: hexane; eluent B: 2-propanol; isocratic: 70%A+30%B; flow: 150 mL/min; temperature: 25°C; UV: 254 nm Analytical chiral HPLC: Rt = 5.46 min Instrument: Waters Alliance 2695; Column: YMC Cellulose SC 3µ, 100x4.6; eluent A: hexane; eluent B: 2-propanol; isocratic: 70%A+30%B; flow: 1.4 mL/min; temperature: 25°C; UV: 254 nm			
74.2	 2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-3-fluoro-anilino)propanamide (enantiomer 2)	Example 74	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.18 (d, *J*=7.35 Hz, 3 H), 5.05 (q, *J*=7.18 Hz, 1 H), 7.28 (s, 1 H), 7.32 (td, *J*=8.30, 2.15 Hz, 1 H), 7.37 - 7.46 (m, 4 H), 7.47 - 7.56 (m, 4 H), 7.60 (s, 1 H), 7.85 - 8.35 (m, 2 H). $[\alpha]_D^{20}$ = +151.0° (c = 1.00, chloroform) 4 % yield

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
Chiral HPLC Example 74.2 HPLC separation of rac-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-3-fluoro-anilino)propanamide (260 mg, 0.64 mmol; Example 74) on a chiral column gave 65 mg (25 % yield) of 2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-3-fluoro-anilino)propanamide, enantiomer 2. Preparative chiral HPLC Instrument: PrepCon Labomatic HPLC; Column: YMC Cellulose SC 10µ, 250x50; eluent A: hexane; eluent B: 2-propanol; isocratic: 70%A+30%B; flow: 150 mL/min; temperature: 25°C; UV: 254 nm Analytical chiral HPLC: Rt = 6.76 min Instrument: Waters Alliance 2695; Column: YMC Cellulose SC 3µ, 100x4.6; eluent A: hexane; eluent B: 2-propanol; isocratic: 70%A+30%B; flow: 1.4 mL/min; temperature: 25°C; UV: 254 nm			
75	 rac-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-2-fluoro-anilino)propanamide	Intermediate 93; rac-2-bromopropanamide	^{1}H-NMR (500 MHz, DMSO-*d6*): δ ppm = 1.22 (d, *J*=7.31 Hz, 3 H), 5.04 (q, *J*=7.10 Hz, 1 H), 6.87 - 7.30 (m, 2 H), 7.32 (td, *J*=7.63, 1.27 Hz, 1 H), 7.34 - 7.43 (m, 4 H), 7.49 - 7.55 (m, 3 H), 7.77 (td, *J*=7.95, 1.59 Hz, 1 H), 7.92 (br s, 2 H). LC-MS (method 2) Rt = 1.04 min; MS (ESIpos): m/z = 385.4 $[M+H]^+$ preparative flash chromatography (method Z, 0-3%) 52 % yield
75.1 and **75.2**	(R)-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-2-fluoro-anilino)propanamide and (S)-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-2-fluoro-anilino)propanamide		

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
75.1	 2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-2-fluoro-anilino)propanamide (enantiomer 1)	Example 75	^{1}H-NMR (500 MHz, DMSO-*d6*): δ ppm = 1.22 (d, *J*=7.31 Hz, 3 H), 5.04 (q, *J*=7.10 Hz, 1 H), 6.87 - 7.30 (m, 2 H), 7.32 (td, *J*=7.63, 1.27 Hz, 1 H), 7.34 - 7.43 (m, 4 H), 7.49 - 7.55 (m, 3 H), 7.77 (td, *J*=7.95, 1.59 Hz, 1 H), 7.92 (br s, 2 H). $[\alpha]_D^{20}$ = -116.9° (c = 1.00, chloroform) 13 % yield

Chiral HPLC Example 75.1

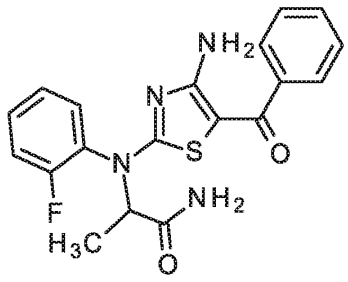
HPLC separation of rac-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-2-fluoro-anilino)propanamide (560 mg, 1.38 mmol; Example 75) on a chiral column gave 135 mg (24 % yield) of 2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-2-fluoro-anilino)propanamide, enantiomer 1.

Preparative chiral HPLC

Instrument: PrepCon Labomatic HPLC; Column: YMC Cellulose SB 5µ, 250x30; eluent A: hexane + 0.1 vol % diethylamine; eluent B: 2-propanol; isocratic: 70%A+30%B; flow: 50 mL/min; temperature: 25°C; UV: 254 nm

Analytical chiral HPLC: Rt = 3.50 min

Instrument: Waters Alliance 2695; Column: YMC Cellulose SB 3µ, 100x4.6; eluent A: hexane + 0.1 vol % diethylamine; eluent B: 2-propanol; isocratic: 70%A+30%B; flow: 1.4 mL/min; temperature: 25°C; UV: 254 nm

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
75.2	 2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-2-fluoro-anilino)propanamide (enantiomer 2)	Example 75	^{1}H-NMR (500 MHz, DMSO-*d6*): δ ppm = 1.22 (d, *J*=7.31 Hz, 3 H), 5.04 (q, *J*=7.10 Hz, 1 H), 6.87 - 7.30 (m, 2 H), 7.32 (td, *J*=7.63, 1.27 Hz, 1 H), 7.34 - 7.43 (m, 4 H), 7.49 - 7.55 (m, 3 H), 7.77 (td, *J*=7.95, 1.59 Hz, 1 H), 7.92 (br s, 2 H). $[\alpha]_D^{20}$ = +109.3° (c = 1.00, chloroform) 15 % yield

Chiral HPLC Example 75.2

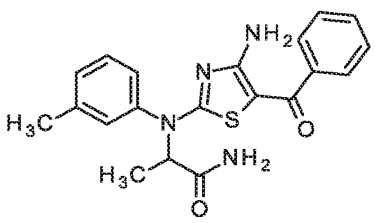
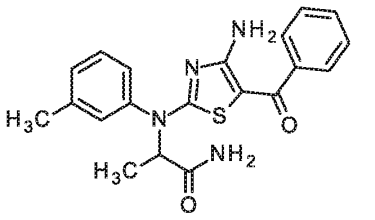
HPLC separation of rac-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-2-fluoro-anilino)propanamide (560 mg, 1.38 mmol; Example 75) on a chiral column gave 165 mg (31 % yield) of 2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-2-fluoro-anilino)propanamide, enantiomer 2.

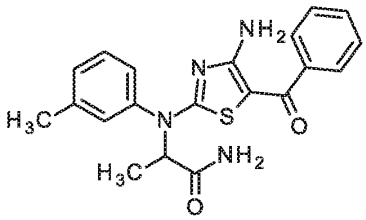
Preparative chiral HPLC

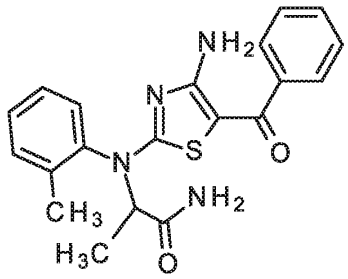
Instrument: PrepCon Labomatic HPLC; Column: YMC Cellulose SB 5µ, 250x30; eluent A: hexane + 0.1 vol % diethylamine; eluent B: 2-propanol; isocratic: 70%A+30%B; flow: 50 mL/min; temperature: 25°C; UV: 254 nm

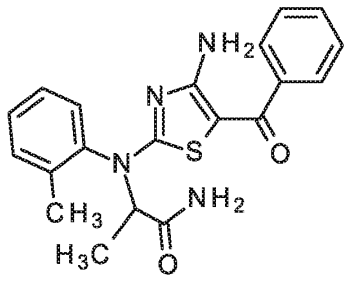
Analytical chiral HPLC: Rt = 4.39 min

Instrument: Waters Alliance 2695; Column: YMC Cellulose SB 3µ, 100x4.6; eluent A: hexane + 0.1 vol % diethylamine; eluent B: 2-propanol; isocratic: 70%A+30%B; flow: 1.4 mL/min; temperature: 25°C; UV: 254 nm

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
76	 rac-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-3-methyl-anilino)propanamide	Intermediate 72; rac-2-bromopropanamide	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.16 (d, *J*=7.35 Hz, 3 H), 2.31 (s, 3 H), 5.05 (q, *J*=7.18 Hz, 1 H), 7.22 (s, 1 H), 7.23 - 7.27 (m, 1 H), 7.33 - 7.41 (m, 6 H), 7.45 - 7.50 (m, 2 H), 7.53 (s, 1 H), 7.70 - 8.47 (m, 2 H). LC-MS (method 2) Rt = 1.10 min; MS (ESIpos): m/z = 381.5 $[M+H]^+$ preparative flash chromatography (method Z, 0-3%) 71 % yield
76.1 and **76.2**	(R)-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-3-methyl-anilino)propanamide and (S)-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-3-methyl-anilino)propanamide		
76.1	 2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-3-methyl-anilino)propanamide (enantiomer 1)	Example 76	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.16 (d, *J*=7.35 Hz, 3 H), 2.31 (s, 3 H), 5.05 (q, *J*=7.18 Hz, 1 H), 7.22 (s, 1 H), 7.23 - 7.27 (m, 1 H), 7.33 - 7.41 (m, 6 H), 7.45 - 7.50 (m, 2 H), 7.53 (s, 1 H), 7.70 - 8.47 (m, 2 H). $[\alpha]_D^{20}$ = +177.3° (c = 1.00, chloroform) 31 % yield

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
Chiral HPLC Example 76.1 HPLC separation of rac-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-3-methyl-anilino)propanamide (1170 mg, 3.00 mmol; Example 76) on a chiral column gave 525 mg (44 % yield) of 2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-3-methyl-anilino)propanamide, enantiomer 1. Preparative chiral HPLC Instrument: PrepCon Labomatic HPLC; Column: YMC Cellulose SC 10µ, 250x50; eluent A: methyl tert-butyl ether; eluent B: acetonitrile; isocratic: 95%A+5%B; flow: 150 mL/min; temperature: 25°C; UV: 254 nm Analytical chiral HPLC: Rt = 6.56 min Instrument: Waters Alliance 2695; Column: YMC Cellulose SC 3µ, 100x4.6; eluent A: methyl tert-butyl ether; eluent B: acetonitrile; isocratic: 95%A+5%B; flow: 1.4 mL/min; temperature: 25°C; UV: 254 nm			
76.2	 2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-3-methyl-anilino)propanamide (enantiomer 2)	Example 76	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.16 (d, *J*=7.35 Hz, 3 H), 2.31 (s, 3 H), 5.05 (q, *J*=7.18 Hz, 1 H), 7.22 (s, 1 H), 7.23 - 7.27 (m, 1 H), 7.33 - 7.41 (m, 6 H), 7.45 - 7.50 (m, 2 H), 7.53 (s, 1 H), 7.70 - 8.47 (m, 2 H). $[\alpha]_D^{20}$ = +177.3° (c = 1.00, chloroform) 34 % yield

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
Chiral HPLC Example 76.2 HPLC separation of rac-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-3-methyl-anilino)propanamide (1170 mg, 3.00 mmol; Example 76) on a chiral column gave 525 mg (45 % yield) of 2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-3-methyl-anilino)propanamide, enantiomer 2. Preparative chiral HPLC Instrument: PrepCon Labomatic HPLC; Column: YMC Cellulose SC 10µ, 250x50; eluent A: methyl tert-butyl ether; eluent B: acetonitrile; isocratic: 95%A+5%B; flow: 150 mL/min; temperature: 25°C; UV: 254 nm Analytical chiral HPLC: Rt = 8.91 min Instrument: Waters Alliance 2695; Column: YMC Cellulose SC 3µ, 100x4.6; eluent A: methyl tert-butyl ether; eluent B: acetonitrile; isocratic: 95%A+5%B; flow: 1.4 mL/min; temperature: 25°C; UV: 254 nm			
77	 rac-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-2-methyl-anilino)propanamide	Intermediate 73; rac-2-bromopropanamide	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 0.97 - 1.08 (m, 3 H), 2.17 (s, 3 H), 4.97 - 5.12 (m, 1 H), 7.24 (br s, 1 H), 7.33 - 7.40 (m, 6 H), 7.46 (br d, *J*=5.32 Hz, 2 H), 7.57 (br s, 1 H), 7.71 - 7.77 (m, 1 H), 7.85 - 8.48 (m, 2 H). LC-MS (method 2) Rt = 1.08 min; MS (ESIpos): m/z = 381.4 $[M+H]^+$ preparative flash chromatography (method Z, 0-3%) 56 % yield
77.1 and **77.2**	(R)-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-2-methyl-anilino)propanamide and (S)-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-2-methyl-anilino)propanamide		

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
77.1	 2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-2-methyl-anilino)propanamide (enantiomer 1)	Example 77	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 0.97 - 1.08 (m, 3 H), 2.17 (s, 3 H), 4.97 - 5.12 (m, 1 H), 7.24 (br s, 1 H), 7.33 - 7.40 (m, 6 H), 7.46 (br d, *J*=5.32 Hz, 2 H), 7.57 (br s, 1 H), 7.71 - 7.77 (m, 1 H), 7.85 - 8.48 (m, 2 H). $[\alpha]_D^{20}$ = +166.1° (c = 1.00, chloroform) 23 % yield

Chiral HPLC Example 77.1

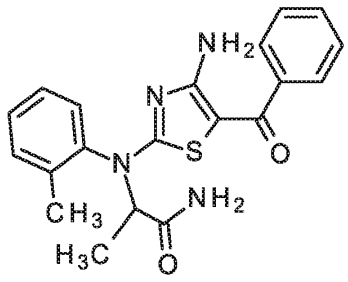
HPLC separation of rac-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-2-methyl-anilino)propanamide (1010 mg, 2.52 mmol; Example 77) on a chiral column gave 420 mg (42 % yield) of 2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-2-methyl-anilino)propanamide, enantiomer 1.

Preparative chiral HPLC

Instrument: PrepCon Labomatic HPLC; Column: Chiralpak IG 5µ, 250x30; eluent A: hexane + 0.1 vol % diethylamine; eluent B: ethanol + 0.1 vol % diethylamine; isocratic: 85%A+15%B; flow: 60 mL/min; temperature: 25°C; UV: 254 nm

Analytical chiral HPLC: Rt = 7.09 min

Instrument: Waters Alliance 2695; Column: Chiralpak IG 3µ, 100x4.6; eluent A: hexane + 0.1 vol % diethylamine; eluent B: ethanol; isocratic: 85%A+15%B; flow: 1.4 mL/min; temperature: 25°C; UV: 254 nm

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
77.2	 2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-2-methyl-anilino)propanamide (enantiomer 1)	Example 77	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 0.97 - 1.08 (m, 3 H), 2.17 (s, 3 H), 4.97 - 5.12 (m, 1 H), 7.24 (br s, 1 H), 7.33 - 7.40 (m, 6 H), 7.46 (br d, *J*=5.32 Hz, 2 H), 7.57 (br s, 1 H), 7.71 - 7.77 (m, 1 H), 7.85 - 8.48 (m, 2 H). $[\alpha]_D^{20}$ = -152.0° (c = 1.00, chloroform) 23 % yield

Chiral HPLC Example 77.2

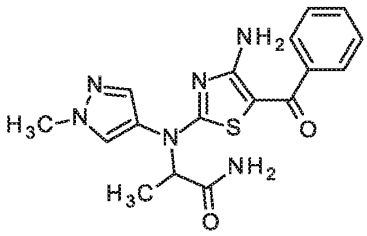
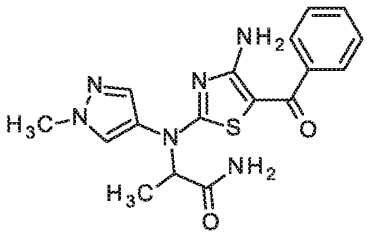
HPLC separation of rac-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-2-methyl-anilino)propanamide (1010 mg, 2.52 mmol; Example 77) on a chiral column gave 420 mg (42 % yield) of 2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-2-methyl-anilino)propanamide, enantiomer 2.

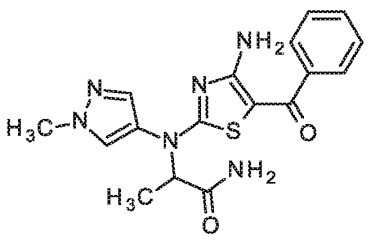
Preparative chiral HPLC

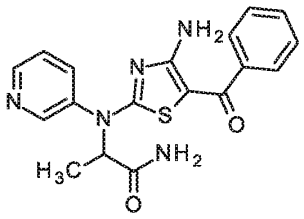
Instrument: PrepCon Labomatic HPLC; Column: Chiralpak IG 5µ, 250x30; eluent A: hexane + 0.1 vol % diethylamine; eluent B: ethanol + 0.1 vol % diethylamine; isocratic: 85%A+15%B; flow: 60 mL/min; temperature: 25°C; UV: 254 nm

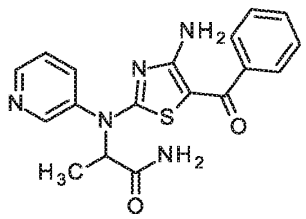
Analytical chiral HPLC: Rt = 10.30 min

Instrument: Waters Alliance 2695; Column: Chiralpak IG 3µ, 100x4.6; eluent A: hexane + 0.1 vol % diethylamine; eluent B: ethanol; isocratic: 85%A+15%B; flow: 1.4 mL/min; temperature: 25°C; UV: 254 nm

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
78	 rac-2-[(4-amino-5-benzoyl-thiazol-2-yl)-(1-methylpyrazol-4-yl)amino]propanamide	Intermediate 94; rac-2-bromopropanamide	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.19 (d, *J*=7.35 Hz, 3 H), 3.83 (s, 3 H), 4.99 - 5.18 (m, 1 H), 7.18 (s, 1 H), 7.37 - 7.44 (m, 3 H), 7.48 (s, 1 H), 7.49 - 7.53 (m, 3 H), 7.80 - 8.48 (m, 2 H), 7.90 (s, 1 H). LC-MS (method 2) Rt = 0.80 min; MS (ESIpos): m/z = 371.3 $[M+H]^+$ preparative flash chromatography (method Z, 0-3%) 17 % yield
78.1 and **78.2**	(R)-2-[(4-amino-5-benzoyl-thiazol-2-yl)-(1-methylpyrazol-4-yl)amino]propanamide and (S)-2-[(4-amino-5-benzoyl-thiazol-2-yl)-(1-methylpyrazol-4-yl)amino]propanamide		
78.1	 2-[(4-amino-5-benzoyl-thiazol-2-yl)-(1-methylpyrazol-4-yl)amino]propanamide (enantiomer 1)	Example 78	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.19 (d, *J*=7.35 Hz, 3 H), 3.83 (s, 3 H), 4.99 - 5.18 (m, 1 H), 7.18 (s, 1 H), 7.37 - 7.44 (m, 3 H), 7.48 (s, 1 H), 7.49 - 7.53 (m, 3 H), 7.80 - 8.48 (m, 2 H), 7.90 (s, 1 H). $[\alpha]_D^{20}$ = -82.8° (c = 1.00, chloroform) 6 % yield

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
Chiral HPLC Example 78.1 HPLC separation of rac-2-[(4-amino-5-benzoyl-thiazol-2-yl)-(1-methylpyrazol-4-yl)amino]propanamide (240 mg, 0.64 mmol; Example 78) on a chiral column gave 89 mg (36 % yield) of 2-[(4-amino-5-benzoyl-thiazol-2-yl)-(1-methylpyrazol-4-yl)amino]propanamide, enantiomer 1. Preparative chiral HPLC Instrument: Sepiatec: Prep SFC100; Column: Chiralpak IC 5µ 250x30mm; eluent A: CO_2; eluent B: methanol + 0.2 vol % aqueous ammonia (32%); isocratic: 40%B; flow: 100 mL/min; temperature: 40°C; BPR: 150bar; UV: 254 nm Analytical chiral HPLC: Rt = 1.77 min Instrument: Agilent: 1260, Aurora SFC-Modul; Column: Chiralpak IC 5µ 100x4.6mm; eluent A: CO_2; eluent B: methanol + 0.2 vol % aqueous ammonia (32%); isocratic: 40%B; flow: 4 mL/min; temperature: 37.5°C; BPR: 100bar; UV: 254 nm			
78.2	 2-[(4-amino-5-benzoyl-thiazol-2-yl)-(1-methylpyrazol-4-yl)amino]propanamide (enantiomer 2)	Example 78	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.19 (d, *J*=7.35 Hz, 3 H), 3.83 (s, 3 H), 4.99 - 5.18 (m, 1 H), 7.18 (s, 1 H), 7.37 - 7.44 (m, 3 H), 7.48 (s, 1 H), 7.49 - 7.53 (m, 3 H), 7.80 - 8.48 (m, 2 H), 7.90 (s, 1 H). $[\alpha]_D^{20}$ = +72.6° (c = 1.00, chloroform) 6 % yield

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
Chiral HPLC Example 78.2 HPLC separation of rac-2-[(4-amino-5-benzoyl-thiazol-2-yl)-(1-methylpyrazol-4-yl)amino]propanamide (240 mg, 0.64 mmol; Example 78) on a chiral column gave 80 mg (33 % yield) of 2-[(4-amino-5-benzoyl-thiazol-2-yl)-(1-methylpyrazol-4-yl)amino]propanamide, enantiomer 2. Preparative chiral HPLC Instrument: Sepiatec: Prep SFC100; Column: Chiralpak IC 5µ 250x30mm; eluent A: CO_2; eluent B: methanol + 0.2 vol % aqueous ammonia (32%); isocratic: 40%B; flow: 100 mL/min; temperature: 40°C; BPR: 150bar; UV: 254 nm Analytical chiral HPLC: Rt = 2.66 min Instrument: Agilent: 1260, Aurora SFC-Modul; Column: Chiralpak IC 5µ 100x4.6mm; eluent A: CO_2; eluent B: methanol + 0.2 vol % aqueous ammonia (32%); isocratic: 40%B; flow: 4 mL/min; temperature: 37.5°C; BPR: 100bar; UV: 254 nm			
79	 rac-2-[(4-amino-5-benzoyl-thiazol-2-yl)-(3-pyridyl)amino]propanamide	Intermediate 95; rac-2-bromopropanamide	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.17 (d, *J*=7.35 Hz, 3 H), 5.07 (q, *J*=7.10 Hz, 1 H), 5.76 (s, 1 H), 7.30 (s, 1 H), 7.35 - 7.43 (m, 3 H), 7.47 - 7.51 (m, 2 H), 7.54 (dd, *J*=8.11, 4.82 Hz, 1 H), 7.64 (s, 1 H), 7.90 - 8.44 (m, 2 H), 8.04 - 8.08 (m, 1 H), 8.63 (dd, *J*=4.56, 1.52 Hz, 1 H), 8.74 (d, *J*=2.03 Hz, 1 H). LC-MS (method 2) Rt = 0.84 min; MS (ESIpos): m/z = 368.5 $[M+H]^+$ preparative flash chromatography (method Z, 0-3%) 10 % yield

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
79.1 and **79.2**	(R)-2-[(4-amino-5-benzoyl-thiazol-2-yl)-(3-pyridyl)amino]propanamide and (S)-2-[(4-amino-5-benzoyl-thiazol-2-yl)-(3-pyridyl)amino]propanamide		
79.1	 2-[(4-amino-5-benzoyl-thiazol-2-yl)-(3-pyridyl)amino]propanamide (enantiomer 1)	Example 79	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.17 (d, *J*=7.35 Hz, 3 H), 5.07 (q, *J*=7.10 Hz, 1 H), 5.76 (s, 1 H), 7.30 (s, 1 H), 7.35 - 7.43 (m, 3 H), 7.47 - 7.51 (m, 2 H), 7.54 (dd, *J*=8.11, 4.82 Hz, 1 H), 7.64 (s, 1 H), 7.90 - 8.44 (m, 2 H), 8.04 - 8.08 (m, 1 H), 8.63 (dd, *J*=4.56, 1.52 Hz, 1 H), 8.74 (d, *J*=2.03 Hz, 1 H). $[\alpha]_D^{20}$ = -119.3° (c = 1.00, chloroform) 3 % yield

Chiral HPLC Example 79.1

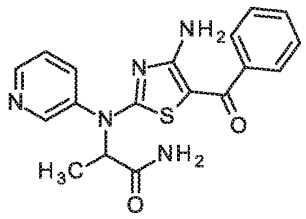
HPLC separation of rac-2-[(4-amino-5-benzoyl-thiazol-2-yl)-(3-pyridyl)amino]propanamide (200 mg, 0.52 mmol; Example 79) on a chiral column gave 50 mg (25 % yield) of 2-[(4-amino-5-benzoyl-thiazol-2-yl)-(3-pyridyl)amino]propanamide, enantiomer 1.

Preparative chiral HPLC

Instrument: PrepCon Labomatic HPLC; Column: YMC Cellulose SB 10µ, 250x50; eluent A: hexane + 0.1 vol % diethylamine; eluent B: ethanol; isocratic: 60%A+40%B; flow: 150 mL/min; temperature: 25°C; UV: 254 nm

Analytical chiral HPLC: Rt = 2.15 min

Instrument: Waters Alliance 2695; Column: YMC Cellulose SB 3µ, 100x4.6; eluent A: hexane + 0.1 vol % diethylamine; eluent B: ethanol; isocratic: 60%A+40%B; flow: 1.4 ml/min; temperature: 25°C; UV: 254 nm

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
79.2	 2-[(4-amino-5-benzoyl-thiazol-2-yl)-(3-pyridyl)amino]propanamide (enantiomer 2)	Example 79	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.17 (d, *J*=7.35 Hz, 3 H), 5.07 (q, *J*=7.10 Hz, 1 H), 5.76 (s, 1 H), 7.30 (s, 1 H), 7.35 - 7.43 (m, 3 H), 7.47 - 7.51 (m, 2 H), 7.54 (dd, *J*=8.11, 4.82 Hz, 1 H), 7.64 (s, 1 H), 7.90 - 8.44 (m, 2 H), 8.04 - 8.08 (m, 1 H), 8.63 (dd, *J*=4.56, 1.52 Hz, 1 H), 8.74 (d, *J*=2.03 Hz, 1 H). $[\alpha]_D^{20}$ = +138.1° (c = 1.00, chloroform) 3 % yield

Chiral HPLC Example 79.2

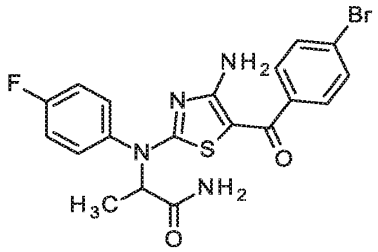
HPLC separation of rac-2-[(4-amino-5-benzoyl-thiazol-2-yl)-(3-pyridyl)amino]propanamide (200 mg, 0.52 mmol; Example 79) on a chiral column gave 50 mg (25 % yield) of 2-[(4-amino-5-benzoyl-thiazol-2-yl)-(3-pyridyl)amino]propanamide, enantiomer 2.

Preparative chiral HPLC

Instrument: PrepCon Labomatic HPLC; Column: YMC Cellulose SB 10µ, 250x50; eluent A: hexane + 0.1 vol % diethylamine; eluent B: ethanol; isocratic: 60%A+40%B; flow: 150 mL/min; temperature: 25°C; UV: 254 nm

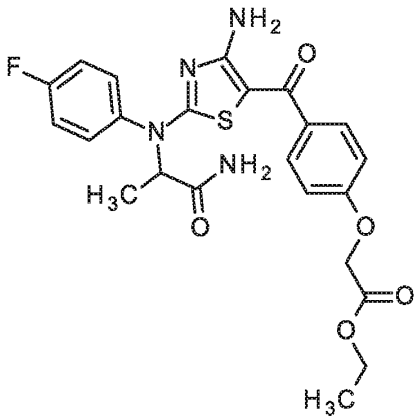
Analytical chiral HPLC: Rt = 2.15 min

Instrument: Waters Alliance 2695; Column: YMC Cellulose SB 3µ, 100x4.6; eluent A: hexane + 0.1 vol % diethylamine; eluent B: ethanol; isocratic: 60%A+40%B; flow: 1.4 ml/min; temperature: 25°C; UV: 254 nm

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
80	 rac-2-(N-[4-amino-5-(4-bromobenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 96; rac-2-bromopropanamide	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.16 (d, *J*=7.35 Hz, 3 H), 5.06 (q, *J*=6.25 Hz, 1 H), 7.25 (s, 1 H), 7.33 (t, *J*=8.74 Hz, 2 H), 7.40 - 7.46 (m, 2 H), 7.57 - 7.67 (m, 5 H), 7.82 - 8.54 (m, 2 H). LC-MS (method 2) Rt = 1.20 min; MS (ESIpos): m/z = 463.4 $[M+H]^+$ preparative flash chromatography (method Z, 0-3%) 19 % yield

Example 81

rac-ethyl 2-[4-[4-amino-2-(4-fluoro-N-[2-amino-1-methyl-2-oxo-ethyl]anilino)thiazole-5-carbonyl]phenoxy]acetate



Ethyl 2-[4-[4-amino-2-(4-fluoroanilino)thiazole-5-carbonyl]phenoxy]acetate (18.54 g, 44.6 mmol; Intermediate 80) was dissolved in N,N-dimethylformamide (493 mL), followed by the addition of potassium carbonate (30.84 g, 223.1 mmol) and rac-2-bromopropanamide (8.14 g, 53.6 mmol). The reaction mixture was stirred at 90°C for 1 h. After cooling down the reaction mixture was partitioned between water and ethyl acetate. The organic layer was separated and washed with saturated aqueous ammonium chloride solution and brine. Afterwards, the organic layer was filtrated by a water repellent filter circle (MN 617 WA) and evaporated to dryness. Water was

added to the residue and the resulting suspension was dried by lyophilization to give 6.16 g (27 % yield) of rac-ethyl 2-[4-[4-amino-2-(4-fluoro-N-[2-amino-1-methyl-2-oxo-ethyl]anilino)thiazole-5-carbonyl]phenoxy]-acetate.

^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.16 (d, *J*=7.86 Hz, 3 H), 1.18 (t, *J*=6.84 Hz, 3 H), 4.15 (q, *J*=7.10 Hz, 2 H), 4.80 (s, 2 H), 5.06 (q, *J*=6.25 Hz, 1 H), 6.91 (d, *J*=8.87 Hz, 2 H), 7.25 (s, 1 H), 7.33 (t, *J*=8.74 Hz, 2 H), 7.47 (d, *J*=8.87 Hz, 2 H), 7.58 (s, 1 H), 7.64 (dd, *J*=8.87, 5.07 Hz, 2 H), 8.15 (br s, 2 H).

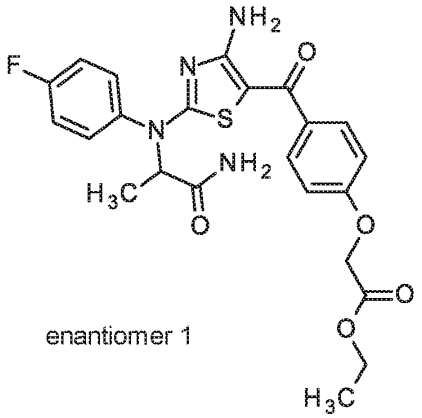
LC-MS (method 2) Rt = 1.09 min; MS (ESIpos): m/z = 487.5 $[M+H]^+$

Example 81.1 and 81.2:

(R)-ethyl 2-[4-[4-amino-2-(4-fluoro-N-[2-amino-1-methyl-2-oxo-ethyl]anilino)thiazole-5-carbonyl]phenoxy]acetate and (S)-ethyl 2-[4-[4-amino-2-(4-fluoro-N-[2-amino-1-methyl-2-oxo-ethyl]anilino)thiazole-5-carbonyl]phenoxy]acetate

Example 81.1

ethyl 2-[4-[4-amino-2-(4-fluoro-N-[2-amino-1-methyl-2-oxo-ethyl]anilino)thiazole-5-carbonyl]phenoxy]acetate (enantiomer 1)



enantiomer 1

HPLC separation of rac-ethyl 2-[4-[4-amino-2-(4-fluoro-N-[2-amino-1-methyl-2-oxo-ethyl]anilino)thiazole-5-carbonyl]phenoxy]acetate (6.16 g, 12.66 mmol; Example 81) on a chiral column gave 2.50 g (39 % yield) of ethyl 2-[4-[4-amino-2-(4-fluoro-N-[2-amino-1-methyl-2-oxo-ethyl]anilino)thiazole-5-carbonyl]phenoxy]acetate, enantiomer 1.

Preparative chiral HPLC

Labomatic HD3000, Knauer Pump 100, Labcol Vario 4000 Plus, Knauer DAD 2600; column: Amylose SB 5µ 250x50mm Nr.34; Eluent A: hexane; Eluent B: ethanol; isocratic: 70%A +

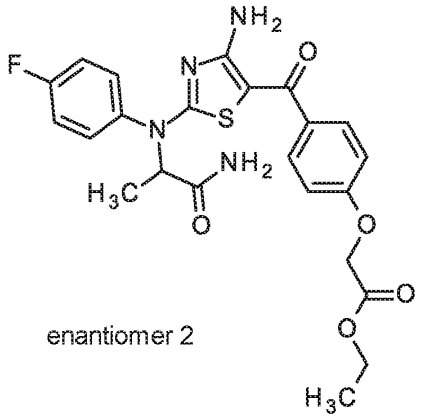
30%B; flow 150.0 mL/min; UV @ 254 nm

Analytical chiral HPLC: Rt = 7.31 min

Instrument: Agilent HPLC 1260; column: Amylose SB 3µ 100x4, 6mm; Eluent A: hexane; Eluent B: ethanol; isocratic: 70%A + 30%B; flow 1.4 mL/min; temperature: 25 °C; DAD 254 nm

Example 81.2

ethyl 2-[4-[4-amino-2-(4-fluoro-N-[2-amino-1-methyl-2-oxo-ethyl]anilino)thiazole-5-carbonyl]phenoxy]acetate (enantiomer 2)



enantiomer 2

HPLC separation of rac-ethyl 2-[4-[4-amino-2-(4-fluoro-N-[2-amino-1-methyl-2-oxo-ethyl]anilino)thiazole-5-carbonyl]phenoxy]acetate (6.16 g, 12.66 mmol; Example 81) on a chiral column gave 2.60 g (40 % yield) of ethyl 2-[4-[4-amino-2-(4-fluoro-N-[2-amino-1-methyl-2-oxo-ethyl]anilino)thiazole-5-carbonyl]phenoxy]acetate, enantiomer 2.

Preparative chiral HPLC

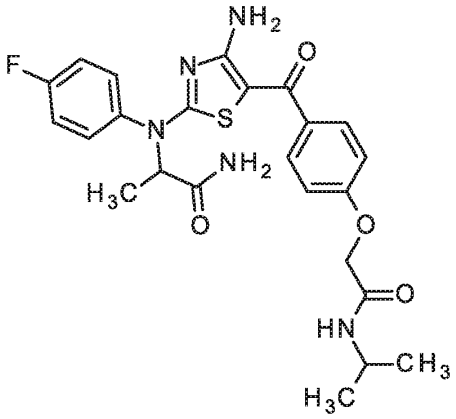
Labomatic HD3000, Knauer Pump 100, Labcol Vario 4000 Plus, Knauer DAD 2600; column: Amylose SB 5µ 250x50mm Nr.34; Eluent A: hexane; Eluent B: ethanol; isocratic: 70%A + 30%B; flow 150.0 mL/min; UV @ 254 nm

Analytical chiral HPLC: Rt = 10.17 min

Instrument: Agilent HPLC 1260; column: Amylose SB 3µ 100x4, 6mm; Eluent A: hexane; Eluent B: ethanol; isocratic: 70%A + 30%B; flow 1.4 mL/min; temperature: 25 °C; DAD 254 nm

Example 82

rac-2-(N-[4-amino-5-[4-[2-(isopropylamino)-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide



Rac-2-[4-[4-amino-2-(N-[2-amino-1-methyl-2-oxo-ethyl]-4-fluoro-anilino)thiazole-5-carbonyl]phenoxy]acetic acid (12 mg, 26 µmol, intermediate 100) and isopropylamine (3 mg, 51 µmol) were dissolved in dimethylformamide (0.4 mL). N,N-diisopropylethylamine (13 mg, 102 µmol), 4-dimethylaminopyridine (0.2 mg, 1 µmol) and HATU (19 mg, 51 µmol) were added. The reaction mixture was stirred at rt for 2 h.

The reaction mixture was filtrated and purified by RP-HPLC (method C, basic) to give 6 mg (42 % yield) of the title compound.

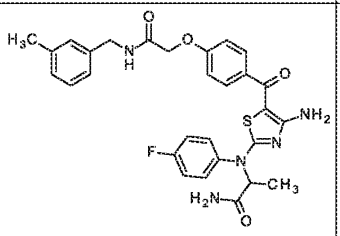
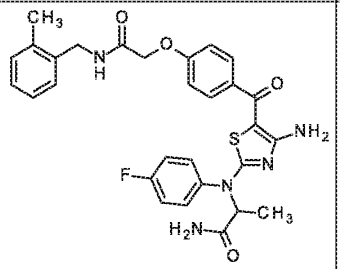
^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.04 - 1.07 (m, 6 H), 1.16 (d, *J*=7.35 Hz, 3 H), 3.86 - 3.97 (m, 1 H), 4.45 (s, 2 H), 5.05 (q, *J*=6.34 Hz, 1 H), 6.92 (d, *J*=8.87 Hz, 2 H), 7.24 (s, 1 H), 7.33 (t, *J*=8.87 Hz, 2 H), 7.47 (d, *J*=8.87 Hz, 2 H), 7.58 (s, 1 H), 7.64 (dd, *J*=8.87, 5.07 Hz, 2 H), 7.88 (br d, *J*=7.86 Hz, 1 H), 8.13 (br s, 2 H).

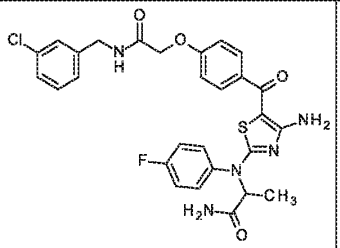
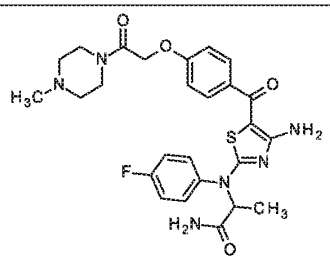
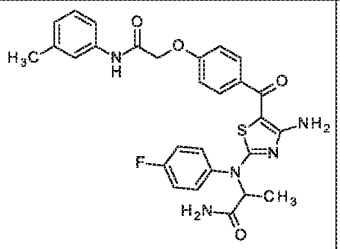
LC-MS (method 2) Rt = 1.00 min; MS (ESIpos): m/z = 500.6 $[M+H]^+$

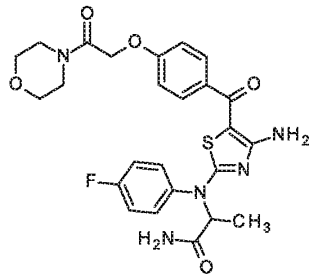
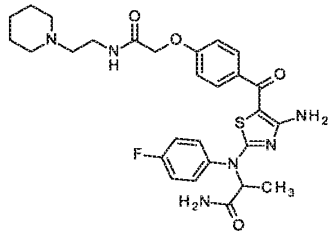
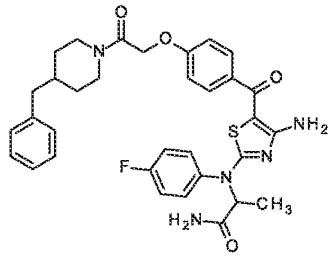
The following examples were prepared from the starting materials stated in Table 7, below, using the procedure as for Example 82.

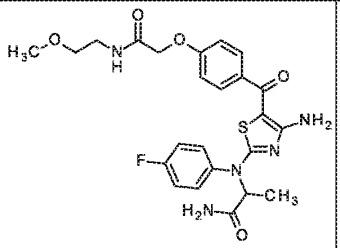
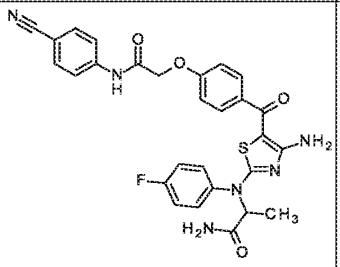
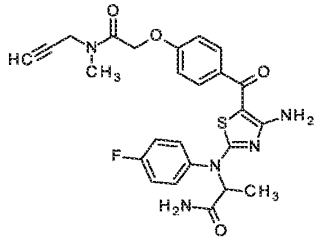
The crude product was purified by method F (individual gradient given, depending on retention time in analytical HPLC) after filtration of the reaction mixture.

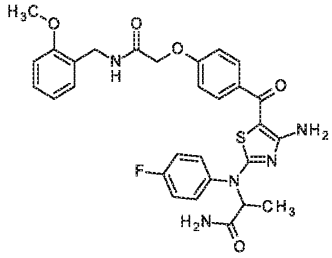
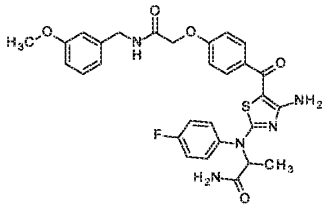
Table 7: Examples 83 – 141

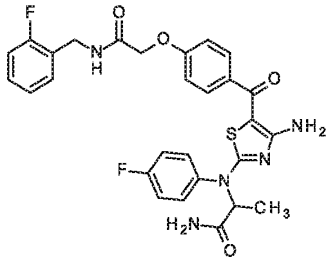
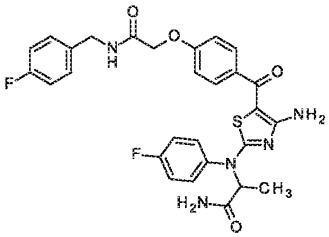
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
83	 rac-2-(N-[4-amino-5-[4-[2-(m-tolylmethylamino)-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 100, 1-(3-methylphenyl)methanamine	LC-MS (method 3) Rt = 1.12 min; MS (ESIpos): m/z = 562.2 $[M+H]^+$ Method F: Prep_30-60% B 11 % yield
84	 rac-2-(N-[4-amino-5-[4-[2-(o-tolylmethylamino)-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 100, 1-(2-methylphenyl)methanamine	LC-MS (method 3) Rt = 1.11 min; MS (ESIpos): m/z = 562.1 $[M+H]^+$ Method F: Prep_30-60% B 11 % yield

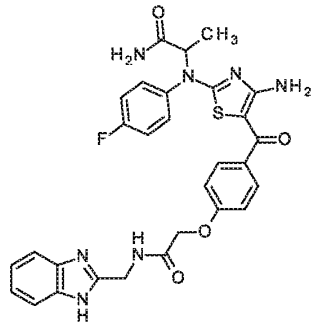
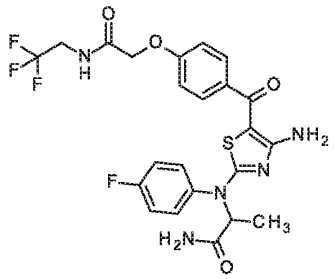
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
85	 rac-2-(N-[4-amino-5-[4-[2-[(3-chlorophenyl)methylamino]-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 100, 1-(3-chlorophenyl)methanamine	LC-MS (method 3) Rt = 1.13 min; MS (ESIpos): m/z = 582.1 $[M+H]^+$ Method F: Prep_35-65% B 10 % yield
86	 rac-2-(N-[4-amino-5-[4-[2-(4-methylpiperazin-1-yl)-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 100, 1-methylpiperazine	LC-MS (method 3) Rt = 0.88 min; MS (ESIpos): m/z = 541.1 $[M+H]^+$ Method F: Prep_20-50% B 12 % yield
87	 rac-2-(N-[4-amino-5-[4-[2-(3-methylanilino)-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 100, m-toluidine	LC-MS (method 3) Rt = 1.15 min; MS (ESIpos): m/z = 548.1 $[M+H]^+$ Method F: Prep_40-70% B 12 % yield

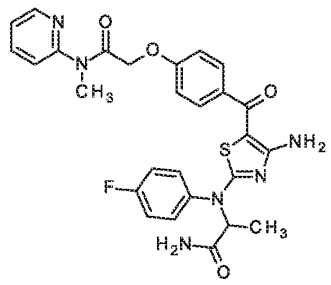
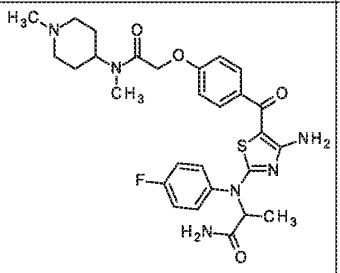
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88	 rac-2-(N-[4-amino-5-[4-(2-morpholino-2-oxo-ethoxy)benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 100, morpholine	LC-MS (method 3) Rt = 0.90 min; MS (ESIpos): m/z = 528.1 $[M+H]^+$ Method F: Prep_20-50% B 13 % yield
89	 rac-2-(N-[4-amino-5-[4-[2-oxo-2-[2-(1-piperidyl)ethylamino]ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 100, 2-(piperidin-1-yl)ethanamine	LC-MS (method 3) Rt = 1.07 min; MS (ESIpos): m/z = 569.2 $[M+H]^+$ Method F: Prep_30-60% B 5 % yield
90	 rac-2-(N-[4-amino-5-[4-[2-(4-benzyl-1-piperidyl)-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 100, 4-benzylpiperidine	LC-MS (method 3) Rt = 1.26 min; MS (ESIpos): m/z = 616.2 $[M+H]^+$ Method F: Prep_45-75% B 5 % yield

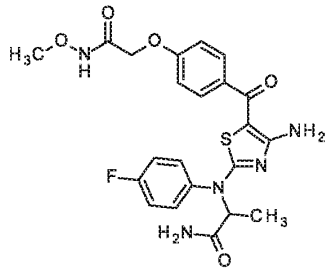
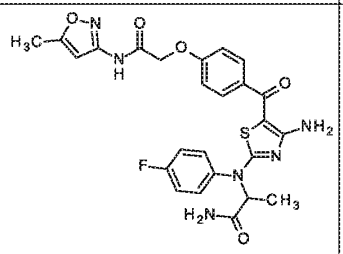
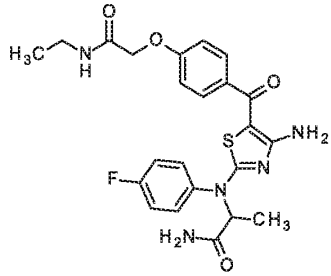
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
91	 rac-2-(N-[4-amino-5-[4-[2-(2-methoxyethylamino)-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 100, 2-methoxyethanamine	LC-MS (method 3) Rt = 0.90 min; MS (ESIpos): m/z = 516.1 $[M+H]^+$ Method F: Prep_20-50% B 5 % yield
92	 rac-2-(N-[4-amino-5-[4-[2-(4-cyanoanilino)-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 100, 4-aminobenzonitrile	LC-MS (method 3) Rt = 1.06 min; MS (ESIpos): m/z = 559.1 $[M+H]^+$ Method F: Prep_30-60% B 9 % yield
93	 rac-2-(N-[4-amino-5-[4-[2-[methyl(prop-2-ynyl)amino]-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 100, N-methylprop-2-yn-1-amine	LC-MS (method 3) Rt = 0.96 min; MS (ESIpos): m/z = 510.1 $[M+H]^+$ Method F: Prep_25-55% B 9 % yield

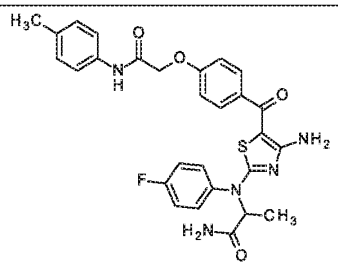
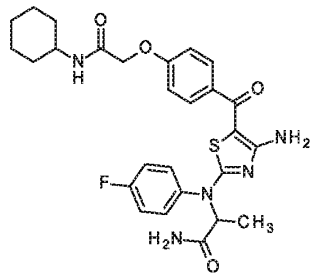
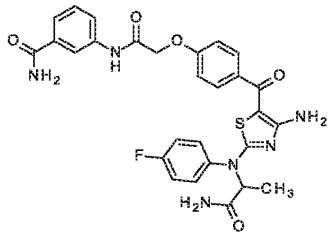
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
94	 rac-2-(N-[4-amino-5-[4-[2-[(2-methoxyphenyl)methylamino]-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 100, 1-(2-methoxyphenyl)methanamine	LC-MS (method 3) Rt = 1.08 min; MS (ESIpos): m/z = 578.1 $[M+H]^+$ Method F: Prep_30-60% B 13 % yield
95	 rac-2-(N-[4-amino-5-[4-[2-[(3-methoxyphenyl)methylamino]-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 100, 1-(3-methoxyphenyl)methanamine	LC-MS (method 3) Rt = 1.06 min; MS (ESIpos): m/z = 578.1 $[M+H]^+$ Method F: Prep_30-60% B 10 % yield

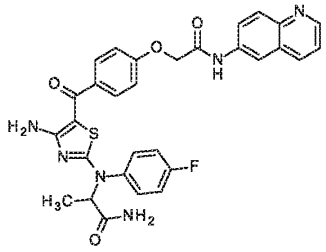
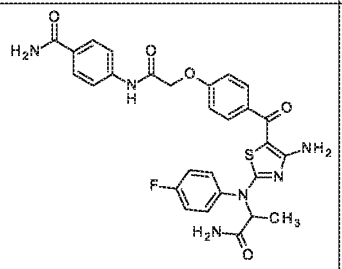
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
96	 rac-2-(N-[4-amino-5-[4-[2-[(2-fluorophenyl)methylamino]-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 100, 1-(2-fluorophenyl)methanamine	LC-MS (method 3) Rt = 1.07 min; MS (ESIpos): m/z = 566.1 $[M+H]^+$ Method F: Prep_30-60% B 10 % yield
97	 rac-2-(N-[4-amino-5-[4-[2-[(4-fluorophenyl)methylamino]-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 100, 1-(4-fluorophenyl)methanamine	LC-MS (method 3) Rt = 1.07 min; MS (ESIpos): m/z = 566.1 $[M+H]^+$ Method F: Prep_30-60% B 13 % yield

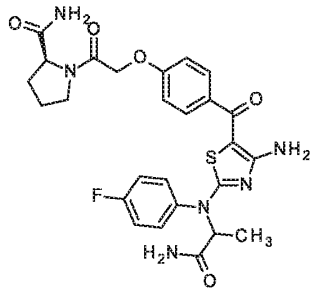
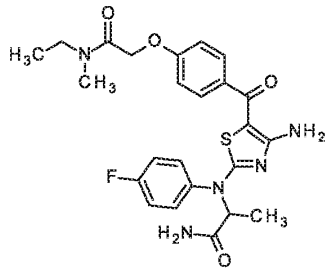
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
98	 rac-2-(N-[4-amino-5-[4-[2-(1H-benzimidazol-2-ylmethylamino)-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 100, 1-(1H-benzimidazol-2-yl)methanamine	LC-MS (method 3) Rt = 0.93 min; MS (ESIpos): m/z = 588.1 $[M+H]^+$ Method F: Prep_25-55% B 7 % yield
99	 rac-2-(N-[4-amino-5-[4-[2-oxo-2-(2,2,2-trifluoroethylamino)ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 100, 2,2,2-trifluoroethanamine	LC-MS (method 3) Rt = 1.00 min; MS (ESIpos): m/z = 540.0 $[M+H]^+$ Method F: Prep_25-55% B 21 % yield

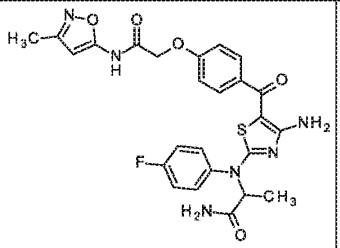
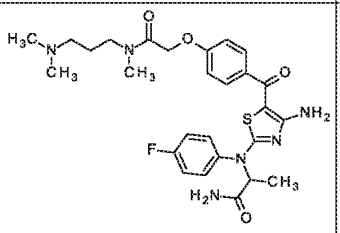
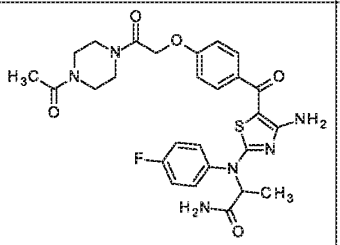
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
100	 rac-2-(N-[4-amino-5-[4-[2-[methyl(2-pyridyl)amino]-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 100, N-methylpyridin-2-amine	LC-MS (method 3) Rt = 0.99 min; MS (ESIpos): m/z = 549.1 $[M+H]^+$ Method F: Prep_25-55% B 9 % yield
101	 rac-2-(N-[4-amino-5-[4-[2-[methyl-(1-methyl-4-piperidyl)amino]-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 100, N,1-dimethylpiperidin-4-amine	LC-MS (method 3) Rt = 0.94 min; MS (ESIpos): m/z = 569.1 $[M+H]^+$ Method F: Prep_25-55% B 23 % yield

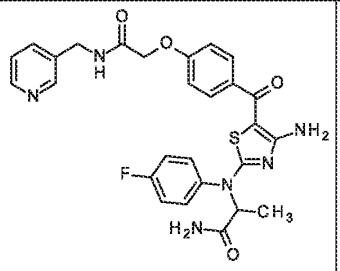
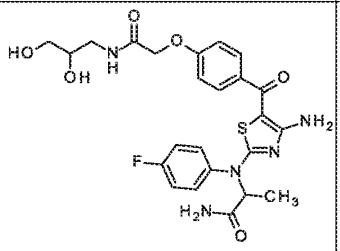
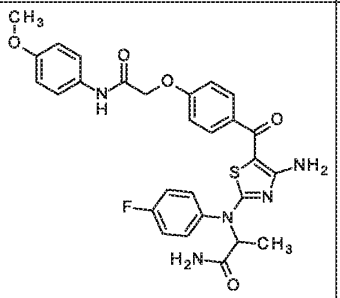
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102	 rac-2-(N-[4-amino-5-[4-[2-(methoxyamino)-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 100, O-methylhydroxylamine	LC-MS (method 3) Rt = 0.90 min; MS (ESIpos): m/z = 488.1 $[M+H]^+$ Method F: Prep_20-50% B 22 % yield
103	 rac-2-(N-[4-amino-5-[4-[2-[(5-methylisoxazol-3-yl)amino]-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 100, 5-methyl-1,2-oxazol-3-amine	LC-MS (method 3) Rt = 0.99 min; MS (ESIpos): m/z = 539.1 $[M+H]^+$ Method F: Prep_25-55% B 7 % yield
104	 rac-2-(N-[4-amino-5-[4-[2-(ethylamino)-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 100, ethanamine	LC-MS (method 3) Rt = 0.92 min; MS (ESIpos): m/z = 486.0 $[M+H]^+$ Method F: Prep_25-55% B 33 % yield

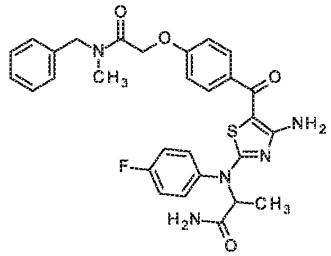
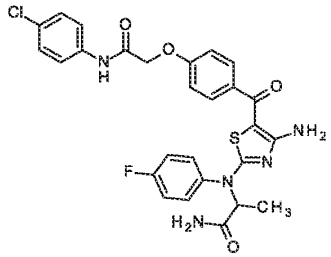
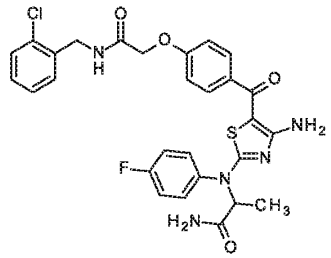
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
105	 rac-2-(N-[4-amino-5-[4-[2-(4-methylanilino)-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 100, p-toluidine	LC-MS (method 3) Rt = 1.15 min; MS (ESIpos): m/z = 548.1 $[M+H]^+$ Method F: Prep_40-70% B 37 % yield
106	 rac-2-(N-[4-amino-5-[4-[2-(cyclohexylamino)-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 100, cyclohexanamine	LC-MS (method 3) Rt = 1.12 min; MS (ESIpos): m/z = 540.1 $[M+H]^+$ Method F: Prep_35-65% B 11 % yield
107	 rac-3-[[2-[4-[4-amino-2-(N-[2-amino-1-methyl-2-oxo-ethyl]-4-fluoro-anilino)thiazole-5-carbonyl]phenoxy]acetyl]amino]benzamide	Intermediate 100, 3-aminobenzamide	LC-MS (method 3) Rt = 0.89 min; MS (ESIpos): m/z = 577.1 $[M+H]^+$ Method F: Prep_20-50% B 20 % yield

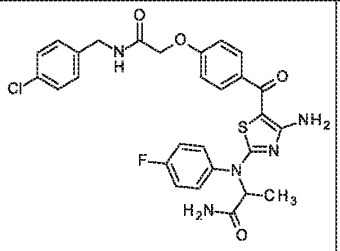
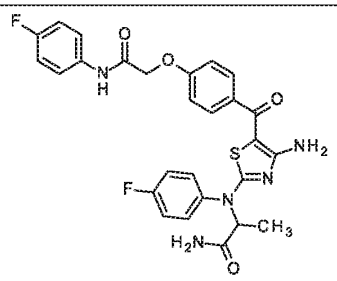
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
108	 rac-2-(N-[4-amino-5-[4-[2-oxo-2-(6-quinolylamino)ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 100, quinolin-6-amine	LC-MS (method 3) Rt = 1.01 min; MS (ESIpos): m/z = 585.1 $[M+H]^+$ Method F: Prep_25-55% B 30 % yield
109	 rac-4-[[2-[4-[4-amino-2-(N-[2-amino-1-methyl-2-oxo-ethyl]-4-fluoro-anilino)thiazole-5-carbonyl]phenoxy]acetyl]amino]benzamide	Intermediate 100, 4-aminobenzamide	LC-MS (method 3) Rt = 1.01 min; MS (ESIpos): m/z = 577.1 $[M+H]^+$ Method F: Prep_20-50% B 7 % yield

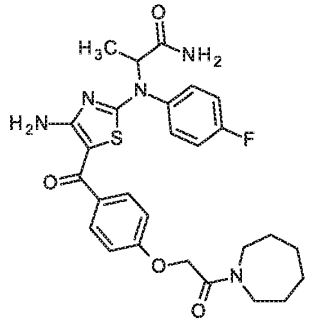
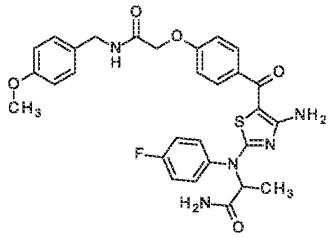
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
110	 (2S)-1-[2-[4-[4-amino-2-(N-[2-amino-(1RS)-methyl-2-oxo-ethyl]-4-fluoro-anilino)thiazole-5-carbonyl]phenoxy]acetyl]pyrrolidine-2-carboxamide (mixture of two diastereomers)	Intermediate 100, L-prolinamide	LC-MS (method 3) Rt = 0.82 min; MS (ESIpos): m/z = 555.1 $[M+H]^+$ Method F: Prep_15-45% B 15 % yield
111	 rac-2-(N-[4-amino-5-[4-[2-[ethyl(methyl)amino]-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 100, N-methylethanamine	LC-MS (method 3) Rt = 0.96 min; MS (ESIpos): m/z = 500.1 $[M+H]^+$ Method F: Prep_25-55% B 23 % yield

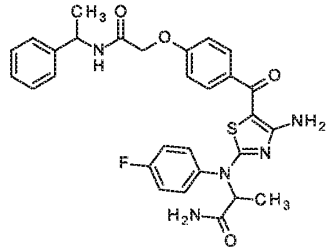
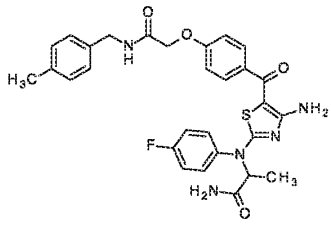
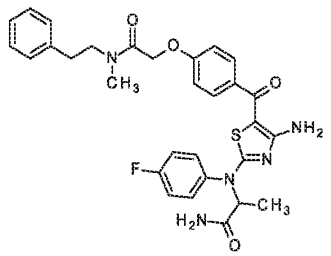
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
112	 rac-2-(N-[4-amino-5-[4-[2-[(3-methylisoxazol-5-yl)amino]-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 100, 3-methyl-1,2-oxazol-5-amine	LC-MS (method 3) Rt = 0.80 min; MS (ESIpos): m/z = 539.1 $[M+H]^+$ Method F: Prep_10-40% B 4 % yield
113	 rac-2-(N-[4-amino-5-[4-[2-[3-(dimethylamino)propyl-methyl-amino]-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 100, N,N,N'-trimethylpropane-1,3-diamine	LC-MS (method 3) Rt = 1.02 min; MS (ESIpos): m/z = 557.2 $[M+H]^+$ Method F: Prep_25-55% B 12 % yield
114	 rac-2-(N-[5-[4-[2-(4-acetylpiperazin-1-yl)-2-oxo-ethoxy]benzoyl]-4-amino-thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 100, 1-(piperazin-1-yl)ethanone	LC-MS (method 3) Rt = 0.84 min; MS (ESIpos): m/z = 569.1 $[M+H]^+$ Method F: Prep_15-45% B 14 % yield

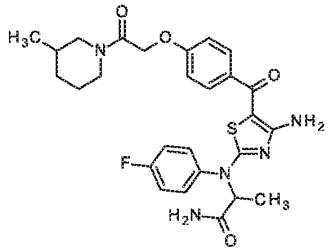
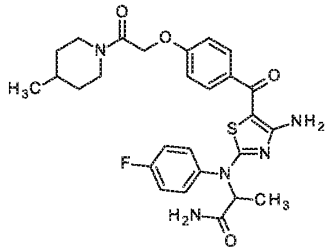
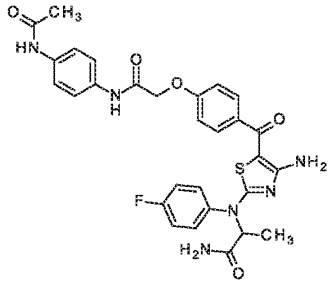
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
115	 rac-2-(N-[4-amino-5-[4-[2-oxo-2-(3-pyridylmethylamino)ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 100, 1-(pyridin-3-yl)methanamine	LC-MS (method 3) Rt = 0.90 min; MS (ESIpos): m/z = 549.1 $[M+H]^+$ Method F: Prep_20-50% B 4 % yield
116	 2-(N-[4-amino-5-[4-[2-(2,3-dihydroxypropylamino)-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide (mixture of stereoisomers)	Intermediate 100, rac-3-aminopropane-1,2-diol	LC-MS (method 3) Rt = 0.77 min; MS (ESIpos): m/z = 532.0 $[M+H]^+$ Method F: Prep_10-40% B 12 % yield
117	 rac-2-(N-[4-amino-5-[4-[2-(4-methoxyanilino)-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 100, 4-methoxyaniline	LC-MS (method 3) Rt = 1.07 min; MS (ESIpos): m/z = 564.1 $[M+H]^+$ Method F: Prep_30-60% B 21 % yield

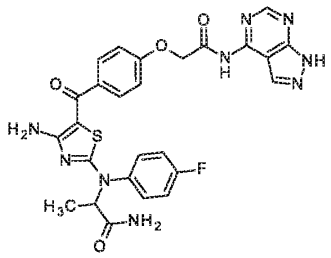
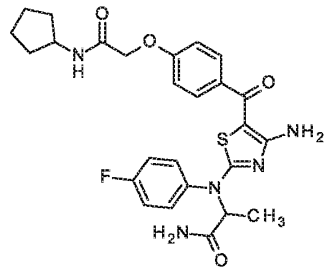
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
118	 rac-2-(N-[4-amino-5-[4-[2-[benzyl(methyl)amino]-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 100, N-methyl-1-phenylmethanamine	LC-MS (method 3) Rt = 1.10 min; MS (ESIpos): m/z = 562.1 $[M+H]^+$ Method F: Prep_30-60% B 14 % yield
119	 rac-2-(N-[4-amino-5-[4-[2-(4-chloroanilino)-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 100, 4-chloroaniline	LC-MS (method 3) Rt = 1.18 min; MS (ESIpos): m/z = 568.1 $[M+H]^+$ Method F: Prep_40-70% B 22 % yield
120	 rac-2-(N-[4-amino-5-[4-[2-[(2-chlorophenyl)methylamino]-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 100, 1-(2-chlorophenyl)methanamine	LC-MS (method 3) Rt = 1.13 min; MS (ESIpos): m/z = 582.1 $[M+H]^+$ Method F: Prep_35-65% B 12 % yield

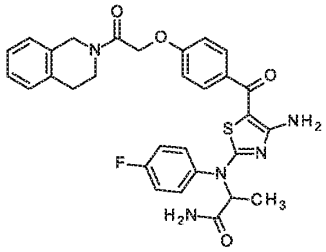
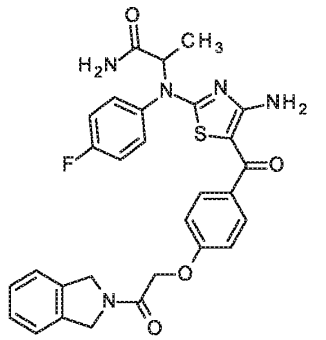
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
121	 rac-2-(N-[4-amino-5-[4-[2-[(4-chlorophenyl)methylamino]-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 100, 1-(4-chlorophenyl)methanamine	LC-MS (method 3) Rt = 1.13 min; MS (ESIpos): m/z = 582.1 $[M+H]^+$ Method F: Prep_35-65% B 15 % yield
122	 rac-2-(N-[4-amino-5-[4-[2-(4-fluoroanilino)-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 100, 4-fluoroaniline	LC-MS (method 3) Rt = 1.10 min; MS (ESIpos): m/z = 552.1 $[M+H]^+$ Method F: Prep_30-60% B 24 % yield

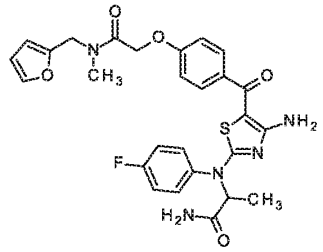
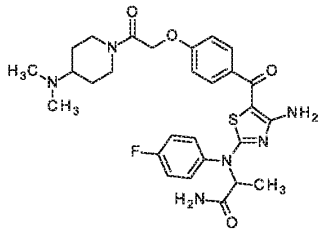
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
123	 rac-2-(N-[4-amino-5-[4-[2-(azepan-1-yl)-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 100, azepane	LC-MS (method 3) Rt = 1.08 min; MS (ESIpos): m/z = 540.1 $[M+H]^+$ Method F: Prep_30-60% B 6 % yield
124	 rac-2-(N-[4-amino-5-[4-[2-[(4-methoxyphenyl)methylamino]-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 100, 1-(4-methoxyphenyl)methanamine	LC-MS (method 3) Rt = 1.05 min; MS (ESIpos): m/z = 578.1 $[M+H]^+$ Method F: Prep_30-60% B 8 % yield

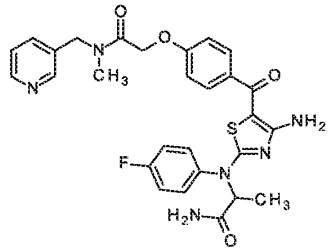
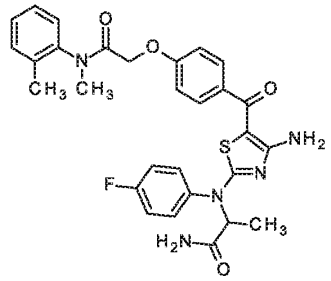
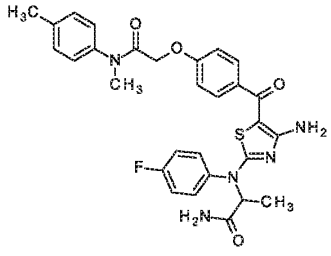
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
125	 2-(N-[4-amino-5-[4-[2-oxo-2-(1-phenylethylamino)ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide (mixture of stereoisomers)	Intermediate 100, rac-1-phenylethanamine	LC-MS (method 3) Rt = 1.10 min; MS (ESIpos): m/z = 562.1 $[M+H]^+$ Method F: Prep_30-60% B 9 % yield
126	 rac-2-(N-[4-amino-5-[4-[2-oxo-2-(p-tolylmethylamino)ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 100, 1-(4-methylphenyl)methanamine	LC-MS (method 3) Rt = 1.12 min; MS (ESIpos): m/z = 562.1 $[M+H]^+$ Method F: Prep_35-65% B 13 % yield
127	 rac-2-(N-[4-amino-5-[4-[2-[methyl(2-phenylethyl)amino]-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 100, N-methyl-2-phenylethanamine	LC-MS (method 3) Rt = 1.11 min; MS (ESIpos): m/z = 576.1 $[M+H]^+$ Method F: Prep_30-60% B 23 % yield

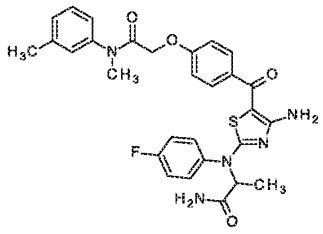
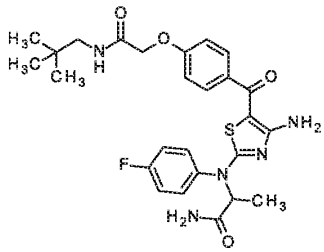
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
128	 2-(N-[4-amino-5-[4-[2-(3-methyl-1-piperidyl)-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide (mixture of stereoisomers)	Intermediate 100, rac-3-methylpiperidine	LC-MS (method 3) Rt = 1.11 min; MS (ESIpos): m/z = 540.1 $[M+H]^+$ Method F: Prep_30-60% B 4 % yield
129	 rac-2-(N-[4-amino-5-[4-[2-(4-methyl-1-piperidyl)-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 100, 4-methylpiperidine	LC-MS (method 3) Rt = 1.11 min; MS (ESIpos): m/z = 540.1 $[M+H]^+$ Method F: Prep_30-60% B 5 % yield
130	 rac-2-(N-[5-[4-[2-(4-acetamidoanilino)-2-oxo-ethoxy]benzoyl]-4-amino-thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 100, N-(4-aminophenyl)acetamide	LC-MS (method 3) Rt = 0.92 min; MS (ESIpos): m/z = 591.1 $[M+H]^+$ Method F: Prep_25-55% B 25 % yield

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
131	 rac-2-(N-[4-amino-5-[4-[2-oxo-2-(1H-pyrazolo[3,4-d]pyrimidin-4-ylamino)ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 100, 1H-pyrazolo[3,4-d]pyrimidin-4-amine	LC-MS (method 3) Rt = 0.80 min; MS (ESIpos): m/z = 576.1 $[M+H]^+$ Method F: Prep_10-40% B 7 % yield
132	 rac-2-(N-[4-amino-5-[4-[2-(cyclopentylamino)-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 100, cyclopentanamine	LC-MS (method 3) Rt = 1.06 min; MS (ESIpos): m/z = 526.1 $[M+H]^+$ Method F: Prep_30-60% B 8 % yield

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
133	 rac-2-(N-[4-amino-5-[4-[2-(3,4-dihydro-1H-isoquinolin-2-yl)-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 100, 1,2,3,4-tetrahydroisoquinoline	LC-MS (method 3) Rt = 1.13 min; MS (ESIpos): m/z = 574.1 $[M+H]^+$ Method F: Prep_35-65% B 8 % yield
134	 rac-2-(N-[4-amino-5-[4-(2-isoindolin-2-yl-2-oxo-ethoxy)benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 100, isoindoline	LC-MS (method 3) Rt = 1.09 min; MS (ESIpos): m/z = 560.1 $[M+H]^+$ Method F: Prep_30-60% B 6 % yield

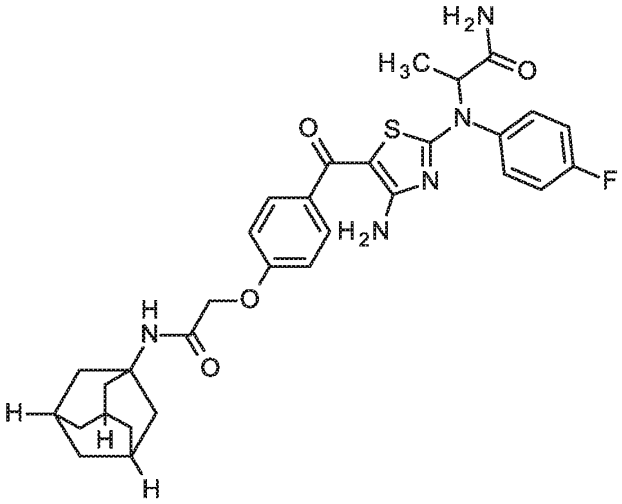
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
135	 rac-2-(N-[4-amino-5-[4-[2-[2-furylmethyl(methyl)amino]-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 100, 1-(2-furyl)-N-methylmethanamine	LC-MS (method 3) Rt = 1.04 min; MS (ESIpos): m/z = 552.1 $[M+H]^+$ Method F: Prep_30-60% B 12 % yield
136	 rac-2-(N-[4-amino-5-[4-[2-[4-(dimethylamino)-1-piperidyl]-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 100, N,N-dimethylpiperidin-4-amine	LC-MS (method 3) Rt = 0.97 min; MS (ESIpos): m/z = 569.2 $[M+H]^+$ Method F: Prep_25-55% B 13 % yield

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
137	 rac-2-(N-[4-amino-5-[4-[2-[methyl(3-pyridylmethyl)amino]-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 100, N-methyl-1-(pyridin-3-yl)methanamine	LC-MS (method 3) Rt = 0.92 min; MS (ESIpos): m/z = 563.1 $[M+H]^+$ Method F: Prep_25-55% B 24 % yield
138	 rac-2-(N-[4-amino-5-[4-[2-(N,2-dimethylanilino)-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 100, N,2-dimethylaniline	LC-MS (method 3) Rt = 1.13 min; MS (ESIpos): m/z = 562.1 $[M+H]^+$ Method F: Prep_35-65% B 13 % yield
139	 rac-2-(N-[4-amino-5-[4-[2-(N,4-dimethylanilino)-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 100, N,4-dimethylaniline	LC-MS (method 3) Rt = 1.16 min; MS (ESIpos): m/z = 562.1 $[M+H]^+$ Method F: Prep_40-70% B 26 % yield

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
140	 rac-2-(N-[4-amino-5-[4-[2-(N,3-dimethylanilino)-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 100, N,3-dimethylaniline	LC-MS (method 3) Rt = 1.15 min; MS (ESIpos): m/z = 562.1 $[M+H]^+$ Method F: Prep_40-70% B 31 % yield
141	 rac-2-(N-[4-amino-5-[4-[2-(2,2-dimethylpropylamino)-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 100, 2,2-dimethylpropan-1-amine	LC-MS (method 3) Rt = 1.08 min; MS (ESIpos): m/z = 528.1 $[M+H]^+$ Method F: Prep_30-60% B 4 % yield

Example 142

2-(N-[5-[4-[2-(1-adamantylamino)-2-oxo-ethoxy]benzoyl]-4-amino-thiazol-2-yl]-4-fluoro-anilino)propanamide (single stereoisomer)



2-[4-[4-amino-2-(N-[2-amino-1-methyl-2-oxo-ethyl]-4-fluoro-anilino)thiazole-5-carbonyl]phenoxy]acetic acid (enantiomer 2) (30 mg, 65 µmol; Intermediate 100.2) and adamantan-1-amine (20 mg, 131 µmol) were dissolved in dimethylformamide (0.5 mL). N,N-diisopropylethylamine (25 mg, 196 µmol), 4-dimethylaminopyridine (0.4 mg, 3 µmol) and HATU (50 mg, 131 µmol) were added. The reaction mixture was stirred overnight at rt.

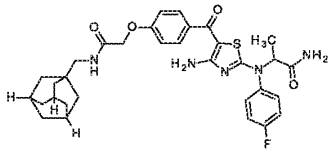
The reaction mixture was filtrated and purified by RP-HPLC (method E, basic) to give 12 mg (29 % yield) of the title compound.

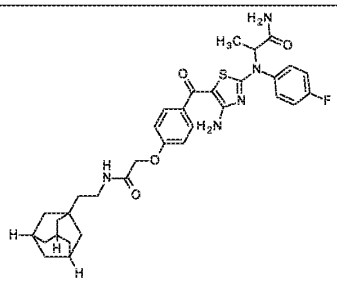
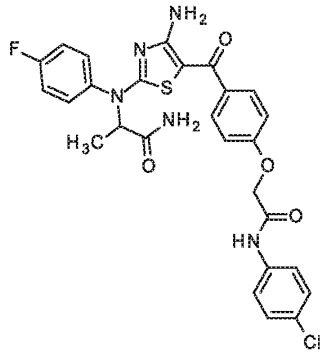
^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.16 (d, *J*=7.60 Hz, 3 H), 1.59 - 1.63 (m, 6 H), 1.92 (d, *J*=2.53 Hz, 6 H), 2.00 (br d, *J*=1.77 Hz, 3 H), 4.41 (s, 2 H), 5.00 - 5.13 (m, 1 H), 6.89 (d, *J*=8.87 Hz, 2 H), 7.24 (s, 1 H), 7.30 - 7.36 (m, 3 H), 7.46 (d, *J*=8.87 Hz, 2 H), 7.57 (s, 1 H), 7.64 (dd, *J*=9.00, 5.20 Hz, 2 H), 8.11 (br s, 2 H).

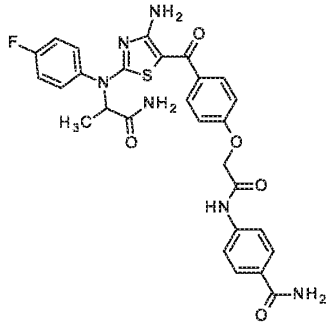
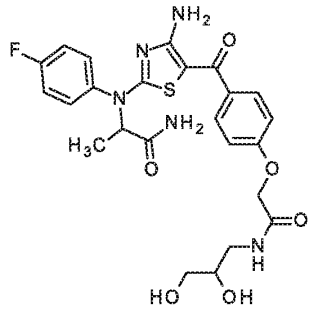
LC-MS (method 2) Rt = 1.32 min; MS (ESIpos): m/z = 592.5 $[M+H]^+$

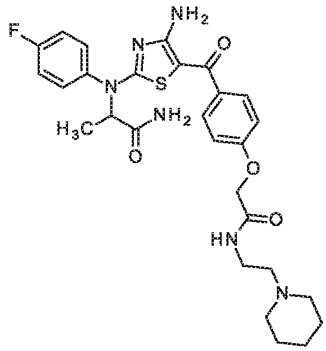
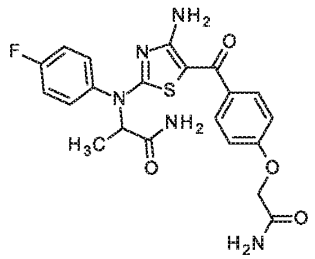
The following examples were prepared from the starting materials stated in Table 8, below, using the procedure as for Example 142.

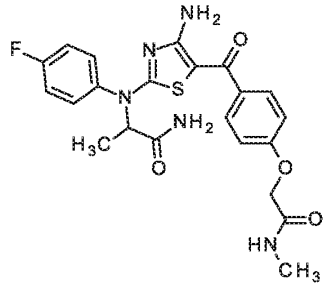
Table 8: Examples 143 – 155

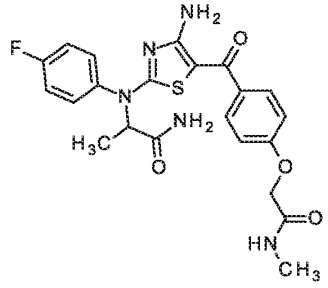
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
143	 2-(N-[5-[4-[2-(1-adamantylmethylamino)-2-oxo-ethoxy]benzoyl]-4-amino-thiazol-2-yl]-4-fluoro-anilino)propanamide (single stereoisomer)	Intermediate 100.2; 1-adamantylmethanamine	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.15 (d, *J*=7.35 Hz, 3 H), 1.31 (d, *J*=2.03 Hz, 6 H), 1.44 - 1.48 (m, 3 H), 1.55 - 1.61 (m, 3 H), 1.80 (br s, 3 H), 2.78 (d, *J*=6.59 Hz, 2 H), 4.54 (s, 2 H), 5.02 - 5.11 (m, 1 H), 6.94 (d, *J*=8.87 Hz, 2 H), 7.25 (s, 1 H), 7.32 (t, *J*=8.74 Hz, 2 H), 7.48 (d, *J*=8.62 Hz, 2 H), 7.57 (s, 1 H), 7.63 (dd, *J*=8.87, 4.82 Hz, 2 H), 7.82 (t, *J*=6.21 Hz, 1 H), 8.19 (br s, 2 H). LC-MS (method 1) Rt = 1.29 min; MS (ESIpos): m/z = 606.5 $[M+H]^+$ RP-HPLC (method E, basic) 41 % yield

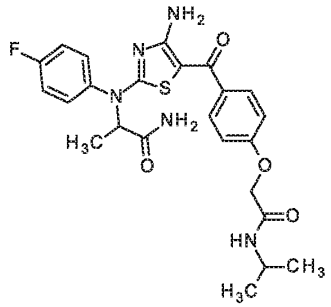
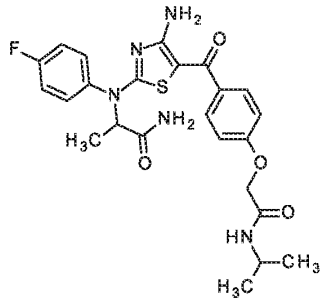
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
144	 2-(N-[5-[4-[2-[2-(1-adamantyl)ethylamino]-2-oxo-ethoxy]benzoyl]-4-amino-thiazol-2-yl]-4-fluoro-anilino)propanamide (single stereoisomer)	Intermediate 100.2; 2-(1-adamantyl)ethanamine	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.13 - 1.17 (m, 3 H), 1.17 - 1.24 (m, 2 H), 1.44 (d, *J*=2.03 Hz, 6 H), 1.55 - 1.61 (m, 3 H), 1.62 - 1.68 (m, 3 H), 1.87 - 1.91 (m, 3 H), 3.07 - 3.15 (m, 2 H), 4.45 (s, 2 H), 5.01 - 5.10 (m, 1 H), 6.92 (d, *J*=8.87 Hz, 2 H), 7.24 (s, 1 H), 7.33 (t, *J*=8.87 Hz, 2 H), 7.47 (d, *J*=8.87 Hz, 2 H), 7.57 (s, 1 H), 7.64 (dd, *J*=8.87, 5.07 Hz, 2 H), 8.30 (br s, 2 H), 7.97 (t, *J*=5.83 Hz, 1 H). LC-MS (method 1) Rt = 1.40 min; MS (ESIpos): m/z = 620.6 $[M+H]^+$ RP-HPLC (method E, basic)
145	 2-(N-[4-amino-5-[4-[2-(4-chloroanilino)-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide (single stereoisomer)	Intermediate 100.2; 4-chloroaniline	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.16 (d, *J*=7.35 Hz, 3 H), 4.73 (s, 2 H), 5.00 - 5.11 (m, 1 H), 6.98 (d, *J*=8.87 Hz, 2 H), 7.24 (s, 1 H), 7.33 (t, *J*=8.87 Hz, 2 H), 7.38 (d, *J*=8.87 Hz, 2 H), 7.49 (d, *J*=8.87 Hz, 2 H), 7.57 (s, 1 H), 7.61 - 7.67 (m, 4 H), 8.08 (br s, 2 H), 10.24 (s, 1 H). LC-MS (method 1) Rt = 1.20 min; MS (ESIpos): m/z = 568.4 $[M+H]^+$ RP-HPLC (method D, basic) 59 % yield

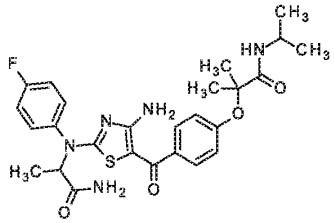
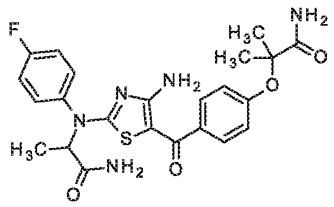
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
146	 4-[[2-[4-[4-amino-2-(4-fluoro-N-[2-amino-1-methyl-2-oxo-ethyl]anilino)thiazole-5-carbonyl]phenoxy]acetyl]amino]benzamide (single stereoisomer)	Intermediate 100.2; 4-aminobenzamide	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.16 (d, *J*=7.35 Hz, 3 H), 4.76 (s, 2 H), 5.01 - 5.09 (m, 1 H), 6.99 (d, *J*=8.87 Hz, 2 H), 7.24 (s, 1 H), 7.26 (br s, 1 H), 7.33 (t, *J*=8.74 Hz, 2 H), 7.49 (d, *J*=8.62 Hz, 2 H), 7.58 (s, 1 H), 7.64 (dd, *J*=9.00, 5.20 Hz, 2 H), 7.68 (d, *J*=8.87 Hz, 2 H), 7.84 (d, *J*=8.87 Hz, 2 H), 7.87 - 7.90 (m, 1 H), 8.10 (br s, 2 H), 10.31 (s, 1 H). LC-MS (method 1) Rt = 0.88 min; MS (ESIpos): m/z = 577.4 [M+H]$^+$ RP-HPLC (method C, basic) 48 % yield
147	 2-(N-[4-amino-5-[4-[2-((2RS),3-dihydroxypropylamino)-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide (mixture of two diastereomers)	Intermediate 100.2; rac-3-aminopropane-1,2-diol	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.16 (d, *J*=7.35 Hz, 3 H), 2.99 - 3.08 (m, 1 H), 3.24 - 3.30 (m, 4 H), 3.48 - 3.56 (m, 2 H), 4.49 - 4.53 (m, 2 H), 4.55 - 4.60 (m, 1 H), 4.75 - 4.85 (m, 1 H), 5.05 (br d, *J*=7.10 Hz, 1 H), 6.92 - 6.96 (m, 2 H), 7.24 (s, 1 H), 7.33 (t, *J*=8.87 Hz, 2 H), 7.48 (d, *J*=8.62 Hz, 2 H), 7.58 (s, 1 H), 7.61 - 7.67 (m, 2 H), 7.93 - 7.99 (m, 1 H). LC-MS (method 1) Rt = 0.78 min; MS (ESIpos): m/z = 532.4 [M+H]$^+$ RP-HPLC (method B, basic) 54 % yield

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
148	 2-(N-[4-amino-5-[4-[2-oxo-2-[2-(1-piperidyl)ethylamino]ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide (single stereoisomer)	Intermediate 100.2; 2-(piperidin-1-yl)ethanamine (salt with hydrogen chloride)	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.16 (d, *J*=7.60 Hz, 3 H), 1.28 - 1.46 (m, 7 H), 2.22 - 2.30 (m, 6 H), 3.16 - 3.24 (m, 2 H), 4.42 - 4.56 (m, 2 H), 4.96 - 5.19 (m, 1 H), 6.90 - 6.95 (m, 2 H), 7.23 - 7.26 (m, 1 H), 7.33 (t, *J*=8.74 Hz, 2 H), 7.45 - 7.50 (m, 2 H), 7.56 - 7.59 (m, 1 H), 7.61 - 7.66 (m, 2 H), 7.87 (t, *J*=5.32 Hz, 1 H). LC-MS (method 1) Rt = 0.77 min; MS (ESIpos): m/z = 569.5 $[M+H]^+$ RP-HPLC (method C, basic) 54 % yield
149	 2-(N-[4-amino-5-[4-(2-amino-2-oxo-ethoxy)benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide (single stereoisomer)	Intermediate 100.2; ammonia in dioxane	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.16 (d, *J*=7.35 Hz, 3 H), 4.44 (s, 2 H), 5.05 (q, *J*=6.84 Hz, 1 H), 6.92 (d, *J*=8.87 Hz, 2 H), 7.24 (s, 1 H), 7.33 (t, *J*=8.87 Hz, 2 H), 7.38 (br s, 1 H), 7.47 (d, *J*=8.87 Hz, 2 H), 7.52 (br s, 1 H), 7.58 (s, 1 H), 7.64 (dd, *J*=8.87, 5.07 Hz, 2 H), 8.07 (br s, 2 H). LC-MS (method 1) Rt = 0.82 min; MS (ESIpos): m/z = 458.3 $[M+H]^+$ RP-HPLC (method B, basic) 60 % yield

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
150 and **151**	(R)-2-(N-[4-amino-5-[4-[2-(methylamino)-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide and (S)-2-(N-[4-amino-5-[4-[2-(methylamino)-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide		
150	 2-(N-[4-amino-5-[4-[2-(methylamino)-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide (enantiomer 1)	Intermediate 100.1; methanamine in tetrahydrofurane 2.0M	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.16 (d, *J*=7.60 Hz, 3 H), 2.63 (d, *J*=4.82 Hz, 3 H), 4.47 (s, 2 H), 5.05 (q, *J*=6.00 Hz, 1 H), 6.93 (d, *J*=8.87 Hz, 2 H), 7.24 (s, 1 H), 7.33 (t, *J*=8.74 Hz, 2 H), 7.48 (d, *J*=8.62 Hz, 2 H), 7.58 (s, 1 H), 7.64 (dd, *J*=8.87, 5.07 Hz, 2 H), 8.15 (br s, 2 H), 8.00 - 8.04 (m, 1 H). LC-MS (method 1) Rt = 0.88 min; MS (ESIpos): m/z = 472.3 $[M+H]^+$ RP-HPLC (method C, basic) 64 % yield

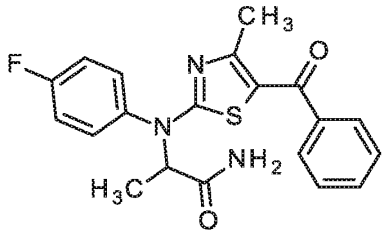
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
151	 2-(N-[4-amino-5-[4-[2-(methylamino)-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide (enantiomer 2)	Intermediate 100.2; methanamine in tetrahydrofurane 2.0M	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.16 (d, *J*=7.60 Hz, 3 H), 2.63 (d, *J*=4.82 Hz, 3 H), 4.47 (s, 2 H), 5.05 (q, *J*=7.35 Hz, 1 H), 6.93 (d, *J*=8.87 Hz, 2 H), 7.25 (s, 1 H), 7.33 (t, *J*=8.74 Hz, 2 H), 7.48 (d, *J*=8.62 Hz, 2 H), 7.58 (s, 1 H), 7.64 (dd, *J*=8.87, 5.07 Hz, 2 H), 8.07 (br s, 2 H), 7.99 - 8.05 (m, 1 H). LC-MS (method 1) Rt = 0.88 min; MS (ESIpos): m/z = 472.3 $[M+H]^+$ RP-HPLC (method C, basic) 29 % yield
152 and **153**	(R)-2-(N-[4-amino-5-[4-[2-(isopropylamino)-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide and (S)-2-(N-[4-amino-5-[4-[2-(isopropylamino)-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide		

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
152	 2-(N-[4-amino-5-[4-[2-(isopropylamino)-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide (enantiomer 1)	Intermediate 100.1; propan-2-amine	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.04 - 1.08 (m, 6 H), 1.16 (d, *J*=7.35 Hz, 3 H), 3.86 - 3.96 (m, 1 H), 4.45 (s, 2 H), 5.05 (br q, *J*=7.10 Hz, 1 H), 6.92 (d, *J*=8.87 Hz, 2 H), 7.24 (s, 1 H), 7.33 (t, *J*=8.87 Hz, 2 H), 7.47 (d, *J*=8.87 Hz, 2 H), 7.57 (s, 1 H), 7.64 (dd, *J*=9.00, 5.20 Hz, 2 H), 8.08 (br s, 2 H), 7.87 (br d, *J*=8.11 Hz, 1 H). LC-MS (method 1) Rt = 1.00 min; MS (ESIpos): m/z = 500.4 $[M+H]^+$ RP-HPLC (method C, basic) 75 % yield
153	 2-(N-[4-amino-5-[4-[2-(isopropylamino)-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide (enantiomer 2)	Intermediate 100.2; propan-2-amine	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.06 (d, *J*=6.59 Hz, 6 H), 1.16 (d, *J*=7.35 Hz, 3 H), 3.87 - 3.96 (m, 1 H), 4.45 (s, 2 H), 5.05 (q, *J*=7.86 Hz, 1 H), 6.92 (d, *J*=8.87 Hz, 2 H), 7.24 (s, 1 H), 7.33 (t, *J*=8.87 Hz, 2 H), 7.47 (d, *J*=8.87 Hz, 2 H), 7.57 (s, 1 H), 7.64 (dd, *J*=9.00, 5.20 Hz, 2 H), 8.06 (br s, 2 H), 7.87 (br d, *J*=7.86 Hz, 1 H). LC-MS (method 1) Rt = 1.00 min; MS (ESIpos): m/z = 500.4 $[M+H]^+$ RP-HPLC (method C, basic) 72 % yield

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
154	 rac-2-[4-[4-amino-2-(N-(2-amino-1-methyl-2-oxo-ethyl)-4-fluoro-anilino)thiazole-5-carbonyl]phenoxy]-N-isopropyl-2-methyl-propanamide	Intermediate 82; propan-2-amine	^{1}H-NMR (400 MHz, DMSO-d_6): δ ppm = 0.94 (d, *J*=6.59 Hz, 6 H), 1.16 (d, *J*=7.35 Hz, 3 H), 1.43 (s, 6 H), 3.83 - 3.96 (m, 1 H), 4.99 - 5.11 (m, 1 H), 6.79 (d, *J*=8.62 Hz, 2 H), 7.24 (s, 1 H), 7.32 (t, *J*=8.87 Hz, 2 H), 7.42 (d, *J*=8.62 Hz, 2 H), 7.57 (s, 1 H), 7.63 (dd, *J*=8.74, 5.20 Hz, 2 H), 7.75 (d, *J*=8.11 Hz, 1 H), 7.80 - 8.50 (m, 2 H). LC-MS (method 1) Rt = 1.10 min; MS (ESIpos): m/z = 528.4 [M+H]$^+$ RP-HPLC (method D, basic) 23 % yield
155	 rac-2-[4-[4-amino-2-(N-(2-amino-1-methyl-2-oxo-ethyl)-4-fluoro-anilino)thiazole-5-carbonyl]phenoxy]-2-methyl-propanamide	Intermediate 82; ammonia	^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.15 (d, *J*=7.35 Hz, 3 H), 1.43 (s, 6 H), 4.99 - 5.11 (m, 1 H), 6.82 (d, *J*=8.87 Hz, 2 H), 7.25 (br d, *J*=7.86 Hz, 2 H), 7.33 (t, *J*=8.87 Hz, 2 H), 7.44 (d, *J*=8.62 Hz, 2 H), 7.50 - 7.52 (m, 1 H), 7.57 - 7.59 (m, 1 H), 7.64 (dd, *J*=8.74, 5.20 Hz, 2 H), 7.82 - 8.34 (m, 2 H). LC-MS (method 1) Rt = 0.93 min; MS (ESIpos): m/z = 486.3 [M+H]$^+$ RP-HPLC (method C, basic) 42 % yield

Example 156

rac-2-(N-(5-benzoyl-4-methyl-thiazol-2-yl)-4-fluoro-anilino)propanamide



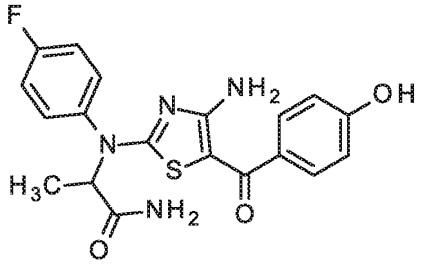
[2-(4-fluoroanilino)-4-methyl-thiazol-5-yl]-phenyl-methanone (40 mg, 0.13 mmol; Intermediate 81) was dissolved in N,N-dimethylformamide (1.4 mL), followed by the addition of potassium carbonate (177 mg, 1.28 mmol) and rac-2-bromopropanamide (97 mg, 0.64 mmol). The reaction mixture was stirred at 90°C for 1 h. The reaction mixture was filtrated and purified by RP-HPLC (method D, basic) to give 24 mg (48 % yield) of the title compound.

^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.16 (d, *J*=7.35 Hz, 3 H), 2.24 - 2.27 (m, 3 H), 5.11 (q, *J*=7.35 Hz, 1 H), 7.20 (s, 1 H), 7.36 (t, *J*=8.87 Hz, 2 H), 7.43 - 7.48 (m, 2 H), 7.51 - 7.57 (m, 3 H), 7.62 (s, 1 H), 7.67 (dd, *J*=9.13, 5.07 Hz, 2 H).

LC-MS (method 2) Rt = 1.16 min; MS (ESIpos): m/z = 384.4 $[M+H]^+$

Example 157

rac-2-(N-[4-amino-5-(4-hydroxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide



Rac-2-(N-[4-amino-5-(4-benzyloxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide (100 mg, 204 µmol, Example 158) was dissolved in ethanol (2.5 mL). Under nitrogen atmosphere was added palladium on carbon (325 mg, 10 % purity, 306 µmol; CAS-RN 7440-05-3) and then the nitrogen atmosphere was evacuated and was replaced with hydrogen. The mixture was stirred for 3.5 h at rt under hydrogen atmosphere. Further palladium on carbon (100 µmol) was added and the mixture was stirred for a further 3 h at rt under hydrogen atmosphere. The reaction mixture was filtered over celite, washed with ethanol and the filtrate was concentrated under

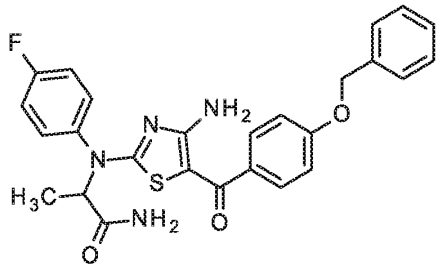
reduced pressure. The residue was purified by RP-HPLC (method B, basic) to give 27 mg (31 % yield) of the title compound.

LC-MS (method 2) Rt = 0.69 min; MS (ESIpos): m/z = 401.2 $[M+H]^+$

^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.16 (d, *J*=7.35 Hz, 3 H), 2.08 (s, 1 H), 5.01 - 5.09 (m, 1 H), 6.70 - 6.75 (m, 2 H), 7.24 (s, 1 H), 7.33 (t, *J*=8.87 Hz, 2 H), 7.37 - 7.41 (m, 2 H), 7.57 (s, 1 H), 7.64 (dd, *J*=9.00, 4.94 Hz, 2 H), 7.76 - 8.21 (m, 2 H), 9.90 (br s, 1 H)

Example 158

rac-2-(N-[4-amino-5-(4-benzyloxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide



[4-amino-2-(4-fluoroanilino)-1,3-thiazol-5-yl][4-(benzyloxy)phenyl]methanone (610 mg, 1.45 mmol, Intermediate 77) was suspended in DMF (10 mL), rac-2-bromopropanamide (265 mg, 1.75 mmol) and potassium carbonate (301 mg, 2.18 mmol) were added. The reaction mixture was stirred for 3.5 h at rt. Further rac-2-bromopropanamide (265 mg, 1.75 mmol) and potassium carbonate (301 mg, 2.18 mmol) were added and the mixture was stirred overnight at rt. The mixture was treated with water and stirred for 30 min. The resulting precipitate was isolated by filtration, washed with water and dried to give 641 mg (98 % purity, 88 % yield) of the title compound.

^{1}H-NMR (400 MHz, DMSO-*d6*): δ ppm = 1.16 (d, *J*=7.35 Hz, 3 H), 5.02 - 5.09 (m, 1 H), 5.11 (s, 2 H), 7.00 (d, *J*=8.87 Hz, 2 H), 7.25 (s, 1 H), 7.31 - 7.45 (m, 7 H), 7.46 - 7.50 (m, 2 H), 7.57 (s, 1 H), 7.64 (dd, *J*=8.87, 5.07 Hz, 2 H), 7.78 - 8.38 (m, 2 H).

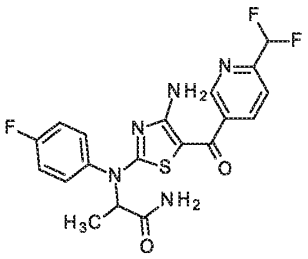
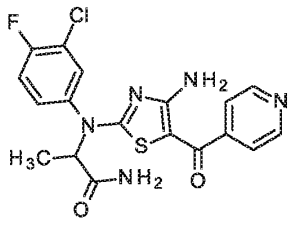
LC-MS (method 2) Rt = 1.25 min; MS (ESIpos): m/z = 491.3 $[M+H]^+$

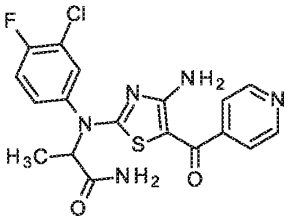
The following examples were prepared from the starting materials stated in Table 9, below, using the procedure as for Example 1.

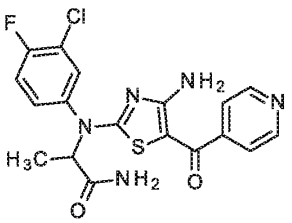
The crude product was either purified by RP-HPLC (methods A-D depending on polarity) or by preparative flash chromatography (methods X, Y or Z depending on polarity) after precipitation, extraction or filtration of the reaction mixture if necessary.

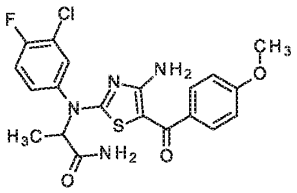
Enantiomers were separated from their racemate by chiral HPLC using the column and solvent conditions stated.

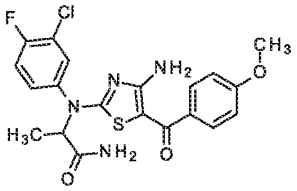
Table 9: Example 159 - 256

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
159	 rac-2-(N-[4-amino-5-[6-(difluoromethyl)pyridine-3-carbonyl]thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 101; rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.16 (d, *J*=7.35 Hz, 3 H), 5.04 – 5.08 (m, 1 H), 6.94 (t, *J*=60 Hz, 1 H), 7.29 – 7.33 (m, 3 H), 7.60 -7.65 (m, 3 H), 7.72 (d, *J*=8.11 Hz, 1 H), 8.04 (dd, *J*=7.98, 2.15 Hz, 1 H), 8.30 8.34 (m, 2 H), 8.76 (d, *J*=1.52 Hz, 1 H). RP-HPLC (method C basic) LC-MS (method 2) Rt = 1.00 min MS (ESIpos): m/z = 436.4 $[M+H]^+$ 48 % yield
160	 rac-2-(N-[4-amino-5-(pyridine-4-carbonyl)thiazol-2-yl]-3-chloro-4-fluoro-anilino)propanamide	Intermediate 102; rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.18 (d, *J*=7.35 Hz, 3 H), 5.00 – 5.04 (m, 1 H), 7.31 (s, 1 H), 7.40 – 7.44 (m, 2 H), 7.55 – 7.58 (m, 1 H), 7.63 – 7.67 (m, 2 H), 7.91 (dd, *J*=6.84, 2.28 Hz, 1 H), 8.27 -8.31 (m, 2 H), 8.60 – 8.64 (m, 2 H). Isolated via precipitation LC-MS (method 2) Rt = 0.94 min MS (ESIpos): m/z = 420.3 $[M+H]^+$ 60 % yield

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
160.1 and **160.2**	(R)- 2-(N-[4-amino-5-(pyridine-4-carbonyl)thiazol-2-yl]-3-chloro-4-fluoro-anilino)propanamide and (S)- 2-(N-[4-amino-5-(pyridine-4-carbonyl)thiazol-2-yl]-3-chloro-4-fluoro-anilino)propanamide		
160.1	 2-(N-[4-amino-5-(pyridine-4-carbonyl)thiazol-2-yl]-3-chloro-4-fluoro-anilino)propanamide (enantiomer 1)	Example 160	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.18 (d, *J*=7.35 Hz, 4 H), 5.00 – 5.05 (m, 1 H), 7.31 (s, 1 H), 7.42 (d, *J*=6.08 Hz, 2 H), 7.57 (m, 1 H), 7.62 – 7.67 (m, 2 H), 7.92 (dd, *J*=6.84, 2.53 Hz, 1 H), 8.25 – 8.29 (m, 2 H), 8.63 (d, *J*=5.83 Hz, 2 H). LC-MS (method 1) Rt = 0.86 min; MS (ESIpos): m/z = 420.3 $[M+H]^+$ 34 % yield

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
Chiral HPLC Example 160.1 HPLC separation of rac-2-(N-[4-amino-5-(pyridine-4-carbonyl)thiazol-2-yl]-3-chloro-4-fluoro-anilino)propanamide (560 mg, 1.33 mmol, Example 160) on a chiral column gave 190 mg (34 % yield) of 2-(N-[4-amino-5-(pyridine-4-carbonyl)thiazol-2-yl]-3-chloro-4-fluoro-anilino)propanamide, enantiomer 1. Preparative chiral HPLC PrepCon Labomatic HPLC; Column: YMC Amylose SA 10µ, 250x50; eluent A: methyl tert-butyl ether + 0.1 vol % diethylamine; eluent B: acetonitrile; isocratic: 50%A+50%B; flow: 120 mL/min; temperature: 25°C; UV: 254 nm Analytical chiral HPLC: Rt = 1.23 min Waters Alliance 2695; Column: YMC Amylose SA 3µ, 100x4.6; eluent A: methyl tert-butyl ether + 0.1 vol % diethylamine; eluent B: acetonitrile; isocratic: 50%A+50%B; flow: 1.4 mL/min; temperature: 25°C; UV: 254 nm			
160.2	 2-(N-[4-amino-5-(pyridine-4-carbonyl)thiazol-2-yl]-3-chloro-4-fluoro-anilino)propanamide (enantiomer 2)	Example 160	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.18 (d, *J*=7.35 Hz, 4 H), 5.00 – 5.04 (m, 1 H), 7.31 (s, 1 H), 7.42 (d, *J*=6.08 Hz, 2 H), 7.55 – 7.59 (m, 1 H), 7.63 – 7.67 (m, 2 H), 7.92 (dd, *J*=6.84, 2.53 Hz, 1 H), 8.24 – 8.30 (m, 2 H), 8.63 (d, *J*=5.83 Hz, 2 H). LC-MS (method 1) Rt = 0.86 min; MS (ESIpos): m/z = 420.3 $[M+H]^+$ 33 % yield

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
Chiral HPLC Example 160.2 HPLC separation of rac-2-(N-[4-amino-5-(pyridine-4-carbonyl)thiazol-2-yl]-3-chloro-4-fluoro-anilino)propanamide (560 mg, 1.33 mmol, Example 160) on a chiral column gave 185 mg (33 % yield) of 2-(N-[4-amino-5-(pyridine-4-carbonyl)thiazol-2-yl]-3-chloro-4-fluoro-anilino)propanamide, enantiomer 2. <u>Preparative chiral HPLC</u> PrepCon Labomatic HPLC; Column: YMC Amylose SA 10µ, 250x50; eluent A: methyl tert-butyl ether + 0.1 vol % diethylamine; eluent B: acetonitrile; isocratic: 50%A+50%B; flow: 120 mL/min; temperature: 25°C; UV: 254 nm <u>Analytical chiral HPLC:</u> Rt = 1.67 min Waters Alliance 2695; Column: YMC Amylose SA 3µ, 100x4.6; eluent A: methyl tert-butyl ether + 0.1 vol % diethylamine; eluent B: acetonitrile; isocratic: 50%A+50%B; flow: 1.4 mL/min; temperature: 25°C; UV: 254 nm			
161	 rac-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-3-chloro-4-fluoro-anilino)propanamide	Intermediate 103; rac-2-bromopropanamide	^{1}H NMR (500 MHz, DMSO-d_6) δ ppm = 1.18 (d, *J*=7.57 Hz, 3 H), 3.76 (s, 3 H), 5.00 – 5.04 (m, 1 H), 6.94 (d, *J*=8.83 Hz, 2 H), 7.29 (s, 1 H), 7.50 (d, *J*=8.83 Hz, 2 H), 7.57 – 7.59 (m, 1 H), 7.63 (s, 1 H), 7.64 – 7.68 (m, 1 H), 7.92 (m, 1 H), 8.12 – 8.17 (m, 2 H). LC-MS (method 2) Rt = 1.17 min Isolated via precipitation MS (ESIpos): m/z = 449.3 $[M+H]^+$ 70 % yield
161.1 and **161.2**	(R)- 2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-3-chloro-4-fluoro-anilino)propanamide and (S)- 2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-3-chloro-4-fluoro-anilino)propanamide		

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
161.1	 2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-3-chloro-4-fluoro-anilino)propanamide (enantiomer 1)	Example 161	^{1}H NMR (500 MHz, DMSO-d_6) δ ppm = 1.18 (d, *J*=7.57 Hz, 3 H), 3.76 (s, 3 H), 5.00 – 5.04 (m, 1 H), 6.94 (d, *J*=8.83 Hz, 2 H), 7.29 (s, 1 H), 7.50 (d, *J*=8.83 Hz, 2 H), 7.55 – 7.59 (m, 1 H), 7.63 (s, 1 H), 7.64 – 7.66 (m, 1 H), 7.90 – 7.94 (m, 1 H), 8.14 (m, 2 H). LC-MS (method 1) Rt = 1.13 min MS (ESIpos): m/z = 449.4 $[M+H]^+$ $[\alpha]_D^{20}$ = 85° c = 10.3 mg/mL in DMSO 31 % yield

Chiral HPLC Example 161.1

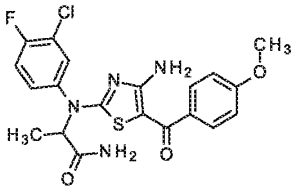
HPLC separation of rac-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-3-chloro-4-fluoro-anilino)propanamide (1300 mg, 2.9 mmol, Example 161) on a chiral column followed by trituration in MTBE gave 401 mg (31 % yield) of 2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-3-chloro-4-fluoro-anilino)propanamide, enantiomer 1.

Preparative chiral HPLC

Instrument: PrepCon Labomatic HPLC; Column: YMC Cellulose SB 5µ, 250x30; eluent A: hexane + 0.1 vol % diethylamine; eluent B: 2-propanol; isocratic: 60%A+40%B; flow: 40 mL/min; temperature: 25°C; UV: 254 nm

Analytical chiral HPLC: Rt = 2.11 min

Instrument: Thermo Fisher UltiMate 3000; Column: YMC Cellulose SB 3µ, 100x4.6; eluent A: hexane + 0.1 vol % diethylamine; eluent B: 2-propanol; isocratic: 60%B+40%B; flow: 1.4 mL/min; temperature: 25°C; UV: 254 nm

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
161.2	 2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-3-chloro-4-fluoro-anilino)propanamide (enantiomer 2)	Example 161	^{1}H NMR (500 MHz, DMSO-d_6) δ ppm = 1.18 (d, *J*=7.57 Hz, 3 H), 3.76 (s, 3 H), 5.00 – 5.04 (m, 1 H), 6.94 (d, *J*=8.83 Hz, 2 H), 7.29 (s, 1 H), 7.50 (d, *J*=8.83 Hz, 2 H), 7.58 (m, 1 H), 7.63 (s, 1 H), 7.66 (m, 1 H), 7.90 – 7.94 (m, 1 H), 8.10 – 8.16 (m, 2 H). LC-MS (method 1) Rt = 1.13 min; MS (ESIpos): m/z = 449.4 $[M+H]^+$ $[\alpha]_D^{20}$ = -89° c = 10.1 mg/mL in DMSO 29 % yield

Chiral HPLC Example 161.2

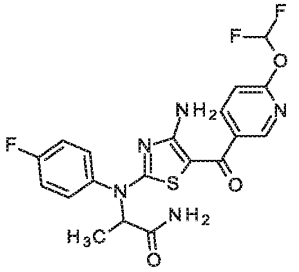
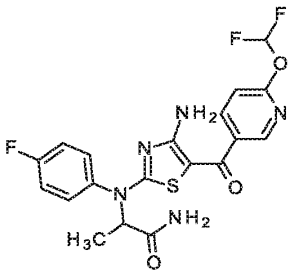
HPLC separation of rac-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-3-chloro-4-fluoro-anilino)propanamide (1300 mg, 2.9 mmol, Example 161) on a chiral column followed by trituration in MTBE gave 375 mg (29 % yield) of 2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-3-chloro-4-fluoro-anilino)propanamide, enantiomer 2.

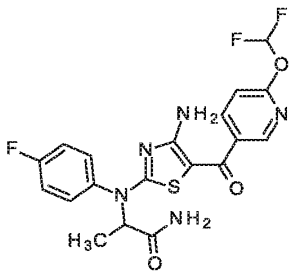
Preparative chiral HPLC

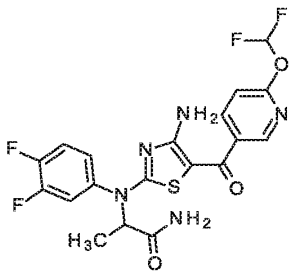
Instrument: PrepCon Labomatic HPLC; Column: YMC Cellulose SB 5µ, 250x30; eluent A: hexane + 0.1 vol % diethylamine; eluent B: 2-propanol; isocratic: 60%A+40%B; flow: 40 mL/min; temperature: 25°C; UV: 254 nm

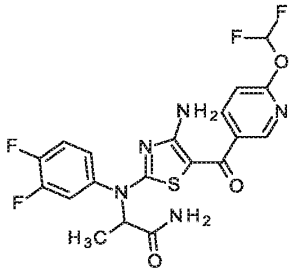
Analytical chiral HPLC: Rt = 5.48 min

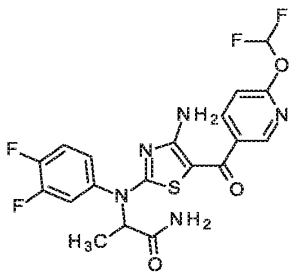
Instrument: Thermo Fisher UltiMate 3000; Column: YMC Cellulose SB 3µ, 100x4.6; eluent A: hexane + 0.1 vol % diethylamine; eluent B: 2-propanol; isocratic: 60%B+40%B; flow: 1.4 mL/min; temperature: 25°C; UV: 254 nm

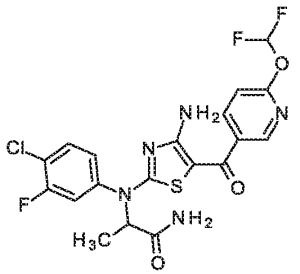
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
162	 rac-2-(N-[4-amino-5-[6-(difluoromethoxy)pyridine-3-carbonyl]thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 104; rac-2-bromopropanamide	^{1}H-NMR (400 MHz, DMSO-d_6): δ ppm = 1.13 – 1.20 (m, 3 H), 5.00 – 5.12 (m, 1 H), 7.10 (d, J=8.62 Hz, 1 H), 7.23 – 7.28 (m, 1 H), 7.34 (t, J=8.87 Hz, 2 H), 7.52 – 7.68 (m, 3 H), 7.97 – 8.03 (m, 1 H), 8.06 – 8.35 (m, 1 H), 8.35 – 8.42 (m, 1 H). LC-MS (method 2) Rt = 1.10 min Isolated via precipitation MS (ESIpos): m/z = 452.2 [M+H]$^+$ 61 % yield
162.1 and **162.2**	(R)-2-(N-[4-amino-5-[6-(difluoromethoxy)pyridine-3-carbonyl]thiazol-2-yl]-4-fluoro-anilino)propanamide and (S)-2-(N-[4-amino-5-[6-(difluoromethoxy)pyridine-3-carbonyl]thiazol-2-yl]-4-fluoro-anilino)propanamide		
162.1	 2-(N-[4-amino-5-[6-(difluoromethoxy)pyridine-3-carbonyl]thiazol-2-yl]-4-fluoro-anilino)propanamide (enantiomer 1)	Example 162	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.16 (d, *J*=7.35 Hz, 3 H), 5.06 (m, 1 H), 7.11 (d, *J*=8.62 Hz, 1 H), 7.26 (s, 1 H), 7.34 (m, 2 H), 7.59 (s, 1 H), 7.65 (br d, *J*=3.80 Hz, 2 H), 7.71 (t, *J*=72 Hz, 1 H), 8.00 (dd, *J*=8.49, 2.41 Hz, 1 H), 8.19 (m, 1 H), 8.38 (d, *J*=2.03 Hz, 1 H), 8.38 (m, 1 H). LC-MS (method 2) Rt = 1.13 min; MS (ESIpos): m/z = 452.3 [M+H]$^+$ $[\alpha]_D^{20}$ = -71° c = 8 mg/mL in DMSO 37 % yield

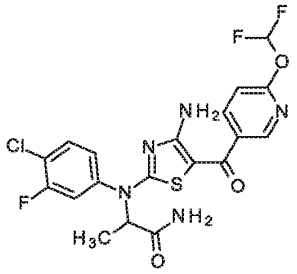
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
Chiral HPLC Example 162.1 HPLC separation of rac-2-(N-[4-amino-5-[6-(difluoromethoxy)pyridine-3-carbonyl]thiazol-2-yl]-4-fluoro-anilino)propanamide (105 mg, 0.23 mmol, Example 162) on a chiral column gave 39 mg (37 % yield) of 2-(N-[4-amino-5-[6-(difluoromethoxy)pyridine-3-carbonyl]thiazol-2-yl]-4-fluoro-anilino)propanamide, enantiomer 1. Preparative chiral HPLC Instrument: PrepCon Labomatic HPLC-4; column: YMC Cellulose SB 5µ, 250x30; eluent A: hexane + 0.1 vol % diethylamine; eluent B: ethanol + 0.1 vol % diethylamine; isocratic: 70%A+30%B; flow: 50 mL/min; temperature: 25°C; UV: 254 nm Analytical chiral HPLC: Rt = 3.07 min Instrument: Waters Alliance 2695; column: YMC Cellulose SB 3µ, 100x4.6; eluent A: hexane + 0.1 vol % diethylamine; eluent B: ethanol; isocratic: 70%A+30%B; flow: 1.4 mL/min; temperature: 25°C; UV: 254 nm			
162.2	 2-(N-[4-amino-5-[6-(difluoromethoxy)pyridine-3-carbonyl]thiazol-2-yl]-4-fluoro-anilino)propanamide (enantiomer 2)	Example 162	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.16 (d, *J*=7.35 Hz, 3 H), 5.02 – 5.08 (m, 1 H), 7.11 (d, *J*=8.62 Hz, 1 H), 7.26 (s, 1 H), 7.34 (m, 2 H), 7.59 (s, 1 H), 7.65 (br d, *J*=3.80 Hz, 2 H), 7.71 (t, *J*=72 Hz, 1 H), 8.00 (dd, *J*=8.49, 2.41 Hz, 1 H), 8.17 – 8.21 (m, 1 H), 8.38 (d, *J*=2.03 Hz, 1 H), 8.38 (m, 1 H). LC-MS (method 2) Rt = 1.13 min; MS (ESIpos): m/z = 452.3 $[M+H]^+$ $[\alpha]_D^{20}$ = 74° c = 8.7 mg/mL in DMSO 39 % yield

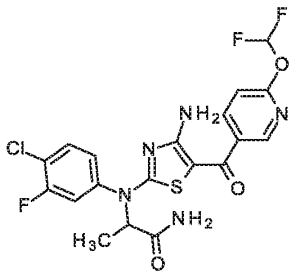
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
Chiral HPLC Example 162.2 HPLC separation of rac-2-(N-[4-amino-5-[6-(difluoromethoxy)pyridine-3-carbonyl]thiazol-2-yl]-4-fluoro-anilino)propanamide (105 mg, 0.23 mmol, Example 162) on a chiral column gave 41 mg (39 % yield) of 2-(N-[4-amino-5-[6-(difluoromethoxy)pyridine-3-carbonyl]thiazol-2-yl]-4-fluoro-anilino)propanamide, enantiomer 2. Preparative chiral HPLC Instrument: PrepCon Labomatic HPLC-4; column: YMC Cellulose SB 5µ, 250x30; eluent A: hexane + 0.1 vol % diethylamine; eluent B: ethanol + 0.1 vol % diethylamine; isocratic: 70%A+30%B; flow: 50 mL/min; temperature: 25°C; UV: 254 nm Analytical chiral HPLC: Rt = 2.40 min Instrument: Waters Alliance 2695; column: YMC Cellulose SB 3µ, 100x4.6; eluent A: hexane + 0.1 vol % diethylamine; eluent B: ethanol; isocratic: 70%A+30%B; flow: 1.4 mL/min; temperature: 25°C; UV: 254 nm			
163	 rac-2-(N-[4-amino-5-[6-(difluoromethoxy)pyridine-3-carbonyl]thiazol-2-yl]-3,4-difluoro-anilino)propanamide	Intermediate 105; rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.19 (d, *J*=8 Hz, 3 H), 5.03 (q, *J*=6.84 Hz, 1 H), 7.09 – 7.12 (m, 1 H), 7.30 (s, 1 H), 7.58 (m, 3 H), 7.71 (t, *J*=72 Hz, 1 H), 7.79 (m, 1 H), 8.02 (dd, *J*=8.49, 2.41 Hz, 1 H), 8.19 – 8.23 (m, 2 H), 8.41 (d, *J*=2.03 Hz, 1 H). LC-MS (method 2) Rt = 1.15 min Biotage (method X) MS (ESIpos): m/z = 470.3 $[M+H]^+$ 56 % yield

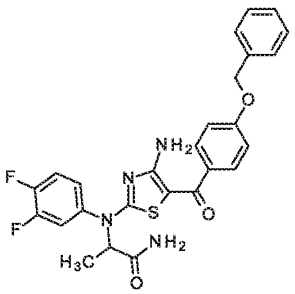
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
163.1 and **163.2**	(R)-(N-[4-amino-5-[6-(difluoromethoxy)pyridine-3-carbonyl]thiazol-2-yl]-3,4-difluoro-anilino)propanamide and (S)-(N-[4-amino-5-[6-(difluoromethoxy)pyridine-3-carbonyl]thiazol-2-yl]-3,4-difluoro-anilino)propanamide		
163.1	 2-(N-[4-amino-5-[6-(difluoromethoxy)pyridine-3-carbonyl]thiazol-2-yl]-3,4-difluoro-anilino)propanamide (enantiomer 1)	Example 163	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.16 (d, *J*=7.35 Hz, 3 H), 5.02 – 5.06 (m, 1 H), 7.11 (d, *J*=8.62 Hz, 1 H), 7.26 (s, 1 H), 7.34 (m, 2 H), 7.59 (s, 1 H), 7.65 (br d, *J*=3.80 Hz, 2 H), 7.71 (t, *J*=72 Hz, 1 H), 8.00 (dd, *J*=8.49, 2.41 Hz, 1 H), 8.17 – 8.22 (m, 1 H), 8.38 (d, *J*=2.03 Hz, 1 H), 8.35 – 8.37 (m, 1 H). LC-MS (method 2) Rt = 1.15 min 41 % yield

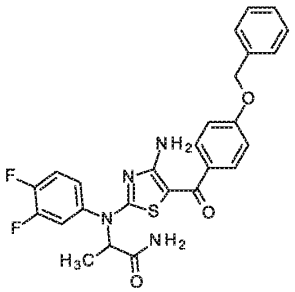
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
Chiral HPLC Example 163.1 HPLC separation of rac-2-(N-[4-amino-5-[6-(difluoromethoxy)pyridine-3-carbonyl]thiazol-2-yl]-3,4-difluoro-anilino)propanamide (120 mg, 0.26 mmol, Example 163) on a chiral column gave 49 mg (41 % yield) of 2-(N-[4-amino-5-[6-(difluoromethoxy)pyridine-3-carbonyl]thiazol-2-yl]-3,4-difluoro-anilino)propanamide, enantiomer 1. Preparative chiral HPLC Instrument: PrepCon Labomatic HPLC-2; Column: YMC Amylose SA 10µ, 250x50; eluent A: methyl tert-butyl ether + 0.1 vol % diethylamine; eluent B: acetonitrile; isocratic: 95%A+5%B; flow: 100 mL/min; temperature: 25°C; UV: 280 nm Analytical chiral HPLC: Rt = 2.42 min Instrument: Thermo Fisher UltiMate 3000; Column: YMC Amylose SA 3µ, 100x4.6; eluent A: methyl tert-butyl ether + 0.1 vol % diethylamine; eluent B: acetonitrile; isocratic: 95%A+5%B; flow: 1.4 mL/min; temperature: 25°C; UV: 280 nm			
163.2	 2-(N-[4-amino-5-[6-(difluoromethoxy)pyridine-3-carbonyl]thiazol-2-yl]-3,4-difluoro-anilino)propanamide (enantiomer 2)	Example 163	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.19 (d, *J*=7.35 Hz, 3 H), 5.02 – 5.06 (m, 1 H), 7.12 (d, *J*=8.62 Hz, 1 H), 7.30 (s, 1 H), 7.48 – 7.52 (m, 1 H), 7.58 – 7.62 (m, 2 H), 7.72 (t, *J*=72 Hz, 1 H), 7.77 – 7.82 (m, 1 H), 8.02 (dd, *J*=8.49, 2.41 Hz, 1 H), 8.20 – 8.25 (m, 2 H), 8.41 (d, *J*=2.53 Hz, 1 H). LC-MS (method 2) Rt = 1.15 min 56 % yield

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
Chiral HPLC Example 163.2 HPLC separation of rac-2-(N-[4-amino-5-[6-(difluoromethoxy)pyridine-3-carbonyl]thiazol-2-yl]-3,4-difluoro-anilino)propanamide (120 mg, 0.26 mmol, Example 163) on a chiral column gave 68 mg (56 % yield) of 2-(N-[4-amino-5-[6-(difluoromethoxy)pyridine-3-carbonyl]thiazol-2-yl]-3,4-difluoro-anilino)propanamide, enantiomer 2. Preparative chiral HPLC Instrument: PrepCon Labomatic HPLC-2; Column: YMC Amylose SA 10µ, 250x50; eluent A: methyl tert-butyl ether + 0.1 vol % diethylamine; eluent B: acetonitrile; isocratic: 95%A+5%B; flow: 100 mL/min; temperature: 25°C; UV: 280 nm Analytical chiral HPLC: Rt = 3.72 min Instrument: Thermo Fisher UltiMate 3000; Column: YMC Amylose SA 3µ, 100x4.6; eluent A: methyl tert-butyl ether + 0.1 vol % diethylamine; eluent B: acetonitrile; isocratic: 95%A+5%B; flow: 1.4 mL/min; temperature: 25°C; UV: 280 nm			
164	 rac-2-(N-[4-amino-5-[6-(difluoromethoxy)pyridine-3-carbonyl]thiazol-2-yl]-4-chloro-3-fluoro-anilino)propanamide	Intermediate 106, rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.20 (d, *J*=8.11 Hz, 3 H), 5.01 – 5.05 (m, 1 H), 7.12 (d, *J*=8.62 Hz, 1 H), 7.32 (s, 1 H), 7.53 (m, 1 H), 7.64 (s, 1 H), 7.71 (t, *J*=72 Hz, 1 H), 7.72 – 7.76 (m, 2 H), 8.03 (dd, *J*=8.62, 2.53 Hz, 1 H), 8.20 – 8.25 (m, 2 H), 8.41 (d, *J*=2.28 Hz, 1 H). Biotage (method X) LC-MS (method 2) Rt = 1.21 min MS (ESIpos): m/z = 486.3 [M+H]$^+$ 53 % yield

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
164.1 and **164.2**	(R)-2-(N-[4-amino-5-[6-(difluoromethoxy)pyridine-3-carbonyl]thiazol-2-yl]-4-chloro-3-fluoro-anilino)propanamide and (S)-2-(N-[4-amino-5-[6-(difluoromethoxy)pyridine-3-carbonyl]thiazol-2-yl]-4-chloro-3-fluoro-anilino)propanamide		
164.1	 2-(N-[4-amino-5-[6-(difluoromethoxy)pyridine-3-carbonyl]thiazol-2-yl]-4-chloro-3-fluoro-anilino)propanamide (enantiomer 1)	Example 164	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.20 (d, *J*=7.35 Hz, 3 H), 5.01 – 5.05 (m, 1 H), 7.12 (m, 1 H), 7.32 (s, 1 H), 7.53 (m, 1 H), 7.64 (s, 1 H), 7.71 (t, *J*=72 Hz, 1 H), 7.72 – 7.77 (m, 2 H), 8.03 (dd, *J*=8.62, 2.53 Hz, 1 H), 8.21 – 8.26 (m, 2 H), 8.39 – 8.42 (m, 1 H). 45 % yield

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
Chiral HPLC Example 164.1 HPLC separation of rac-2-(N-[4-amino-5-[6-(difluoromethoxy)pyridine-3-carbonyl]thiazol-2-yl]-4-chloro-3-fluoro-anilino)propanamide (113 mg, 0.23 mmol, Example 164) on a chiral column gave 51 mg (45 % yield) of 2-(N-[4-amino-5-[6-(difluoromethoxy)pyridine-3-carbonyl]thiazol-2-yl]-4-chloro-3-fluoro-anilino)propanamide, enantiomer 1. Preparative chiral HPLC Instrument: PrepCon Labomatic HPLC-2; Column: YMC Amylose SA 10µ, 250x50; eluent A: methyl tert-butyl ether + 0.1 vol % diethylamine; eluent B: acetonitrile; isocratic: 95%A+5%B; flow: 100 mL/min; temperature: 25°C; UV: 280 nm Analytical chiral HPLC: Rt = 2.6 min Instrument: Thermo Fisher UltiMate 3000; Column: YMC Amylose SA 3µ, 100x4.6; eluent A: methyl tert-butyl ether + 0.1 vol % diethylamine; eluent B: acetonitrile; isocratic: 95%A+5%B; flow: 1.4 mL/min; temperature: 25°C; UV: 280 nm			
164.2	 2-(N-[4-amino-5-[6-(difluoromethoxy)pyridine-3-carbonyl]thiazol-2-yl]-4-chloro-3-fluoro-anilino)propanamide (enantiomer 2)	Example 164	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.20 (d, *J*=7.35 Hz, 3 H), 5.01 – 5.05 (m, 1 H), 7.10 – 7.14 (m, 1 H), 7.32 (s, 1 H), 7.50 – 7.56 (m, 1 H), 7.64 (s, 1 H), 7.71 (t, *J*=72 Hz, 1 H), 7.70 – 7.78 (m, 2 H), 8.03 (dd, *J*=8.62, 2.53 Hz, 1 H), 8.20 – 8.25 (m, 2 H), 8.40 – 8.43 (m, 1 H). 45 % yield

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
Chiral HPLC Example 164.2 HPLC separation of rac-2-(N-[4-amino-5-[6-(difluoromethoxy)pyridine-3-carbonyl]thiazol-2-yl]-4-chloro-3-fluoro-anilino)propanamide (113 mg, 0.23 mmol, Example 164) on a chiral column gave 51 mg (45 % yield) of 2-(N-[4-amino-5-[6-(difluoromethoxy)pyridine-3-carbonyl]thiazol-2-yl]-4-chloro-3-fluoro-anilino)propanamide, enantiomer 2. Preparative chiral HPLC Instrument: PrepCon Labomatic HPLC-2; Column: YMC Amylose SA 10µ, 250x50; eluent A: methyl tert-butyl ether + 0.1 vol % diethylamine; eluent B: acetonitrile; isocratic: 95%A+5%B; flow: 100 mL/min; temperature: 25°C; UV: 280 nm Analytical chiral HPLC: Rt = 3.87 min Instrument: Thermo Fisher UltiMate 3000; Column: YMC Amylose SA 3µ, 100x4.6; eluent A: methyl tert-butyl ether + 0.1 vol % diethylamine; eluent B: acetonitrile; isocratic: 95%A+5%B; flow: 1.4 mL/min; temperature: 25°C; UV: 280 nm			
165	 rac-2-(N-[4-amino-5-(4-benzyloxybenzoyl)thiazol-2-yl]-3,4-difluoro-anilino)propanamide	Intermediate 107, rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.18 (d, *J*=7.35 Hz, 3 H), 5.00 – 5.04 (m, 1 H), 5.12 (s, 2 H), 7.00 – 7.05 (m, 2 H), 7.24 – 7.64 (m, 11 H), 7.77 – 7.81 (m, 1 H), 8.03 – 8.07 (m, 2 H). Biotage (method X) LC-MS (method 2) Rt = 1.32 min MS (ESIpos): m/z = 509.4 $[M+H]^+$ 57 % yield
165.1 and **165.2**	(R)-2-(N-[4-amino-5-(4-benzyloxybenzoyl)thiazol-2-yl]-3,4-difluoro-anilino)propanamide and (S)-2-(N-[4-amino-5-(4-benzyloxybenzoyl)thiazol-2-yl]-3,4-difluoro-anilino)propanamide		

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
165.1	 2-(N-[4-amino-5-(4-benzyloxybenzoyl)thiazol-2-yl]-3,4-difluoro-anilino)propanamide (enantiomer 1)	Example 165	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.19 (d, *J*=7.35 Hz, 4 H), 5.00 – 5.04 (m, 1 H), 5.12 (s, 2 H), 7.00 – 7.05 (m, 2 H), 7.28 (s, 1 H), 7.36 – 7.44 (m, 5 H), 7.47 – 7.52 (m, 3 H), 7.59 – 7.63 (m, 2 H), 7.78 (ddd, *J*=11.34, 7.54, 2.41 Hz, 1 H), 8.02 – 8.06 (m, 2 H) 46 % yield

Chiral HPLC Example 165.1

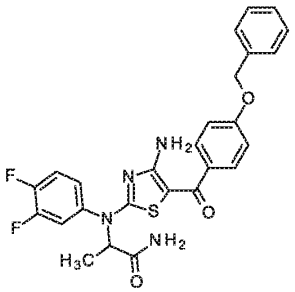
HPLC separation of rac-2-(N-[4-amino-5-(4-benzyloxybenzoyl)thiazol-2-yl]-3,4-difluoro-anilino)propanamide (340 mg, 0.67 mmol, Example 165) on a chiral column gave 155 mg (46 % yield) of 2-(N-[4-amino-5-(4-benzyloxybenzoyl)thiazol-2-yl]-3,4-difluoro-anilino)propanamide, enantiomer 1.

Preparative chiral HPLC

Instrument: PrepCon Labomatic HPLC-4; Column: YMC Amylose SA 5µ, 250x30;
eluent A: methyl tert-butyl ether + 0.1 vol % diethylamine; eluent B: acetonitrile; isocratic: 80%A+20%B; flow: 50 mL/min; temperature: 25°C; UV: 280 nm

Analytical chiral HPLC: Rt = 1.73 min

Instrument: Waters Alliance 2695; Column: YMC Amylose SA 3µ, 100x4.6;
eluent A: methyl tert-butyl ether + 0.1 vol % diethylamine; eluent B: acetonitrile; isocratic: 80%A+20%B; flow: 1.4 mL/min; temperature: 25°C; UV: 280 nm

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
165.2	 2-(N-[4-amino-5-(4-benzyloxybenzoyl)thiazol-2-yl]-3,4-difluoro-anilino)propanamide (enantiomer 2)	Example 165	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.19 (d, *J*=7.35 Hz, 4 H), 5.00 – 5.04 (m, 1 H), 5.12 (s, 2 H), 7.02 (m, 2 H), 7.28 (s, 1 H), 7.35 – 7.45 (m, 5 H), 7.47 – 7.52 (m, 3 H), 7.58 – 7.62 (m, 2 H), 7.78 (ddd, *J*=11.34, 7.54, 2.41 Hz, 1 H), 8.02 – 8.05 (m, 2 H) 46 % yield

Chiral HPLC Example 165.2

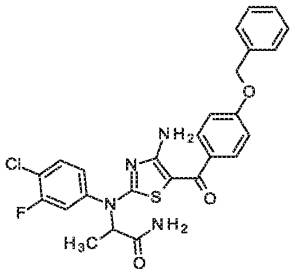
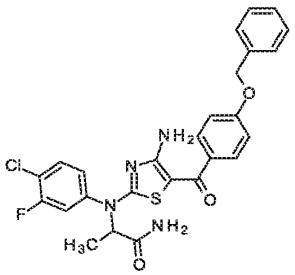
HPLC separation of rac-2-(N-[4-amino-5-(4-benzyloxybenzoyl)thiazol-2-yl]-3,4-difluoro-anilino)propanamide (340 mg, 0.67 mmol, Example 165) on a chiral column gave 156 mg (46 % yield) of 2-(N-[4-amino-5-(4-benzyloxybenzoyl)thiazol-2-yl]-3,4-difluoro-anilino)propanamide, enantiomer 2.

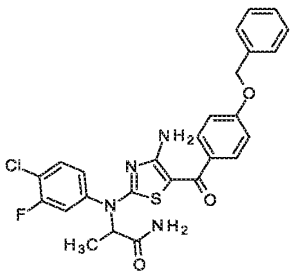
Preparative chiral HPLC

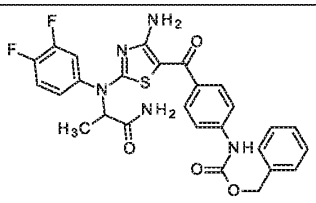
Instrument: PrepCon Labomatic HPLC-4; Column: YMC Amylose SA 5µ, 250x30;
eluent A: methyl tert-butyl ether + 0.1 vol % diethylamine; eluent B: acetonitrile; isocratic: 80%A+20%B; flow: 50 mL/min; temperature: 25°C; UV: 280 nm

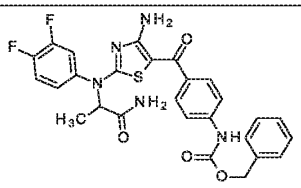
Analytical chiral HPLC: Rt = 2.32 min

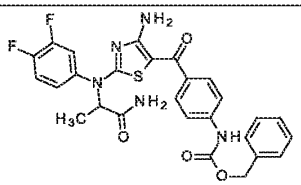
Instrument: Waters Alliance 2695; Column: YMC Amylose SA 3µ, 100x4.6;
eluent A: methyl tert-butyl ether + 0.1 vol % diethylamine; eluent B: acetonitrile; isocratic: 80%A+20%B; flow: 1.4 mL/min; temperature: 25°C; UV: 280 nm

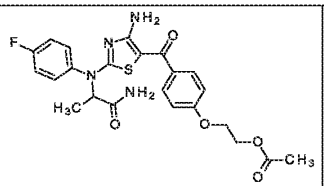
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
166	 rac-2-(N-[4-amino-5-(4-benzyloxybenzoyl)thiazol-2-yl]-4-chloro-3-fluoro-anilino)propanamide	Intermediate 108, rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.20 (d, *J*=7.35 Hz, 3 H), 5.00 – 5.04 (m, 1 H), 5.12 (s, 2 H), 7.00 – 7.05 (m, 2 H), 7.30 – 7.42 (m, 6 H), 7.47 – 7.52 (m, 3 H), 7.63 (s, 1 H), 7.73 – 7.77 (m, 2 H), 8.09 – 8.13 (m, 2 H) Biotage (method X) LC-MS (method 2) Rt = 1.36 min MS (ESIpos): m/z = 525.3 [M+H]$^+$ 57 % yield
166.1 and **166.2**	(R)-2-(N-[4-amino-5-(4-benzyloxybenzoyl)thiazol-2-yl]-4-chloro-3-fluoro-anilino)propanamide and (S)-2-(N-[4-amino-5-(4-benzyloxybenzoyl)thiazol-2-yl]-4-chloro-3-fluoro-anilino)propanamide		
166.1	 2-(N-[4-amino-5-(4-benzyloxybenzoyl)thiazol-2-yl]-4-chloro-3-fluoro-anilino)propanamide (enantiomer 1)	Example 166	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.20 (d, *J*=7.35 Hz, 3 H), 5.01 – 5.04 (m, 1 H), 5.12 (s, 2 H), 7.00 – 7.05 (m, 2 H), 7.35 – 7.45 (m, 9 H), 7.63 (s, 1 H), 7.73 – 7.77 (m, 2 H), 8.08 – 8.13 (m, 2 H) 39 % yield

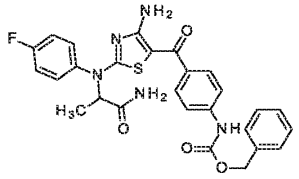
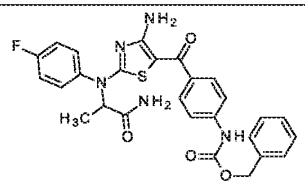
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
Chiral HPLC Example 166.1 HPLC separation of rac-2-(N-[4-amino-5-(4-benzyloxybenzoyl)thiazol-2-yl]-4-chloro-3-fluoro-anilino)propanamide (790 mg, 1.5 mmol, Example 166) on a chiral column gave 313 mg (39 % yield) of 2-(N-[4-amino-5-(4-benzyloxybenzoyl)thiazol-2-yl]-4-chloro-3-fluoro-anilino)propanamide, enantiomer 1. Preparative chiral HPLC Instrument: PrepCon Labomatic HPLC-4; Column: YMC Cellulose SC 10µ, 250x50; eluent A: methyl tert-butyl ether + 0.1 vol % diethylamine; eluent B: acetonitrile; isocratic: 90%A+10%B; flow: 100 mL/min; temperature: 25°C; UV: 325 nm Analytical chiral HPLC: Rt = 2.94 min Instrument: Thermo Fisher UltiMate 3000; Column: YMC Cellulose SC 3µ, 100x4.6; eluent A: methyl tert-butyl ether + 0.1 vol % diethylamine; eluent B: acetonitrile; isocratic: 90%A+10%B; flow: 1.4 mL/min; temperature: 25°C; UV: 325 nm			
166.2	 2-(N-[4-amino-5-(4-benzyloxybenzoyl)thiazol-2-yl]-4-chloro-3-fluoro-anilino)propanamide (enantiomer 2)	Example 166	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.20 (d, *J*=7.35 Hz, 3 H), 5.01 – 5.05 (m, 1 H), 5.12 (s, 2 H), 7.00 – 7.05 (m, 2 H), 7.35 – 7.45 (m, 9 H), 7.63 (s, 1 H), 7.73 – 7.77 (m, 2 H), 8.08 – 8.13 (m, 2 H) 35 % yield

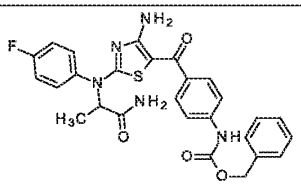
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
HPLC separation of rac-2-(N-[4-amino-5-(4-benzyloxybenzoyl)thiazol-2-yl]-4-chloro-3-fluoro-anilino)propanamide (790 mg, 1.5 mmol, Example 166) on a chiral column gave 276 mg (35 % yield) of 2-(N-[4-amino-5-(4-benzyloxybenzoyl)thiazol-2-yl]-4-chloro-3-fluoro-anilino)propanamide, enantiomer 2. Preparative chiral HPLC Instrument: PrepCon Labomatic HPLC-4; Column: YMC Cellulose SC 10µ, 250x50; eluent A: methyl tert-butyl ether + 0.1 vol % diethylamine; eluent B: acetonitrile; isocratic: 90%A+10%B; flow: 100 mL/min; temperature: 25°C; UV: 325 nm Analytical chiral HPLC: Rt = 3.51 min Instrument: Thermo Fisher UltiMate 3000; Column: YMC Cellulose SC 3µ, 100x4.6; eluent A: methyl tert-butyl ether + 0.1 vol % diethylamine; eluent B: acetonitrile; isocratic: 90%A+10%B; flow: 1.4 mL/min; temperature: 25°C; UV: 325 nm			
167	 rac-benzyl N-[4-[4-amino-2-(N-(2-amino-1-methyl-2-oxo-ethyl)-3,4-difluoro-anilino)thiazole-5-carbonyl]phenyl]carbamate	Intermediate 109, rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.18 (d, *J*=7.60 Hz, 3 H), 5.01 (br d, *J*=7.35 Hz, 1 H), 5.15 (s, 2 H), 7.28 (s, 1 H), 7.40 (m, 6 H), 7.48 (m, 5 H), 7.57 (m, 1 H), 7.61 (s, 1 H), 7.77 (ddd, *J*=11.41, 7.48, 2.41 Hz, 1 H), 7.95 (m, 2 H) Biotage (method X) LC-MS (method 2) Rt = 1.22 min MS (ESIpos): m/z = 552.4 $[M+H]^+$ 64 % yield

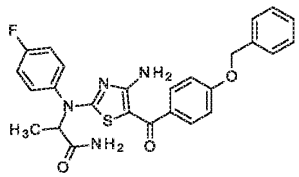
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
167.1 and **167.2**	(R)-benzyl N-[4-[4-amino-2-(N-(2-amino-1-methyl-2-oxo-ethyl)-3,4-difluoro-anilino)thiazole-5-carbonyl]phenyl]carbamate and (S)-benzyl N-[4-[4-amino-2-(N-(2-amino-1-methyl-2-oxo-ethyl)-3,4-difluoro-anilino)thiazole-5-carbonyl]phenyl]carbamate		
167.1	 Benzyl N-[4-[4-amino-2-(N-(2-amino-1-methyl-2-oxo-ethyl)-3,4-difluoro-anilino)thiazole-5-carbonyl]phenyl]carbamate (enantiomer 1)	Example 167	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.18 (d, *J*=7.35 Hz, 3 H), 5.01 (q, *J*=7.35 Hz, 1 H), 5.15 (s, 2 H), 5.76 (s, 1 H), 7.28 (s, 1 H), 7.35 – 7.42 (m, 5 H), 7.46 – 7.52 (m, 5 H), 7.57 (m, 1 H), 7.61 (s, 1 H), 7.78 (m, 1 H), 8.18 (m, 2 H), 10.00 (s, 1 H) 32 % yield

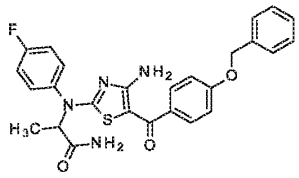
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
Chiral HPLC Example 167.1 HPLC separation of rac-benzyl N-[4-[4-amino-2-(N-(2-amino-1-methyl-2-oxo-ethyl)-3,4-difluoro-anilino)thiazole-5-carbonyl]phenyl]carbamate (385 mg, 0.7 mmol, Example 167) on a chiral column followed by trituration in MTBE gave 123 mg (32 % yield) of benzyl N-[4-[4-amino-2-(N-(2-amino-1-methyl-2-oxo-ethyl)-3,4-difluoro-anilino)thiazole-5-carbonyl]phenyl]carbamate, enantiomer 1. Preparative chiral HPLC Instrument: PrepCon Labomatic HPLC-3; Column: YMC Amylose SA 10µ, 250x50; eluent A: methyl tert-butyl ether + 0.1 vol % diethylamine; eluent B: acetonitrile; isocratic: 90%A+10%B; flow: 100 mL/min; temperature: 25°C; UV: 280 nm Analytical chiral HPLC: Rt = 2.87 min Instrument: Thermo Fisher UltiMate 3000; Column: YMC Cellulose SC 3µ, 100x4.6; eluent A: methyl tert-butyl ether + 0.1 vol % diethylamine; eluent B: acetonitrile; isocratic: 90%A+10%B; flow: 1.4 mL/min; temperature: 25°C; UV: 325 nm			
167.2	 Benzyl N-[4-[4-amino-2-(N-(2-amino-1-methyl-2-oxo-ethyl)-3,4-difluoro-anilino)thiazole-5-carbonyl]phenyl]carbamate (enantiomer 2)	Example 167	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.18 (d, *J*=7.35 Hz, 3 H), 5.01 (q, *J*=7.35 Hz, 1 H), 5.15 (s, 2 H), 5.76 (s, 1 H), 7.28 (s, 1 H), 7.40 (m, 5 H), 7.48 (m, 5 H), 7.57 (m, 1 H), 7.61 (s, 1 H), 7.78 (m, 1 H), 8.18 (m, 2 H), 10.00 (s, 1 H) 34 % yield

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
Chiral HPLC Example 167.2 HPLC separation of rac-benzyl N-[4-[4-amino-2-(N-(2-amino-1-methyl-2-oxo-ethyl)-3,4-difluoro-anilino)thiazole-5-carbonyl]phenyl]carbamate (385 mg, 0.7 mmol, Example 167) on a chiral column followed by trituration in MTBE gave 129 mg (34 % yield) of benzyl N-[4-[4-amino-2-(N-(2-amino-1-methyl-2-oxo-ethyl)-3,4-difluoro-anilino)thiazole-5-carbonyl]phenyl]carbamate, enantiomer 2. Preparative chiral HPLC Instrument: PrepCon Labomatic HPLC-3; Column: YMC Amylose SA 10µ, 250x50; eluent A: methyl tert-butyl ether + 0.1 vol % diethylamine; eluent B: acetonitrile; isocratic: 90%A+10%B; flow: 100 mL/min; temperature: 25°C; UV: 280 nm Analytical chiral HPLC: Rt = 3.90 min Instrument: Thermo Fisher UltiMate 3000; Column: YMC Cellulose SC 3µ, 100x4.6; eluent A: methyl tert-butyl ether + 0.1 vol % diethylamine; eluent B: acetonitrile; isocratic: 90%A+10%B; flow: 1.4 mL/min; temperature: 25°C; UV: 325 nm			
168	 rac-2-[4-[4-amino-2-(N-(2-amino-1-methyl-2-oxo-ethyl)-4-fluoro-anilino)thiazole-5-carbonyl]phenoxy]ethyl acetate	Intermediate 112, rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.15 (d, *J*=7.60 Hz, 3 H), 2.01 (s, 3 H), 4.18 (dd, *J*=5.32, 3.55 Hz, 2 H), 4.30 (dd, *J*=5.45, 3.42 Hz, 2 H), 5.06 (m, 1 H), 6.94 (m, 2 H), 7.23 (s, 1 H), 7.33 (t, *J*=8.74 Hz, 2 H), 7.47 (d, *J*=8.87 Hz, 2 H), 7.58 (s, 1 H), 7.63 (m, 2 H), 8.06 (m, 2 H) RP-HPLC (method C basic) LC-MS (method 1) Rt = 1.04 min MS (ESIpos): m/z = 487.6 $[M+H]^+$ 54 % yield

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
169	 rac-benzyl N-[4-[4-amino-2-(N-(2-amino-1-methyl-2-oxo-ethyl)-4-fluoro-anilino)thiazole-5-carbonyl]phenyl]carbamate	Intermediate 132, rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.16 (d, *J*=7.35 Hz, 3 H), 5.05 (q, *J*=7.35 Hz, 1 H), 5.15 (s, 2 H), 7.25 (s, 1 H), 7.40 (m, 11 H), 7.58 (s, 1 H), 7.64 (m, 2 H), 8.12 (m, 2 H), 9.99 (m, 1 H) Biotage (method X) LC-MS (method 1) Rt = 1.19 min MS (ESIpos): m/z = 534.4 $[M+H]^+$ 65 % yield
169.1 and **169.2**	(R)-benzyl N-[4-[4-amino-2-(N-(2-amino-1-methyl-2-oxo-ethyl)-4-fluoro-anilino)thiazole-5-carbonyl]phenyl]carbamate and (S)-benzyl N-[4-[4-amino-2-(N-(2-amino-1-methyl-2-oxo-ethyl)-4-fluoro-anilino)thiazole-5-carbonyl]phenyl]carbamate		
169.1	 Benzyl N-[4-[4-amino-2-(N-(2-amino-1-methyl-2-oxo-ethyl)-4-fluoro-anilino)thiazole-5-carbonyl]phenyl]carbamate (enantiomer 1)	Example 169	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.16 (d, *J*=7.35 Hz, 3 H), 5.05 (q, *J*=7.35 Hz, 1 H), 5.15 (s, 2 H), 7.25 (s, 1 H), 7.40 (m, 11 H), 7.58 (s, 1 H), 7.64 (m, 2 H), 8.12 (m, 2 H), 9.99 (m, 1 H) LC-MS (method 1) Rt = 1.19 min MS (ESIpos): m/z = 534.4 $[M+H]^+$ 14 % yield

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
Chiral HPLC Example 169.1 HPLC separation of rac-benzyl N-[4-[4-amino-2-(N-(2-amino-1-methyl-2-oxo-ethyl)-4-fluoro-anilino)thiazole-5-carbonyl]phenyl]carbamate (422 mg, 0.76 mmol, Example 169) on a chiral column followed by trituration in MTBE gave 88 mg (14 % yield) of benzyl N-[4-[4-amino-2-(N-(2-amino-1-methyl-2-oxo-ethyl)-4-fluoro-anilino)thiazole-5-carbonyl]phenyl]carbamate, enantiomer 1. Preparative chiral HPLC Instrument: PrepCon Labomatic HPLC-3; Column: YMC Amylose SA 10µ, 250x50; eluent A: methyl tert-butyl ether + 0.1 vol % diethylamine; eluent B: acetonitrile; isocratic: 50%A+50%B; flow: 80 mL/min; temperature: 25°C; UV: 280 nm Analytical chiral HPLC: Rt = 1.39 min Instrument: Thermo Fisher UltiMate 3000; Column: YMC Amylose SA 3µ, 100x4.6; eluent A: methyl tert-butyl ether + 0.1 vol % diethylamine; eluent B: acetonitrile; isocratic: 50%A+50%B; flow: 1.4 mL/min; temperature: 25°C; UV: 280 nm			
169.2	 Benzyl N-[4-[4-amino-2-(N-(2-amino-1-methyl-2-oxo-ethyl)-4-fluoro-anilino)thiazole-5-carbonyl]phenyl]carbamate (enantiomer 2)	Example 169	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.16 (d, *J*=7.35 Hz, 3 H), 5.05 (q, *J*=7.35 Hz, 1 H), 5.15 (s, 2 H), 7.25 (s, 1 H), 7.40 (m, 11 H), 7.58 (s, 1 H), 7.64 (m, 2 H), 8.12 (m, 2 H), 9.99 (m, 1 H) LC-MS (method 1) Rt = 1.19 min MS (ESIpos): m/z = 534.4 $[M+H]^+$ 16 % yield

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
Chiral HPLC Example 169.2 HPLC separation of rac-benzyl N-[4-[4-amino-2-(N-(2-amino-1-methyl-2-oxo-ethyl)-4-fluoro-anilino)thiazole-5-carbonyl]phenyl]carbamate (422 mg, 0.76 mmol, Example 169) on a chiral column followed by trituration in MTBE gave 106 mg (14 % yield) of benzyl N-[4-[4-amino-2-(N-(2-amino-1-methyl-2-oxo-ethyl)-4-fluoro-anilino)thiazole-5-carbonyl]phenyl]carbamate, enantiomer 2. Preparative chiral HPLC Instrument: PrepCon Labomatic HPLC-3; Column: YMC Amylose SA 10µ, 250x50; eluent A: methyl tert-butyl ether + 0.1 vol % diethylamine; eluent B: acetonitrile; isocratic: 50%A+50%B; flow: 80 mL/min; temperature: 25°C; UV: 280 nm Analytical chiral HPLC: Rt = 1.80 min Instrument: Thermo Fisher UltiMate 3000; Column: YMC Amylose SA 3µ, 100x4.6; eluent A: methyl tert-butyl ether + 0.1 vol % diethylamine; eluent B: acetonitrile; isocratic: 50%A+50%B; flow: 1.4 mL/min; temperature: 25°C; UV: 280 nm			
170	 rac-2-(N-[4-amino-5-(4-benzyloxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 110, rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.16 (d, *J*=7.35 Hz, 3 H), 5.05 (m, 1 H), 5.11 (s, 2 H), 7.00 (m, 2 H), 7.25 (s, 1 H), 7.37 (m, 7 H), 7.48 (m, 2 H), 7.57 (s, 1 H), 7.64 (m, 2 H), 8.11 (m, 2H) RP-HPLC (method B basic) LC-MS (method 2) Rt = 1.25 min MS (ESIpos): m/z = 491.3 $[M+H]^+$ 88 % yield
170.1 and **170.2**	(R)-2-(N-[4-amino-5-(4-benzyloxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide and (S)-2-(N-[4-amino-5-(4-benzyloxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide		

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
170.1	 2-(N-[4-amino-5-(4-benzyloxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide (enantiomer 1)	Example 170	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.16 (d, *J*=7.35 Hz, 3 H), 5.02 – 5.06 (m, 1 H), 5.11 (s, 2 H), 7.00 (m, 2 H), 7.25 (s, 1 H), 7.30 – 7.40 (m, 7 H), 7.46 – 7.50 (m, 2 H), 7.57 (s, 1 H), 7.62 – 7.66 (m, 2 H), 8.08 – 8.12 (m, 2H) LC-MS (method 2) Rt = 1.25 min MS (ESIpos): m/z = 491.3 $[M+H]^+$ 35 % yield

Chiral HPLC Example 170.1

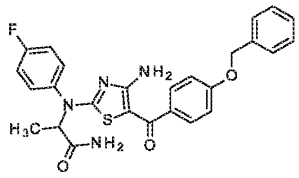
HPLC separation of rac-2-(N-[4-amino-5-(4-benzyloxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide (150 mg, 0.3 mmol, Example 170) on a chiral column gave 53 mg (35 % yield) of 2-(N-[4-amino-5-(4-benzyloxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, enantiomer 1.

Preparative chiral HPLC

Instrument: Sepiatec: Prep SFC100; Column: Chiralpak IB 5µ 250x30mm; eluent A: CO_2; eluent B: 2-propanol + 0.4 vol % diethylamine; isocratic: 35%B; flow: 100 mL/min; temperature: 40°C; BPR: 150bar; UV: 254 nm

Analytical chiral HPLC: Rt = 3.08 min

Instrument: Agilent: 1260, Aurora SFC-Modul; Column: Chiralpak IB 5µ 100x4.6mm; eluent A: CO_2; eluent B: 2-propanol + 0.4 vol % diethylamine; isocratic: 35%B; flow: 4 mL/min; temperature: 37.5°C; BPR: 100bar; UV: 254 nm

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
170.2	 2-(N-[4-amino-5-(4-benzyloxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide (enantiomer 2)	Example 170	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.16 (d, *J*=7.35 Hz, 3 H), 5.04 – 5.07 (m, 1 H), 5.11 (s, 2 H), 6.97 – 7.02 (m, 2 H), 7.25 (s, 1 H), 7.30 – 7.40 (m, 7 H), 7.46 – 7.50 (m, 2 H), 7.57 (s, 1 H), 7.62 – 7.66 (m, 2 H), 8.09 – 8.11 (m, 2H) LC-MS (method 2) Rt = 1.25 min MS (ESIpos): m/z = 491.3 $[M+H]^+$ 34 % yield

Chiral HPLC Example 170.2

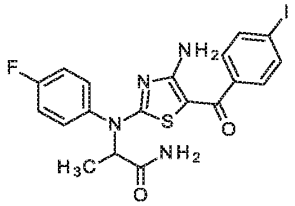
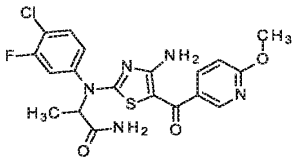
HPLC separation of rac-2-(N-[4-amino-5-(4-benzyloxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide (150 mg, 0.3 mmol, Example 170) on a chiral column gave 51 mg (34 % yield) of 2-(N-[4-amino-5-(4-benzyloxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, enantiomer 2.

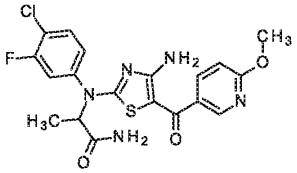
Preparative chiral HPLC

Instrument: Sepiatec: Prep SFC100; Column: Chiralpak IB 5µ 250x30mm; eluent A: CO_2; eluent B: 2-propanol + 0.4 vol % diethylamine; isocratic: 35%B; flow: 100 mL/min; temperature: 40°C; BPR: 150bar; UV: 254 nm

Analytical chiral HPLC: Rt = 4.42 min

Instrument: Agilent: 1260, Aurora SFC-Modul; Column: Chiralpak IB 5µ 100x4.6mm; eluent A: CO_2; eluent B: 2-propanol + 0.4 vol % diethylamine; isocratic: 35%B; flow: 4 mL/min; temperature: 37.5°C; BPR: 100bar; UV: 254 nm

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
171	 rac-2-(N-[4-amino-5-(4-iodobenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 111, rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.16 (d, *J*=7.35 Hz, 3 H), 5.07 (q, *J*=7.35 Hz, 1 H), 7.29 (m, 5 H), 7.58 (m, 1 H), 7.63 (m, 2 H), 7.76 (m, 2 H), 8.21 (m, 2 H) Biotage (method X) LC-MS (method 2) Rt = 1.21 min MS (ESIpos): m/z = 511.0 [M+H]$^+$ 39 % yield
172	 rac-2-(N-[4-amino-5-(6-methoxypyridine-3-carbonyl)thiazol-2-yl]-4-chloro-3-fluoro-anilino)propanamide	Intermediate 113, rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.20 (d, *J*=7.35 Hz, 3 H), 3.87 (s, 3 H), 5.03 (q, *J*=7.35 Hz, 1 H), 6.85 (dd, *J*=8.62, 0.76 Hz, 1 H), 7.31 (s, 1 H), 7.52 (m, 1 H), 7.64 (s, 1 H), 7.76 (m, 2 H), 7.84 (dd, *J*=8.49, 2.41 Hz, 1 H), 8.14 (m, 2 H), 8.37 (m, 1 H) Biotage (method Y) LC-MS (method 2) Rt = 1.14 min MS (ESIpos): m/z = 450.3 [M+H]$^+$ 38 % yield
172.1 and **172.2**	(R)-2-(N-[4-amino-5-(6-methoxypyridine-3-carbonyl)thiazol-2-yl]-4-chloro-3-fluoro-anilino)propanamide and (S)-2-(N-[4-amino-5-(6-methoxypyridine-3-carbonyl)thiazol-2-yl]-4-chloro-3-fluoro-anilino)propanamide		

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
172.1	 2-(N-[4-amino-5-(6-methoxypyridine-3-carbonyl)thiazol-2-yl]-4-chloro-3-fluoro-anilino)propanamide (enantiomer 1)	Example 172	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.20 (d, *J*=7.35 Hz, 3 H), 3.87 (s, 3 H), 5.03 (q, *J*=7.35 Hz, 1 H), 6.85 (dd, *J*=8.62, 0.76 Hz, 1 H), 7.31 (s, 1 H), 7.52 (m, 1 H), 7.64 (s, 1 H), 7.76 (m, 2 H), 7.84 (dd, *J*=8.49, 2.41 Hz, 1 H), 8.14 (m, 2 H), 8.37 (m, 1 H) LC-MS (method 2) Rt = 1.14 min MS (ESIpos): m/z = 450.3 $[M+H]^+$ 24 % yield

Chiral HPLC Example 172.1

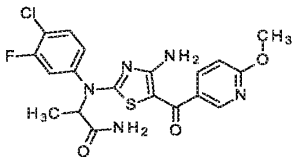
HPLC separation of rac-2-(N-[4-amino-5-(6-methoxypyridine-3-carbonyl)thiazol-2-yl]-4-chloro-3-fluoro-anilino)propanamide (312 mg, 0.69 mmol, Example 172) on a chiral column gave 78 mg (24 % yield) of 2-(N-[4-amino-5-(6-methoxypyridine-3-carbonyl)thiazol-2-yl]-4-chloro-3-fluoro-anilino)propanamide, enantiomer 1.

Preparative chiral HPLC

Instrument: Sepiatec: Prep SFC100; Column: Chiralpak IG 5µ 250x30mm; eluent A: CO_2; eluent B: methanol + 0.2 vol % aqueous ammonia (32%); isocratic: 30%B; flow: 100 mL/min; temperature: 40°C; BPR: 150bar; UV: 254 nm

Analytical chiral HPLC: Rt = 2.61 min

Instrument: Agilent: 1260, Aurora SFC-Modul; Column: Chiralpak IG 5µ 100x4.6mm; eluent A: CO_2; eluent B: methanol + 0.2 vol % aqueous ammonia (32%); isocratic: 30%B; flow: 4 mL/min; temperature: 37.5°C; BPR: 100bar; UV: 254 nm

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
172.2	 2-(N-[4-amino-5-(6-methoxypyridine-3-carbonyl)thiazol-2-yl]-4-chloro-3-fluoro-anilino)propanamide (enantiomer 2)	Example 172	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.20 (d, *J*=7.35 Hz, 3 H), 3.87 (s, 3 H), 5.03 (q, *J*=7.35 Hz, 1 H), 6.85 (dd, *J*=8.62, 0.76 Hz, 1 H), 7.31 (s, 1 H), 7.52 (m, 1 H), 7.64 (s, 1 H), 7.76 (m, 2 H), 7.84 (dd, *J*=8.49, 2.41 Hz, 1 H), 8.14 (m, 2 H), 8.37 (m, 1 H) LC-MS (method 2) Rt = 1.14 min MS (ESIpos): m/z = 450.3 $[M+H]^+$ 23 % yield

Chiral HPLC Example 172.2

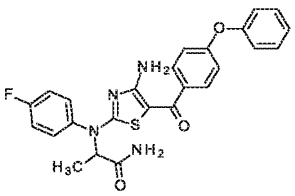
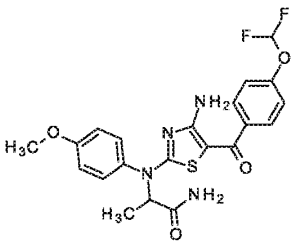
HPLC separation of rac-2-(N-[4-amino-5-(6-methoxypyridine-3-carbonyl)thiazol-2-yl]-4-chloro-3-fluoro-anilino)propanamide (312 mg, 0.69 mmol, Example 172) on a chiral column gave 73 mg (23 % yield) of 2-(N-[4-amino-5-(6-methoxypyridine-3-carbonyl)thiazol-2-yl]-4-chloro-3-fluoro-anilino)propanamide, enantiomer 2.

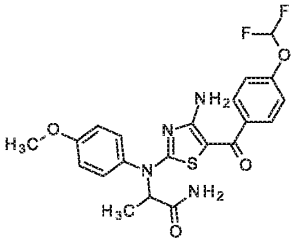
Preparative chiral HPLC

Instrument: Sepiatec: Prep SFC100; Column: Chiralpak IG 5µ 250x30mm; eluent A: CO_2; eluent B: methanol + 0.2 vol % aqueous ammonia (32%); isocratic: 30%B; flow: 100 mL/min; temperature: 40°C; BPR: 150bar; UV: 254 nm

Analytical chiral HPLC: Rt = 3.40 min

Instrument: Agilent: 1260, Aurora SFC-Modul; Column: Chiralpak IG 5µ 100x4.6mm; eluent A: CO_2; eluent B: methanol + 0.2 vol % aqueous ammonia (32%); isocratic: 30%B; flow: 4 mL/min; temperature: 37.5°C; BPR: 100bar; UV: 254 nm

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
173	 rac-2-(N-[4-amino-5-(4-phenoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 114, rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.16 (d, *J*=7.35 Hz, 3 H), 5.07 (m, 1 H), 6.94 (m, 2 H), 7.06 (m, 2 H), 7.20 (m, 1 H), 7.25 (s, 1 H), 7.33 (dd, *J*=8.87 Hz, 2 H), 7.41 (m, 2 H), 7.53 (m, 2 H), 7.58 (s, 1 H), 7.64 (m, 2 H), 8.14 (m, 2 H) Biotage (method X) LC-MS (method 2) Rt = 1.26 min MS (ESIpos): m/z = 477.2 $[M+H]^+$ 56 % yield
174	 rac-2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-methoxy-anilino)propanamide	Intermediate 115, rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.15 (d, *J*=7.35 Hz, 3 H), 3.73 (s, 3H), 5.06 (q, *J*=7.35 Hz, 1 H), 7.01 (d, *J*=9.13 Hz, 2 H), 7.16 (m, 2 H), 7.21 (s, 1 H), 7.27 (t, *J*=72 Hz, 1 H), 7.46 (m, 2 H), 7.54 (m, 3 H), 8.15 (m, 2 H) Biotage (method X) LC-MS (method 2) Rt = 1.08 min MS (ESIpos): m/z = 463.2 $[M+H]^+$ 77 % yield
174.1 and **174.2**	(R)-2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-methoxy-anilino)propanamide and (S)-2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-methoxy-anilino)propanamide		

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
174.1	 2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-methoxy-anilino)propanamide (enantiomer 1)	Example 174	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.15 (d, *J*=7.35 Hz, 3 H), 3.73 (s, 3H), 5.06 (q, *J*=7.35 Hz, 1 H), 7.01 (d, *J*=9.13 Hz, 2 H), 7.16 (m, 2 H), 7.21 (s, 1 H), 7.27 (t, *J*=72 Hz, 1 H), 7.46 (m, 2 H), 7.54 (m, 3 H), 8.15 (m, 2 H) LC-MS (method 2) Rt = 1.08 min MS (ESIpos): m/z = 463.2 $[M+H]^+$ 31 % yield

Chiral HPLC Example 174.1

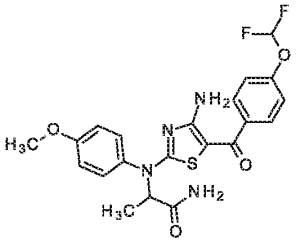
HPLC separation of rac-2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-methoxy-anilino)propanamide (316 mg, 0.66 mmol, Example 174 on a chiral column gave 121 mg (31 % yield) of 2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-methoxy-anilino)propanamide, enantiomer 1.

Preparative chiral HPLC

Instrument: PrepCon Labomatic HPLC-3; Column: YMC Amylose SA 10µ, 250x50; eluent A: methyl tert-butyl ether + 0.1 vol % diethylamine; eluent B: methanol; isocratic: 50%A+50%B; flow: 100 mL/min; temperature: 25°C; UV: 254 nm

Analytical chiral HPLC: Rt = 1.28 min

Instrument: Thermo Fisher UltiMate 3000; Column: YMC Amylose SA 3µ, 100x4.6; eluent A: methyl tert-butyl ether + 0.1 vol % diethylamine; eluent B: acetonitrile; isocratic: 50%A+50%B; flow: 1.4 mL/min; temperature: 25°C; UV: 254 nm

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
174.2	 2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-methoxy-anilino)propanamide (enantiomer 2)	Example 174	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.15 (d, *J*=7.35 Hz, 3 H), 3.73 (s, 3H), 5.06 (q, *J*=7.35 Hz, 1 H), 7.01 (d, *J*=9.13 Hz, 2 H), 7.16 (m, 2 H), 7.21 (s, 1 H), 7.27 (t, *J*=72 Hz, 1 H), 7.46 (m, 2 H), 7.54 (m, 3 H), 8.15 (m, 2 H) LC-MS (method 2) Rt = 1.08 min MS (ESIpos): m/z = 463.2 $[M+H]^+$ 31 % yield

Chiral HPLC Example 174.2

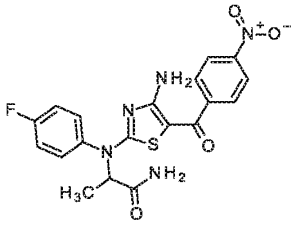
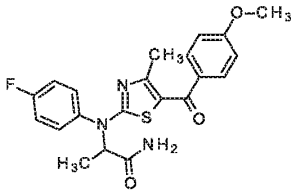
HPLC separation of rac-2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-methoxy-anilino)propanamide (316 mg, 0.66 mmol, Example 174 on a chiral column gave 121 mg (31 % yield) of 2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-methoxy-anilino)propanamide, enantiomer 2.

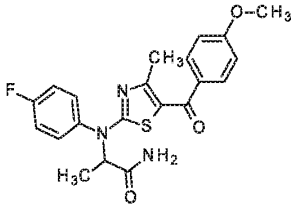
Preparative chiral HPLC

Instrument: PrepCon Labomatic HPLC-3; Column: YMC Amylose SA 10µ, 250x50; eluent A: methyl tert-butyl ether + 0.1 vol % diethylamine; eluent B: methanol; isocratic: 50%A+50%B; flow: 100 mL/min; temperature: 25°C; UV: 254 nm

Analytical chiral HPLC: Rt = 1.62 min

Instrument: Thermo Fisher UltiMate 3000; Column: YMC Amylose SA 3µ, 100x4.6; eluent A: methyl tert-butyl ether + 0.1 vol % diethylamine; eluent B: acetonitrile; isocratic: 50%A+50%B; flow: 1.4 mL/min; temperature: 25°C; UV: 254 nm

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
175	 rac-2-(N-[4-amino-5-(4-nitrobenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 116, rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.16 (d, J=7.35 Hz, 3 H), 5.07 (q, J=7.35 Hz, 1 H), 7.26 (br s, 1 H), 7.33 (m, 3 H), 7.59 (br s, 1 H), 7.63 (m, 3 H), 7.71 (m, 2 H), 8.23 (m, 3 H), 8.38 (m, 1 H) Biotage (method X) LC-MS (method 2) Rt = 1.05 min MS (ESIpos): m/z = 430.1 [M+H]$^+$ 66 % yield
176	 rac-2-(4-fluoro-N-[5-(4-methoxybenzoyl)-4-methyl-thiazol-2-yl]anilino)propanamide	Intermediate 117, rac-2-bromopropanamide	^{1}H NMR (500 MHz, DMSO-d_6) δ ppm = 1.16 (d, *J*=7.57 Hz, 3 H), 2.29 (s, 3 H), 3.80 (s, 3 H), 5.11 (q, *J*=7.35 Hz, 1 H), 6.99 (d, *J*=8.83 Hz, 2 H), 7.20 (s, 1 H), 7.36 (dd, *J*=8.83 Hz, 2 H), 7.58 (m, 2 H), 7.61 (s, 1 H), 7.68 (m, 2 H) LC-MS (method 2) Rt = 1.16 min MS (ESIpos): m/z = 414.5 [M+H]$^+$ 79 % yield
176.1 and **176.2**	(R)-2-(4-fluoro-N-[5-(4-methoxybenzoyl)-4-methyl-thiazol-2-yl]anilino)propanamide and (S)-2-(4-fluoro-N-[5-(4-methoxybenzoyl)-4-methyl-thiazol-2-yl]anilino)propanamide		

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
176.1	 2-(4-fluoro-N-[5-(4-methoxybenzoyl)-4-methyl-thiazol-2-yl]anilino)propanamide (enantiomer 1)	Example 176	^{1}H NMR (500 MHz, DMSO-d_6) δ ppm = 1.16 (d, *J*=7.57 Hz, 3 H), 2.29 (s, 3 H), 3.80 (s, 3 H), 5.11 (q, *J*=7.35 Hz, 1 H), 6.99 (d, *J*=8.83 Hz, 2 H), 7.20 (s, 1 H), 7.36 (dd, *J*=8.83 Hz, 2 H), 7.58 (m, 2 H), 7.61 (s, 1 H), 7.68 (m, 2 H) LC-MS (method 2) Rt = 1.16 min MS (ESIpos): m/z = 414.5 $[M+H]^+$ 49 % yield

Chiral HPLC Example 176.1

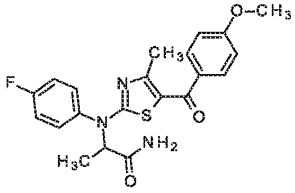
HPLC separation of rac-2-(4-fluoro-N-[5-(4-methoxybenzoyl)-4-methyl-thiazol-2-yl]anilino)propanamide (80 mg, 0.19 mmol, Example 176 on a chiral column gave 39 mg (49 % yield) of 2-(4-fluoro-N-[5-(4-methoxybenzoyl)-4-methyl-thiazol-2-yl]anilino)propanamide, enantiomer 1.

Preparative chiral HPLC

Instrument: PrepCon Labomatic HPLC-4; Column: YMC Cellulose SC 10µ, 250x50; eluent A: hexane + 0.1 vol % diethylamine; eluent B: ethanol; isocratic: 80%A+20%B; flow: 100 mL/min; temperature: 25°C; UV: 254 nm

Analytical chiral HPLC: Rt = 4.20 min

Instrument: Thermo Fisher UltiMate 3000; Column: YMC Cellulose SC 3µ, 100x4.6; eluent A: hexane + 0.1 vol % diethylamine; eluent B: ethanol; isocratic: 80%A+20%B; flow: 1.4 mL/min; temperature: 25°C; UV: 254 nm

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
176.2	 2-(4-fluoro-N-[5-(4-methoxybenzoyl)-4-methyl-thiazol-2-yl]anilino)propanamide (enantiomer 2)	Example 176	^{1}H NMR (500 MHz, DMSO-d_6) δ ppm = 1.16 (d, *J*=7.57 Hz, 3 H), 2.29 (s, 3 H), 3.80 (s, 3 H), 5.11 (q, *J*=7.35 Hz, 1 H), 6.99 (d, *J*=8.83 Hz, 2 H), 7.20 (s, 1 H), 7.36 (dd, *J*=8.83 Hz, 2 H), 7.58 (m, 2 H), 7.61 (s, 1 H), 7.68 (m, 2 H) LC-MS (method 2) Rt = 1.16 min MS (ESIpos): m/z = 414.5 $[M+H]^+$ 49 % yield

Chiral HPLC Example 176.2

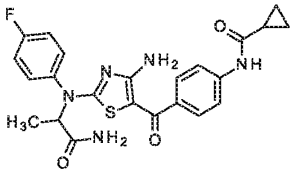
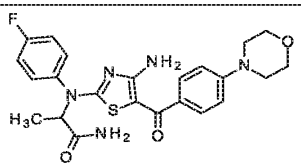
HPLC separation of rac-2-(4-fluoro-N-[5-(4-methoxybenzoyl)-4-methyl-thiazol-2-yl]anilino)propanamide (80 mg, 0.19 mmol, Example 176 on a chiral column gave 31 mg (39 % yield) of 2-(4-fluoro-N-[5-(4-methoxybenzoyl)-4-methyl-thiazol-2-yl]anilino)propanamide, enantiomer 2.

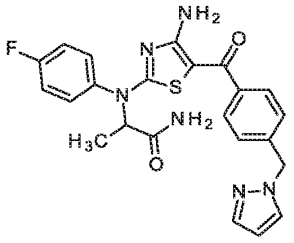
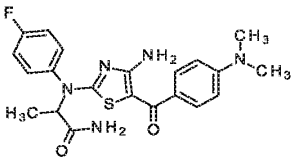
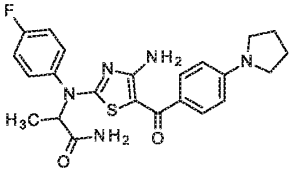
Preparative chiral HPLC

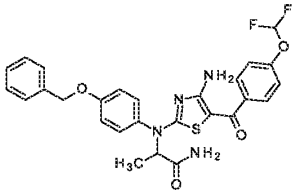
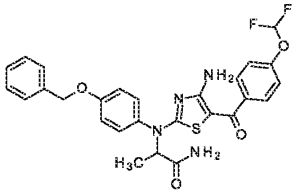
Instrument: PrepCon Labomatic HPLC-4; Column: YMC Cellulose SC 10µ, 250x50; eluent A: hexane + 0.1 vol % diethylamine; eluent B: ethanol; isocratic: 80%A+20%B; flow: 100 mL/min; temperature: 25°C; UV: 254 nm

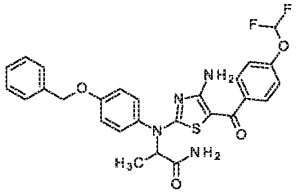
Analytical chiral HPLC: Rt = 4.84 min

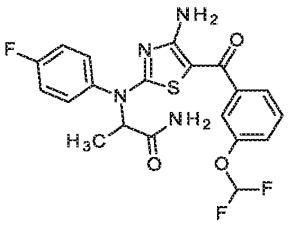
Instrument: Thermo Fisher UltiMate 3000; Column: YMC Cellulose SC 3µ, 100x4.6; eluent A: hexane + 0.1 vol % diethylamine; eluent B: ethanol; isocratic: 80%A+20%B; flow: 1.4 mL/min; temperature: 25°C; UV: 254 nm

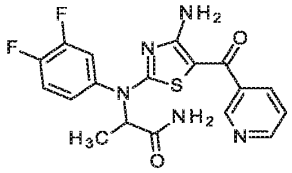
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
177	 rac-4-[4-[4-amino-2-(N-(2-amino-1-methyl-2-oxo-ethyl)-4-fluoro-anilino)thiazole-5-carbonyl]phenyl]cyclopropanecarboxamide	Intermediate 118, rac-2-bromopropanamide	^{1}H NMR (500 MHz, DMSO-d_6) δ ppm = 0.75 – 0.80 (m, 4 H), 1.16 (d, *J*=7.31 Hz, 3 H), 1.77 (m, 1 H), 5.05 (m, 1 H), 7.24 (br s, 1 H), 7.32 (dd, *J*=8.74 Hz, 2 H), 7.45 (d, *J*=8.58 Hz, 2 H), 7.57 (m, 3 H), 7.64 (dd, *J*=8.74, 4.93 Hz, 2 H), 8.11 (m, 2 H), 10.34 (s, 1 H) RP-HPLC (method C basic) LC-MS (method 1) Rt = 0.99 min MS (ESIpos): m/z = 468.5 $[M+H]^+$ 57 % yield
178	 rac-2-(N-[4-amino-5-(4-morpholinobenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 119, rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.16 (d, *J*=7.35 Hz, 3 H), 3.16 (m, 4 H), 3.70 (m, 4 H), 5.06 (q, *J*=7.35 Hz, 1 H), 6.90 (d, *J*=8.87 Hz, 2 H), 7.24 (br s, 1 H), 7.34 (dd, *J*=8.74 Hz, 2 H), 7.43 (m, *J*=8.87 Hz, 2 H), 7.57 (br s, 1 H), 7.65 (m, 2 H), 7.97 (m, 2 H) LC-MS (method 2) Rt = 1.01 min MS (ESIpos): m/z = 470.3 $[M+H]^+$ 48 % yield

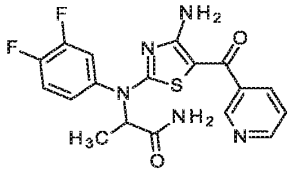
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
179	 rac-2-(N-[4-amino-5-[4-(pyrazol-1-ylmethyl)benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 120, rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.14 (d, *J*=7.35 Hz, 3 H), 5.04 (q, *J*=7.35 Hz, 1 H), 5.32 (m, 2 H), 6.27 (dd, *J*=2.03 Hz, 1 H), 7.15 (d, *J*=8.36 Hz, 2 H), 7.23 (s, 1 H), 7.31 (m, 2 H), 7.43 (m, 2 H), 7.45 (m, 1 H), 7.60 (m, 3 H), 7.82 (dd, *J*=2.28, 0.76 Hz, 1 H), 8.18 (m, 2 H) RP-HPLC (method C basic) LC-MS (method 1) Rt = 1.0 min MS (ESIpos): m/z = 465.6 [M+H]$^+$ 66 % yield
180	 rac-2-(N-[4-amino-5-[4-(dimethylamino)benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 121, rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.16 (d, *J*=7.35 Hz, 3 H), 2.92 (s, 6 H), 5.05 (q, *J*=7.35 Hz, 1 H), 6.65 (m, 2 H), 7.23 (s, 1 H), 7.34 (dd, *J*=8.87 Hz, 2 H), 7.43 (m, 2 H), 7.57 (br d, *J*=0.76 Hz, 1 H), 7.65 (m, 2 H), 7.96 (m, 2 H) RP-HPLC (method D basic) LC-MS (method 2) Rt = 1.13 min MS (ESIpos): m/z = 428.5 [M+H]$^+$ 63 % yield
181	 rac-2-(N-[4-amino-5-(4-pyrrolidin-1-ylbenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 122, rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.16 (br d, *J*=7.35 Hz, 3 H), 1.93 (m, 4 H), 3.23 (m, 4 H), 5.06 (m, 1 H), 6.47 (br d, *J*=8.62 Hz, 2 H), 7.24 (m, 1 H), 7.34 (s, 2 H), 7.42 (br d, *J*=8.36 Hz, 2 H), 7.57 (br s, 1 H), 7.65 (m, 2 H), 7.97 (m, 2 H) LC-MS (method 2) Rt = 1.21 min MS (ESIpos): m/z = 454.3 [M+H]$^+$ 82 % yield

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
182	 rac-2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-benzyloxy-anilino)propanamide	Intermediate 123, rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.15 (d, *J*=7.35 Hz, 3 H), 5.03 – 5.06 (m, 1 H), 5.08 – 5.12 (m, 2 H), 7.09 – 7.14 (m, 4 H), 7.22 (s, 1 H), 7.28 (s, 1 H), 7.35 – 7.45 – 7.62 (m, 10 H), 8.10 – 8.15 (m, 2 H) Biotage (method X) LC-MS (method 2) Rt = 1.29 min MS (ESIpos): m/z = 539.4 [M+H]$^+$ 73 % yield
182.1 and **182.2**	(R)-2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-benzyloxy-anilino)propanamide and (S)-2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-benzyloxy-anilino)propanamide		
182.1	 2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-benzyloxy-anilino)propanamide (enantiomer 1)	Example 182	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.15 (d, *J*=7.35 Hz, 3 H), 5.05 (m, 1 H), 5.11 (m, 2 H), 7.13 (m, 4 H), 7.22 (s, 1 H), 7.28 (s, 1 H), 7.35 – 7.55 (m, 10 H), 8.13 (m, 2 H) LC-MS (method 2) Rt = 1.29 min MS (ESIpos): m/z = 539.4 [M+H]$^+$ 44 % yield

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
Chiral HPLC Example 182.1 HPLC separation of rac-2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-benzyloxy-anilino)propanamide (813 mg, 1.51 mmol, Example 182) on a chiral column gave 360 mg (44 % yield) of 2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-benzyloxy-anilino)propanamide, enantiomer 1. Preparative chiral HPLC Instrument: PrepCon Labomatic HPLC-3; Column: YMC Cellulose SB 10µ, 250x50; eluent A: hexane + 0.1 vol % diethylamine; eluent B: ethanol + 0.1 vol % diethylamine; isocratic: 60%A+40%B; flow: 100 mL/min; temperature: 25°C; UV: 254 nm Analytical chiral HPLC: Rt = 2.76 min Instrument: Waters Alliance 2695; Column: YMC Cellulose SB 3µ, 100x4.6; eluent A: hexane + 0.1 vol % diethylamine; eluent B: ethanol; isocratic: 60%A+40%B; flow: 1.4 mL/min; temperature: 25°C; UV: 254 nm			
182.2	 2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-benzyloxy-anilino)propanamide (enantiomer 2)	Example 182	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.15 (d, *J*=7.35 Hz, 3 H), 5.03 – 5.06 (m, 1 H), 5.09 – 5.12 (m, 2 H), 7.09 – 7.14 (m, 4 H), 7.22 (s, 1 H), 7.28 (s, 1 H), 7.35 – 7.55 (m, 10 H), 8.10 – 8.15 (m, 2 H) LC-MS (method 2) Rt = 1.29 min MS (ESIpos): m/z = 539.4 $[M+H]^+$ 45 % yield

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
Chiral HPLC Example 182.2 HPLC separation of rac-2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-benzyloxy-anilino)propanamide (813 mg, 1.51 mmol, Example 182) on a chiral column gave 365 mg (45 % yield) of 2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-benzyloxy-anilino)propanamide, enantiomer 2. Preparative chiral HPLC Instrument: PrepCon Labomatic HPLC-3; Column: YMC Cellulose SB 10µ, 250x50; eluent A: hexane + 0.1 vol % diethylamine; eluent B: ethanol + 0.1 vol % diethylamine; isocratic: 60%A+40%B; flow: 100 mL/min; temperature: 25°C; UV: 254 nm Analytical chiral HPLC: Rt = 3.49 min Instrument: Waters Alliance 2695; Column: YMC Cellulose SB 3µ, 100x4.6; eluent A: hexane + 0.1 vol % diethylamine; eluent B: ethanol; isocratic: 60%A+40%B; flow: 1.4 mL/min; temperature: 25°C; UV: 254 nm			
183	 rac-2-(N-[4-amino-5-[3-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 124, rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.15 (d, *J*=7.35 Hz, 3 H), 5.03 – 5.06 (m, 1 H), 7.20 – 7.28 (m, 4 H), 7.33 (d, *J*=8.87 Hz, 3 H), 7.42 (d, *J*=8.11 Hz, 1 H), 7.59 – 7.63 (m, 3 H), 8.17 – 8.21 (m, 2 H) RP-HPLC (method D basic) LC-MS (method 2) Rt = 1.13 min MS (ESIpos): m/z = 451.5 $[M+H]^+$ 41 % yield

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
184	 rac-2-(N-[4-amino-5-(pyridine-3-carbonyl)thiazol-2-yl]-3,4-difluoro-anilino)propanamide	Intermediate 125, rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.19 (d, *J*=7.35 Hz, 3 H), 4.97 – 5.09 (m, 1 H), 7.30 (s, 1 H), 7.40 – 7.48 (m, 1 H), 7.48 – 7.53 (m, 1 H), 7.55 – 7.61 (m, 1 H), 7.63 (s, 1 H), 7.74 – 7.81 (m, 1 H), 7.85 – 7.90 (m, 1 H), 8.07 – 8.41 (m, 2 H), 8.61 (dd, *J*=4.82, 1.52 Hz, 1 H), 8.69 (dd, *J*=2.28, 0.76 Hz, 1 H) RP-HPLC (method D basic) LC-MS (method 2) Rt = 0.92 min MS (ESIpos): m/z = 404.3 $[M+H]^+$ 54 % yield
184.1 and **184.2**	(R)-2-(N-[4-amino-5-(pyridine-3-carbonyl)thiazol-2-yl]-3,4-difluoro-anilino)propanamide and (S)-2-(N-[4-amino-5-(pyridine-3-carbonyl)thiazol-2-yl]-3,4-difluoro-anilino)propanamide		

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
184.1	 2-(N-[4-amino-5-(pyridine-3-carbonyl)thiazol-2-yl]-3,4-difluoro-anilino)propanamide (enantiomer 1)	Example 184	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.19 (d, *J*=7.35 Hz, 3 H), 4.97 – 5.09 (m, 1 H), 7.30 (s, 1 H), 7.40 – 7.48 (m, 1 H), 7.48 – 7.53 (m, 1 H), 7.55 – 7.61 (m, 1 H), 7.63 (s, 1 H), 7.74 – 7.81 (m, 1 H), 7.85 – 7.90 (m, 1 H), 8.07 – 8.41 (m, 2 H), 8.61 (dd, *J*=4.82, 1.52 Hz, 1 H), 8.69 (dd, *J*=2.28, 0.76 Hz, 1 H) LC-MS (method 2) Rt = 0.92 min MS (ESIpos): m/z = 404.3 $[M+H]^+$ 39 % yield

Chiral HPLC Example 184.1

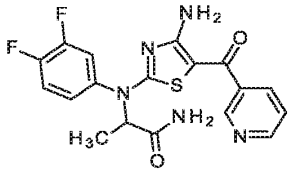
HPLC separation of rac-2-(N-[4-amino-5-(pyridine-3-carbonyl)thiazol-2-yl]-3,4-difluoro-anilino)propanamide (115 mg, 0.29 mmol, Example 184) on a chiral column gave 45 mg (39 % yield) of 2-(N-[4-amino-5-(pyridine-3-carbonyl)thiazol-2-yl]-3,4-difluoro-anilino)propanamide, enantiomer 1.

Preparative chiral HPLC

Instrument: PrepCon Labomatic HPLC-4; Column: YMC Cellulose SC 10µ, 250x50; eluent A: methyl tert-butyl ether + 0.1 vol % diethylamine; eluent B: acetonitrile; isocratic: 50%A+50%B; flow: 100 mL/min; temperature: 25°C; UV: 280 nm

Analytical chiral HPLC: Rt = 2.11 min

Instrument: Thermo Fisher UltiMate 3000; Column: YMC Cellulose SC 3µ, 100x4.6; eluent A: methyl tert-butyl ether + 0.1 vol % diethylamine; eluent B: acetonitrile; isocratic: 50%A+50%B; flow: 1.4 mL/min; temperature: 25°C; UV: 254 nm

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
184.2	 2-(N-[4-amino-5-(pyridine-3-carbonyl)thiazol-2-yl]-3,4-difluoro-anilino)propanamide (enantiomer 2)	Example 184	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.19 (d, *J*=7.35 Hz, 3 H), 4.97 – 5.09 (m, 1 H), 7.30 (s, 1 H), 7.40 – 7.48 (m, 1 H), 7.48 – 7.53 (m, 1 H), 7.55 – 7.61 (m, 1 H), 7.63 (s, 1 H), 7.74 – 7.81 (m, 1 H), 7.85 – 7.90 (m, 1 H), 8.07 – 8.41 (m, 2 H), 8.61 (dd, *J*=4.82, 1.52 Hz, 1 H), 8.69 (dd, *J*=2.28, 0.76 Hz, 1 H) LC-MS (method 2) Rt = 0.92 min MS (ESIpos): m/z = 404.3 $[M+H]^+$ 43 % yield

Chiral HPLC Example 184.2

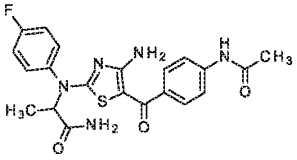
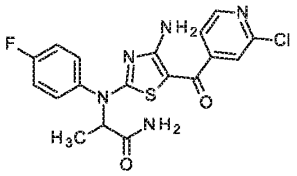
HPLC separation of rac-2-(N-[4-amino-5-(pyridine-3-carbonyl)thiazol-2-yl]-3,4-difluoro-anilino)propanamide (115 mg, 0.29 mmol, Example 184) on a chiral column gave 50 mg (43 % yield) of 2-(N-[4-amino-5-(pyridine-3-carbonyl)thiazol-2-yl]-3,4-difluoro-anilino)propanamide, enantiomer 2.

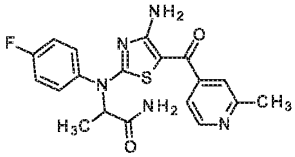
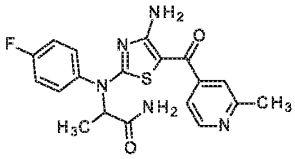
Preparative chiral HPLC

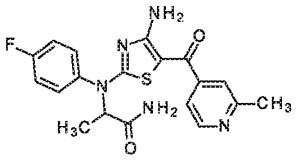
Instrument: PrepCon Labomatic HPLC-4; Column: YMC Cellulose SC 10µ, 250x50; eluent A: methyl tert-butyl ether + 0.1 vol % diethylamine; eluent B: acetonitrile; isocratic: 50%A+50%B; flow: 100 mL/min; temperature: 25°C; UV: 280 nm

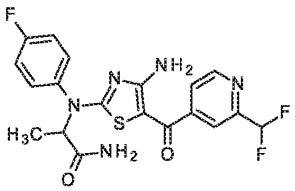
Analytical chiral HPLC: Rt = 2.83 min

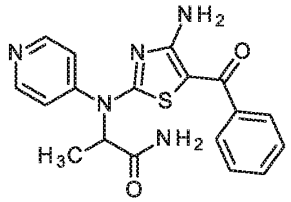
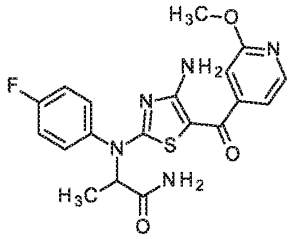
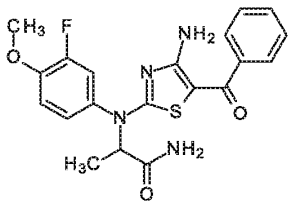
Instrument: Thermo Fisher UltiMate 3000; Column: YMC Cellulose SC 3µ, 100x4.6; eluent A: methyl tert-butyl ether + 0.1 vol % diethylamine; eluent B: acetonitrile; isocratic: 50%A+50%B; flow: 1.4 mL/min; temperature: 25°C; UV: 254 nm

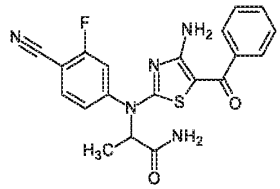
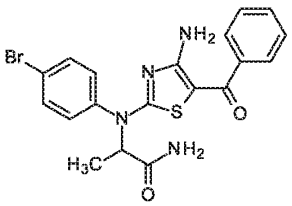
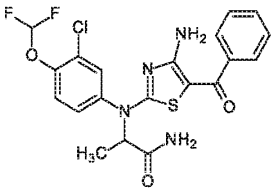
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
185	 rac-2-(N-[5-(4-acetamidobenzoyl)-4-amino-thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 126, rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.15 (d, *J*=7.35 Hz, 3 H), 2.03 (s, 3 H), 5.05 (q, *J*=7.35 Hz, 1 H), 7.24 (s, 1 H), 7.32 (dd, *J*=8.87 Hz, 2 H), 7.44 (d, *J*=8.87 Hz, 2 H), 7.55 (d, *J*=8.62 Hz, 2 H), 7.58 (br s, 1 H), 7.61 – 7.66 (m, 2 H), 7.81 – 8.39 (m, 2 H), 10.11 (br s, 1 H) RP-HPLC (method C basic) LC-MS (method 1) Rt = 0.87 min MS (ESIpos): m/z = 442.4 $[M+H]^+$ 54 % yield
186	 rac-2-(N-[4-amino-5-(2-chloropyridine-4-carbonyl)thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 127, rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.16 (d, *J*=7.60 Hz, 3 H), 5.00 – 5.13 (m, 1 H), 7.27 (s, 1 H), 7.34 (dd, *J*=8.87 Hz, 2 H), 7.41 (dd, *J*=5.07, 1.27 Hz, 1 H), 7.49 (s, 1 H), 7.59 (s, 1 H), 7.64 (dd, *J*=8.87, 5.07 Hz, 2 H), 8.20 – 8.42 (m, 2 H), 8.45 (d, *J*=5.07 Hz, 1 H) RP-HPLC (method C basic) LC-MS (method 2) Rt = 1.03 min MS (ESIpos): m/z = 420.3 $[M+H]^+$ 25 % yield

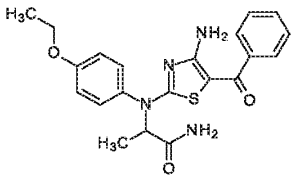
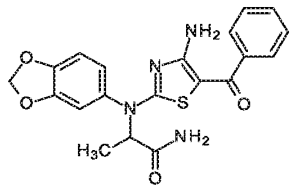
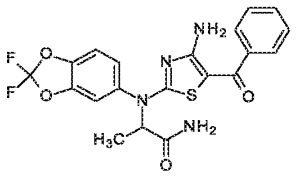
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
187	 rac-2-(N-[4-amino-5-(2-methylpyridine-4-carbonyl)thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 128, rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.15 (d, *J*=7.60 Hz, 3 H), 2.45 (s, 3 H), 5.06 (br s, 1 H), 7.10 – 7.23 (m, 1 H), 7.23 – 7.28 (m, 2 H), 7.33 (dd, *J*=8.74 Hz, 2 H), 7.59 (br s, 1 H), 7.63 (dd, *J*=8.87, 5.07 Hz, 2 H), 8.05 – 8.42 (m, 2 H), 8.46 (d, *J*=5.07 Hz, 1 H) RP-HPLC (method C basic) LC-MS (method 2) Rt = 0.90 min MS (ESIpos): m/z = 400.5 $[M+H]^+$ 66 % yield
187.1 and **187.2**	(R)-2-(N-[4-amino-5-(2-methylpyridine-4-carbonyl)thiazol-2-yl]-4-fluoro-anilino)propanamide and (S)-2-(N-[4-amino-5-(2-methylpyridine-4-carbonyl)thiazol-2-yl]-4-fluoro-anilino)propanamide		
187.1	 2-(N-[4-amino-5-(2-methylpyridine-4-carbonyl)thiazol-2-yl]-4-fluoro-anilino)propanamide (enantiomer 1)	Example 187	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.15 (d, *J*=7.60 Hz, 3 H), 2.45 (s, 3 H), 5.06 (br s, 1 H), 7.10 – 7.23 (m, 1 H), 7.23 – 7.28 (m, 2 H), 7.33 (dd, *J*=8.74 Hz, 2 H), 7.59 (br s, 1 H), 7.63 (dd, *J*=8.87, 5.07 Hz, 2 H), 8.05 – 8.42 (m, 2 H), 8.46 (d, *J*=5.07 Hz, 1 H) 32 % yield

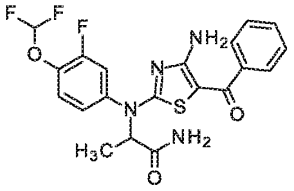
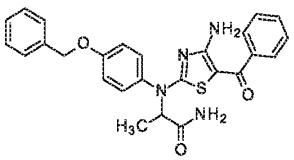
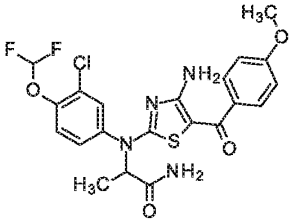
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
Chiral HPLC Example 187.1 HPLC separation of rac-2-(N-[4-amino-5-(2-methylpyridine-4-carbonyl)thiazol-2-yl]-4-fluoro-anilino)propanamide (333 mg, 0.83 mmol, Example 187) on a chiral column gave 105 mg (32 % yield) of 2-(N-[4-amino-5-(2-methylpyridine-4-carbonyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, enantiomer 1. Preparative chiral HPLC Instrument: Sepiatec: Prep SFC100; Column: Chiralpak IG 5µ 250x30mm; eluent A: CO_2; eluent B: ethanol + 0.2 vol % aqueous ammonia (32%); isocratic: 15%B; flow: 100 mL/min; temperature: 40°C; BPR: 150bar; UV: 254 nm Analytical chiral HPLC: Rt = 2.81 min Instrument: Agilent: 1260, Aurora SFC-Modul; Column: Chiralpak IG 5µ 100x4.6mm; eluent A: CO_2; eluent B: ethanol + 0.2 vol % aqueous ammonia (32%); isocratic: 25%B; flow: 4 mL/min; temperature: 37.5°C; BPR: 100bar; UV: 254 nm			
187.2	 2-(N-[4-amino-5-(2-methylpyridine-4-carbonyl)thiazol-2-yl]-4-fluoro-anilino)propanamide (enantiomer 2)	Example 187	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.15 (d, *J*=7.60 Hz, 3 H), 2.45 (s, 3 H), 5.06 (br s, 1 H), 7.10 – 7.23 (m, 1 H), 7.23 – 7.28 (m, 2 H), 7.33 (dd, *J*=8.74 Hz, 2 H), 7.59 (br s, 1 H), 7.63 (dd, *J*=8.87, 5.07 Hz, 2 H), 8.05 – 8.42 (m, 2 H), 8.46 (d, *J*=5.07 Hz, 1 H) 23 % yield

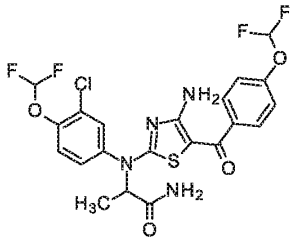
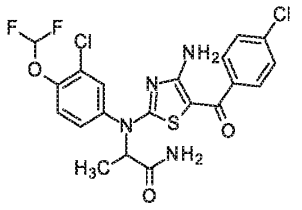
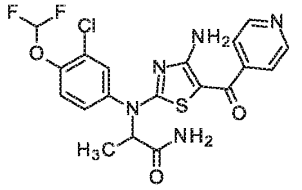
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
Chiral HPLC Example 187.2 HPLC separation of rac-2-(N-[4-amino-5-(2-methylpyridine-4-carbonyl)thiazol-2-yl]-4-fluoro-anilino)propanamide (333 mg, 0.83 mmol, Example 187) on a chiral column gave 78 mg (23 % yield) of 2-(N-[4-amino-5-(2-methylpyridine-4-carbonyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, enantiomer 2. Preparative chiral HPLC Instrument: Sepiatec: Prep SFC100; Column: Chiralpak IG 5µ 250x30mm; eluent A: CO_2; eluent B: ethanol + 0.2 vol % aqueous ammonia (32%); isocratic: 15%B; flow: 100 mL/min; temperature: 40°C; BPR: 150bar; UV: 254 nm Analytical chiral HPLC: Rt = 3.56 min Instrument: Agilent: 1260, Aurora SFC-Modul; Column: Chiralpak IG 5µ 100x4.6mm; eluent A: CO_2; eluent B: ethanol + 0.2 vol % aqueous ammonia (32%); isocratic: 25%B; flow: 4 mL/min; temperature: 37.5°C; BPR: 100bar; UV: 254 nm			
188	 rac-2-(N-[4-amino-5-[2-(difluoromethyl)pyridine-4-carbonyl]thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 129, rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.16 (d, *J*=7.35 Hz, 3 H), 4.99 – 5.13 (m, 1 H), 6.97 (t, *J*=52 Hz, 1 H), 7.27 (s, 1 H), 7.33 (t, *J*=8.87 Hz, 2 H), 7.56 – 7.61 (m, 2 H), 7.64 (dd, *J*=8.87, 5.07 Hz, 2 H), 7.67 (s, 1 H), 8.20 – 8.57 (m, 2 H), 8.73 (d, *J*=4.56 Hz, 1 H) RP-HPLC (method C basic) LC-MS (method 2) Rt = 1.00 min MS (ESIpos): m/z = 436.3 $[M+H]^+$ 13 % yield

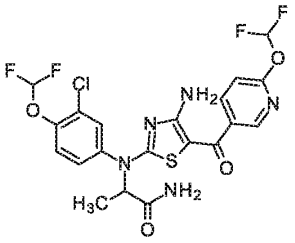
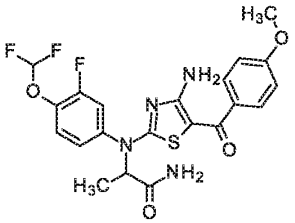
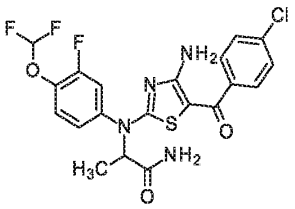
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
189	 rac-2-[(4-amino-5-benzoyl-thiazol-2-yl)-(4-pyridyl)amino]propanamide	Intermediate 130, rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.22 (d, *J*=7.35 Hz, 3 H), 5.05 (q, *J*=7.35 Hz, 1 H), 5.74 (s, 1 H), 7.32 (s, 1 H), 7.37 – 7.44 (m, 2 H), 7.48 – 7.55 (m, 2 H), 7.56 – 7.65 (m, 3 H), 8.06 – 8.42 (m, 2 H), 8.68 – 8.73 (m, 2 H) RP-HPLC (method C basic) LC-MS (method 2) Rt = 0.80 min MS (ESIpos): m/z = 368.2 [M+H]$^+$ 17 % yield
190	 rac-2-(N-[4-amino-5-(2-methoxypyridine-4-carbonyl)thiazol-2-yl]-4-fluoro-anilino)propanamide	Intermediate 131, rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.15 (d, *J*=7.35 Hz, 3 H), 3.83 (s, 3H), 5.00 – 5.11 (m, 1 H), 6.76 (s, 1 H), 6.99 (dd, *J*=5.20, 1.39 Hz, 1 H), 7.26 (s, 1 H), 7.30 – 7.37 (m, 2 H), 7.59 (s, 1 H), 7.63 (dd, *J*=8.87, 5.07 Hz, 2 H), 8.17 – 8.20 (m, 1 H), 8.21 – 8.48 (m, 2 H) RP-HPLC (method C basic) LC-MS (method 2) Rt = 0.98 min MS (ESIpos): m/z = 416.2 [M+H]$^+$ 29 % yield
191	 rac-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-3-fluoro-4-methoxy-anilino)propanamide	Intermediate 133; rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 8.12 (br s, 2H), 7.57 (s, 1H), 7.46-7.53 (m, 3H), 7.34-7.44 (m, 4H), 7.21-7.28 (m, 2H), 4.98-5.10 (m, 1H), 3.87 (s, 3H), 1.16 (d, J = 7.4 Hz, 3H). LC-MS (method 2) Rt = 1.06 min MS (ESIpos): m/z = 415.3 [M+H]$^+$ 78 % yield

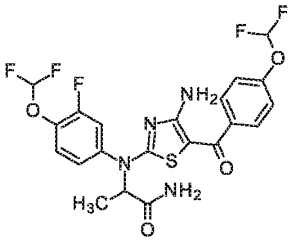
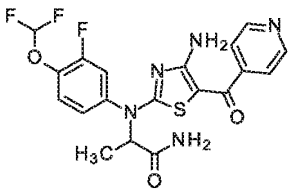
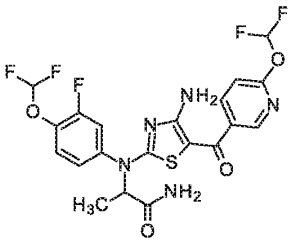
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
192	 rac-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-4-cyano-3-fluoro-anilino)propanamide	Intermediate 134; rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1H NMR (400 MHz, DMSO-d6, 22ºC): Shift = 7.95-8.40 (m, 3H), 7.86 (dd, J = 10.4, 1.8 Hz, 1H), 7.64-7.72 (m, 2H), 7.50-7.55 (m, 2H), 7.38-7.48 (m, 3H), 7.36 (s, 1H), 5.01 (q, J = 7.4 Hz, 1H), 1.22 (d, J = 7.4 Hz, 3H) LC-MS (method 2) Rt = 1.04 min MS (ESIpos): m/z = 410.3 [M+H]$^+$ 18 % yield
193	 rac-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-4-bromo-anilino)propanamide	Intermediate 135; rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 8.17 (br s, 2H), 7.66-7.72 (m, 2H), 7.59 (s, 1H), 7.51-7.57 (m, 2H), 7.46-7.51 (m, 2H), 7.36-7.44 (m, 3H), 7.26 (s, 1H), 5.05 (q, J = 7.3 Hz, 1H), 1.16 (d, J = 7.6 Hz, 3H). LC-MS (method 2) Rt = 1.19 min MS (ESIpos): m/z = 445.3 [M+H]$^+$ 47 % yield
194	 rac-2-[N-(4-amino-5-benzoyl-thiazol-2-yl)-3-chloro-4-(difluoromethoxy)anilino]propanamide	Intermediate 136; rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 8.13 (br s, 2H), 7.90 (d, J = 2.5 Hz, 1H), 7.60-7.68 (m, 2H), 7.45-7.52 (m, 3H), 7.39-7.44 (m, 3H), 7.39 (t, J = 73.0 Hz, 1H), 7.29 (s, 1H), 5.02 (q, J = 7.1 Hz, 1H), 1.18 (d, J = 7.4 Hz, 3H). LC-MS (method 2) Rt = 1.18 min MS (ESIpos): m/z = 467.4 [M+H]$^+$ 68 % yield

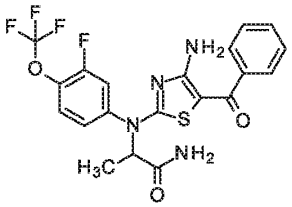
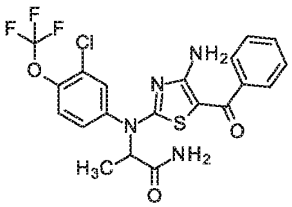
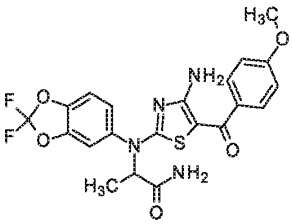
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
195	 rac-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-4-ethoxy-anilino)propanamide	Intermediate 137; rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 8.11 (br s, 2H), 7.52 (s, 1H), 7.41-7.49 (m, 4H), 7.34-7.41 (m, 3H), 7.20 (s, 1H), 6.98 (d, J = 9.1 Hz, 2H), 5.00-5.12 (m, 1H), 4.03 (q, J = 6.8 Hz, 2H), 1.32 (t, J = 7.0 Hz, 3H), 1.14 (d, J = 7.4 Hz, 3H). LC-MS (method 2) Rt = 1.15 min MS (ESIpos): m/z = 411.5 [M+H]$^+$ 61 % yield
196	 rac-2-[(4-amino-5-benzoyl-thiazol-2-yl)-(1,3-benzodioxol-5-yl)amino]propanamide	Intermediate 138; rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 8.08 (br s, 2H), 7.54 (s, 1H), 7.46-7.51 (m, 2H), 7.36-7.44 (m, 3H), 7.22 (s, 1H), 7.14 (d, J = 1.8 Hz, 1H), 7.01-7.07 (m, 1H), 6.96-7.00 (m, 1H), 6.10 (s, 2H), 4.97-5.09 (m, 1H), 1.18 (d, J = 7.4 Hz, 3H). LC-MS (method 2) Rt = 1.03 min MS (ESIpos): m/z = 411.4 [M+H]$^+$ 67 % yield
197	 rac-2-[(4-amino-5-benzoyl-thiazol-2-yl)-(2,2-difluoro-1,3-benzodioxol-5-yl)amino]propanamide	Intermediate 139; rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 8.13 (br s, 2H), 7.71 (d, J = 2.0 Hz, 1H), 7.61 (s, 1H), 7.45-7.56 (m, 4H), 7.35-7.44 (m, 3H), 7.28 (s, 1H), 5.03 (br d, J = 6.8 Hz, 1H), 1.18 (d, J = 7.4 Hz, 3H). LC-MS (method 2) Rt = 1.2 min MS (ESIpos): m/z = 447.3 [M+H]$^+$ 51 % yield

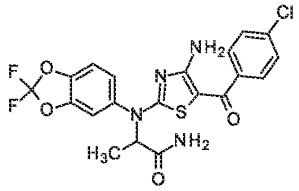
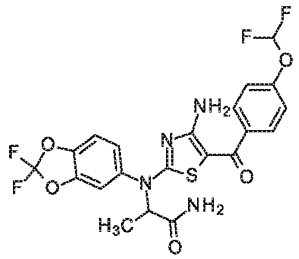
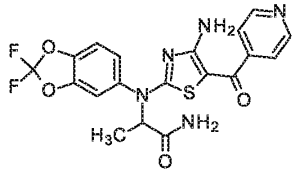
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
198	 rac-2-[N-(4-amino-5-benzoyl-thiazol-2-yl)-4-(difluoromethoxy)-3-fluoro-anilino]propanamide	Intermediate 140; rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 8.14 (br s, 2H), 7.69-7.76 (m, 1H), 7.62 (s, 1H), 7.46-7.52 (m, 4H), 7.36-7.46 (m, 3H), 7.34 (t, J = 73.0 Hz, 1H), 7.29 (s, 1H), 5.03 (q, J = 7.1 Hz, 1H), 1.18 (d, J = 7.4 Hz, 3H). LC-MS (method 2) Rt = 1.12 min MS (ESIpos): m/z = 451.3 $[M+H]^+$ 49 % yield
199	 rac-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-4-benzyloxy-anilino)propanamide	Intermediate 141; rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 8.12 (br s, 2H), 7.53 (s, 1H), 7.44-7.51 (m, 6H), 7.32-7.43 (m, 6H), 7.21 (s, 1H), 7.09 (d, J = 9.1 Hz, 2H), 4.99-5.15 (m, 3H), 1.15 (d, J = 7.4 Hz, 3H). LC-MS (method 2) Rt = 1.28 min MS (ESIpos): m/z = 473.4 $[M+H]^+$ 57 % yield
200	 rac-2-[N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-3-chloro-4-(difluoromethoxy)anilino]propanamide	Intermediate 142; rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 7.93-8.45 (m, 2H), 7.91 (d, J = 2.3 Hz, 1H), 7.63-7.67 (m, 1H), 7.62 (s, 1H), 7.47-7.53 (m, 3H), 7.40 (t, J = 73.0 Hz, 1H), 7.29 (s, 1H), 6.92-6.96 (m, 2H), 4.98-5.07 (m, 1H), 3.76 (s, 3H), 1.18 (d, J = 7.4 Hz, 3H). LC-MS (method 2) Rt = 1.17 min MS (ESIpos): m/z = 497.3 $[M+H]^+$ 63 % yield

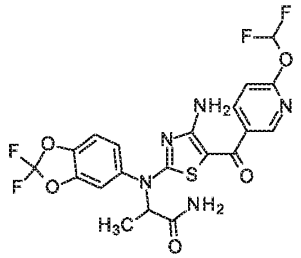
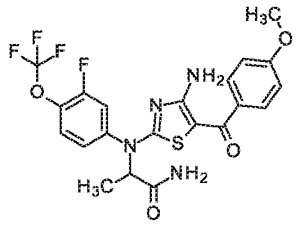
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
201	 rac-2-[N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-3-chloro-4-(difluoromethoxy)anilino]propanamide	Intermediate 143; rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 7.93-8.54 (m, 2H), 7.91 (d, J = 2.5 Hz, 1H), 7.61-7.68 (m, 2H), 7.55-7.61 (m, 2H), 7.08-7.53 (m, 6H), 4.98-5.08 (m, 1H), 1.18 (d, J = 7.4 Hz, 3H). LC-MS (method 2) Rt = 1.21 min MS (ESIpos): m/z = 533.3 [M+H]$^+$ 58 % yield
202	 rac-2-[N-[4-amino-5-(4-chlorobenzoyl)thiazol-2-yl]-3-chloro-4-(difluoromethoxy)anilino]propanamide	Intermediate 144; rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 7.92-8.51 (m, 2H), 7.90 (d, J = 2.5 Hz, 1H), 7.60-7.68 (m, 2H), 7.50-7.55 (m, 2H), 7.45-7.50 (m, 3H), 7.39 (t, J = 73.0 Hz, 1H), 7.30 (s, 1H), 4.98-5.08 (m, 1H), 1.18 (d, J = 7.4 Hz, 3H). LC-MS (method 2) Rt = 1.28 min MS (ESIpos): m/z = 501.3 [M+H]$^+$ 56 % yield
203	 rac-2-[N-[4-amino-5-(pyridine-4-carbonyl)thiazol-2-yl]-3-chloro-4-(difluoromethoxy)anilino]propanamide	Intermediate 145; rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 8.61-8.66 (m, 2H), 8.06-8.54 (m, 2H), 7.90 (d, J = 2.5 Hz, 1H), 7.61-7.67 (m, 2H), 7.48 (d, J = 8.6 Hz, 1H), 7.40-7.45 (m, 2H), 7.39 (t, J = 72.7 Hz, 1H), 7.31 (s, 1H), 4.98-5.07 (m, 1H), 1.18 (d, J = 7.4 Hz, 3H). LC-MS (method 2) Rt = 0.98 min MS (ESIpos): m/z = 468.3 [M+H]$^+$ 47 % yield

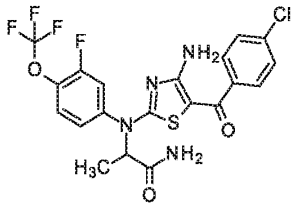
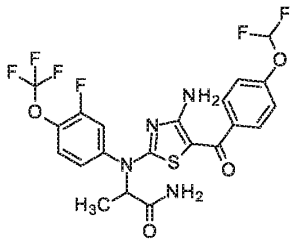
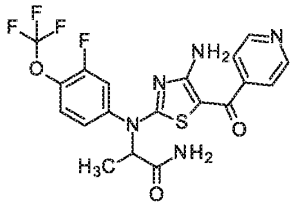
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
204	 rac-2-[N-[4-amino-5-[6-(difluoromethoxy)pyridine-3-carbonyl]thiazol-2-yl]-3-chloro-4-(difluoromethoxy)anilino]propanamide	Intermediate 146; rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 8.41 (d, J = 1.8 Hz, 1H), 8.05-8.38 (m, 2H), 8.02 (dd, J = 8.6, 2.5 Hz, 1H), 7.91 (d, J = 2.5 Hz, 1H), 7.72 (t, J = 72.5 Hz, 1H), 7.61-7.68 (m, 2H), 7.47-7.52 (m, 1H), 7.40 (t, J = 72.8 Hz, 1H), 7.31 (s, 1H), 7.10-7.15 (m, 1H), 4.98-5.08 (m, 1H), 1.19 (d, J = 7.4 Hz, 3H). LC-MS (method 2) Rt = 1.21 min MS (ESIpos): m/z = 534.3 $[M+H]^+$ 42 % yield
205	 rac-2-[N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-(difluoromethoxy)-3-fluoro-anilino]propanamide	Intermediate 147; rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 7.77-8.42 (m, 2H), 7.74 (dd, J = 11.4, 1.3 Hz, 1H), 7.62 (s, 1H), 7.47-7.53 (m, 4H), 7.35 (t, J = 73.0 Hz, 1H), 6.91-6.97 (m, 2H), 4.99-5.08 (m, 1H), 3.76 (s, 3H), 1.19 (d, J = 7.4 Hz, 3H). LC-MS (method 2) Rt = 1.13 min MS (ESIpos): m/z = 481.3 $[M+H]^+$ 57 % yield
206	 rac-2-[N-[4-amino-5-(4-chlorobenzoyl)thiazol-2-yl]-4-(difluoromethoxy)-3-fluoro-anilino]propanamide	Intermediate 148; rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 7.80-8.55 (m, 2H), 7.73 (dd, J = 11.3, 1.4 Hz, 1H), 7.62 (s, 1H), 7.46-7.55 (m, 6H), 7.35 (t, J = 72.8 Hz, 1H), 7.30 (s, 1H), 4.99-5.08 (m, 1H), 1.19 (d, J = 7.4 Hz, 3H). LC-MS (method 2) Rt = 1.24 min MS (ESIpos): m/z = 485.3 $[M+H]^+$ 53 % yield

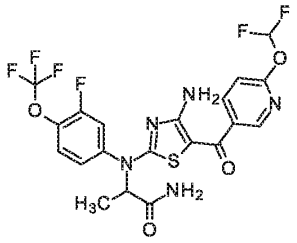
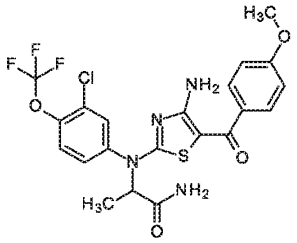
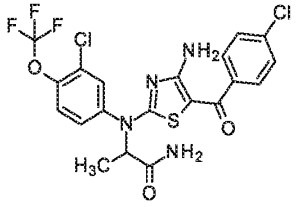
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
207	 rac-2-[N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-(difluoromethoxy)-3-fluoro-anilino]propanamide	Intermediate 149; rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 7.78-8.47 (m, 2H), 7.73 (dd, J = 11.2, 1.3 Hz, 1H), 7.62 (s, 1H), 7.55-7.60 (m, 2H), 7.34-7.54 (m, 3H), 7.09-7.32 (m, 4H), 4.98-5.08 (m, 1H), 1.19 (d, J = 7.4 Hz, 3H). LC-MS (method 2) Rt = 1.18 min MS (ESIpos): m/z = 517.3 $[M+H]^+$ 50 % yield
208	 rac-2-[N-[4-amino-5-(pyridine-4-carbonyl)thiazol-2-yl]-4-(difluoromethoxy)-3-fluoro-anilino]propanamide	Intermediate 150; rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 8.61-8.65 (m, 2H), 8.30 (br s, 2H), 7.73 (dd, J = 11.0, 1.4 Hz, 1H), 7.63 (s, 1H), 7.48-7.52 (m, 2H), 7.39-7.45 (m, 2H), 7.35 (t, J = 73.0 Hz, 1H), 7.31 (s, 1H), 4.98-5.08 (m, 1H), 1.19 (d, J = 7.4 Hz, 3H). LC-MS (method 2) Rt = 0.94 min MS (ESIpos): m/z = 452.3 $[M+H]^+$ 48 % yield
209	 rac-2-[N-[4-amino-5-[6-(difluoromethoxy)pyridine-3-carbonyl]thiazol-2-yl]-4-(difluoromethoxy)-3-fluoro-anilino]propanamide	Intermediate 151; rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 8.41 (d, J = 2.0 Hz, 1H), 8.02 (dd, J = 8.5, 2.4 Hz, 3H), 7.74 (dd, J = 11.4, 1.3 Hz, 1H), 7.72 (t, J = 72.5 Hz, 1H), 7.63 (s, 1H), 7.49-7.53 (m, 2H), 7.36 (t, J = 73.0 Hz, 1H), 7.31 (s, 1H), 7.10-7.15 (m, 1H), 4.99-5.09 (m, 1H), 1.19 (d, J = 7.4 Hz, 3H). LC-MS (method 2) Rt = 1.18 min MS (ESIpos): m/z = 518.3 $[M+H]^+$ 51 % yield

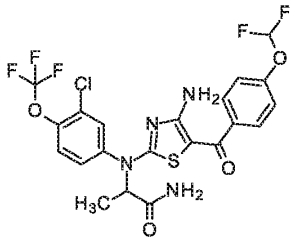
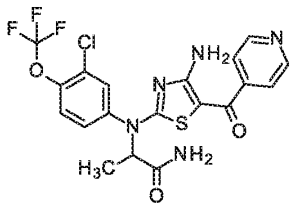
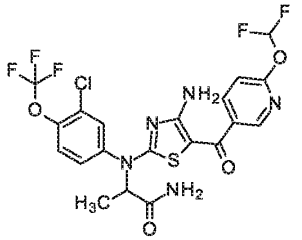
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
210	 rac-2-[N-[4-amino-5-[6-(difluoromethoxy)pyridine-3-carbonyl]thiazol-2-yl]-4-(difluoromethoxy)-3-fluoro-anilino]propanamide	Intermediate 152; rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 8.41 (d, J = 2.0 Hz, 1H), 8.02 (dd, J = 8.5, 2.4 Hz, 3H), 7.74 (dd, J = 11.4, 1.3 Hz, 1H), 7.72 (t, J = 72.5 Hz, 1H), 7.63 (s, 1H), 7.49-7.53 (m, 2H), 7.36 (t, J = 73.0 Hz, 1H), 7.31 (s, 1H), 7.10-7.15 (m, 1H), 4.99-5.09 (m, 1H), 1.19 (d, J = 7.4 Hz, 3H). LC-MS (method 2) Rt = 1.18 min MS (ESIpos): m/z = 518.3 $[M+H]^+$ 51 % yield
211	 rac-2-[N-(4-amino-5-benzoyl-thiazol-2-yl)-3-chloro-4-(trifluoromethoxy)anilino]propanamide	Intermediate 153; rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 8.01 (dd, J = 1.9, 0.9 Hz, 3H), 7.74 (d, J = 1.8 Hz, 2H), 7.66 (s, 1H), 7.49-7.55 (m, 2H), 7.37-7.47 (m, 3H), 7.32 (s, 1H), 4.95-5.05 (m, 1H), 1.19 (d, J = 7.4 Hz, 3H). LC-MS (method 2) Rt = 1.29 min MS (ESIpos): m/z = 485.3 $[M+H]^+$ 48 % yield
212	 rac-2-[[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-(2,2-difluoro-1,3-benzodioxol-5-yl)amino]propanamide	Intermediate 154; rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 7.80-8.36 (m, 2H), 7.72 (d, J = 1.8 Hz, 1H), 7.61 (s, 1H), 7.46-7.57 (m, 4H), 7.28 (s, 1H), 6.90-6.97 (m, 2H), 5.03 (br d, J = 7.6 Hz, 1H), 3.76 (s, 3H), 1.18 (d, J = 7.4 Hz, 3H). LC-MS (method 2) Rt = 1.19 min MS (ESIpos): m/z = 476.3 $[M+H]^+$ 67 % yield

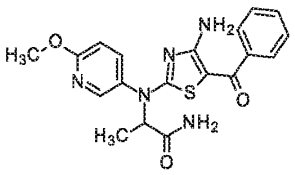
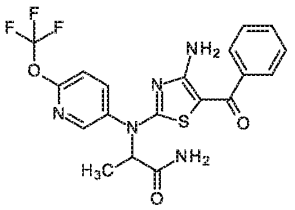
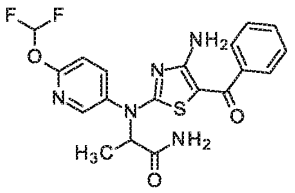
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
213	 rac-2-[[4-amino-5-(4-chlorobenzoyl)thiazol-2-yl]-(2,2-difluoro-1,3-benzodioxol-5-yl)amino]propanamide	Intermediate 155; rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 8.19 (br s, 2H), 7.71 (d, J = 2.0 Hz, 1H), 7.61 (s, 1H), 7.44-7.56 (m, 6H), 7.29 (s, 1H), 4.98-5.09 (m, 1H), 1.18 (d, J = 7.4 Hz, 3H). LC-MS (method 2) Rt = 1.31 min MS (ESIpos): m/z = 481.2 [M+H]$^+$ 59 % yield
214	 rac-2-[[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-(2,2-difluoro-1,3-benzodioxol-5-yl)amino]propanamide	Intermediate 156; rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 7.80-8.54 (m, 2H), 7.72 (d, J = 1.8 Hz, 1H), 7.61 (s, 1H), 7.53-7.60 (m, 3H), 7.47-7.52 (m, 1H), 7.30 (br s, 1H), 7.28 (t, J = 73.8 Hz, 1H), 7.18 (d, J = 8.6 Hz, 2H), 5.04 (br d, J = 6.3 Hz, 1H), 1.18 (d, J = 7.4 Hz, 3H). LC-MS (method 2) Rt = 1.23 min MS (ESIpos): m/z = 513.3 [M+H]$^+$ 37 % yield
215	 rac-2-[[4-amino-5-(pyridine-4-carbonyl)thiazol-2-yl]-(2,2-difluoro-1,3-benzodioxol-5-yl)amino]propanamide	Intermediate 157; rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 8.60-8.65 (m, 2H), 8.07-8.53 (m, 2H), 7.71 (d, J = 2.0 Hz, 1H), 7.63 (s, 1H), 7.52-7.58 (m, 1H), 7.46-7.51 (m, 1H), 7.39-7.45 (m, 2H), 7.30 (s, 1H), 4.95-5.13 (m, 1H), 1.18 (d, J = 7.4 Hz, 3H). LC-MS (method 2) Rt = 0.99 min MS (ESIpos): m/z = 448.3 [M+H]$^+$ 64 % yield

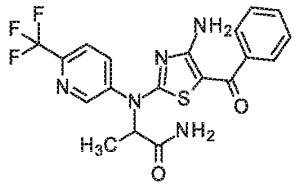
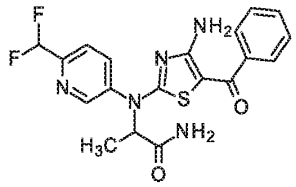
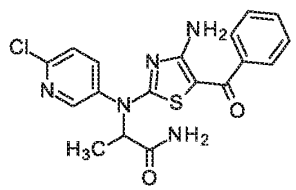
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
216	 rac-2-[[4-amino-5-[6-(difluoromethoxy)pyridine-3-carbonyl]thiazol-2-yl]-(2,2-difluoro-1,3-benzodioxol-5-yl)amino]propanamide	Intermediate 158; rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 8.41 (d, J = 2.3 Hz, 3H), 8.02 (dd, J = 8.5, 2.4 Hz, 1H), 7.72 (d, J = 2.0 Hz, 1H), 7.71 (t, J = 72.5 Hz, 1H), 7.62 (s, 1H), 7.54-7.58 (m, 1H), 7.51 (d, J = 1.8 Hz, 1H), 7.30 (s, 1H), 7.11 (d, J = 8.4 Hz, 1H), 4.96-5.12 (m, 1H), 1.19 (d, J = 7.4 Hz, 3H). LC-MS (method 2) Rt = 1.23 min MS (ESIpos): m/z = 514.3 $[M+H]^+$ 59 % yield
217	 rac-2-[N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-3-fluoro-4-(trifluoromethoxy)anilino]propanamide	Intermediate 159; rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 7.88-8.42 (m, 2H), 7.85 (dd, J = 11.2, 2.5 Hz, 1H), 7.75 (td, J = 8.7, 1.0 Hz, 1H), 7.64 (s, 1H), 7.58-7.63 (m, 1H), 7.48-7.55 (m, 2H), 7.32 (s, 1H), 6.91-6.97 (m, 2H), 5.01 (q, J = 7.4 Hz, 1H), 3.77 (s, 3H), 1.20 (d, J = 7.4 Hz, 3H). LC-MS (method 2) Rt = 1.23 min MS (ESIpos): m/z = 499.3 $[M+H]^+$ 55 % yield

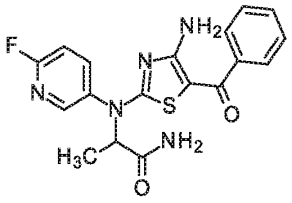
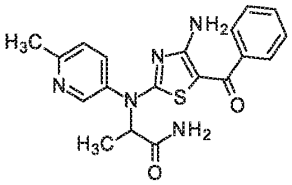
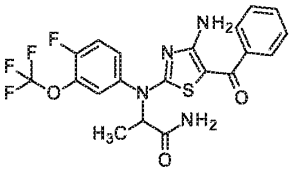
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
218	 rac-2-[N-[4-amino-5-(4-chlorobenzoyl)thiazol-2-yl]-3-fluoro-4-(trifluoromethoxy)anilino]propanamide	Intermediate 160; rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 7.90-8.49 (m, 2H), 7.85 (dd, J = 11.2, 2.3 Hz, 1H), 7.75 (td, J = 8.7, 1.0 Hz, 1H), 7.65 (s, 1H), 7.58-7.62 (m, 1H), 7.51-7.56 (m, 2H), 7.45-7.50 (m, 2H), 7.32 (s, 1H), 4.97-5.06 (m, 1H), 1.20 (d, J = 7.4 Hz, 3H). LC-MS (method 2) Rt = 1.34 min MS (ESIpos): m/z = 503.3 $[M+H]^+$ 46 % yield
219	 rac-2-[N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-3-fluoro-4-(trifluoromethoxy)anilino]propanamide	Intermediate 161; rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 7.89-8.50 (m, 2H), 7.85 (dd, J = 11.2, 2.3 Hz, 1H), 7.70-7.80 (m, 1H), 7.65 (s, 1H), 7.57-7.63 (m, 3H), 7.32 (s, 1H), 7.29 (t, J = 73.8 Hz, 1H), 7.19 (d, J = 8.6 Hz, 2H), 5.02 (q, J = 7.4 Hz, 1H), 1.20 (d, J = 7.4 Hz, 3H). LC-MS (method 2) Rt = 1.26 min MS (ESIpos): m/z = 525.3 $[M+H]^+$ 40 % yield
220	 rac-2-[N-[4-amino-5-(pyridine-4-carbonyl)thiazol-2-yl]-3-fluoro-4-(trifluoromethoxy)anilino]propanamide	Intermediate 162; rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 8.61-8.66 (m, 2H), 8.05-8.54 (m, 2H), 7.85 (dd, J = 11.2, 2.3 Hz, 1H), 7.71-7.78 (m, 1H), 7.66 (s, 1H), 7.60 (dd, J = 8.7, 1.4 Hz, 1H), 7.41-7.46 (m, 2H), 7.33 (s, 1H), 4.97-5.06 (m, 1H), 1.20 (d, J = 7.4 Hz, 3H). LC-MS (method 2) Rt = 1.04 min MS (ESIpos): m/z = 470.3 $[M+H]^+$ 40 % yield

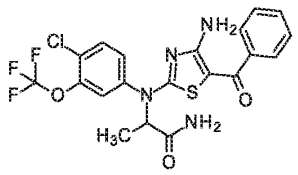
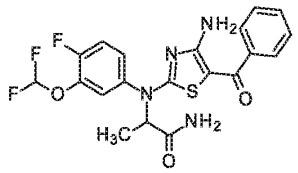
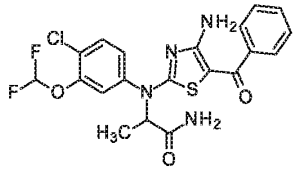
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
221	 rac-2-[N-[4-amino-5-[6-(difluoromethoxy)pyridine-3-carbonyl]thiazol-2-yl]-3-fluoro-4-(trifluoromethoxy)anilino]propanamide	Intermediate 163; rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 8.42 (d, J = 2.0 Hz, 1H), 8.23 (br s, 2H), 8.03 (dd, J = 8.5, 2.4 Hz, 1H), 7.86 (dd, J = 11.2, 2.3 Hz, 1H), 7.73-7.79 (m, 1H), 7.72 (t, J = 72.5 Hz, 1H), 7.66 (s, 1H), 7.58-7.64 (m, 1H), 7.34 (s, 1H), 7.13 (dd, J = 8.6, 0.8 Hz, 1H), 4.97-5.06 (m, 1H), 1.20 (d, J = 7.4 Hz, 3H). LC-MS (method 2) Rt = 1.29 min MS (ESIpos): m/z = 536.3 $[M+H]^+$ 51 % yield
222	 rac-2-[N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-3-chloro-4-(trifluoromethoxy)anilino]propanamide	Intermediate 164; rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 7.78-8.36 (m, 2H), 7.74 (s, 2H), 7.66 (s, 1H), 7.49-7.55 (m, 2H), 7.32 (s, 1H), 6.91-6.98 (m, 2H), 5.00 (q, J = 7.0 Hz, 1H), 3.77 (s, 3H), 1.19 (d, J = 7.4 Hz, 3H). LC-MS (method 2) Rt = 1.29 min MS (ESIpos): m/z = 515.3 $[M+H]^+$ 46 % yield
223	 rac-2-[N-[4-amino-5-(4-chlorobenzoyl)thiazol-2-yl]-3-chloro-4-(trifluoromethoxy)anilino]propanamide	Intermediate 165; rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 8.03-8.45 (m, 2H), 8.01 (t, J = 1.4 Hz, 1H), 7.74 (s, 2H), 7.66 (s, 1H), 7.51-7.57 (m, 2H), 7.45-7.50 (m, 2H), 7.33 (s, 1H), 4.96-5.05 (m, 1H), 1.19 (d, J = 7.4 Hz, 3H). LC-MS (method 2) Rt = 1.4 min MS (ESIpos): m/z = 519.2 $[M+H]^+$ 40 % yield

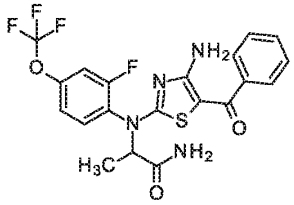
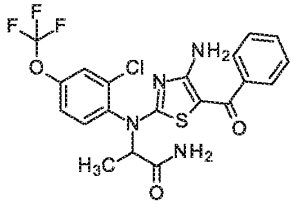
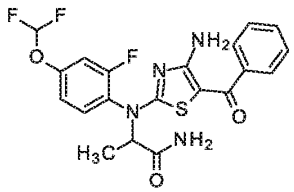
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
224	 rac-2-[N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-3-chloro-4-(trifluoromethoxy)anilino]propanamide	Intermediate 166; rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 8.04-8.37 (m, 2H), 8.01 (t, J = 1.3 Hz, 1H), 7.74 (s, 2H), 7.66 (s, 1H), 7.57-7.62 (m, 2H), 7.33 (s, 1H), 7.29 (t, J = 73.8 Hz, 1H), 7.19 (d, J = 8.6 Hz, 2H), 5.00 (q, J = 7.0 Hz, 1H), 1.19 (d, J = 7.6 Hz, 3H). LC-MS (method 2) Rt = 1.32 min MS (ESIpos): m/z = 551,3 $[M+H]^+$ 42 % yield
225	 rac-2-[N-[4-amino-5-(pyridine-4-carbonyl)thiazol-2-yl]-3-chloro-4-(trifluoromethoxy)anilino]propanamide	Intermediate 167; rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 8.62-8.66 (m, 2H), 8.03-8.60 (m, 2H), 8.01 (t, J = 1.4 Hz, 1H), 7.74 (s, 2H), 7.67 (s, 1H), 7.41-7.46 (m, 2H), 7.34 (s, 1H), 4.95-5.04 (m, 1H), 1.19 (d, J = 7.4 Hz, 3H). LC-MS (method 2) Rt = 1.09 min MS (ESIpos): m/z = 486.2 $[M+H]^+$ 42 % yield
226	 rac-2-[N-[4-amino-5-[6-(difluoromethoxy)pyridine-3-carbonyl]thiazol-2-yl]-3-chloro-4-(trifluoromethoxy)anilino]propanamide	Intermediate 168; rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 8.42 (d, J = 1.8 Hz, 1H), 8.07-8.40 (m, 2H), 8.01-8.06 (m, 2H), 7.75 (s, 2H), 7.72 (t, J = 72.2 Hz, 1H), 7.67 (s, 1H), 7.34 (s, 1H), 7.13 (d, J = 9.1 Hz, 1H), 4.96-5.05 (m, 1H), 1.20 (d, J = 7.6 Hz, 3H). LC-MS (method 2) Rt = 1.33 min MS (ESIpos): m/z = 552.2 $[M+H]^+$ 34 % yield

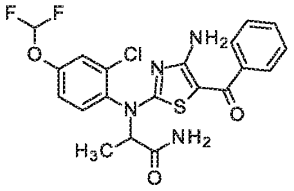
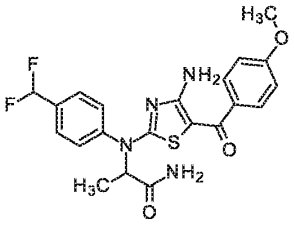
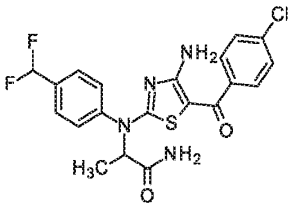
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
227	 rac-2-[(4-amino-5-benzoyl-thiazol-2-yl)-(6-methoxy-3-pyridyl)amino]propanamide	Intermediate 169; rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 8.32 (d, J = 2.5 Hz, 1H), 7.93 (dd, J = 8.9, 2.8 Hz, 3H), 7.61 (s, 1H), 7.47-7.52 (m, 2H), 7.35-7.44 (m, 3H), 7.26 (s, 1H), 6.93 (d, J = 8.9 Hz, 1H), 4.98-5.16 (m, 1H), 3.87 (s, 3H), 1.17 (d, J = 7.4 Hz, 3H). LC-MS (method 2) Rt = 1.01 min MS (ESIpos): m/z = 398.3 [M+H]$^+$ 75 % yield
228	 rac-2-[(4-amino-5-benzoyl-thiazol-2-yl)-[6-(trifluoromethoxy)-3-pyridyl]amino]propanamide	Intermediate 170; rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 8.56 (d, J = 2.5 Hz, 1H), 8.30 (dd, J = 8.7, 2.7 Hz, 1H), 8.15 (br s, 2H), 7.68 (s, 1H), 7.52 (dd, J = 7.6, 1.5 Hz, 2H), 7.37-7.48 (m, 4H), 7.33 (s, 1H), 4.97-5.07 (m, 1H), 1.19 (d, J = 7.4 Hz, 3H). LC-MS (method 2) Rt = 1.16 min MS (ESIpos): m/z = 452.3 [M+H]$^+$ 50 % yield
229	 rac-2-[(4-amino-5-benzoyl-thiazol-2-yl)-[6-(difluoromethoxy)-3-pyridyl]amino]propanamide	Intermediate 171; rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 8.46 (d, J = 2.3 Hz, 1H), 8.18 (dd, J = 8.7, 2.7 Hz, 3H), 7.74 (t, J = 72.2 Hz, 1H), 7.66 (s, 1H), 7.47-7.53 (m, 2H), 7.36-7.46 (m, 3H), 7.31 (s, 1H), 7.23 (d, J = 8.6 Hz, 1H), 5.04 (br d, J = 5.6 Hz, 1H), 1.18 (d, J = 7.4 Hz, 3H). LC-MS (method 2) Rt = 1.1 min MS (ESIpos): m/z = 434.3 [M+H]$^+$ 68 % yield

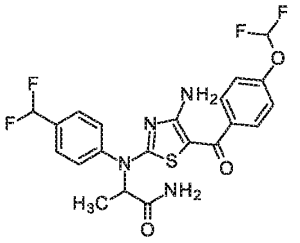
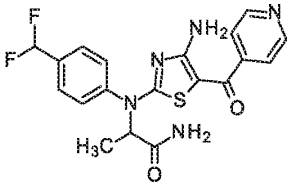
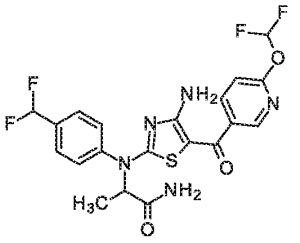
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
230	 rac-2-[(4-amino-5-benzoyl-thiazol-2-yl)-[6-(trifluoromethyl)-3-pyridyl]amino]propanamide	Intermediate 172; rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 8.95 (s, 1H), 8.35-8.40 (m, 1H), 8.09 (br d, J = 8.4 Hz, 3H), 7.72 (s, 1H), 7.50-7.56 (m, 2H), 7.34-7.47 (m, 4H), 4.97-5.04 (m, 1H), 1.21 (br d, J = 7.1 Hz, 3H). LC-MS (method 2) Rt = 1.1 min MS (ESIpos): m/z = 436.3 [M+H]$^+$ 20 % yield
231	 rac-2-[(4-amino-5-benzoyl-thiazol-2-yl)-[6-(difluoromethyl)-3-pyridyl]amino]propanamide	Intermediate 173; rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 8.86 (d, J = 2.3 Hz, 1H), 7.89-8.50 (m, 3H), 7.86 (d, J = 8.4 Hz, 1H), 7.70 (s, 1H), 7.49-7.54 (m, 2H), 7.37-7.46 (m, 3H), 7.34 (s, 1H), 7.03 (t, J = 54.7 Hz, 1H), 5.03 (q, J = 7.4 Hz, 1H), 1.19 (d, J = 7.4 Hz, 3H). LC-MS (method 2) Rt = 1.0 min MS (ESIpos): m/z = 418.3 [M+H]$^+$ 39 % yield
232	 rac-2-[(4-amino-5-benzoyl-thiazol-2-yl)-(6-chloro-3-pyridyl)amino]propanamide	Intermediate 174; rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 8.61 (d, J = 2.8 Hz, 1H), 8.14 (dd, J = 8.4, 2.8 Hz, 3H), 7.69 (d, J = 8.6 Hz, 2H), 7.48-7.55 (m, 2H), 7.37-7.46 (m, 3H), 7.33 (br s, 1H), 4.96-5.07 (m, 1H), 1.19 (d, J = 7.4 Hz, 3H). LC-MS (method 2) Rt = 1.03 min MS (ESIpos): m/z = 402.2 [M+H]$^+$ 49 % yield

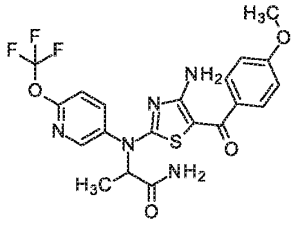
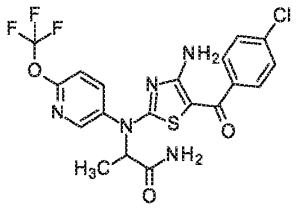
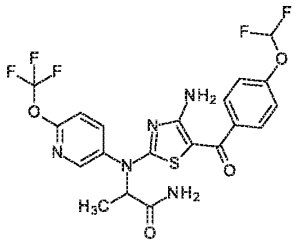
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
233	 rac-2-[(4-amino-5-benzoyl-thiazol-2-yl)-(6-fluoro-3-pyridyl)amino]propanamide	Intermediate 175; rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 8.46 (d, J = 2.3 Hz, 1H), 7.72-8.42 (m, 3H), 7.67 (s, 1H), 7.48-7.54 (m, 2H), 7.33-7.47 (m, 4H), 7.32 (s, 1H), 4.97-5.10 (m, 1H), 1.19 (d, J = 7.6 Hz, 3H). LC-MS (method 2) Rt = 0.97 min MS (ESIpos): m/z = 386.3 [M+H]$^+$ 65 % yield
234	 rac-2-[(4-amino-5-benzoyl-thiazol-2-yl)-(6-methyl-3-pyridyl)amino]propanamide	Intermediate 176; rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 8.58 (d, J = 2.3 Hz, 1H), 7.90 (dd, J = 8.1, 2.5 Hz, 3H), 7.62 (s, 1H), 7.46-7.52 (m, 2H), 7.35-7.44 (m, 4H), 7.27 (s, 1H), 5.01-5.12 (m, 1H), 1.16 (d, J = 7.6 Hz, 3H). LC-MS (method 2) Rt = 0.91 min MS (ESIpos): m/z = 382.3 [M+H]$^+$ 69 % yield
235	 rac-2-[N-(4-amino-5-benzoyl-thiazol-2-yl)-4-fluoro-3-(trifluoromethoxy)anilino]propanamide	Intermediate 177; rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 7.78-8.47 (m, 3H), 7.73 (td, J = 4.3, 2.5 Hz, 1H), 7.62-7.70 (m, 2H), 7.47-7.54 (m, 2H), 7.35-7.46 (m, 3H), 7.30 (s, 1H), 5.02 (br d, J = 6.8 Hz, 1H), 1.17 (d, J = 7.4 Hz, 3H). LC-MS (method 2) Rt = 1.26 min MS (ESIpos): m/z = 469.3 [M+H]$^+$ 52 % yield

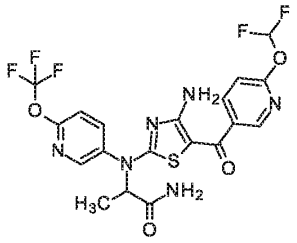
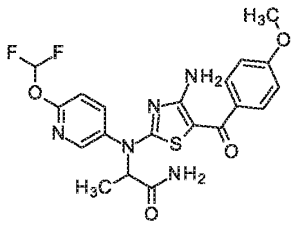
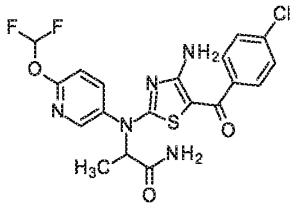
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
236	 rac-2-[N-(4-amino-5-benzoyl-thiazol-2-yl)-4-chloro-3-(trifluoromethoxy)anilino]propanamide	Intermediate 178; rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 7.97 (dd, J = 2.0, 1.3 Hz, 3H), 7.85 (d, J = 8.6 Hz, 1H), 7.65-7.73 (m, 2H), 7.48-7.55 (m, 2H), 7.36-7.47 (m, 3H), 7.32 (s, 1H), 5.03 (q, J = 7.4 Hz, 1H), 1.18 (d, J = 7.6 Hz, 3H). LC-MS (method 2) Rt = 1.33 min MS (ESIpos): m/z = 485.2 $[M+H]^+$ 44 % yield
237	 rac-2-[N-(4-amino-5-benzoyl-thiazol-2-yl)-3-(difluoromethoxy)-4-fluoro-anilino]propanamide	Intermediate 179; rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 7.77-8.54 (m, 2H), 7.72 (d, J = 7.6 Hz, 1H), 7.62 (s, 1H), 7.48-7.58 (m, 4H), 7.36-7.44 (m, 3H), 7.27 (s, 1H), 7.26 (t, J = 72.8 Hz, 1H), 4.97-5.08 (m, 1H), 1.18 (d, J = 7.4 Hz, 3H). LC-MS (method 2) Rt = 1.15 min MS (ESIpos): m/z = 451.3 $[M+H]^+$ 66 % yield
238	 rac-2-[N-(4-amino-5-benzoyl-thiazol-2-yl)-4-chloro-3-(difluoromethoxy)anilino]propanamide	Intermediate 180; rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 7.78-8.54 (m, 2H), 7.69-7.77 (m, 2H), 7.63 (s, 1H), 7.48-7.55 (m, 3H), 7.36-7.45 (m, 3H), 7.09-7.33 (m, 2H), 5.02 (q, J = 7.4 Hz, 1H), 1.19 (d, J = 7.6 Hz, 3H). LC-MS (method 2) Rt = 1.22 min MS (ESIpos): m/z = 467.3 $[M+H]^+$ 51 % yield

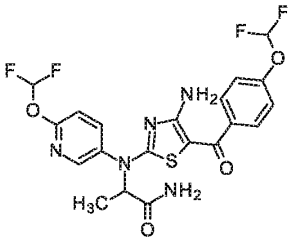
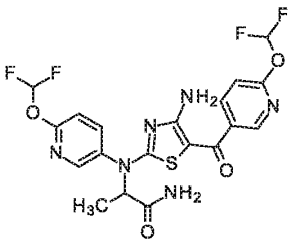
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
239	 rac-2-[N-(4-amino-5-benzoyl-thiazol-2-yl)-2-fluoro-4-(trifluoromethoxy)anilino]propanamide	Intermediate 181; rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 8.03-8.39 (m, 2H), 7.93-8.03 (m, 1H), 7.61-7.72 (m, 2H), 7.52 (br d, J = 4.3 Hz, 2H), 7.42 (br d, J = 7.1 Hz, 4H), 7.34 (br s, 1H), 4.65-5.38 (m, 1H), 1.09-1.27 (m, 3H). LC-MS (method 2) Rt = 1.19 min MS (ESIpos): m/z = 469.2 [M+H]$^+$ 50 % yield
240	 rac-2-[N-(4-amino-5-benzoyl-thiazol-2-yl)-2-chloro-4-(trifluoromethoxy)anilino]propanamide	Intermediate 182; rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 7.88-8.43 (m, 3H), 7.64-7.87 (m, 2H), 7.60 (br d, J = 8.4 Hz, 1H), 7.27-7.56 (m, 6H), 4.93-5.30 (m, 1H), 1.09 (d, J = 7.4 Hz, 3H). LC-MS (method 2) Rt = 1.24 min MS (ESIpos): m/z = 485.1 [M+H]$^+$ 41 % yield
241	 rac-2-[N-(4-amino-5-benzoyl-thiazol-2-yl)-4-(difluoromethoxy)-2-fluoro-anilino]propanamide	Intermediate 183; rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 7.94-8.49 (m, 2H), 7.88 (br s, 1H), 7.63 (br s, 1H), 7.50 (br s, 2H), 7.39-7.45 (m, 3H), 7.38 (t, J = 73.3 Hz, 1H), 7.35 (br d, J = 2.0 Hz, 1H), 7.31 (br s, 1H), 7.18 (br d, J = 8.9 Hz, 1H), 4.82-5.40 (m, 1H), 1.15 (br d, J = 1.3 Hz, 3H). LC-MS (method 2) Rt = 1.09 min MS (ESIpos): m/z = 451.2 [M+H]$^+$ 38 % yield

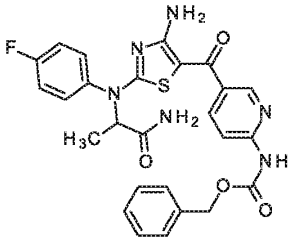
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
242	 rac-2-[N-(4-amino-5-benzoyl-thiazol-2-yl)-2-chloro-4-(difluoromethoxy)anilino]propanamide	Intermediate 184; rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 8.01 (d, J = 8.9 Hz, 3H), 7.60-7.72 (m, 1H), 7.20-7.59 (m, 9H), 4.97-5.21 (m, 1H), 1.09 (d, J = 7.4 Hz, 3H). LC-MS (method 2) Rt = 1.13 min MS (ESIpos): m/z = 467.1 $[M+H]^+$ 44 % yield
243	 rac-2-[N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-(difluoromethyl)anilino]propanamide	Intermediate 185; rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 7.77-8.41 (m, 2H), 7.67-7.76 (m, 4H), 7.60 (s, 1H), 7.45-7.52 (m, 2H), 7.27 (s, 1H), 7.10 (t, J = 55.8 Hz, 1H), 6.90-6.95 (m, 2H), 5.08 (q, J = 7.3 Hz, 1H), 3.75 (s, 3H), 1.17 (d, J = 7.4 Hz, 3H). LC-MS (method 2) Rt = 1.05 min MS (ESIpos): m/z = 447.2 $[M+H]^+$ 54 % yield
244	 rac-2-[N-[4-amino-5-(4-chlorobenzoyl)thiazol-2-yl]-4-(difluoromethyl)anilino]propanamide	Intermediate 186; rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 7.81-8.54 (m, 2H), 7.67-7.75 (m, 4H), 7.60 (s, 1H), 7.48-7.53 (m, 2H), 7.43-7.48 (m, 2H), 7.28 (s, 1H), 7.09 (t, J = 55.5 Hz, 1H), 5.08 (q, J = 7.3 Hz, 1H), 1.17 (d, J = 7.4 Hz, 3H). LC-MS (method 2) Rt = 1.15 min MS (ESIpos): m/z = 451.1 $[M+H]^+$ 48 % yield

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
245	 rac-2-[N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-(difluoromethyl)anilino]propanamide	Intermediate 187; rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 7.76-8.57 (m, 2H), 7.67-7.76 (m, 4H), 7.61 (s, 1H), 7.52-7.59 (m, 2H), 7.14-7.20 (m, 2H), 6.93-7.48 (m, 3H), 5.08 (q, J = 7.5 Hz, 1H), 1.17 (d, J = 7.4 Hz, 3H). LC-MS (method 2) Rt = 1,09 min MS (ESIpos): m/z = 483.2 [M+H]$^+$ 45 % yield
246	 rac-2-[N-[4-amino-5-(pyridine-4-carbonyl)thiazol-2-yl]-4-(difluoromethyl)anilino]propanamide	Intermediate 188; rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 8.59-8.64 (m, 2H), 8.06-8.55 (m, 2H), 7.67-7.76 (m, 4H), 7.62 (s, 1H), 7.37-7.43 (m, 2H), 7.29 (s, 1H), 7.09 (t, J = 55.8 Hz, 1H), 5.02-5.13 (m, 1H), 1.17 (d, J = 7.4 Hz, 3H). LC-MS (method 2) Rt = 0.85 min MS (ESIpos): m/z = 418.2 [M+H]$^+$ 49 % yield
247	 rac-2-[N-[4-amino-5-[6-(difluoromethoxy)pyridine-3-carbonyl]thiazol-2-yl]-4-(difluoromethyl)anilino]propanamide	Intermediate 189; rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 8.03-8.53 (m, 3H), 8.00 (dd, J = 8.5, 2.4 Hz, 1H), 7.50-7.91 (m, 6H), 7.29 (s, 1H), 6.94-7.26 (m, 2H), 5.08 (q, J = 7.1 Hz, 1H), 1.18 (d, J = 7.6 Hz, 3H). LC-MS (method 2) Rt = 1.13 min MS (ESIpos): m/z = 484.5 [M+H]$^+$ 53 % yield

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
248	 rac-2-[[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-[6-(trifluoromethoxy)-3-pyridyl]amino]propanamide	Intermediate 190; rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 8.57 (d, J = 2.5 Hz, 1H), 8.31 (dd, J = 8.6, 2.5 Hz, 1H), 7.90-8.28 (m, 2H), 7.65-7.71 (m, 1H), 7.50-7.55 (m, 2H), 7.46 (d, J = 8.6 Hz, 1H), 7.33 (s, 1H), 6.92-6.97 (m, 2H), 5.03 (q, J = 6.8 Hz, 1H), 3.77 (s, 3H), 1.20 (d, J = 7.4 Hz, 3H). LC-MS (method 2) Rt = 1.14 min MS (ESIpos): m/z = 482.4 [M+H]$^+$ 47 % yield
249	 rac-2-[[4-amino-5-(4-chlorobenzoyl)thiazol-2-yl]-[6-(trifluoromethoxy)-3-pyridyl]amino]propanamide	Intermediate 191; rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 8.56 (d, J = 2.5 Hz, 1H), 8.30 (dd, J = 8.7, 2.7 Hz, 3H), 7.69 (s, 1H), 7.51-7.57 (m, 2H), 7.43-7.50 (m, 3H), 7.34 (s, 1H), 5.03 (br d, J = 7.1 Hz, 1H), 1.19 (d, J = 7.4 Hz, 3H). LC-MS (method 2) Rt = 1.24 min MS (ESIpos): m/z = 486.3 [M+H]$^+$ 23 % yield
250	 rac-2-[[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-[6-(trifluoromethoxy)-3-pyridyl]amino]propanamide	Intermediate 192; rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 8.57 (d, J = 2.5 Hz, 1H), 8.30 (dd, J = 8.7, 2.7 Hz, 1H), 8.11 (br s, 2H), 7.68 (s, 1H), 7.57-7.62 (m, 2H), 7.45 (d, J = 9.1 Hz, 1H), 7.34 (s, 1H), 7.29 (t, J = 73.8 Hz, 1H), 7.19 (d, J = 8.6 Hz, 2H), 5.03 (br d, J = 6.6 Hz, 1H), 1.20 (d, J = 7.4 Hz, 3H). LC-MS (method 2) Rt = 1.19 min MS (ESIpos): m/z = 518.3 [M+H]$^+$ 31 % yield

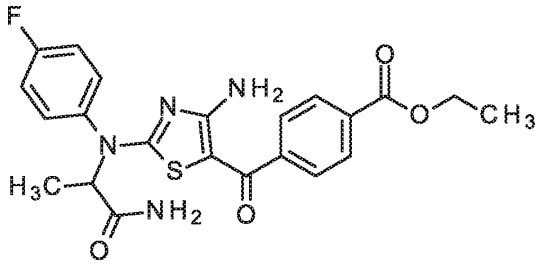
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
251	 rac-2-[[4-amino-5-[6-(difluoromethoxy)pyridine-3-carbonyl]thiazol-2-yl]-[6-(trifluoromethoxy)-3-pyridyl]amino]propanamide	Intermediate 293; rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 8.57 (d, J = 2.5 Hz, 1H), 8.43 (d, J = 2.3 Hz, 1H), 8.31 (dd, J = 8.7, 2.7 Hz, 3H), 8.04 (dd, J = 8.5, 2.4 Hz, 1H), 7.72 (t, J = 72.5 Hz, 1H), 7.70 (s, 1H), 7.46 (d, J = 9.1 Hz, 1H), 7.35 (s, 1H), 7.13 (d, J = 9.1 Hz, 1H), 5.03 (br d, J = 6.8 Hz, 1H), 1.20 (d, J = 7.4 Hz, 3H). LC-MS (method 2) Rt = 1.21 min MS (ESIpos): m/z = 519.4 [M+H]$^+$ 26 % yield
252	 rac-2-[[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-[6-(difluoromethoxy)-3-pyridyl]amino]propanamide	Intermediate 194; rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 8.47 (d, J = 2.5 Hz, 1H), 8.19 (dd, J = 8.6, 2.8 Hz, 3H), 7.75 (t, J = 72.2 Hz, 1H), 7.65 (s, 1H), 7.48-7.53 (m, 2H), 7.30 (s, 1H), 7.25 (d, J = 8.1 Hz, 1H), 6.92-6.96 (m, 2H), 5.05 (br d, J = 5.8 Hz, 1H), 3.76 (s, 3H), 1.19 (d, J = 7.4 Hz, 3H). LC-MS (method 2) Rt = 1.09 min MS (ESIpos): m/z = 464.3 [M+H]$^+$ 65 % yield
253	 rac-2-[[4-amino-5-(4-chlorobenzoyl)thiazol-2-yl]-[6-(difluoromethoxy)-3-pyridyl]amino]propanamide	Intermediate 195; rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 8.46 (d, J = 2.3 Hz, 1H), 8.18 (dd, J = 8.7, 2.7 Hz, 3H), 7.74 (t, J = 72.5 Hz, 1H), 7.66 (s, 1H), 7.50-7.55 (m, 2H), 7.44-7.49 (m, 2H), 7.31 (s, 1H), 7.22-7.27 (m, 1H), 5.05 (br s, 1H), 1.18 (d, J = 7.4 Hz, 3H). LC-MS (method 2) Rt = 1.19 min MS (ESIpos): m/z = 468.3 [M+H]$^+$ 51 % yield

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
254	 rac-2-[[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-[6-(difluoromethoxy)-3-pyridyl]amino]propanamide	Intermediate 196; rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 8.47 (d, J = 2.5 Hz, 1H), 8.19 (dd, J = 8.7, 2.7 Hz, 3H), 7.75 (t, J = 72.5 Hz, 1H), 7.66 (s, 1H), 7.56-7.61 (m, 2H), 7.31 (s, 1H), 7.29 (t, J = 73.8 Hz, 1H), 7.25 (d, J = 8.6 Hz, 1H), 7.18 (d, J = 8.6 Hz, 2H), 5.05 (br s, 1H), 1.19 (d, J = 7.4 Hz, 3H). LC-MS (method 2) Rt = 1.14 min MS (ESIpos): m/z = 500.4 $[M+H]^+$ 44 % yield
255	 rac-2-[[4-amino-5-[6-(difluoromethoxy)pyridine-3-carbonyl]thiazol-2-yl]-[6-(difluoromethoxy)-3-pyridyl]amino]propanamide	Intermediate 197; rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 8.47 (d, J = 2.5 Hz, 1H), 8.41 (d, J = 2.0 Hz, 1H), 8.19 (dd, J = 8.6, 2.5 Hz, 3H), 8.03 (dd, J = 8.6, 2.5 Hz, 1H), 7.75 (t, J = 72.5 Hz, 1H), 7.72 (t, J = 72.3 Hz, 1H), 7.67 (s, 1H), 7.32 (s, 1H), 7.25 (d, J = 9.1 Hz, 1H), 7.12 (d, J = 8.6 Hz, 1H), 5.06 (br s, 1H), 1.19 (d, J = 7.4 Hz, 3H). LC-MS (method 2) Rt = 1.13 min MS (ESIpos): m/z = 501.5 $[M+H]^+$ 56 % yield

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
256	 rac-benzyl N-[5-[4-amino-2-(N-(2-amino-1-methyl-2-oxo-ethyl)-4-fluoro-anilino)thiazole-5-carbonyl]-2-pyridyl]carbamate	Intermediate 217, rac-2-bromopropanamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.17 (d, *J*=7.35 Hz, 3 H), 5.05 (m, *J*=6.34 Hz, 1 H), 5.18 (s, 2 H), 7.26 (s, 1 H), 7.29 - 7.44 (m, 7 H), 7.59 (s, 1 H), 7.64 (dd, *J*=8.87, 5.07 Hz, 2 H), 7.80 - 7.85 (m, 1 H), 7.85 - 7.91 (m, 1 H), 7.94 - 8.36 (m, 2 H), 8.40 (d, *J*=1.77 Hz, 1 H), 10.49 (s, 1 H) RP-HPLC (method C) LC-MS (method 2) Rt = 1.16 min MS (ESIpos): m/z = 535.4 $[M+H]^+$ 7 % yield

Example 257

rac-Ethyl 4-[4-amino-2-(N-(2-amino-1-methyl-2-oxo-ethyl)-4-fluoro-anilino)thiazole-5-carbonyl]benzoate

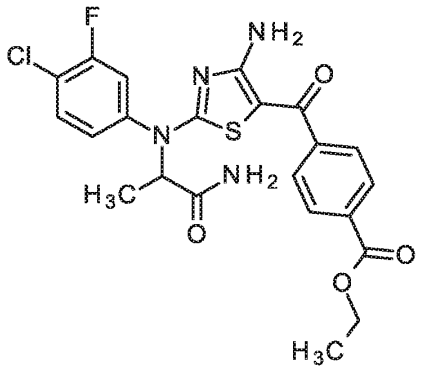


Ethyl 4-[4-amino-2-(4-fluoroanilino)thiazole-5-carbonyl]benzoate (14.2 g, 36.9 mmol, Intermediate 210) was suspended in DMF (300 mL) and treated with rac-2-bromo propionamide (7.9 g, 52 mmol) and potassium carbonate (9 g, 65 mmol). The reaction mixture was stirred at rt overnight and then treated with water. After 30 min the reaction mixture was extracted three times with ethyl acetate. The combined organic phases were washed with brine, filtered through a water repellent filter circle (MN 617 WA) and evaporated to dryness to give 15.47 g (33 mmol, 89 % yield) of the title compound.

LC-MS (method 2): Rt = 1.17 min; MS(ESIpos) m/z = 457.3 $[M+H]^+$

Example 258

rac-Ethyl 4-[4-amino-2-(N-(2-amino-1-methyl-2-oxo-ethyl)-4-chloro-3-fluoro-anilino)thiazole-5-carbonyl]benzoate



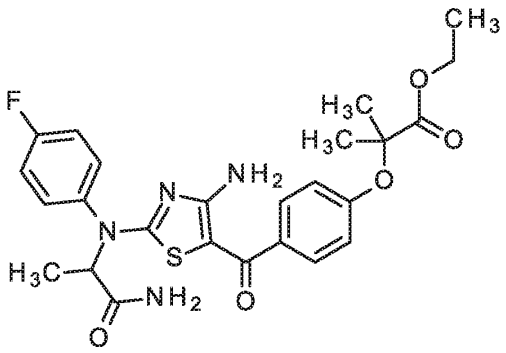
Ethyl 4-[4-amino-2-(4-chloro-3-fluoro-anilino)thiazole-5-carbonyl]benzoate (1.24 g, 2.52 mmol, Intermediate 212) was suspended in DMF (18 mL) and treated with rac-2-bromo propionamide (765.5 mg, 5.04 mmol) and potassium carbonate (522 mg, 3.78 mmol). The reaction mixture was stirred for 3 h and then treated with water. After 30 min the reaction mixture was extracted three times with ethyl acetate. The combined organic phases were washed with brine, filtered through a water repellent filter circle (MN 617 WA) and evaporated to dryness. The crude product was purified by Biotage (method X) to give 1.02 g (82 % yield) of the title compound.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.19 (m, *J*=8.0 Hz, 3 H), 1.31 (t, *J*=7.1 Hz, 3 H), 4.30 (q, *J*=7.10 Hz, 2 H), 5.02 (m, 1 H), 7.31 (s, 1 H), 7.51 (dt, *J*=8.49, 1.20 Hz, 1 H), 7.62 (m, 3 H), 7.74 (m, 2 H), 7.97 (m, 2 H), 8.28 (m, 2 H).

LC-MS (method 2): Rt = 1.20 min; MS(ESIpos) m/z = 491.2 $[M+H]^+$

Example 259

rac-Ethyl 2-[4-[4-amino-2-(N-(2-amino-1-methyl-2-oxo-ethyl)-4-fluoro-anilino)thiazole-5-carbonyl]phenoxy]-2-methyl-propanoate



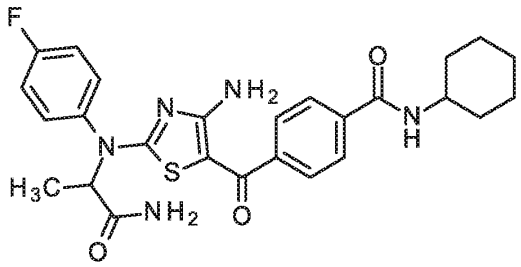
rac-Ethyl 2-[4-[4-amino-2-(4-fluoroanilino)thiazole-5-carbonyl]phenoxy]-2-methyl-propanoate (1.01 g, 2.28 mmol, Intermediate 214) was suspended in DMF (20 mL) and treated with rac-2-bromo propionamide (519 mg, 3.4 mmol) and potassium carbonate (1.57 g, 11.4 mmol). The reaction mixture was stirred overnight at rt and then treated with water. After 30 min the reaction mixture was extracted three times with ethyl acetate. The combined organic phases were washed with brine, filtered through a water repellent filter circle (MN 617 WA) and evaporated to dryness. The crude product was purified by Biotage (method X) to give 926 mg (1.79 mmol, 78 % yield) of the title compound.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.07 (t, *J*=7.1 Hz, 3 H), 1.16 (d, *J*=7.35 Hz, 3 H), 1.53 (s, 6 H), 4.13 (q, *J*=7.1 Hz, 2 H), 5.06 (m, 1 H), 6.74 (m, 2 H), 7.24 (s, 1 H), 7.33 (t, *J*=8.74 Hz, 2 H), 7.44 (m, 2 H), 7.57 (s, 1 H), 7.63 (m, 2 H), 8.13 (m, 2 H).

LC-MS (method 2): Rt = 1.22 min; MS(ESIpos) m/z = 515.5 $[M+H]^+$

Example 260

rac-4-[4-amino-2-(N-(2-amino-1-methyl-2-oxo-ethyl)-4-fluoro-anilino)thiazole-5-carbonyl]-N-cyclohexyl-benzamide



4-[(4-amino-2-{[(2RS)-1-amino-1-oxopropan-2-yl](4-fluorophenyl)amino}-1,3-thiazol-5-yl)carbonyl]benzoic acid (Intermediate 211, 75 mg, 0.175 mmol) and cyclohexane amine (35 mg, 0.35 mmol) were solved in 1 mL DMF and treated with HATU (133 mg, 0.35 mmol), N,N-diisopropylethylamine (68 mg, 0.53 mmol) and DMAP (1 mg, 9 µM). The reaction mixture was stirred at rt overnight, filtrated and purified by RP-HPLC (method D) to yield 48 mg (0.09 mmol, 53%) of the title compound.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.06 - 1.14 (m, 1 H), 1.16 (d, *J*=7.35 Hz, 3 H), 1.20 - 1.36 (m, 4 H), 1.55 - 1.64 (m, 1 H), 1.68 - 1.76 (m, 2 H), 1.76 - 1.83 (m, 2 H), 3.66 - 3.79 (m, 1 H), 5.01 - 5.12 (m, 1 H), 7.25 (s, 1 H), 7.32 (t, *J*=8.74 Hz, 2 H), 7.52 (d, *J*=8.36 Hz, 2 H), 7.58 (s, 1 H), 7.64 (dd, *J*=8.87, 5.07 Hz, 2 H), 7.78 (d, *J*=8.36 Hz, 2 H), 7.98 – 8.12 (br s, 1H), 8.23 (d, *J*=7.86 Hz, 1 H), 8.20 – 8.50 (br s, 1H).

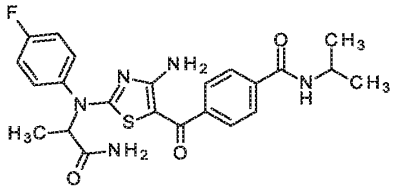
LC-MS (method 2): Rt = 1.15 min; MS(ESIpos) m/z = 510.4 $[M+H]^+$

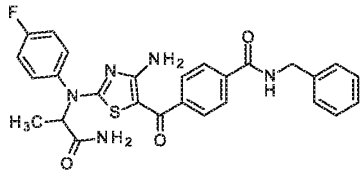
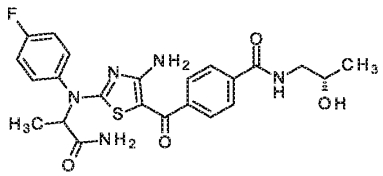
The following examples were prepared from the starting materials stated in Table 10, below, using the procedure as for Example 260.

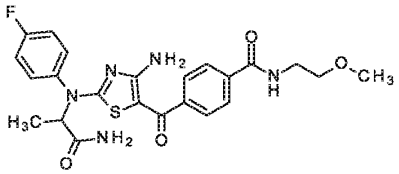
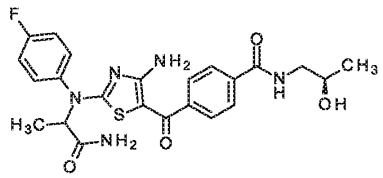
The crude product was either purified by RP-HPLC (methods A-D depending on polarity) or by preparative flash chromatography (methods X, Y or Z depending on polarity) after precipitation, extraction or filtration of the reaction mixture if necessary.

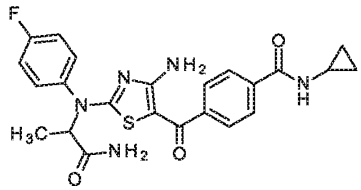
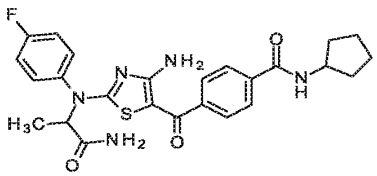
Enantiomers were separated from their racemate by chiral HPLC using the column and solvent conditions stated.

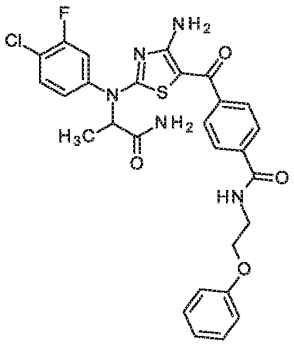
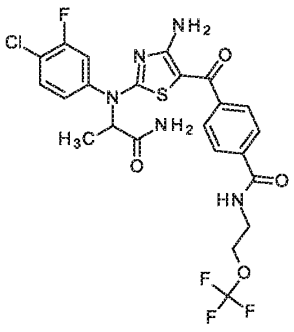
Table 10: Examples 261 – 273

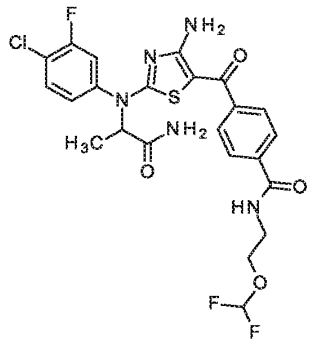
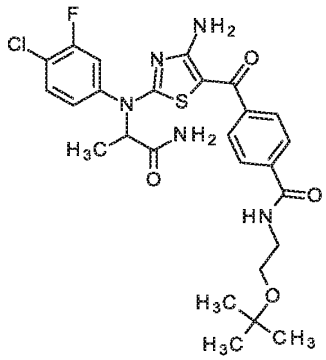
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
261	 rac-4-[4-amino-2-(N-(2-amino-1-methyl-2-oxo-ethyl)-4-fluoro-anilino)thiazole-5-carbonyl]-N-isopropyl-benzamide	Intermediate 211, propan-2-amine	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.11 - 1.19 (m, 9 H), 3.99 - 4.11 (m, 1 H), 5.00 - 5.13 (m, 1 H), 7.25 (s, 1 H), 7.32 (t, *J*=8.87 Hz, 2 H), 7.53 (d, *J*=8.62 Hz, 2 H), 7.58 (s, 1 H), 7.60 - 7.67 (m, 2 H), 7.79 (d, *J*=8.36 Hz, 2 H), 7.94 - 8.22 (m, 1 H), 8.24 (d, *J*=7.86 Hz, 1 H), 8.27 - 8.48 (m, 1 H) RP-HPLC (method C basic) LC-MS (method 2) Rt = 1.00 min MS (ESIpos): m/z = 470.7 $[M+H]^+$ 73 % yield

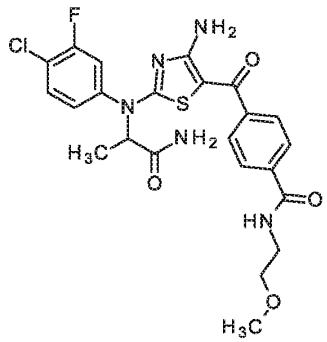
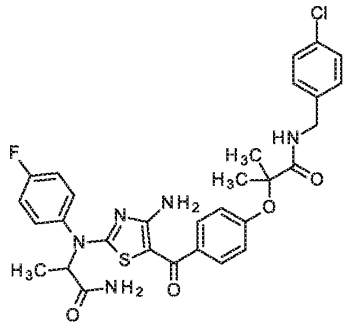
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
262	 rac-4-[4-amino-2-(N-(2-amino-1-methyl-2-oxo-ethyl)-4-fluoro-anilino)thiazole-5-carbonyl]-N-benzyl-benzamide	Intermediate 211, 1-phenylmethanamine	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.16 (d, *J*=7.35 Hz, 3 H), 4.46 (d, *J*=6.08 Hz, 2 H), 5.01 - 5.11 (m, 1 H), 7.21 - 7.28 (m, 2 H), 7.28 - 7.35 (m, 6 H), 7.53 - 7.57 (m, 2 H), 7.58 (s, 1 H), 7.60 - 7.66 (m, 2 H), 7.83 – 7.87 (m, 2 H), 8.09 (br s, 1 H), 8.38 (br s, 1 H), 9.07 (t, *J*=5.96 Hz, 1 H) RP-HPLC (method C basic) LC-MS (method 2) Rt = 1.10 min MS (ESIpos): m/z = 518.4 $[M+H]^+$ 59 % yield
263	 4-[4-amino-2-(N-(2-amino-1-methyl-2-oxo-ethyl)-4-fluoro-anilino)thiazole-5-carbonyl]-N-[(2S)-2-hydroxypropyl]benzamide (mixture of stereoisomers)	Intermediate 211, S-1-aminopropan-2-ol	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.04 (d, *J*=6.34 Hz, 3 H), 1.13 - 1.19 (m, 3 H), 3.17 (td, *J*=5.96, 1.52 Hz, 2 H), 3.70 - 3.81 (m, 1 H), 4.73 (d, *J*=4.82 Hz, 1 H), 5.01 - 5.13 (m, 1 H), 7.26 (s, 1 H), 7.32 (t, *J*=8.74 Hz, 2 H), 7.53 (d, *J*=8.36 Hz, 2 H), 7.58 (s, 1 H), 7.61 - 7.66 (m, 2 H), 7.81 (d, *J*=8.62 Hz, 2 H), 7.91 - 8.14 (m, 1 H), 8.17 - 8.38 (m, 1 H), 8.43 (t, *J*=5.83 Hz, 1 H) RP-HPLC (method C basic) LC-MS (method 2) Rt = 0.83 min MS (ESIpos): m/z = 486.6 $[M+H]^+$ 73 % yield

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
264	 rac-4-[4-amino-2-(N-(2-amino-1-methyl-2-oxo-ethyl)-4-fluoro-anilino)thiazole-5-carbonyl]-N-(2-methoxyethyl)benzamide	Intermediate 211, 2-methoxyethanamine	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.16 (d, *J*=7.35 Hz, 3 H), 3.25 (s, 3 H), 3.36 - 3.46 (m, 4 H), 5.00 - 5.12 (m, 1 H), 7.26 (s, 1 H), 7.29 - 7.36 (m, 2 H), 7.54 (d, *J*=8.36 Hz, 2 H), 7.58 (s, 1 H), 7.63 (dd, *J*=8.87, 5.07 Hz, 2 H), 7.80 (d, *J*=8.36 Hz, 2 H), 7.90 - 8.16 (m, 1 H), 8.17 - 8.47 (m, 1 H), 8.55 (t, *J*=5.20 Hz, 1 H) RP-HPLC (method C basic) LC-MS (method 2) Rt = 0.90 min MS (ESIpos): m/z = 486.6 $[M+H]^+$ 68 % yield
265	 4-[4-amino-2-(N-(2-amino-1-methyl-2-oxo-ethyl)-4-fluoro-anilino)thiazole-5-carbonyl]-N-[(2R)-2-hydroxypropyl]benzamide (mixture of stereoisomers)	Intermediate 211, R-1-aminopropan-2-ol	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.04 (d, *J*=6.08 Hz, 3 H), 1.16 (d, *J*=7.60 Hz, 3 H), 3.17 (td, *J*=6.02, 1.65 Hz, 2 H), 3.70 - 3.80 (m, 1 H), 4.73 (d, *J*=4.82 Hz, 1 H), 5.01 - 5.12 (m, 1 H), 7.25 (s, 1 H), 7.32 (t, *J*=8.74 Hz, 2 H), 7.51 - 7.57 (m, 2 H), 7.58 (s, 1 H), 7.60 - 7.67 (m, 2 H), 7.81 (d, *J*=8.36 Hz, 2 H), 7.92 - 8.17 (m, 1 H), 8.18 - 8.38 (m, 1 H), 8.43 (t, *J*=5.70 Hz, 1 H) RP-HPLC (method C basic) LC-MS (method 2) Rt = 0.83 min MS (ESIpos): m/z = 486.6 $[M+H]^+$ 64 % yield

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
266	 rac-4-[4-amino-2-(N-(2-amino-1-methyl-2-oxo-ethyl)-4-fluoro-anilino)thiazole-5-carbonyl]-N-cyclopropyl-benzamide	Intermediate 211, cyclopropanamine	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 0.51 - 0.58 (m, 2 H), 0.64 - 0.71 (m, 2 H), 1.16 (d, *J*=7.35 Hz, 3 H), 2.82 (m, *J*=4.06 Hz, 1 H), 5.06 (m, *J*=7.10 Hz, 1 H), 7.25 (s, 1 H), 7.32 (t, *J*=8.87 Hz, 2 H), 7.52 (d, *J*=8.36 Hz, 2 H), 7.58 (s, 1 H), 7.61 - 7.67 (m, 2 H), 7.73 - 7.81 (m, 2 H), 7.92 - 8.17 (m, 1 H), 8.18 - 8.40 (m, 1 H), 8.44 (d, *J*=4.31 Hz, 1 H) RP-HPLC (method C basic) LC-MS (method 2) Rt = 0.93 min MS (ESIpos): m/z = 468.5 $[M+H]^+$ 68 % yield
267	 rac-4-[4-amino-2-(N-(2-amino-1-methyl-2-oxo-ethyl)-4-fluoro-anilino)thiazole-5-carbonyl]-N-cyclopentyl-benzamide	Intermediate 211, cyclopentanamine	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.16 (d, *J*=7.35 Hz, 3 H), 1.47 - 1.58 (m, 4 H), 1.63 - 1.73 (m, 2 H), 1.81 - 1.93 (m, 2 H), 4.14 - 4.26 (m, 1 H), 5.01 - 5.13 (m, 1 H), 7.25 (s, 1 H), 7.32 (t, *J*=8.87 Hz, 2 H), 7.50 - 7.55 (m, 2 H), 7.58 (s, 1 H), 7.61 - 7.66 (m, 2 H), 7.75 - 7.82 (m, 2 H), 7.94 - 8.11 (m, 1 H), 8.12 - 8.27 (m, 1 H), 8.31 (d, *J*=7.35 Hz, 1 H) RP-HPLC (method C basic) LC-MS (method 2) Rt = 1.08 min MS (ESIpos): m/z = 496.4 $[M+H]^+$ 47 % yield

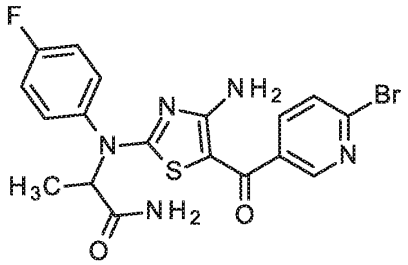
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
268	 rac-4-[4-amino-2-(N-(2-amino-1-methyl-2-oxo-ethyl)-4-chloro-3-fluoro-anilino)thiazole-5-carbonyl]-N-(2-phenoxyethyl)benzamide	Intermediate 213, 2-phenoxyethanamine	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.19 (d, *J*=7.35 Hz, 3 H), 3.58 - 3.65 (m, 2 H), 4.09 (t, *J*=5.83 Hz, 2 H), 4.98 - 5.08 (m, 1 H), 6.90 - 6.97 (m, 3 H), 7.23 - 7.34 (m, 3 H), 7.48 - 7.53 (m, 1 H), 7.55 - 7.59 (m, 2 H), 7.61 - 7.66 (m, 1 H), 7.71 - 7.78 (m, 2 H), 7.81 - 7.87 (m, 2 H), 7.96 - 8.57 (m, 2 H), 8.71 - 8.77 (m, 1 H) RP-HPLC (method D basic) LC-MS (method 2) Rt = 1.15 min MS (ESIpos): m/z = 582.2 $[M+H]^+$ 16 % yield
269	 rac-4-[4-amino-2-(N-(2-amino-1-methyl-2-oxo-ethyl)-4-chloro-3-fluoro-anilino)thiazole-5-carbonyl]-N-[2-(trifluoromethoxy)ethyl]benzamide	Intermediate 213, 2-(trifluoromethoxy)ethanamine hydrochloride (1:1)	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.20 (d, *J*=7.35 Hz, 3 H), 3.55 (q, *J*=5.35 Hz, 2 H), 4.18 (dd, *J*=5.35 Hz, 2 H), 4.99 - 5.07 (m, 1 H), 7.30 (s, 1 H), 7.51 (dt, *J*=8.62, 1.14 Hz, 1 H), 7.56 - 7.61 (m, 2 H), 7.63 (s, 1 H), 7.72 - 7.78 (m, 2 H), 7.79 - 7.88 (m, 2 H), 8.02 - 8.47 (m, 2 H), 8.78 (t, *J*=5.58 Hz, 1 H) RP-HPLC (method D basic) LC-MS (method 2) Rt = 1.11 min MS (ESIpos): m/z = 574.1 $[M+H]^+$ 32 % yield

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
270	 rac-4-[4-amino-2-(N-(2-amino-1-methyl-2-oxo-ethyl)-4-chloro-3-fluoro-anilino)thiazole-5-carbonyl]-N-[2-(difluoromethoxy)ethyl]benzamide	Intermediate 213, 2-(difluoromethoxy)ethanamine	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.20 (d, *J*=7.35 Hz, 3 H), 3.48 (q, *J*=5.58 Hz, 2 H), 3.91 - 3.96 (m, 2 H), 4.98 - 5.09 (m, 1 H), 6.68 (t, J=76 Hz, 1 H), 7.30 (s, 1 H), 7.48 - 7.53 (m, 1 H), 7.56 - 7.60 (m, 2 H), 7.63 (s, 1 H), 7.70 - 7.79 (m, 2 H), 7.79 - 7.86 (m, 2 H), 7.95 - 8.51 (m, 2 H), 8.66 - 8.71 (m, 1 H) RP-HPLC (method D basic) LC-MS (method 2) Rt = 1.02 min MS (ESIpos): m/z = 556.1 $[M+H]^+$ 18 % yield
271	 rac-4-[4-amino-2-(N-(2-amino-1-methyl-2-oxo-ethyl)-4-chloro-3-fluoro-anilino)thiazole-5-carbonyl]-N-(2-tert-butoxyethyl)benzamide	Intermediate 213, 2-tert-butoxyethanamine hydrochloride (1:1)	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.12 (s, 9 H), 1.20 (d, *J*=7.35 Hz, 3 H), 3.27 - 3.33 (m, 2 H), 3.37 - 3.43 (m, 2 H), 4.98 - 5.07 (m, 1 H), 7.30 (s, 1 H), 7.47 - 7.54 (m, 1 H), 7.54 - 7.59 (m, 2 H), 7.63 (s, 1 H), 7.71 - 7.78 (m, 2 H), 7.79 - 7.84 (m, 2 H), 7.97 - 8.45 (m, 2 H), 8.52 (t, *J*=5.58 Hz, 1 H) RP-HPLC (method D basic) LC-MS (method 2) Rt = 1.02 min MS (ESIpos): m/z = 562.2 $[M+H]^+$ 33 % yield

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
272	 rac-4-[4-amino-2-(N-(2-amino-1-methyl-2-oxo-ethyl)-4-chloro-3-fluoro-anilino)thiazole-5-carbonyl]-N-(2-methoxyethyl)benzamide	Intermediate 213, 2-methoxyethanamine	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.20 (d, *J*=7.35 Hz, 3 H), 3.25 (s, 3 H), 3.37 - 3.47 (m, 4 H), 4.98 - 5.08 (m, 1 H), 7.31 (s, 1 H), 7.49 - 7.54 (m, 1 H), 7.54 - 7.59 (m, 2 H), 7.63 (s, 1 H), 7.71 - 7.78 (m, 2 H), 7.80 - 7.85 (m, 2 H), 7.97 - 8.46 (m, 2 H), 8.53 - 8.59 (m, 1 H) RP-HPLC (method C basic) LC-MS (method 2) Rt = 0.95 min MS (ESIpos): m/z = 520.2 $[M+H]^+$ 17 % yield
273	 rac-2-[4-[4-amino-2-(N-(2-amino-1-methyl-2-oxo-ethyl)-4-fluoro-anilino)thiazole-5-carbonyl]phenoxy]-N-[(4-chlorophenyl)methyl]-2-methyl-propanamide	Intermediate 215, 1-(4-chlorophenyl)methanamine	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.16 (d, *J*=7.35 Hz, 3 H), 1.45 (s, 6 H), 4.23 (d, *J*=6.08 Hz, 2 H), 5.00 - 5.13 (m, 1 H), 6.77 - 6.82 (m, 2 H), 7.13 - 7.19 (m, 2 H), 7.24 (s, 1 H), 7.27 - 7.36 (m, 4 H), 7.38 - 7.45 (m, 2 H), 7.57 (s, 1 H), 7.64 (dd, *J*=8.87, 5.07 Hz, 2 H), 7.80 - 8.57 (m, 2 H), 8.68 (t, *J*=6.08 Hz, 1 H) RP-HPLC (method C basic) LC-MS (method 2) Rt = 1.23 min MS (ESIpos): m/z = 610.4 $[M+H]^+$ 77 % yield

Example 274

rac-2-(N-[4-amino-5-(6-bromopyridine-3-carbonyl)thiazol-2-yl]-4-fluoro-anilino)propanamide



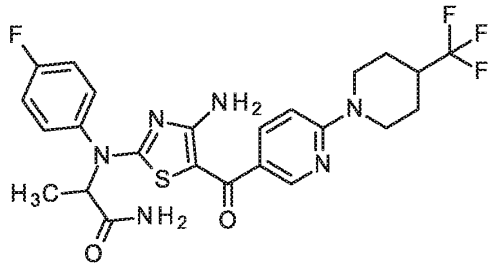
[4-amino-2-(4-fluoroanilino)-1,3-thiazol-5-yl](6-bromopyridin-3-yl)methanone (2.52 g, 6.4 mmol, Intermediate 218) was suspended in DMF (100 mL) and treated with rac-2-bromo propionamide (1.46 g, 9.6 mmol) and potassium carbonate (4.43 g, 32 mmol). The reaction mixture was stirred overnight at rt and then treated with water. After 30 min the precipitate was filtered off, washed with water and dried in vacuo to give 2.2 g (4.4 mmol, 69 % yield) of the title compound.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.16 (d, *J*=7.35 Hz, 3 H), 5.05 (m, 1 H), 7.27 (m, 1 H), 7.34 (t, *J*=8.87 Hz, 2 H), 7.65 (m, 4 H), 7.80 (dd, *J*=8.24, 2.41 Hz, 1 H), 8.25 (m, 2 H), 8.48 (d, *J*=2.03 Hz, 1 H).

LC-MS (method 2): Rt = 1.08 min; MS(ESIpos) m/z = 466.1 $[M+H]^+$

Example 275

rac-2-(N-[4-amino-5-[6-[4-(trifluoromethyl)-1-piperidyl]pyridine-3-carbonyl]thiazol-2-yl]-4-fluoro-anilino)propanamide



2-(N-[4-amino-5-(6-bromopyridine-3-carbonyl)thiazol-2-yl]-4-fluoro-anilino)propanamide (50 mg, 0.11 mmol, Example 274), 4-(trifluoromethyl)piperidine (25 mg, 0.16 mmol), tetrabutylammonium iodide (4 mg, 0.01 mmol) and potassium carbonate (18 mg, 0.13 mmol)

were suspended in DMSO and stirred overnight at 50°C. The reaction mixture was filtrated and purified by RP-HPLC (method D) to yield 24 mg (0.04 mmol, 41 %) of the title compound.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.17 (d, *J*=7.35 Hz, 3 H), 1.30 - 1.43 (m, 2 H), 1.84 (br d, *J*=11.15 Hz, 2 H), 2.56 - 2.65 (m, 1 H), 2.87 (td, *J*=12.86, 2.15 Hz, 2 H), 4.42 - 4.51 (m, 2 H), 5.00 - 5.11 (m, 1 H), 6.84 (d, *J*=8.87 Hz, 1 H), 7.25 (s, 1 H), 7.35 (t, *J*=8.87 Hz, 2 H), 7.58 (s, 1 H), 7.61 - 7.72 (m, 3 H), 7.80 - 8.26 (m, 2 H), 8.31 (d, *J*=2.28 Hz, 1 H).

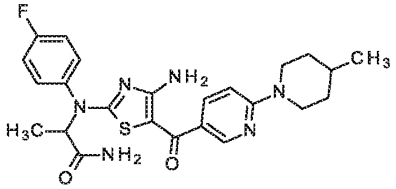
LC-MS (method 2): Rt = 1.25 min; MS(ESIpos) m/z = 537.5 $[M+H]^+$

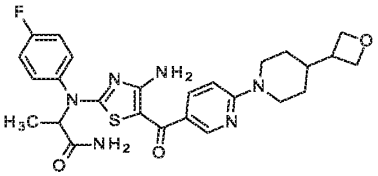
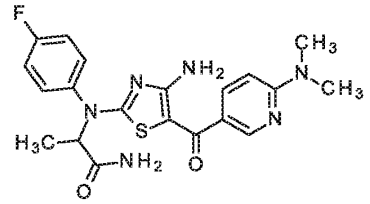
The following examples were prepared from the starting materials stated in Table 11, below, using the procedure as for Example 275.

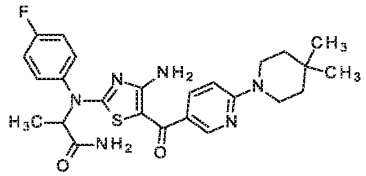
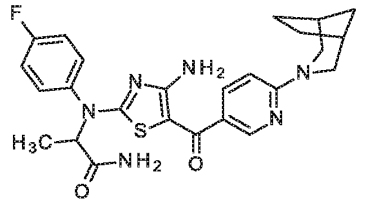
The crude product was either purified by RP-HPLC (methods A-D depending on polarity) or by preparative flash chromatography (methods X, Y or Z depending on polarity) after precipitation, extraction or filtration of the reaction mixture if necessary.

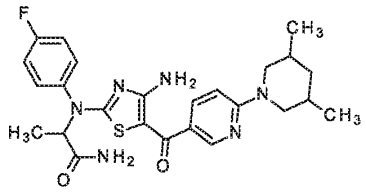
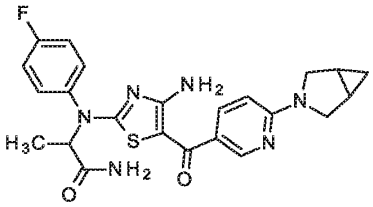
Enantiomers were separated from their racemate by chiral HPLC using the column and solvent conditions stated.

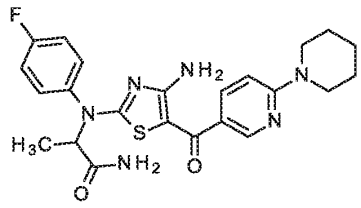
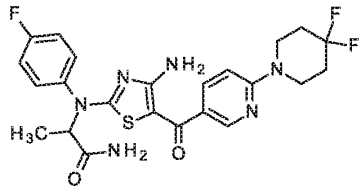
Table 11: Examples 276 – 285.2

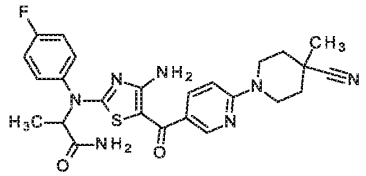
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
276	 rac-2-(N-[4-amino-5-[6-(4-methyl-1-piperidyl)pyridine-3-carbonyl]thiazol-2-yl]-4-fluoro-anilino)propanamide	Example 274, 4-methylpiperidine	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 0.89 (d, *J*=6.08 Hz, 3 H), 0.97 - 1.09 (m, 2 H), 1.17 (d, *J*=7.35 Hz, 3 H), 1.57 - 1.68 (m, 3 H), 2.76 - 2.87 (m, 2 H), 4.32 (br d, *J*=13.18 Hz, 2 H), 5.01 - 5.10 (m, 1 H), 6.78 (d, *J*=8.87 Hz, 1 H), 7.25 (s, 1 H), 7.35 (t, *J*=8.87 Hz, 2 H), 7.58 (br s, 1 H), 7.62 - 7.69 (m, 3 H), 7.86 - 8.24 (m, 2 H), 8.29 (d, *J*=2.28 Hz, 1 H) RP-HPLC (method D basic) LC-MS (method 2) Rt = 1.28 min MS (ESIpos): m/z = 438.3 $[M+H]^+$ 56 % yield

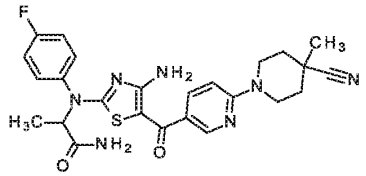
Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
277	 rac-2-(N-[4-amino-5-[6-[4-(oxetan-3-yl)-1-piperidyl]pyridine-3-carbonyl]thiazol-2-yl]-4-fluoro-anilino)propanamide	Example 274, 4-(oxetan-3-yl)piperidine	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 0.94 (br dd, *J*=12.29, 3.42 Hz, 2 H), 1.16 (d, *J*=7.35 Hz, 3 H), 1.61 (br d, *J*=11.15 Hz, 2 H), 1.81 - 1.94 (m, 1 H), 2.63 - 2.73 (m, 1 H), 2.79 - 2.89 (m, 2 H), 4.30 - 4.40 (m, 4 H), 4.59 (dd, *J*=7.86, 6.08 Hz, 2 H), 5.05 (q, *J*=7.10 Hz, 1 H), 6.79 (d, *J*=8.87 Hz, 1 H), 7.25 (s, 1 H), 7.34 (t, *J*=8.87 Hz, 2 H), 7.58 (s, 1 H), 7.60 - 7.70 (m, 3 H), 7.80 - 8.23 (m, 2 H), 8.29 (d, *J*=2.53 Hz, 1 H) RP-HPLC (method D basic) LC-MS (method 2) Rt = 1.06 min MS (ESIpos): m/z = 525.5 $[M+H]^+$ 60 % yield
278	 rac-2-(N-[4-amino-5-[6-(dimethylamino)pyridine-3-carbonyl]thiazol-2-yl]-4-fluoro-anilino)propanamide	Example 274, N-methylmethanamine	^{1}H NMR (500 MHz, DMSO-d_6) δ ppm = 1.17 (d, *J*=7.25 Hz, 3 H), 3.03 (s, 6 H), 5.01 - 5.09 (m, 1 H), 6.61 (d, *J*=8.83 Hz, 1 H), 7.25 (s, 1 H), 7.35 (t, *J*=8.83 Hz, 2 H), 7.58 (s, 1 H), 7.63 - 7.70 (m, 3 H), 7.82 - 8.26 (m, 2 H), 8.30 (d, *J*=2.21 Hz, 1 H) RP-HPLC (method D basic) LC-MS (method 2) Rt = 1.04 min MS (ESIpos): m/z = 429.5 $[M+H]^+$ 51 % yield

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
279	 rac-2-(N-[4-amino-5-[6-(4,4-dimethyl-1-piperidyl)pyridine-3-carbonyl]thiazol-2-yl]-4-fluoro-anilino)propanamide	Example 274, 4,4-dimethylpiperidine hydrochloride (1:1)	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 0.95 (s, 6 H), 1.17 (d, *J*=7.35 Hz, 3 H), 1.28 - 1.34 (m, 4 H), 3.52 - 3.60 (m, 4 H), 5.00 - 5.12 (m, 1 H), 6.78 (d, *J*=9.13 Hz, 1 H), 7.25 (s, 1 H), 7.35 (t, *J*=8.87 Hz, 2 H), 7.55 - 7.61 (m, 1 H), 7.62 - 7.69 (m, 3 H), 7.80 - 8.24 (m, 2 H), 8.29 (d, *J*=2.53 Hz, 1 H) RP-HPLC (method D basic) LC-MS (method 2) Rt = 1.37 min MS (ESIpos): m/z = 497.5 $[M+H]^+$ 59 % yield
280	 rac-2-(N-[4-amino-5-[6-(3-azabicyclo[3.2.1]octan-3-yl)pyridine-3-carbonyl]thiazol-2-yl]-4-fluoro-anilino)propanamide	Example 274, 3-azabicyclo[3.2.1]octane hydrochloride (1:1)	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.16 (d, *J*=7.35 Hz, 3 H), 1.37 - 1.46 (m, 2 H), 1.50 - 1.56 (m, 2 H), 1.56 - 1.67 (m, 2 H), 2.26 - 2.32 (m, 2 H), 2.85 (d, *J*=10.39 Hz, 2 H), 3.93 (br d, *J*=10.65 Hz, 2 H), 4.99 - 5.10 (m, 1 H), 6.67 (d, *J*=8.87 Hz, 1 H), 7.25 (s, 1 H), 7.34 (t, *J*=8.87 Hz, 2 H), 7.58 (s, 1 H), 7.61 - 7.69 (m, 3 H), 7.75 - 8.25 (m, 2 H), 8.29 (d, *J*=2.53 Hz, 1 H) RP-HPLC (method D basic) LC-MS (method 2) Rt = 1.29 min MS (ESIpos): m/z = 495.3 $[M+H]^+$ 60 % yield

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
281	 rac-2-(N-[4-amino-5-[6-(3,5-dimethyl-1-piperidyl)pyridine-3-carbonyl]thiazol-2-yl]-4-fluoro-anilino)propanamide	Example 274, 3,5-dimethylpiperidine	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 0.87 (d, *J*=6.59 Hz, 6 H), 1.17 (d, *J*=7.60 Hz, 3 H), 1.44 - 1.57 (m, 2 H), 1.75 (br d, *J*=12.42 Hz, 1 H), 2.25 - 2.34 (m, 2 H), 4.34 (br d, *J*=9.89 Hz, 2 H), 5.01 - 5.12 (m, 1 H), 6.80 (d, *J*=8.87 Hz, 1 H), 7.25 (s, 1 H), 7.35 (t, *J*=8.74 Hz, 2 H), 7.58 (s, 1 H), 7.62 - 7.70 (m, 3 H), 7.81 - 8.26 (m, 2 H), 8.29 (d, *J*=2.53 Hz, 1 H), 0.78 (q, J=12 Hz, 1 H) RP-HPLC (method D basic) LC-MS (method 2) Rt = 1.37 min MS (ESIpos): m/z = 497.3 $[M+H]^+$ 59 % yield
282	 rac-2-(N-[4-amino-5-[6-(3-azabicyclo[3.1.0]hexan-3-yl)pyridine-3-carbonyl]thiazol-2-yl]-4-fluoro-anilino)propanamide	Example 274, 3-azabicyclo[3.1.0] hexane hydrochloride (1:1)	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 0.13 (d, *J*=4.31 Hz, 1 H), 0.72 (td, *J*=7.67, 4.69 Hz, 1 H), 1.16 (d, *J*=7.35 Hz, 3 H), 1.63 - 1.69 (m, 2 H), 3.34 - 3.41 (m, 2 H), 3.63 (br d, *J*=10.39 Hz, 2 H), 5.05 (br d, *J*=7.35 Hz, 1 H), 6.42 (d, *J*=8.62 Hz, 1 H), 7.25 (s, 1 H), 7.34 (t, *J*=8.74 Hz, 2 H), 7.58 (s, 1 H), 7.60 - 7.70 (m, 3 H), 7.83 - 8.22 (m, 2 H), 8.27 (d, *J*=2.28 Hz, 1 H) RP-HPLC (method D basic) LC-MS (method 2) Rt = 1.12 min MS (ESIpos): m/z = 467.3 $[M+H]^+$ 72 % yield

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
283	 rac-2-(N-[4-amino-5-[6-(1-piperidyl)pyridine-3-carbonyl]thiazol-2-yl]-4-fluoro-anilino)propanamide	Example 274, piperidine	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.17 (d, *J*=7.35 Hz, 3 H), 1.45 - 1.55 (m, 4 H), 1.56 - 1.64 (m, 2 H), 3.53 - 3.59 (m, 4 H), 5.00 - 5.10 (m, 1 H), 6.78 (d, *J*=9.12 Hz, 1 H), 7.25 (s, 1 H), 7.35 (t, *J*=8.74 Hz, 2 H), 7.58 (s, 1 H), 7.62 - 7.70 (m, 3 H), 7.80 - 8.23 (m, 2 H), 8.29 (d, *J*=2.28 Hz, 1 H) RP-HPLC (method D basic) LC-MS (method 2) Rt = 1.22 min MS (ESIpos): m/z = 469.5 $[M+H]^+$ 100 % yield
284	 rac-2-(N-[4-amino-5-[6-(4,4-difluoro-1-piperidyl)pyridine-3-carbonyl]thiazol-2-yl]-4-fluoro-anilino)propanamide	Example 274, 4,4-difluoropiperidine hydrochloride (1:1)	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.17 (d, *J*=7.60 Hz, 3 H), 1.90 - 2.03 (m, 4 H), 3.69 - 3.76 (m, 4 H), 5.00 - 5.11 (m, 1 H), 6.93 (d, *J*=9.13 Hz, 1 H), 7.25 (s, 1 H), 7.35 (t, *J*=8.74 Hz, 2 H), 7.58 (s, 1 H), 7.62 - 7.72 (m, 3 H), 7.80 - 8.26 (m, 2 H), 8.31 - 8.34 (m, 1 H) RP-HPLC (method D basic) LC-MS (method 2) Rt = 1.09 min MS (ESIpos): m/z = 466.2 $[M+H]^+$ 26 % yield

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
285	 rac-2-(N-[4-amino-5-[6-(4-cyano-4-methyl-1-piperidyl)pyridine-3-carbonyl]thiazol-2-yl]-4-fluoro-anilino)propanamide	Example 274, 4-methylpiperidine-4-carbonitrile hydrochloride (1:1)	^{1}H NMR (500 MHz, DMSO-d_6) δ ppm = 1.17 (d, *J*=7.25 Hz, 3 H), 1.35 (s, 3 H), 1.49 (td, *J*=12.77, 4.10 Hz, 2 H), 1.90 (br d, *J*=13.87 Hz, 2 H), 2.97 - 3.05 (m, 2 H), 4.36 (br d, *J*=13.87 Hz, 2 H), 5.01 - 5.10 (m, 1 H), 6.86 (d, *J*=8.83 Hz, 1 H), 7.25 (s, 1 H), 7.35 (t, *J*=8.83 Hz, 2 H), 7.58 (s, 1 H), 7.63 - 7.70 (m, 3 H), 7.78 - 8.29 (m, 2 H), 8.31 (d, *J*=2.21 Hz, 1 H) RP-HPLC (method D basic) LC-MS (method 2) Rt = 1.04 min MS (ESIpos): m/z = 508.8 $[M+H]^+$ 64 % yield
285.1 and **285.2**	(R)-2-(N-[4-amino-5-[6-(4-cyano-4-methyl-1-piperidyl)pyridine-3-carbonyl]thiazol-2-yl]-4-fluoro-anilino)propanamide and (S)-2-(N-[4-amino-5-[6-(4-cyano-4-methyl-1-piperidyl)pyridine-3-carbonyl]thiazol-2-yl]-4-fluoro-anilino)propanamide		

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
285.1	 2-(N-[4-amino-5-[6-(4-cyano-4-methyl-1-piperidyl)pyridine-3-carbonyl]thiazol-2-yl]-4-fluoro-anilino)propanamide (enantiomer 1)	Example 285	^{1}H NMR (500 MHz, DMSO-d_6) δ ppm = 1.17 (d, *J*=7.25 Hz, 3 H), 1.35 (s, 3 H), 1.49 (td, *J*=12.77, 4.10 Hz, 2 H), 1.90 (br d, *J*=13.87 Hz, 2 H), 2.97 - 3.05 (m, 2 H), 4.36 (br d, *J*=13.87 Hz, 2 H), 5.01 - 5.10 (m, 1 H), 6.86 (d, *J*=8.83 Hz, 1 H), 7.25 (s, 1 H), 7.35 (t, *J*=8.83 Hz, 2 H), 7.58 (s, 1 H), 7.63 - 7.70 (m, 3 H), 7.78 - 8.29 (m, 2 H), 8.31 (d, *J*=2.21 Hz, 1 H) LC-MS (method 2) Rt = 1.04 min MS (ESIpos): m/z = 508.8 $[M+H]^+$ 39 % yield

Chiral HPLC Example 285.1

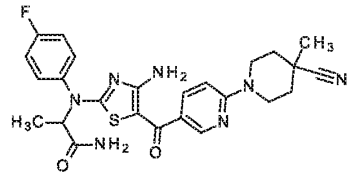
HPLC separation of rac-2-(N-[4-amino-5-[6-(4-cyano-4-methyl-1-piperidyl)pyridine-3-carbonyl]thiazol-2-yl]-4-fluoro-anilino)propanamide (98 mg, 0.19 mmol, Example 285) on a chiral column gave 38 mg (39 % yield) of 2-(N-[4-amino-5-[6-(4-cyano-4-methyl-1-piperidyl)pyridine-3-carbonyl]thiazol-2-yl]-4-fluoro-anilino)propanamide, enantiomer 1.

Preparative chiral HPLC

Instrument: PrepCon Labomatic HPLC-4; Column: YMC Cellulose SC 10µ, 250x50; eluent A: methyl tert-butyl ether + 0.1 vol % diethylamine; eluent B: acetonitrile; isocratic: 50%A+50%B; flow: 100 mL/min; temperature: 25°C; UV: 254 nm

Analytical chiral HPLC: Rt = 2.37 min

Instrument: Thermo Fisher UltiMate 3000; Column: YMC Cellulose SC 3µ, 100x4.6; eluent A: methyl tert-butyl ether + 0.1 vol % diethylamine; eluent B: acetonitrile; isocratic: 50%A+50%B; flow: 1.4 mL/min; temperature: 25°C; UV: 254 nm

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
285.2	 2-(N-[4-amino-5-[6-(4-cyano-4-methyl-1-piperidyl)pyridine-3-carbonyl]thiazol-2-yl]-4-fluoro-anilino)propanamide (enantiomer 2)	Example 285	^{1}H NMR (500 MHz, DMSO-d_6) δ ppm = 1.17 (d, *J*=7.25 Hz, 3 H), 1.35 (s, 3 H), 1.49 (td, *J*=12.77, 4.10 Hz, 2 H), 1.90 (br d, *J*=13.87 Hz, 2 H), 2.97 - 3.05 (m, 2 H), 4.36 (br d, *J*=13.87 Hz, 2 H), 5.01 - 5.10 (m, 1 H), 6.86 (d, *J*=8.83 Hz, 1 H), 7.25 (s, 1 H), 7.35 (t, *J*=8.83 Hz, 2 H), 7.58 (s, 1 H), 7.63 - 7.70 (m, 3 H), 7.78 - 8.29 (m, 2 H), 8.31 (d, *J*=2.21 Hz, 1 H) LC-MS (method 2) Rt = 1.04 min MS (ESIpos): m/z = 508.8 $[M+H]^+$ 42 % yield

Chiral HPLC Example 285.2

HPLC separation of rac-2-(N-[4-amino-5-[6-(4-cyano-4-methyl-1-piperidyl)pyridine-3-carbonyl]thiazol-2-yl]-4-fluoro-anilino)propanamide (98 mg, 0.19 mmol, Example 285) on a chiral column gave 41 mg (42 % yield) of 2-(N-[4-amino-5-[6-(4-cyano-4-methyl-1-piperidyl)pyridine-3-carbonyl]thiazol-2-yl]-4-fluoro-anilino)propanamide, enantiomer 2.

Preparative chiral HPLC

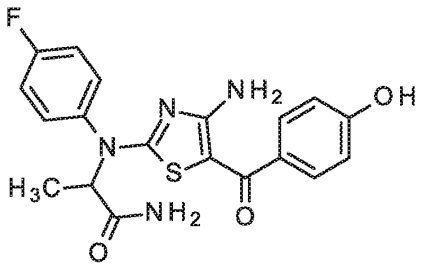
Instrument: PrepCon Labomatic HPLC-4; Column: YMC Cellulose SC 10µ, 250x50; eluent A: methyl tert-butyl ether + 0.1 vol % diethylamine; eluent B: acetonitrile; isocratic: 50%A+50%B; flow: 100 mL/min; temperature: 25°C; UV: 254 nm

Analytical chiral HPLC: Rt = 3.22 min

Instrument: Thermo Fisher UltiMate 3000; Column: YMC Cellulose SC 3µ, 100x4.6; eluent A: methyl tert-butyl ether + 0.1 vol % diethylamine; eluent B: acetonitrile; isocratic: 50%A+50%B; flow: 1.4 mL/min; temperature: 25°C; UV: 254 nm

Example 286

2-(N-[4-amino-5-(4-hydroxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide (single enantiomer)



2-(N-[4-amino-5-(4-benzyloxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide (enantiomer 2, example 170.2, 41 mg, 0.084 mmol) was solved in ethanol (1 mL). Under nitrogen, Pd/C (133 mg) was added and the reaction mixture was purged with H_2 and stirred under atmospheric H_2 for 5 h at rt. The mixture was filtrated via Celite and the solvent was evaporated under reduced pressure. The residue was purified by RP-HPLC (method B) to yield 22 mg (0.05 mmol, 61 %) of the title compound.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.16 (d, *J*=7.35 Hz, 3 H), 4.99 - 5.10 (m, 1 H), 6.70 - 6.75 (m, 2 H), 7.24 (s, 1 H), 7.30 - 7.40 (m, 4 H), 7.57 (s, 1 H), 7.61 - 7.66 (m, 2 H), 7.84 - 8.32 (m, 2 H), 9.90 (br s, 1 H).

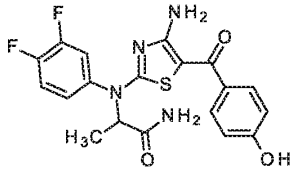
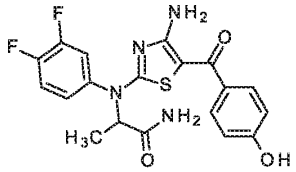
LC-MS (method 2): Rt = 0.68 min; MS(ESIpos) m/z = 401.3 $[M+H]^+$

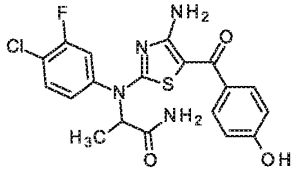
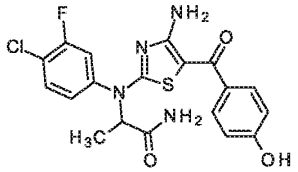
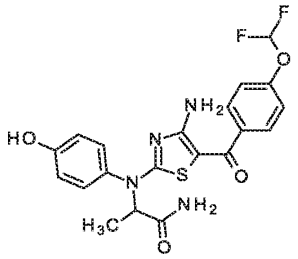
The following examples were prepared from the starting materials stated in Table 12, below, using the procedure as for Example 286.

The crude product was either purified by RP-HPLC (methods A-D depending on polarity) or by preparative flash chromatography (methods X, Y or Z depending on polarity) after precipitation, extraction or filtration of the reaction mixture if necessary.

Enantiomers were separated from their racemate by chiral HPLC using the column and solvent conditions stated.

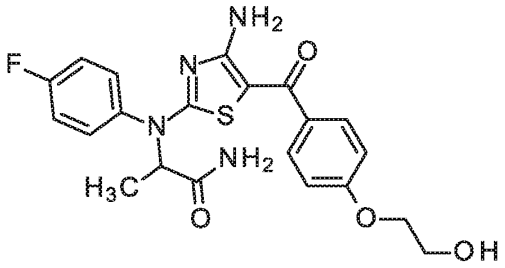
Table 12: Examples 287 – 291

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
287	 2-(N-[4-amino-5-(4-hydroxybenzoyl)thiazol-2-yl]-3,4-difluoro-anilino)propanamide (enantiomer 1)	Example 165.1	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.18 (d, *J*=7.35 Hz, 3 H), 4.96 - 5.06 (m, 1 H), 6.72 (d, *J*=8.62 Hz, 2 H), 7.28 (s, 1 H), 7.37 - 7.43 (m, 2 H), 7.48 - 7.54 (m, 1 H), 7.55 - 7.64 (m, 2 H), 7.72 - 7.83 (m, 1 H), 7.83 - 8.25 (m, 2 H) RP-HPLC (method B basic) LC-MS (method 2) Rt = 0.68 min MS (ESIpos): m/z = 419.3 [M+H]$^+$ 49 % yield
288	 2-(N-[4-amino-5-(4-hydroxybenzoyl)thiazol-2-yl]-3,4-difluoro-anilino)propanamide (enantiomer 2)	Example 165.2	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.18 (d, *J*=7.35 Hz, 3 H), 4.96 - 5.06 (m, 1 H), 6.72 (d, *J*=8.62 Hz, 2 H), 7.28 (s, 1 H), 7.37 - 7.43 (m, 2 H), 7.48 - 7.54 (m, 1 H), 7.55 - 7.64 (m, 2 H), 7.72 - 7.83 (m, 1 H), 7.83 - 8.25 (m, 2 H) RP-HPLC (method B basic) LC-MS (method 2) Rt = 0.68 min MS (ESIpos): m/z = 419.3 [M+H]$^+$ 43 % yield

Example number	Chemical structure Compound name	Starting materials	Analytics/purification/yield
289	 2-(N-[4-amino-5-(4-hydroxybenzoyl)thiazol-2-yl]-4-chloro-3-fluoro-anilino)propanamide (enantiomer 1)	Example 166.1	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.19 (d, *J*=7.35 Hz, 3 H), 4.97 - 5.06 (m, 1 H), 6.72 - 6.78 (m, 2 H), 7.29 (s, 1 H), 7.38 - 7.46 (m, 2 H), 7.51 (dt, *J*=8.49, 1.20 Hz, 1 H), 7.62 (s, 1 H), 7.71 - 7.79 (m, 2 H), 7.83 - 8.26 (m, 2 H), 9.93 (s, 1 H) Biotage (method X) LC-MS (method 2) Rt = 0.76 min MS (ESIpos): m/z = 435.2 $[M+H]^+$ 21 % yield
290	 2-(N-[4-amino-5-(4-hydroxybenzoyl)thiazol-2-yl]-4-chloro-3-fluoro-anilino)propanamide (enantiomer 2)	Example 166.2	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.19 (d, *J*=7.35 Hz, 3 H), 4.97 - 5.06 (m, 1 H), 6.72 - 6.78 (m, 2 H), 7.29 (s, 1 H), 7.38 - 7.46 (m, 2 H), 7.51 (dt, *J*=8.49, 1.20 Hz, 1 H), 7.62 (s, 1 H), 7.71 - 7.79 (m, 2 H), 7.83 - 8.26 (m, 2 H), 9.93 (s, 1 H) Biotage (method X) LC-MS (method 2) Rt = 0.76 min MS (ESIpos): m/z = 435.2 $[M+H]^+$ 27 % yield
291	 2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-hydroxy-anilino)propanamide (single enantiomer)	Example 182.2	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.14 (d, *J*=7.35 Hz, 3 H), 4.96 - 5.13 (m, 1 H), 6.80 (d, *J*=8.87 Hz, 2 H), 7.14 - 7.21 (m, 3 H), 7.27 (t, J=72 Hz, 1H), 7.32 (d, *J*=8.62 Hz, 2 H), 7.49 (s, 1 H), 7.52 - 7.58 (m, 2 H), 7.78 - 8.55 (m, 2 H), 9.85 (s, 1 H) RP-HPLC (method B basic) LC-MS (method 2) Rt = 0.68 min MS (ESIpos): m/z = 449.3 $[M+H]^+$ 47 % yield

Example 292

rac-2-(N-[4-amino-5-[4-(2-hydroxyethoxy)benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide



[4-amino-2-(4-fluoroanilino)thiazol-5-yl]-[4-(2-hydroxyethoxy)phenyl]methanone (Intermediate 209, 74 mg, 0.2 mmol) was suspended in DMF (4 mL) and treated with rac-2-bromopropamide (30 mg, 0.2 mmol) and potassium carbonate (137 mg, 0.2 mmol). The reaction mixture was stirred at rt for 4 days. The filtrate was purified by RP-HPLC (method C, basic) to give 47 mg (53 % yield) of the title compound.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 1.15 (d, *J*=7.35 Hz, 3 H) 3.64 - 3.71 (m, 2 H) 3.98 (t, *J*=4.94 Hz, 2 H) 4.87 - 4.93 (m, 1 H) 5.00 - 5.11 (m, 1 H) 6.88 - 6.95 (m, 2 H) 7.23 (s, 1 H) 7.30 - 7.36 (m, 2 H) 7.44 - 7.49 (m, 2 H) 7.56 - 7.60 (m, 1 H) 7.61 - 7.66 (m, 2 H) 7.74 - 8.34 (m, 2 H) 9.02 - 9.07 (m, 1 H).

LC-MS (method 1): Rt = 0.84 min; MS(ESIpos) m/z = 445.6 $[M+H]^+$.

EXPERIMENTAL SECTION – DETERMINATION OF ABSOLUTE STEREOCHEMISTRY BY MEANS OF X-RAY-ANALYSIS

Determination of the absolute configuration of Example 49.2

(R)-2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-3,4-difluoro-anilino)propanamide

The crystallographic data of Example 49.2 as well as a figure depicting the thermal ellipsoids and numbering of the structure, are shown in Table 13 and Figure 6. Colorless crystals of Example 49.2 were obtained by slow evaporation of an ethanol solution. A single crystal was mounted on a cryoloop using a protective oil. Single-crystal X-ray diffraction data were collected at 100 K on a Rigaku XtaLAB Synergy S system with a kappa goniometer and a HyPix-6000HE hybrid photon detector using Cu X-ray radiation (CuKα, = 1.54178 Å). Data were integrated using the program CrysAlisPRO. SHELXM was used for structure solution and SHELXL was used for full-matrix least-squares refinement on F2. In the asymmetric unit two molecules of Example 49.2 and two water molecules are present. The di-fluorinated phenyl rings in both molecules are disordered via a 180° rotation of the ring systems. The occupancies for the alternative positions were refined to 0.25 / 0.75 in Molecule A and 0.35 / 0.65 in Molecule B, respectively. All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were added in calculated positions and refined riding on their resident atoms. Hydrogens attached to the nitrogen atoms in 49.2 as well as at the water molecules were located in the difference Fourier map and placed manually. The isotropic temperature factors of the hydrogen atoms were refined as 1.2 and 1.5 times the size of the temperature factors of the corresponding heavy atoms, respectively. The absolute stereochemistry (R-configuration) could be assigned unambiguously with a Flack Parameter of 0.008(7). The program XP was used for molecular representations.

Table 13: Crystal data and structure refinement for Example 49.2

Identification code	Example 49.2	
Empirical formula	C40 H36 F8 N8 O8 S2	
Formula weight	972.89	
Temperature	100(2) K	
Wavelength	1.54184 Å	
Crystal system	Triclinic	
Space group	P1	
Unit cell dimensions	a = 7.59740(10) Å	a= 78.1410(10)°.
	b = 9.28630(10) Å	b= 89.0340(10)°.
	c = 15.1835(2) Å	g = 83.8330(10)°.
Volume	1042.28(2) $Å^3$	
Z	1	
Density (calculated)	1.550 Mg/m^3	
Absorption coefficient	2.049 mm^{-1}	
F(000)	500	
Crystal size	0.050 x 0.040 x 0.160 mm^3	
Theta range for data collection	2.974 to 68.246°.	
Index ranges	-9<=h<=9, -11<=k<=11, -18<=l<=18	
Reflections collected	74868	
Independent reflections	7441 [R(int) = 0.0428]	
Completeness to theta = 67.684°	99.9 %	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	7441 / 153 / 651	
Goodness-of-fit on F^2	1.044	
Final R indices [I>2sigma(I)]	R1 = 0.0425, wR2 = 0.1062	
R indices (all data)	R1 = 0.0437, wR2 = 0.1072	
Absolute structure parameter	0.008(7)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.879 and -0.502 $e.Å^{-3}$	

Determination of the absolute configuration of Example 59.1

(R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-chloro-3-fluoro-anilino)propanamide

The crystallographic data of Example 59.1 as well as a figure depicting the thermal ellipsoids and numbering of the structure, are shown in Table 14 and Figure 7. Colorless crystals of Example 59.1 were obtained by slow evaporation from a toluene solution. A single crystal was mounted on a cryoloop using a protective oil. Single-crystal X-ray diffraction data were collected at 100 K on a Rigaku XtaLAB Synergy S system with a kappa goniometer and a HyPix-6000HE hybrid photon detector using Cu X-ray radiation (CuKα, = 1.54178 Å). Data were integrated using the program CrysAlisPRO. SHELXM was used for structure solution and SHELXL was used for full-matrix least-squares refinement on F2. In the asymmetric unit four molecules of Example 59.1 and one disordered toluene molecules are present. The fluorinated phenyl ring systems in three of the four molecules are disordered via a 180° rotation of the ring systems. The occupancies for the alternative positions were refined to 0.30 / 0.70 in Molecule B, 0.20 / 0.80 in Molecule C and 0.15 / 0.85 in Molecule D, respectively. The toluene solvent molecule is disordered over a pseudo 2-fold axis and the occupancies for both alternative positions refined with a ratio of 0.45 / 0.55. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were added in calculated positions and refined riding on their resident atoms. Hydrogens attached to amine and amide nitrogen atoms were either located in the difference Fourier map and placed manually or were refined using the riding model. The isotropic temperature factors of the hydrogen atoms were refined as 1.2 and 1.5 times the size of the temperature factors of the corresponding heavy atoms, respectively. The absolute stereochemistry (R-configuration) could be assigned unambiguously with a Flack Parameter of 0.015(11). The program XP was used for molecular representations.

Table 14: Crystal data and structure refinement for Example 59.1

	Identification code	59.1	
	Empirical formula	C20 H18 N4 O3 F Cl S + 0.25 (C7 H8)	
	Formula weight	448.9 + 23.0	
	Temperature	100(2) K	
	Wavelength	1.54178 Å	
	Crystal system	Triclinic	
	Space group	P1	
	Unit cell dimensions	a = 8.9781(2) Å	a= 103.099(2)°.
		b = 13.3867(3) Å	b= 92.827(2)°.
		c = 18.9350(3) Å	g = 101.417(2)°.
	Volume	2162.07(8) $Å^3$	
	Z	4	
	Density (calculated)	1.450 Mg/m^3	
	Absorption coefficient	2.827 mm^{-1}	
	F(000)	978	
	Crystal size	0.070 x 0.060 x 0.005 mm^3	
	Theta range for data collection	2.407 to 68.401°.	
	Index ranges	-10<=h<=10, -16<=k<=16, -22<=l<=22	
	Reflections collected	76934	
	Independent reflections	15381 [R(int) = 0.0650]	
	Completeness to theta = 67.679°	100.0 %	
	Refinement method	Full-matrix least-squares on F^2	
	Data / restraints / parameters	15381 / 1400 / 1272	
	Goodness-of-fit on F^2	1.003	
	Final R indices [I>2sigma(I)]	R1 = 0.0496, wR2 = 0.1120	
	R indices (all data)	R1 = 0.0605, wR2 = 0.1185	
	Absolute structure parameter	0.015(11)	
	Extinction coefficient	n/a	
	Largest diff. peak and hole	0.462 and -0.430 $e.Å^{-3}$	

Determination of the absolute configuration of Example 61.2

(R)-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-4-fluoro-anilino)propanamide

The crystallographic data of Example 61.2 as well as a figure depicting the thermal ellipsoids and numbering of the structure, are shown in Table 15 and Figure 8. Colorless crystals of Example 61.2 were obtained by slow evaporation from an acetonitrile solution. A single crystal was mounted on a cryoloop using a protective oil. Single-crystal X-ray diffraction data were collected at 100 K on a Rigaku XtaLAB Synergy S system with a kappa goniometer and a HyPix-6000HE hybrid photon detector using Cu X-ray radiation (CuKα, = 1.54178 Å). Data were integrated using the program CrysAlisPRO. SHELXM was used for structure solution and SHELXL was used for full-matrix least-squares refinement on F2. In the asymmetric unit eight molecules of Example 61.2 and two water molecules are present. All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were added in calculated positions and refined riding on their resident atoms. Hydrogens attached to amine and amide nitrogen atoms were either located in the difference Fourier map and placed manually or were refined using the riding model. The isotropic temperature factors of the hydrogen atoms were refined as 1.2 and 1.5 times the size of the temperature factors of the corresponding heavy atoms, respectively. The absolute stereochemistry (R-configuration) could be assigned unambiguously with a Flack Parameter of 0.027(11). The program XP was used for molecular representations.

Table 15: Crystal data and structure refinement for Example 61.2

Identification code	Example 61.2	
Empirical formula	C19 H20 F N4 O2 S + 0.1875 H2 O	
Formula weight	390.45	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Tetragonal	
Space group	P4(1)	
Unit cell dimensions	a = 17.135 Å	a= 90°.
	b = 17.135 Å	b= 90°.
	c = 49.3911(2) Å	g = 90°.
Volume	14502.48(6) $Å^3$	
Z	32	
Density (calculated)	1.431 Mg/m^3	
Absorption coefficient	1.886 mm^{-1}	
F(000)	6544	
Crystal size	0,3 x 0,2 x 0,1 mm^3	
Theta range for data collection	2.58 to 77.25°.	
Index ranges	-14<=h<=15, 0<=k<=21, -59<=l<=61	
Reflections collected	178451	
Independent reflections	26790 [R(int) = 0.0513]	
Completeness to theta = 77.25°	91.2 %	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	26790 / 1889 / 2043	
Goodness-of-fit on F^2	1.315	
Final R indices [I>2sigma(I)]	R1 = 0.0508, wR2 = 0.1276	
R indices (all data)	R1 = 0.0538, wR2 = 0.1292	
Absolute structure parameter	0.027(11)	
Largest diff. peak and hole	0.475 and -0.425 $e.Å^{-3}$	

Determination of the absolute configuration of Example 62.2

(R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide

The crystallographic data of Example 62.2 as well as a figure depicting the thermal ellipsoids and numbering of the structure, are shown in Table 16 and Figure 9. Colorless crystals of Example 62.2 were already present in the purified sample. A single crystal was mounted on a cryoloop using a protective oil. Single-crystal X-ray diffraction data were collected at 100 K on a Rigaku XtaLAB Synergy S system with a kappa goniometer and a HyPix-6000HE hybrid photon detector using Cu X-ray radiation (CuKα, = 1.54178 Å). Data were integrated using the program CrysAlisPRO. SHELXM was used for structure solution and SHELXL was used for full-matrix least-squares refinement on F2. In the asymmetric unit two molecules of Example 62.2 are present. All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were added in calculated positions and refined riding on their resident atoms. Hydrogens attached to the nitrogen atoms were located in the difference Fourier map and placed manually. The isotropic temperature factors of the hydrogen atoms were refined as 1.2 and 1.5 times the size of the temperature factors of the corresponding heavy atoms, respectively. The absolute stereochemistry (R-configuration) could be assigned unambiguously with a Flack Parameter of 0.004(3). The program XP was used for molecular representations.

Table 16: Crystal data and structure refinement for Example 62.2

Identification code	Example 62.2	
Empirical formula	C40 H38 F2 N8 O6 S2	
Formula weight	828.90	
Temperature	100(2) K	
Wavelength	1.54184 Å	
Crystal system	Monoclinic	
Space group	I2	
Unit cell dimensions	a = 14.128 Å	a= 90°.
	b = 13.01730(10) Å	b= 92.60°.
	c = 21.74910(10) Å	g = 90°.
Volume	3995.63(4) $Å^3$	
Z	4	
Density (calculated)	1.378 Mg/m^3	
Absorption coefficient	1.778 mm^{-1}	
F(000)	1728	
Crystal size	0.100 x 0.070 x 0.020 mm^3	
Theta range for data collection	3.656 to 77.353°.	
Index ranges	-17<=h<=17, -16<=k<=15, -27<=l<=27	
Reflections collected	75900	
Independent reflections	8071 [R(int) = 0.0302]	
Completeness to theta = 67.684°	100.0 %	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	8071 / 1 / 551	
Goodness-of-fit on F^2	1.065	
Final R indices [I>2sigma(I)]	R1 = 0.0226, wR2 = 0.0591	
R indices (all data)	R1 = 0.0227, wR2 = 0.0592	
Absolute structure parameter	-0.004(3)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.151 and -0.239 $e.Å^{-3}$	

EXPERIMENTAL SECTION – BIOLOGICAL ASSAYS AND BIOLOGICAL DATA

Table 17, below, lists the abbreviations used in this paragraph and in the Assays section as far as they are not explained within the text body. Other abbreviations have their meanings customary *per se* to the skilled person.

Table 17: Abbreviations

nL	nanoliter
µL	microliter
mL	milliliter
nM	nanomolar
µM	micromolar
mM	millimolar
min	minute(s)
s	second(s)
kDa	kilodalton
MW	molecular weight
cAMP	cyclic adenosine monophosphat
ADP	adenosine diphosphate
ATP	adenosine triphosphate
FCS	fetal calf serum
FBS	fetal bovine serum
PBS	phosphate buffered saline
RPMI	Roswell Park Memorial Institute
ACK lysing buffer	ammonium-chloride-potassium lysis buffer
DMEM	Dulbecco's Modified Eagle's Medium
HEPES	2-[4-(2-hydroxyethyl)piperazin-1-yl]ethanesulfonic acid
MOPS	3-(N-morpholino)propanesulfonic acid
Pen/Strep	penicillin and streptomycin
HBS-P+	buffer containing 0.1 M HEPES, 1.5 M NaCl and 0.5% v/v Surfactant P20

DTT	DL-Dithiothreitol
BGG	bovine gamma globulin
PBMC	peripheral blood mononuclear cells
APC	antigen presenting cells
CD	cluster of differentiation
IgG	immunoglobulin G
OKT3	CD3 monoclonal antibody
FLAG-Tag	amino acid sequence DYKDDDDK
DNA	deoxyribonucleic acid
CFSE	carboxyfluorescein succinimidyl ester
OVA	ovalbumin antigen
FACS	fluorescence-activated cell sorting
s.c.	subcutaneous
i.v.	intravenous
i.p.	intraperitoneal
n.d.	not determined

Examples were tested in selected biological assays one or more times. When tested more than once, data are reported as either average values or as median values, wherein

- the average value, also referred to as the arithmetic mean value, represents the sum of the values obtained divided by the number of times tested, and
- the median value represents the middle number of the group of values when ranked in ascending or descending order. If the number of values in the data set is odd, the median is the middle value. If the number of values in the data set is even, the median is the arithmetic mean of the two middle values.

Examples were synthesized one or more times. When synthesized more than once, data from biological assays represent average values or median values calculated utilizing data sets obtained from testing of one or more synthetic batch.

The *in vitro* activity of the compounds of the present invention can be demonstrated in the following assays:

Human DGKζ kinase activity inhibition assay.

Human diacylglycerol kinase zeta (DGKζ) inhibitory activity of compounds of the present invention was quantified employing the human DGKζ kinase activity assay as described in the following paragraphs. In essence, the enzyme activity was measured by quantification of the adenosine-di-phosphate (ADP) generated as a co-product of the enzyme reaction via the "ADP-Glo™ Kinase Assay" kit from the company Promega. This detection system works as follows: In a first step the adenosine-tri-phosphate (ATP) not consumed in the kinase reaction is quantitatively converted to cyclic adenosine-mono-phosphate (cAMP) employing an adenylate cyclase ("ADP-Glo-reagent"), then the adenylate cyclase is stopped and the ADP generated in the kinase reaction is converted to ATP, which subsequently generates in a luciferase-based reaction a glow-luminescence signal ("Kinase Detection Reagent").

C-terminally FLAG-tagged, recombinant full-length human DGKζ (inhouse expressed in baculovirus infected insect cells, purified using anti-Flag pulldown and size exclusion chromatography) was used as enzyme. As an alternative, commercially available enzyme by Carnabio can be used. As substrate for the kinase, 1,2-dioleoyl-*sn*-glycerol, reconstituted in octyl-β-D-glucopyranoside micelles, was used. For the preparation of the micelles, 1 volume of a 16.1 mM solution of 1,2-dioleoyl-*sn*-glycerol (Avanti, Cat. # O8001-25G) in chloroform was slowly evaporated using a nitrogen stream. Subsequently, 22.55 volumes of a 510 mM solution of octyl-β-D-glucopyranoside (Sigma-Aldrich, Cat. # O8001-10G) in 50 mM MOPS buffer (pH 7.4) were added, and the mixture was sonicated in an ultrasonic bath for 20 s. Then 35 volumes of 50 mM MOPS buffer (pH 7.4) were added to yield a solution of 0.28 mM 1,2 dioleoyl-sn-glycerol and 200 mM octyl-β-D-glucopyranoside, which was aliquoted, flash-frozen in liquid nitrogen, and stored at -20°C until use. For each experiment, a fresh aliquot was quickly thawed and diluted 24-fold with aqueous assay buffer (described below) containing 95.7 µM adenosine triphosphate (Promega) to yield a 1.67-fold concentrated substrate solution.

For the assay 50 nl of a 100-fold concentrated solution of the test compound in dimethyl sulfoxide (DMSO, Sigma) was pipetted into either a white 1536-well or a white low-volume 384-well microtiter plate (both Greiner Bio-One, Frickenhausen, Germany). Subsequently, 2 µl of a solution of human DGKζ in aqueous assay buffer [50 mM (3-(N-morpholino)propanesulfonic acid (MOPS, pH 7.4, Sigma-Aldrich), 1 mM dithiothreitol (DTT, Sigma-Aldrich), 100 mM NaCl (Sigma-Aldrich), 10 mM $MgCl_2$ (Sigma-Aldrich), 0.1 % (w/v) bovine gamma globulin (BGG, Sigma-Aldrich), 1 µM $CaCl_2$ (Sigma-Aldrich)] were added to the wells, and the mixture was incubated for 15 min at 22°C to allow pre-binding of the test compounds to the enzyme. The reaction was initiated by the addition of 3 µL of substrate solution [preparation described above; 11.7 µM 1,2-dioleoyl-*sn*-glycerol (=> final conc. in the 5 µL assay volume is 7 µM), 8.33 mM octyl-β-D-

glucopyranoside (=> final conc. in 5 µL assay volume is 5 mM), and 91.67 µM adenosine triphosphate (=> final conc. in 5 µL assay volume is 55 µM) in assay buffer] and the resulting mixture was incubated for a reaction time of 20 min at 22°C. The concentration of DGKζ was adjusted depending of the activity of the enzyme lot and was chosen appropriate to have the assay in the linear range, a typical concentration is about 0.1 nM. The reaction was stopped by the addition of 2.5 µL of "ADP-Glo-reagent" (1 to 1.5 diluted with water) and the resulting mixture was incubated at 22°C for 1 h to convert the ATP not consumed in the kinase reaction completely to cAMP. Subsequently 2.5 µl of the "kinase detection reagent" (1.2fold more concentrated than recommended by the producer) were added, the resulting mixture was incubated at 22°C for 1 h and then the luminescence measured with a suitable measurement instrument (e.g. Viewlux™ from Perkin-Elmer). The amount of emitted light was taken as a measure for the amount of ADP generated and thereby for the activity of the DGKζ.

The data were normalised (enzyme reaction without inhibitor = 0 % inhibition, all other assay components but no enzyme = 100 % inhibition). Usually the test compounds were tested on the same microtiterplate in 11 different concentrations in the range of 20 µM to 0.07 nM (20 µM, 5.7 µM, 1.6 µM, 0.47 µM, 0.13 µM, 38 nM, 11 nM, 3.1 nM, 0.9 nM, 0.25 nM and 0.07 nM, the dilution series prepared separately before the assay on the level of the 100fold concentrated solutions in DMSO by serial dilutions, exact concentrations may vary depending pipettors used) in duplicate values for each concentration and IC_{50} values were calculated using Genedata Screener™ software.

Table 18: IC_{50} values of examples in *in vitro* human DGKζ kinase activity inhibition assays.

Example number	IC_{50} [nM]
1	946
2	935
3	927
4	833
5	757
6	740
7	705
8	618
9	536

Example number	IC_{50} [nM]
10	425
11	406
12	364
13	357
14	334
15	266
16	283
17	261
18	207
19	200
20	161
21	142
21.1	5510
21.2	51
22	130
23	130
24	115
25	101
26	74.8
27	69.6
27.1	8650
27.2	43.6
28	61
29	58.4
29.1	12500
29.2	46.2
30	57.5

Example number	IC_{50} [nM]
31	43.5
32	38.7
33	42.8
33.1	8610
33.2	22.8
34	34.4
35	25.3
36	22.2
37	19.8
37.1	2000
37.2	9.46
38	19.3
38.1	2000
38.2	7.37
39	19
40	15.4
40.1	792
40.2	7.08
41	13.5
41.1	2930
41.2	7.73
42	11.3
43	11.1
43.1	2730
43.2	5.93
44	8.83
44.1	1390

Example number	IC_{50} [nM]
44.2	6.72
45	338
45.1	201
45.2	8910
45.3	1050
45.4	> 20000
46	7.07
46.1	1470
46.2	5.69
47	3.77
47.1	1020
47.2	1.96
48	3.72
48.1	1.76
48.2	120
49	2.76
49.1	1030
49.2	2.1
50	378
50.1	127
50.2	14300
51	16.6
51.1	8.85
51.2	872
52	99.2
52.1	72.7
52.2	11400

Example number	IC_{50} [nM]
53	30.8
53.1	20.3
53.2	1780
54	20.7
55	9.74
55.1	6
55.2	835
56	120
56.1	50.5
56.2	7640
57	155
57.1	137
57.2	14638
58	16.7
58.1	8
58.2	1047
59	10.3
59.1	4
59.2	424
60	403
61	93.2
61.1	5180
61.2	108
62	32.2
62.1	4620
62.2	23.2
63	33.9

Example number	IC_{50} [nM]
63.1	5170
63.2	18.5
64	55.8
65	101
66	363
67	2270
68	457
69	64.1
70	196
71	2310
72	985
73	148
73.1	3720
73.2	82.1
74	190
74.1	17100
74.2	81.4
75	419
75.1	> 20000
75.2	214
76	252
76.1	114
76.2	11000
77	533
77.1	234
77.2	10200
78	7220

Example number	IC_{50} [nM]
78.1	> 20000
78.2	7550
79	6790
79.1	1660
79.2	2390
80	10.8
81	8.71
81.1	1020
81.2	10.1
82	89.6
83	24.3
84	24.6
85	20.3
86	759
87	8.53
88	667
89	131
90	63.3
91	701
92	16.7
93	187
94	25.7
95	39
96	31.4
97	24.7
98	73.5
99	75.8

Example number	IC_{50} [nM]
100	176
101	329
102	506
103	41.9
104	234
105	6.45
106	33.3
107	77.3
108	19.4
109	51.7
110	366
111	334
112	300
113	703
114	658
115	272
116	581
117	14.9
118	22.4
119	4.54
120	16.7
121	19.9
122	9.07
123	100
124	48.3
125	44
126	28.8

Example number	IC_{50} [nM]
127	73.1
128	72.2
129	97.1
130	46.5
131	180
132	93.3
133	42.5
134	76.8
135	49.5
136	740
137	238
138	61.6
139	56.9
140	37.5
141	389
142	14.5
143	12.7
144	8.79
145	2.66
146	21.6
147	291
148	76.4
149	405
150	372
151	387
152	111
153	107

Example number	IC_{50} [nM]
154	55.6
155	200
156	231
157	190
158	6.71
159	214
160	187
160.1	115
160.2	8448
161	15
161.1	9
161.2	2573
162	22
162.1	12
162.2	6574
163	9
163.1	5
163.2	1091
164	7
164.1	5
164.2	944
165	3
165.1	2
165.2	331
166	3
166.1	2
166.2	129

Example number	IC_{50} [nM]
167	2
167.1	3
167.2	303
168	19
169	3
169.1	3
169.2	859
170	7
170.1	5
170.2	1000
171	11
172	46
172.1	24
172.2	4892
173	25
174	51
174.1	26
174.2	3793
175	20
176	91
176.1	34
176.2	672
177	40
178	48
179	57
180	62
181	65

Example number	IC_{50} [nM]
182	91
182.1	84
182.2	10527
183	222
184	428
184.1	297
184.2	> 20000
185	301
186	392
187	1400
187.1	553
187.2	> 20000
188	1240
189	6352
190	553
191	356
192	224
193	35
194	66
195	1000
196	128
197	90
198	88
199	396
200	70
201	25
202	69

Example number	IC_{50} [nM]
203	381
204	73
205	54
206	48
207	22
208	672
209	45
210	69
211	183
212	41
213	42
214	16
215	279
216	32
217	41
218	64
219	13
220	219
221	31
222	108
223	235
224	45
225	252
226	87
227	393
228	218
229	193

Example number	IC_{50} [nM]
230	199
231	662
232	112
233	267
234	1640
235	542
236	730
237	749
238	667
239	236
240	1328
241	382
242	2031
243	51
244	30
245	22
246	662
247	40
248	136
249	120
250	36
251	87
252	106
253	59
254	32
255	76
256	9

Example number	IC_{50} [nM]
257	n.d.
258	19
259	19
260	29
261	90
262	6
263	539
264	376
265	459
266	287
267	63
268	3
269	12
270	13
271	18
272	39
273	20
274	107
275	29
276	29
277	494
278	230
279	48
280	43
281	98
282	53
283	36

Example number	IC_{50} [nM]
284	33
285	68
285.1	34
285.2	432
286	31
287	18
288	3442
289	10
290	936
291	178
292	282

Table 19: IC_{50} values of intermediates in *in vitro* human DGKζ kinase activity inhibition assays.

Intermediate number	IC_{50} [nM]
41	> 20000
43	> 20000
62	> 20000
63	> 20000
64	> 20000
65	> 20000
66	> 20000
67	> 20000

Transactivation Assay in Jurkat IL2-reporter cell line

Transactivation assays were carried out in Jurkat cells purchased from Promega (Promega, #CS187001) stably transfected with a firefly luciferase reporter gene construct under the control of the IL2-promoter. Cells were cultured as specified by the manufacturer. Bulk cells were harvested at a culture density of approx. 1E+06 cells/mL, suspended in cryo-storage medium (70%RPMI/20%FCS/10%DMSO), frozen at controlled rate of -1°/min in 1.8 mL cryo-vials with cell densities of 1E+07 to 1E+08 cells per vial, and stored at -150°C or below until further use. Frozen cells were thawed and cultured in medium at a starting density of 3.5E+05 cells/mL for 6 days. On day 6 cells were centrifuged for 5 min at 300 x g, medium was decanted and cell concentration was adjusted to 5.0E+06 cells/mL with fresh assay medium (500 mL RPMI (Gibco, # 22400) + 5 mL L-Glutamin (Sigma, #G7513) + 5 mL Penicillin / Streptomycin (Sigma #P0781) + 5 mL Non-essential amino acids (Invitrogen, #11140) + 5 mL sodium-pyruvate (Gibco #1136088), 5 mL FBS (Biochrom, #S0615)). Cell working stock was split in two parts: neutral control and compounds with EC30 stimulation, high control with EC100 stimulation.

An antibody premix was prepared by diluting anti-CD3 (BD Pharmingen, #555329), anti-CD28 (BD Pharmingen, #555725) and goat anti mouse anti-IgG (ThermoFisher, #31160) antibodies at 1/1/4 ratio in assay medium at 2-fold of final concentration (final concentrations depend on cell batch, typically for neutral control 0.055/0.055/0.22 µg/mL, for high control 0.5/0.5/2 mg/mL). The premix solutions were added to the cells in 1+1 volume prior use.

Fifty nL of a 100-fold concentrated solution of the test compounds in DMSO were transferred into a white microtiter test plate (384, Greiner Bio-One, Germany). For this, either a Hummingbird liquid handler (Digilab, USA) or an Echo acoustic system (Labcyte, USA) was used. Five µL of the freshly prepared cell suspension was added to the wells of a test plate and incubated at 37°C in a 5% CO_2 atmosphere. After completion of the incubation for 4 hours, 3 µl of Bio-Glo Luciferase assay reagent (Promega, #G7941, prepared as recommended by the supplier) were added to all wells. The test plate was incubated at 20°C for 10 min before measurement of the luminescence in a microplate reader (typically Pherastar by BMG, Germany, or ViewLux by Perkin-Elmer, USA). Data were normalized (neutral control = 0% effect, high control = 100% effect). Compounds were tested in duplicates at up to 11 concentrations (typically 20 µM, 5,7 µM, 1,6 µM, 0,47 µM, 0,13 µM, 38 nM, 11 nM, 3,1 nM, 0,89 nM, 0,25 nM and 0,073 nM). Dilution series were made prior to the assay in a 100-fold concentrated form by serial dilution. EC_{50} values were calculated by 4-Parameter fitting using a commercial software package (Genedata Analyzer, Switzerland).

Polyclonal activation of human PBMCs

To test the effect of DGKζ inhibitors of the present invention on IL-2 and IFN-γ secretion of human Peripheral Blood Mononuclear Cells (PBMCs) a 24h human PBMC assay was performed as screening assay. For this, a 96 well flat bottom plate was coated with a suboptimal stimulation condition (EC 10-30) of human aCD3 (Invitrogen, clone OKT3) antibody in 50 µL PBS/well at 4°C overnight. PBMCs isolated and frozen at liquid N_2 from leucapherese samples was thawed and resuspended in culture medium (X-Vivo-20). 4 x 10^5 cells/well were plated. Wells were treated with the DGKζ inhibitors of the present invention at the respective concentrations (5-fold dilution steps from 10 µM to 3 nM) and the final DMSO concentration per well is 0.1%. Medium+ DMSO (0.1%) was used as baseline value. As positive controls 1000 ng/mL aCD3 + aCD28 (1 µg/mL) and a DGKζ reference inhibitor was used. After 24 h the medium was collected and hIL-2 or hIFN-γ ELISA were performed. The following parameters were calculated: EC_{50} value, concentration at 50% increase; max increase in % and respective concentration and maximum effect normalized to max concentration (10 µM) of a selected DGKζ reference inhibitor.

***In vitro* activation of mouse OT-I antigen-specific T-cells**

To test the effect of DGKζ inhibitors of the present invention in murine antigen-specific T-cells, spleens and lymph nodes of OT-I mice were collected and mashed through a 40 µm cell strainer and incubated for 1 min in 1 mL ACK lysing buffer (Gibco)/spleen. 4x106 cells/mL were incubated in medium containing 0.05 ng/mL SIINFEKL (figure 2) in a 50 mL falcon at 37°C for 30 min. Afterwards cells were centrifuged and 4x106 cells/mL were resuspended in fresh medium (DMEM; 10% FCS, 1% Pen/Strep, 0.1% β-mercaptoethanol, 1% HEPES). 4x105 cells were plated per well in a 96-well round bottom plate. Wells were treated with DGKζ inhibitors of the present invention at the respective concentrations (5-fold dilution steps from 10 µM to 3 nM) in a final DMSO concentration of 0.1%. Medium + DMSO (0.1%) was used as baseline value. As positive controls cells incubated with the 4x SIINFEKL concentration (0.2ng/ml) and a DGKζ reference inhibitor were used. The plates were centrifuged to reduce the distance between T-cells and APCs before incubation. After 24 h the medium was collected and mIL-2 or mIFN-γ ELISAs were performed. The following parameters were calculated: EC_{50} value, concentration at 50% increase; max increase in % and respective concentration and maximum effect normalized to max concentration (10 µM) of a selected DGKζ reference inhibitor.

DGKζ Surface Plasmon Resonance Interaction Assay

The ability of the compounds described in this invention to bind to DGKζ were determined using surface plasmon resonance (SPR). This allows for the quantification of binding in terms of the equilibrium dissociation constant (K_D [M]), as well as association and dissociation rate constants (k_{on} [1/Ms] and k_{off} [1/s], respectively). The measurements were performed using Biacore® T200, Biacore® S200 or Biacore® 8K (GE Healthcare).

All buffers described in this section were prepared with 10 x HBS-P+ Buffer (GE Healthcare, #BR100671) supplemented with additional buffer components as indicated below, dithiothreitol (DTT from Sigma, #D0632-25G), Adenosine 5′-triphosphate (ATP from Sigma, #A26209-10G), $MgCl_2$ (Sigma, #M1028-100ML), dimethyl sulfoxide (DMSO from Biomol, #54686.500).

For SPR measurements, recombinant and biotinylated human DGKζ (obtained from Carna Biosciences, Product number: 12-410-20N) was immobilized via the streptavidin-biotin interaction onto a Series S Sensor Chip SA (GE Healthcare, # BR-1005-31). Briefly, DGKζ was diluted to a concentration of 10 µg/mL in Immobilization Buffer (10 mM HEPES, 150 mM NaCl, 0.05% v/v Surfactant P20, 2 mM $MgCl_2$, 1 mM DTT, pH 7.4) and captured on the SA Chip surface using a flow rate of 10 µL/min for 500 seconds at a temperature of 10°C. Immobilization levels of approximately 6000 RU were typically achieved. The reference surface consisted of a streptavidin surface without immobilized protein. Compounds were diluted from 10 mM DMSO stock solution into Running Buffer (10 mM HEPES, 150 mM NaCl, 0.05% v/v Surfactant P20, 2 mM $MgCl_2$, 1 mM DTT, 0.2 mM ATP and 1% v/v DMSO, pH 7.4). For SPR-binding measurements serial dilutions (typically 1:3 dilutions resulting in 8 concentrations up to 2 µM or 20 µM) were injected over immobilized protein. Binding affinity and kinetics were measured at 18°C and at a flow rate of 100 µL/min.

A variation of the assay with an additional regeneration step was performed by injection of Regeneration Buffer without ATP (10 mM HEPES, 150 mM NaCl, 0.05% v/v Surfactant P20, 1 mM DTT and 1% v/v DMSO, pH 7.4) for 200 s at a flow rate of 30 µL/min

The double-referenced sensorgrams were fit to a simple reversible Langmuir 1:1 reaction mechanism as implemented in the Biacore® T200, S200 and 8K evaluation software (Biacore T200 Evaluation Software version 2.0, Biacore S200 Evaluation Software version 1.0, Biacore 8K Evaluation Software, GE Healthcare).

Expression of DGKζ in insect cells using the Baculovirus system

Expression constructs:

The cDNA encoding the full length sequence of human DGKζ (Uniprot **Q13574-2**) was optimized for expression in eukaryotic cells and synthesized by the GeneArt Technology at Life Technologies.

The DNA sequence encoded the following sequence:

Construct DGKζ_hu amino acid M1 to V928

Additionally the expression construct encoded: a Kozak DNA sequence for translation initiation (GCCACC), a translational start codon for methionine followed by amino acid glycine, a Flag (DYKDDDDK) sequence at the N-terminus of DGKζ, and at the C-terminus of DGKζ two stop codons and moreover 5' and 3' att-DNA sequences for Gateway Cloning.

The DGKζ construct was subcloned using the Gateway Technology into the Destination vector pD-INS. The vector pD-INS is a Baculovirus transfer vector (based on vector pVL1393, Pharmingen) which enables the expression of the Flag-DGKζ protein. The respective protein was named DGKz_hu_1.

Generation of recombinant Baculovirus

The DGKζ transfer vector was co-transfected in Sf9 cells with Baculovirus DNA (Flashbac Gold DNA, Oxford Expression Technologies) using Fugene HD (Roche). After 5 days the supernatant of the transfected cells containing the recombinant Baculovirus encoding the various DGK proteins was used for further infection of Sf9 cells for virus amplification whereby the virus titer was monitored using qPCR.

DGKζ expression in Sf9 cells using bioreactor

Sf9 cells cultured (Insect-xpress medium, Lonza, 27 °C) in a Wave-bioreactor with a disposable culture bag were infected at a cell density of 10^6 cells/mL with one of the recombinant baculovirus stocks at a multiplicity of infection of 1 and incubated for 72. Subsequently, the cells were harvested by centrifugation (800 xg) and the cell pellet frozen at -80 °C.

Purification of the DGKz_hu_1 protein:

Purification of the DGKz_hu_1 protein was achieved by a two-step chromatography procedure as follows.

The pelleted cells (from 8 L cell culture) were resuspended in Lysis-Buffer (25 mM Tris HCl 8.0; 500 mM NaCl; 250 mM Sucrose, 1 mM DTT; 0.1 % Triton X-100; Complete Protease Inhibitor Cocktail-(Roche)) and lysed by a freeze-thaw cycle followed by an incubation on ice for 60 min in the presence of Benzonase (25 U/mL). The lysate was centrifuged at 63.000 xg for 30 min at 4 °C. The soluble supernatant was than incubated with 40 mL anti-Flag M2 Agarose (Sigma) in a plastic flask rotating for 16 h at 4 °C for binding of the tagged DGKζ proteins, subsequently rinsed with 5 x 50 mL Wash-Buffer (25 mM Tris HCl 8.0; 500 mM NaCl; 250 mM Sucrose; 1 mM

DTT) and finally the bound protein was eluted using Elution-Buffer (Wash-Buffer with 250 µg/mL FLAG-Peptide, incubated 30 min. at 4 °C with 3 x25 mL).

The elution fractions from the affinity chromatography were concentrated (using Amicon Ultra 15, Centrifugal Filters, 30 kDa MW cut-off; Millipore #UFC903024) to 25 mL and applied to a size exclusion chromatography column (S200 prep grade 26/60, GE Healthcare) and the resulting monomeric peak fraction was collected, pooled and again concentrated. Wash-buffer with 300 mM NaCl was used for size exclusion chromatography and the final concentrated sample. The final protein sample concentration was 5 to 10 mg/mL and the yield was 5 mg final protein per L cell culture.

The *in vivo* activity of the compounds of the present invention can be demonstrated in the following assays:

***In vivo* activation of murine antigen specific OT-I T cells**

Oral Administration of compounds enhances antigen-specific T cell activation *in vivo*.

Direct detection of antigen-specific T cell proliferation *in vivo* is technically challenging, since it requires the presence of T cells specific for a cognate antigen and also a specific measurement procedure for cell proliferation. Both these requirements are fulfilled in the OT-I transfer model, which utilizes the direct transfer of CD8 T cells transgenic for a T cell receptor recognizing an Ovalbumin-derived peptide as antigen.

Before transfer, the OT-I T cells were labeled with the fluorescent dye CFSE, which was diluted by every cell division and therefore allowed detection of cell proliferation. After transfer of the CFSE-labeled T cells, mice were vaccinated with the Ovalbumin antigen OVA-30 (figure 3). Only transferred OT-I cells were able to recognize the OVA-antigen presented by APC and only these transferred T cells then got activated. Flow cytometric analysis of CFSE-levels in the OT-I cells can be combined with measurement of multiple activation markers like CD69, CD25 and PD1.

In particular, Wild type C57Bl6 mice received 2x10x6 CFSE-labeled OT-I T cells and were vaccinated one day later by intravenous application of 2.5 µg OVA-30. Mice were then divided into groups which received vehicle only, DGKζ inhibitors of the present invention alone or in combination with other immune modulating agents. Mice were treated for 2 to 20 days and T cell composition (incl. transferred OT-1 cells) of spleen, blood and lymph nodes were analysed by FACS.

***In vivo* syngeneic tumor models**

Mice were assigned to a study at the age of 6-8 weeks. Animal husbandry, feeding and health conditions were according to animal welfare guidelines. Syngeneic tumor cell lines were cultivated with appropriate medium and split at least 3 times before inoculation. Female mice were inoculated with appropriate amount of tumor cells in medium or a medium /matrigel mixture s.c, i.v., or i.p, depending on the model. After 4-10 days the mice were randomized and therapeutic treatment started when tumors had reached a size of approx. 40-70mm^2.

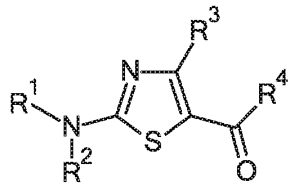
Tumor size was measured using calipers determining length (a) and width (b). Tumor volume was calculated according to:

v=(a x b^2)/2

Significance of monotherapies and combination treatment was calculated *versus* control group as determined by 2-Way ANOVA analysis.

CLAIMS

1. A compound of general formula (I):



(I)

in which :

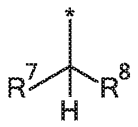
R^1 represents a phenyl or 6-membered heteroaryl group optionally substituted, one, two, or three times, each substituent independently selected from a halogen atom or a group selected from hydroxy, cyano, nitro, C_1-C_6-alkyl, (phenyl)-(C_1-C_3-alkyl)-, C_1-C_6-haloalkyl, C_1-C_6-alkoxy, (phenyl)-(C_1-C_3-alkoxy)-, C_1-C_6-haloalkoxy, -N(R^5)(R^6),

wherein the phenyl groups in said (phenyl)-(C_1-C_3-alkyl)- and (phenyl)-(C_1-C_3-alkoxy)- groups are optionally substituted one or two times, each substituent independently selected from a halogen atom or a group selected from cyano, methyl, ethyl, trifluoromethyl, methoxy, ethoxy, dimethylamino and trifluoromethoxy,

or two substituents attached to adjacent carbon atoms of said phenyl or 6-membered heteroaryl group together form a bivalent group selected from –(CH_2)$_3$-, -(CH_2)$_4$-, -(CH_2)$_2$-O-, -(CH_2)$_3$-O-, -CH_2-O-CH_2-, -(CH_2)$_2$-O-CH_2-, -O-CH_2-O-, -O-CH_2-CH_2-O-, -O-CF_2-O-, -O-CH_2-CF_2-O-, and -O-CF_2-CF_2-O-,

or

R^1 represents a 5-membered heteroaryl group optionally substituted one or two times, each substituent independently selected from a halogen atom or a group selected from cyano, C_1-C_3-alkyl, and C_1-C_3-alkoxy;

R^2 represents a group  ,

wherein "*" indicates the point of attachment to the nitrogen atom to which R^2 is attached;

R^3 represents a group selected from methyl and -NH_2;

R^4 represents a phenyl or 6-membered heteroaryl group optionally substituted, one, two, or three times, each substituent independently selected from a halogen atom or a group selected from cyano, nitro, C_1-C_6-alkyl, (phenyl)-(C_1-C_3-alkyl)-, (5- or 6-membered heteroaryl)-(C_1-C_3-alkyl)-, (C_3-C_7-cycloalkyl)-(C_1-C_3-alkyl)-, ((R^9)O)-(C_1-C_6-alkyl)-, C_1-C_6-haloalkyl, C_3-C_7-cycloalkyl, -OR^9, -$N(R^{10})(R^{11})$, ((R^{10})(R^{11})N)-(C_1-C_3-alkyl)-, -C(=O)-$N(R^{12})(R^{13})$, -$S(=O)_n$-R^{14}, -C(=O)R^{14}, -C(=O)-OR^{17}, and a 5- or 6-membered heteroaryl group which itself is optionally substituted with one or two substituents selected from a halogen atom and a methyl group,

or two substituents attached to adjacent carbon atoms of said phenyl or 6-membered heteroaryl group together form a bivalent group selected from –$(CH_2)_3$-, -$(CH_2)_4$-, -$(CH_2)_2$-O-, -$(CH_2)_3$-O-, -CH_2-O-CH_2-, -$(CH_2)_2$-O-CH_2-, -O-CH_2-O-, -O-CH_2-CH_2-O-, -O-CF_2-O-, -O-CH_2-CF_2-O-, and -O-CF_2-CF_2-O-;

R^5 and R^6 represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_4-alkyl, (C_1-C_4-alkyl)-C(=O)-, C_3-C_4-cycloalkyl and (phenyl)-(C_1-C_3-alkyl)-,

or

R^5 and R^6, together with the nitrogen atom to which they are attached, represent a monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group which is optionally substituted one, two or three times, each substituent independently selected from a halogen atom or a group selected from oxo, hydroxy, C_1-C_4-alkyl, (C_1-C_4-alkyl)-C(=O)-, C_3-C_4-cycloalkyl and C_1-C_4-alkoxy;

R^7 represents a hydrogen atom or a C_1-C_2-alkyl group;

R^8 represents a group selected from -C(=O)-NH_2 and -$S(=O)_2$-NH_2;

R^9 represents a hydrogen atom or a group selected from C_1-C_6-alkyl, (5- or 6-membered heteroaryl)-(C_1-C_3-alkyl)-, (phenyl)-(C_1-C_3-alkyl)-, C_1-C_6-haloalkyl, C_2-C_4-hydroxyalkyl, (C_1-C_3-alkoxy)-C_2-C_3-alkyl-, ((C_1-C_3-alkyl)-C(=O)-O)-C_2-C_3-alkyl-, -$C(R^{18})(R^{19})$-C(=O)-OR^{17}, -$C(R^{18})(R^{19})$-C(=O)-$N(R^{20})(R^{21})$, -C(=O)-$N(R^{20})(R^{21})$, phenyl and 5- or 6-membered heteroaryl group,

wherein the phenyl group within said (phenyl)-(C_1-C_3-alkyl)- group and said phenyl group itself, and the 5- or 6-membered heteroaryl group within said (5- or 6-membered heteroaryl)-(C_1-C_3-alkyl)- group and said 5- or 6-membered heteroaryl group itself are optionally substituted one or two times, each substituent independently selected from a halogen atom or a group selected from cyano, methyl, ethyl, trifluoromethyl, methoxy, ethoxy, dimethylamino and trifluoromethoxy;

R^{10} and R^{11} represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_2-C_4-hydroxyalkyl, (C_1-C_3-alkoxy)-C_2-C_3-alkyl-, ((R^{22})(R^{23})N)-C_2-C_3-alkyl, (C_3-C_7-cycloalkyl)-(C_1-C_3-alkyl)-, (C_1-C_4-alkyl)-C(=O)-, C_3-C_7-cycloalkyl, (C_3-C_7-cycloalkyl)-C(=O)-, (phenyl)-(C_1-C_3-alkyl)-, (phenyl)-(C_1-C_3-alkyl)-C(=O)-, (phenyl)-(C_1-C_3-alkyl)-O-C(=O)-, phenyl and a 5- or 6-membered heteroaryl group,

wherein C_3-C_7-cycloalkyl, and the C_3-C_7-cycloalkyl within said (C_3-C_7-cycloalkyl)-(C_1-C_3-alkyl)- and (C_3-C_7-cycloalkyl)-C(=O)- groups are optionally substituted one or two times, each substituent independently selected from a fluorine atom or a group selected from cyano, C_1-C_2-alkyl and C_1-C_2-haloalkyl,

and wherein said phenyl and said 5- or 6-membered heteroaryl group, and the phenyl groups within said (phenyl)-(C_1-C_3-alkyl)-, (phenyl)-(C_1-C_3-alkyl)-C(=O)- and (phenyl)-(C_1-C_3-alkyl)-O-C(=O)- groups, are optionally substituted one or two times, each substituent independently selected from a halogen atom or a group selected from cyano, methyl, ethyl, trifluoromethyl, methoxy, ethoxy, dimethylamino and trifluoromethoxy,

or

R^{10} and R^{11}, together with the nitrogen atom to which they are attached, represent a monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group, or a bicyclic nitrogen containing 5- to 11-membered heterocycloalkyl group, which are optionally substituted one, two or three times, each substituent independently selected from a halogen atom or a group selected from cyano, oxo, hydroxy, C_1-C_4-alkyl, C_1-C_4-haloalkyl, (C_1-C_4-alkyl)-C(=O)-, C_3-C_7-cycloalkyl, C_1-C_4-alkoxy, -N(R^{22})(R^{23}), and a monocyclic 4- to 7-membered heterocycloalkyl group;

R^{12} and R^{13} represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-hydroxyalkyl, (C_1-C_4-alkoxy)-C_2-C_3-alkyl-, (C_1-C_4-haloalkoxy)-C_2-C_3-alkyl-, (phenoxy)-C_2-C_3-alkyl-, C_3-C_7-cycloalkyl, monocyclic 4- to 7-membered heterocycloalkyl and (phenyl)-(C_1-C_3-alkyl)-,

wherein C_3-C_7-cycloalkyl and monocyclic 4- to 7-membered heterocycloalkyl are optionally substituted one, two or three times, each substituent independently selected from a halogen atom or a group selected from cyano, oxo, hydroxy, C_1-C_4-alkyl, (C_1-C_4-alkyl)-C(=O)-, C_3-C_4-cycloalkyl and C_1-C_4-alkoxy,

and wherein the phenyl groups within said (phenoxy)-C_2-C_3-alkyl- group and said (phenyl)-(C_1-C_3-alkyl)- group are optionally substituted one or two times, each substituent independently selected from a halogen atom or a group selected from cyano, methyl, ethyl, trifluoromethyl, methoxy, ethoxy, dimethylamino and trifluoromethoxy,

or

R^{12} and R^{13}, together with the nitrogen atom to which they are attached, represent a monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group which is optionally substituted one, two or three times, each substituent independently selected from a halogen atom or a group selected from cyano, oxo, hydroxy, C_1-C_4-alkyl, (C_1-C_4-alkyl)-C(=O)-, C_3-C_4-cycloalkyl and C_1-C_4-alkoxy;

R^{14} represents a group selected from C_1-C_4-alkyl, C_1-C_4-haloalkyl and phenyl,

wherein the phenyl group is optionally substituted one or two times, each substituent independently selected from a halogen atom or a group selected from cyano, methyl, ethyl, trifluoromethyl, methoxy, ethoxy, dimethylamino and trifluoromethoxy;

R^{17} represents a C_1-C_4-alkyl group;

R^{18} and R^{19} represent, independently from each occurrence, a hydrogen atom or a C_1-C_4-alkyl group;

R^{20} represents a hydrogen atom or a group selected from C_1-C_6-alkyl, C_3-C_4-alkenyl, C_3-C_4-alkynyl, C_1-C_3-alkoxy, C_3-C_7-cycloalkyl, bicyclic C_5-C_{11}-cycloalkyl, adamantyl, monocyclic 4- to 7-membered heterocycloalkyl, bicyclic 5- to 11-membered heterocycloalkyl, phenyl, naphthyl, and 5- to 10-membered heteroaryl,

wherein said C_1-C_6-alkyl group is optionally substituted one, two or three times, each substituent independently selected from a halogen atom or a group selected from hydroxy, cyano, C_1-C_3-alkoxy, -N(R^{22})(R^{23}), C_3-C_7-cycloalkyl, bicyclic C_5-C_{11}-cycloalkyl, adamantyl, monocyclic 4- to 7-membered heterocycloalkyl, bicyclic 5- to 11-membered heterocycloalkyl, phenyl, and 5- to 10-membered heteroaryl, said phenyl and 5- to 10-membered heteroaryl substituents themselves being optionally substituted one or two times, each substituent independently selected from a halogen atom or a group selected from cyano, methyl, ethyl, trifluoromethyl, methoxy, ethoxy, dimethylamino and trifluoromethoxy,

and wherein C_3-C_7-cycloalkyl, bicyclic C_5-C_{11}-cycloalkyl, adamantyl, monocyclic 4- to 7-membered heterocycloalkyl and bicyclic 5- to 11-membered heterocycloalkyl

are optionally substituted one, two or three times, each substituent independently selected from a halogen atom or a group selected from cyano, oxo, hydroxy, C_1-C_4-alkyl, (C_1-C_4-alkyl)-C(=O)-, C_3-C_4-cycloalkyl and C_1-C_4-alkoxy,

and wherein said phenyl, naphthyl and 5- to 10-membered heteroaryl groups are optionally substituted one, two or three times, each substituent independently selected from a halogen atom or a group selected from cyano, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, -N(R^{22})(R^{23}) and -C(=O)-N(R^{24})(R^{25}),

R^{21} represents a hydrogen atom or a C_1-C_4-alkyl group,

or

R^{20} and R^{21}, together with the nitrogen atom to which they are attached, represent a monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group which is optionally benzocondensed, and which is optionally substituted one, two or three times, each substituent independently selected from a halogen atom or a group selected from cyano, oxo, hydroxy, C_1-C_4-alkyl, C_1-C_4-haloalkyl, (phenyl)-(C_1-C_3-alkyl)-, (C_1-C_4-alkyl)-C(=O)-, C_3-C_4-cycloalkyl, C_1-C_4-alkoxy, C_1-C_3-haloalkoxy, -N(R^{22})(R^{23}) and -C(=O)-N(R^{24})(R^{25});

R^{22} and R^{23} represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_2-alkyl and (C_1-C_2-alkyl)-C(=O)-;

R^{24} and R^{25} represent, independently from each occurrence, a hydrogen atom or a C_1-C_4-alkyl group, and

n represents an integer 0, 1, or 2,

or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

2. The compound according to claim 1, wherein:

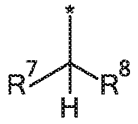
R^1 represents a phenyl or pyridinyl group optionally substituted, one, two, or three times, each substituent independently selected from a halogen atom or a group selected from hydroxy, cyano, nitro, C_1-C_4-alkyl, (phenyl)-(C_1-C_2-alkyl)-, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, (phenyl)-(C_1-C_2-alkoxy)-, C_1-C_4-haloalkoxy, -N(R^5)(R^6),

wherein the phenyl groups in said (phenyl)-(C_1-C_2-alkyl)- and (phenyl)-(C_1-C_2-alkoxy)- groups are optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a bromine atom, or a group selected from methyl, trifluoromethyl and methoxy,

or two substituents attached to adjacent carbon atoms of said phenyl or pyridinyl group together form a bivalent group selected from –$(CH_2)_3$-, -$(CH_2)_4$-, -$(CH_2)_2$-O-, -$(CH_2)_3$-O-, -CH_2-O-CH_2-, -O-CH_2-O-, -O-CH_2-CH_2-O- and -O-CF_2-O-,

or

R^1 represents a pyrazolyl group optionally substituted one or two times, each substituent independently selected from a halogen atom or a group selected from cyano, C_1-C_2-alkyl, and C_1-C_2-alkoxy;

R^2 represents a group  ,

wherein "*" indicates the point of attachment to the nitrogen atom to which R^2 is attached;

R^3 represents a group selected from methyl and -NH_2;

R^4 represents a phenyl or pyridinyl group optionally substituted, one, two, or three times, each substituent independently selected from a halogen atom or a group selected from cyano, nitro, C_1-C_4-alkyl, (phenyl)-(C_1-C_2-alkyl)-, (5-membered heteroaryl)-(C_1-C_2-alkyl)-, (C_3-C_7-cycloalkyl)-(C_1-C_2-alkyl)-, ((R^9)O)-(C_1-C_4-alkyl)-, C_1-C_4-haloalkyl, C_3-C_7-cycloalkyl, -OR^9, -N(R^{10})(R^{11}), ((R^{10})(R^{11})N)-(C_1-C_3-alkyl)-, -C(=O)-N(R^{12})(R^{13}), S(=O)$_n$-R^{14}, -C(=O)R^{14}, -C(=O)-OR^{17}, and a 5-membered heteroaryl group which itself is optionally substituted with one or two methyl groups,

or two substituents attached to adjacent carbon atoms of said phenyl or pyridinyl group together form a bivalent group selected from –$(CH_2)_3$-, -$(CH_2)_4$-, -$(CH_2)_2$-O-, -$(CH_2)_3$-O-, -CH_2-O-CH_2-, -O-CH_2-O-, -O-CH_2-CH_2-O- and -O-CF_2-O-;

R^5 and R^6 represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_2-alkyl and (C_1-C_2-alkyl)-C(=O)-,

or

R^5 and R^6, together with the nitrogen atom to which they are attached, represent a monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group which is optionally substituted one or two times, each substituent independently selected from a fluorine

atom, a chlorine atom and a bromine atom, or a group selected from oxo, hydroxy, C_1-C_2-alkyl and (C_1-C_2-alkyl)-C(=O)-;

R^7 represents a hydrogen atom or a C_1-C_2-alkyl group;

R^8 represents a -C(=O)-NH_2 group;

R^9 represents a hydrogen atom or a group selected from C_1-C_4-alkyl, (phenyl)-(C_1-C_2-alkyl)-, C_1-C_4-haloalkyl, C_2-C_3-hydroxyalkyl, (C_1-C_2-alkoxy)-C_2-alkyl-, ((C_1-C_2-alkyl)-C(=O)-O)-C_2-alkyl-, -C(R^{18})(R^{19})-C(=O)-OR^{17}, -C(R^{18})(R^{19})-C(=O)-N(R^{20})(R^{21}), -C(=O)-N(R^{20})(R^{21}) and phenyl,

wherein the phenyl group within said (phenyl)-(C_1-C_2-alkyl)- group and said phenyl group itself are optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a bromine atom, or a group selected from cyano, methyl, trifluoromethyl and methoxy;

R^{10} and R^{11} represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_2-alkyl, C_1-C_2-haloalkyl, C_2-C_3-hydroxyalkyl, (C_1-C_2-alkoxy)-C_2-alkyl-, ((R^{22})(R^{23})N)-C_2-alkyl, (C_3-C_7-cycloalkyl)-(C_1-C_2-alkyl)-, (C_1-C_2-alkyl)-C(=O)-, C_3-C_7-cycloalkyl, (C_3-C_7-cycloalkyl)-C(=O)-, (phenyl)-(C_1-C_2-alkyl)-, (phenyl)-(C_1-C_2-alkyl)-C(=O)- and (phenyl)-(C_1-C_2-alkyl)-O-C(=O)-,

wherein C_3-C_7-cycloalkyl, and the C_3-C_7-cycloalkyl within said (C_3-C_7-cycloalkyl)-(C_1-C_2-alkyl)- and (C_3-C_7-cycloalkyl)-C(=O)- groups are optionally substituted one or two times, each substituent independently selected from a fluorine atom or a group selected from cyano, C_1-C_2-alkyl and C_1-C_2-haloalkyl,

and wherein the phenyl groups within said (phenyl)-(C_1-C_2-alkyl)-, (phenyl)-(C_1-C_2-alkyl)-C(=O)- and (phenyl)-(C_1-C_2-alkyl)-O-C(=O)- groups are optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a bromine atom, or a group selected from methyl, trifluoromethyl and methoxy,

or

R^{10} and R^{11}, together with the nitrogen atom to which they are attached, represent a monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group, or a bicyclic nitrogen containing 5- to 10-membered heterocycloalkyl group, which are optionally substituted one, two or three times, each substituent independently selected from a halogen atom or a group selected from cyano, oxo, hydroxy, C_1-C_2-alkyl, C_1-C_2-haloalkyl, (C_1-C_2-alkyl)-

C(=O)-, C_1-C_2-alkoxy, -N(R^{22})(R^{23}), and a monocyclic 4- to 7-membered heterocycloalkyl group;

R^{12} and R^{13} represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-hydroxyalkyl, (C_1-C_4-alkoxy)-C_2-C_3-alkyl-, (C_1-C_4-haloalkoxy)-C_2-C_3-alkyl-, (phenoxy)-C_2-C_3-alkyl-, C_3-C_7-cycloalkyl, monocyclic 4- to 7-membered heterocycloalkyl and (phenyl)-(C_1-C_3-alkyl)-,

wherein C_3-C_7-cycloalkyl and monocyclic 4- to 7-membered heterocycloalkyl are optionally substituted one or two times, each substituent independently selected from a halogen atom or a group selected from oxo, C_1-C_2-alkyl and (C_1-C_2-alkyl)-C(=O)-,

and wherein the phenyl groups within said (phenoxy)-C_2-C_3-alkyl- group and said (phenyl)-(C_1-C_3-alkyl)- group are optionally substituted one or two times, each substituent independently selected from fluorine atom, a chlorine atom and a bromine atom, or a group selected from cyano, methyl, trifluoromethyl and methoxy,

or

R^{12} and R^{13}, together with the nitrogen atom to which they are attached, represent a monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group which is optionally substituted one or two times, each substituent independently selected from a halogen atom or a group selected from oxo, C_1-C_2-alkyl and (C_1-C_2-alkyl)-C(=O)-;

R^{14} represents a group selected from C_1-C_2-alkyl, C_1-C_2-haloalkyl and phenyl,

wherein the phenyl group is optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a bromine atom, or a group selected from methyl, trifluoromethyl and methoxy;

R^{17} represents a C_1-C_4-alkyl group;

R^{18} and R^{19} represent, independently from each occurrence, a hydrogen atom or a C_1-C_2-alkyl group;

R^{20} represents a hydrogen atom or a group selected from C_1-C_6-alkyl, C_3-C_4-alkenyl, C_3-C_4-alkynyl, C_1-C_3-alkoxy, C_3-C_7-cycloalkyl, bicyclic C_5-C_{11}-cycloalkyl, adamantyl, monocyclic 4- to 7-membered heterocycloalkyl, bicyclic 5- to 10-membered heterocycloalkyl, phenyl, naphthyl, and 5- to 10-membered heteroaryl,

wherein said C_1-C_6-alkyl group is optionally substituted one, two or three times, each substituent independently selected from a halogen atom or a group selected from hydroxy, cyano, C_1-C_3-alkoxy, -N(R^{22})(R^{23}), C_3-C_7-cycloalkyl, bicyclic C_5-C_{11}-cycloalkyl, adamantyl, monocyclic 4- to 7-membered heterocycloalkyl, bicyclic 5- to 10-membered heterocycloalkyl, phenyl, and 5- to 10-membered heteroaryl, said phenyl and 5- to 10-membered heteroaryl substituents themselves being optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a bromine atom, or a group selected from methyl, trifluoromethyl and methoxy,

and wherein C_3-C_7-cycloalkyl, bicyclic C_5-C_{11}-cycloalkyl, adamantyl, monocyclic 4- to 7-membered heterocycloalkyl, bicyclic 5- to 10-membered heterocycloalkyl are optionally substituted one or two or three times, each substituent independently selected from a halogen atom or a group selected from cyano, oxo, hydroxy, C_1-C_2-alkyl and (C_1-C_2-alkyl)-C(=O)-,

and wherein said phenyl, naphthyl and 5- to 10-membered heteroaryl groups are optionally substituted one, two or three times, each substituent independently selected from a halogen atom or a group selected from cyano, C_1-C_2-alkyl, C_1-C_2-haloalkyl, C_1-C_2-alkoxy, C_1-C_2-haloalkoxy, -N(R^{22})(R^{23}) and -C(=O)-N(R^{24})(R^{25}),

R^{21} represents a hydrogen atom or a C_1-C_2-alkyl group,

or

R^{20} and R^{21}, together with the nitrogen atom to which they are attached, represent a monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group which is optionally benzocondensed, and which is optionally substituted one, two or three times, each substituent independently selected from a halogen atom or a group selected from cyano, oxo, hydroxy, C_1-C_2-alkyl, C_1-C_2-haloalkyl, (phenyl)-(C_1-C_2-alkyl)-, (C_1-C_2-alkyl)-C(=O)-, C_3-C_4-cycloalkyl, C_1-C_2-alkoxy, C_1-C_2-haloalkoxy, -N(R^{22})(R^{23}) and -C(=O)-N(R^{24})(R^{25});

R^{22} and R^{23} represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_2-alkyl and (C_1-C_2-alkyl)-C(=O)-;

R^{24} and R^{25} represent, independently from each occurrence, a hydrogen atom or a C_1-C_2-alkyl group, and

n represents an integer 0, 1, or 2,

or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

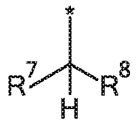
3. The compound according to claim 1 or 2, wherein:

R^1 represents a phenyl or pyridinyl group optionally substituted, one, two, or three times, each substituent independently selected from a fluorine atom, a chlorine atom and a bromine atom, or a group selected from hydroxy, cyano, C_1-C_4-alkyl, C_1-C_2-fluoroalkyl, C_1-C_2-alkoxy, (phenyl)-(C_1-C_2-alkoxy)-, C_1-C_2-fluoroalkoxy and -N(R^5)(R^6),

or two substituents attached to adjacent carbon atoms of said phenyl or pyridinyl group together form a bivalent group selected from –$(CH_2)_3$-, -O-CH_2-O- and -O-CF_2-O-,

or

R^1 represents a pyrazolyl group optionally substituted with one methyl group;

R^2 represents a group  ,

wherein "*" indicates the point of attachment to the nitrogen atom to which R^2 is attached;

R^3 represents a group selected from methyl and -NH_2;

R^4 represents a phenyl or pyridinyl group optionally substituted, one, two, or three times, each substituent independently selected from a halogen atom or a group selected from cyano, C_1-C_3-alkyl, ((R^9)O)-(C_1-C_3-alkyl)-, C_1-C_3-fluoroalkyl, -OR^9, -N(R^{10})(R^{11}), -C(=O)-N(R^{12})(R^{13}), S(=O)$_n$-R^{14} and -C(=O)-OR^{17},

or two substituents attached to adjacent carbon atoms of said phenyl or pyridinyl group together form a bivalent group selected from –$(CH_2)_3$-, -O-CH_2-O- and -O-CF_2-O-;

R^5 and R^6 represent, independently from each occurrence, a hydrogen atom or a C_1-C_2-alkyl group,

or

R^5 and R^6, together with the nitrogen atom to which they are attached, represent a monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group which is optionally substituted one or two times, each substituent independently selected from a fluorine atom or a group selected from hydroxy and C_1-C_2-alkyl;

R^7 represents a hydrogen atom or a C_1-C_2-alkyl group;

R^8 represents a -C(=O)-NH_2 group;

R^9 represents a hydrogen atom or a group selected from C_1-C_2-alkyl, benzyl, C_1-C_2-fluoroalkyl, C_2-hydroxyalkyl, (C_1-C_2-alkoxy)-C_2-alkyl-, ((C_1-C_2-alkyl)-C(=O)-O)-C_2-alkyl-, -$C(R^{18})(R^{19})$-C(=O)-OR^{17}, -$C(R^{18})(R^{19})$-C(=O)-$N(R^{20})(R^{21})$, -C(=O)-$N(R^{20})(R^{21})$ and phenyl,

wherein the phenyl group within said benzyl group and said phenyl group itself are optionally substituted one or two times, each substituent independently selected from a fluorine atom and a chlorine atom, or a group selected from cyano and methyl;

R^{10} and R^{11} represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_2-alkyl, C_1-C_2-fluoroalkyl, (C_3-C_5-cycloalkyl)-(C_1-C_2-alkyl)- (C_1-C_2-alkyl)-C(=O)-, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-(C=O)-, (phenyl)-(C_1-C_2-alkyl)-, (phenyl)-(C_1-C_2-alkyl)-C(=O)- and (phenyl)-(C_1-C_2-alkyl)-O-C(=O)-,

wherein C_3-C_7-cycloalkyl, and the C_3-C_5-cycloalkyl within said (C_3-C_5-cycloalkyl)-(C_1-C_2-alkyl)- and the C_3-C_7-cycloalkyl within the C_3-C_7-cycloalkyl-(C=O)- groups are optionally substituted one or two times, each substituent independently selected from a fluorine atom or a group selected from cyano, C_1-C_2-alkyl and C_1-C_2-fluoroalkyl,

and wherein the phenyl groups within said (phenyl)-(C_1-C_2-alkyl)-, (phenyl)-(C_1-C_2-alkyl)-C(=O)- and (phenyl)-(C_1-C_2-alkyl)-O-C(=O)- groups are optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a methyl group,

or

R^{10} and R^{11}, together with the nitrogen atom to which they are attached, represent a monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group which is optionally substituted one or two times, each substituent independently selected from a fluorine atom or a group selected from cyano, oxo, C_1-C_2-alkyl, C_1-C_2-fluoroalkyl and (C_1-C_2-alkyl)-C(=O)-;

R^{12} and R^{13} represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_4-alkyl, C_1-C_4-fluoroalkyl, C_1-C_4-hydroxyalkyl, (C_1-C_4-alkoxy)-C_2-C_3-alkyl-, (C_1-C_2-fluoroalkoxy)-C_2-C_3-alkyl-, (phenoxy)-C_2-C_3-alkyl-, C_3-C_7-cycloalkyl, monocyclic 4- to 7-membered heterocycloalkyl and (phenyl)-(C_1-C_2-alkyl)-,

wherein C_3-C_7-cycloalkyl and monocyclic 4- to 7-membered heterocycloalkyl are optionally substituted one or two times, each substituent independently selected from a fluorine atom or a group selected from oxo, C_1-C_2-alkyl and (C_1-C_2-alkyl)-C(=O)-,

and wherein the phenyl groups within said (phenoxy)-C_2-C_3-alkyl- group and said (phenyl)-(C_1-C_2-alkyl)- group are optionally substituted one or two times, each substituent independently selected from a fluorine atom and a chlorine atom, or a group selected from methyl, trifluoromethyl and methoxy,

or

R^{12} and R^{13}, together with the nitrogen atom to which they are attached, represent a monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group which is optionally substituted one or two times, each substituent independently selected from a halogen atom or a group selected from oxo, C_1-C_2-alkyl and (C_1-C_2-alkyl)-C(=O)-;

R^{14} represents a group selected from methyl and trifluoromethyl;

R^{17} represents a C_1-C_2-alkyl group;

R^{18} and R^{19} represent, independently from each occurrence, a hydrogen atom or a methyl group;

R^{20} represents a hydrogen atom or a group selected from optionally substituted C_1-C_3-alkyl, unsubstituted C_4-C_6-alkyl, prop-2-ynyl, methoxy, C_3-C_6-cycloalkyl, adamantyl, monocyclic 4- to 7-membered heterocycloalkyl, phenyl, and 5- to 10-membered heteroaryl,

wherein said C_1-C_3-alkyl group is optionally substituted one, two or three times, each substituent independently selected from a halogen atom or a group selected from hydroxy, cyano, C_1-C_3-alkoxy, -N(R^{22})(R^{23}), C_3-C_6-cycloalkyl, adamantyl, monocyclic 4- to 7-membered heterocycloalkyl, phenyl, and 5- to 10-membered heteroaryl, said phenyl and 5- to 10-membered heteroaryl substituents themselves being optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a methyl group,

and wherein said C_3-C_6-cycloalkyl, adamantyl and monocyclic 4- to 7-membered heterocycloalkyl groups are optionally substituted one or two or three times, each substituent independently selected from a fluorine atom or a group selected from oxo, C_1-C_2-alkyl and (C_1-C_2-alkyl)-C(=O)-,

and wherein said phenyl and 5- to 10-membered heteroaryl groups are optionally substituted one, two or three times, each substituent independently selected from a fluorine atom and a chlorine atom or a group selected from cyano, C_1-C_2-alkyl, C_1-C_2-fluoroalkyl, C_1-C_2-alkoxy, C_1-C_2-fluoroalkoxy, -N(R^{22})(R^{23}) and -C(=O)-N(R^{24})(R^{25}),

R^{21} represents a hydrogen atom or a C_1-C_2-alkyl group,

or

R^{20} and R^{21}, together with the nitrogen atom to which they are attached, represent a monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group which is optionally benzocondensed, and which is optionally substituted one, two or three times, each substituent independently selected from a halogen atom or a group selected from cyano, oxo, hydroxy, C_1-C_2-alkyl, C_1-C_2-fluoroalkyl, benzyl, (C_1-C_2-alkyl)-C(=O)-, C_3-C_4-cycloalkyl, C_1-C_2-alkoxy, C_1-C_2-fluoroalkoxy, -N(R^{22})(R^{23}) and -C(=O)-N(R^{24})(R^{25});

R^{22} and R^{23} represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_2-alkyl and (C_1-C_2-alkyl)-C(=O)-;

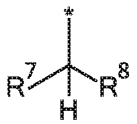
R^{24} and R^{25} represent, independently from each occurrence, a hydrogen atom or a C_1-C_2-alkyl group, and

n represents an integer 2,

or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

4. The compound according to claim 1, 2 or 3, wherein:

R^1 represents a phenyl or pyridinyl group optionally substituted, one or two times, each substituent independently selected from a fluorine atom and a chlorine atom, or a group selected from cyano, C_1-C_2-alkyl, C_1-C_2-fluoroalkyl, C_1-C_2-alkoxy, C_1-C_2-fluoroalkoxy;

R^2 represents a group  ,

wherein "*" indicates the point of attachment to the nitrogen atom to which R^2 is attached;

R^3 represents a group selected from methyl and -NH_2;

R^4 represents a phenyl or pyridinyl group optionally substituted, one or two times, each substituent independently selected from a fluorine atom and a chlorine atom, or a group selected from C_1-C_2-alkyl, C_1-C_2-fluoroalkyl, -OR^9;

R^7 represents a hydrogen atom or a C_1-C_2-alkyl group;

R^8 represents a -C(=O)-NH_2 group, and

R^9 represents a group selected from C_1-C_2-alkyl, benzyl, C_1-C_2-fluoroalkyl, (C_1-C_2-alkoxy)-C_2-alkyl- and phenyl,

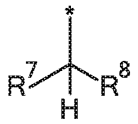
wherein the phenyl group within said benzyl group and said phenyl group itself are optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a methyl group;

or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

5. The compound according to claim 1, 2 or 3, wherein:

R^1 represents a phenyl or pyridinyl group optionally substituted, one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a bromine atom, or a group selected from cyano, difluoromethyl, trifluoromethyl, methoxy, benzyloxy, difluoromethoxy and trifluoromethoxy,

or two substituents attached to adjacent carbon atoms of said phenyl or pyridinyl group together form a bivalent group -O-CF_2-O-;

R^2 represents a group  ,

wherein "*" indicates the point of attachment to the nitrogen atom to which R^2 is attached;

R^3 represents a group selected from methyl and -NH_2;

R^4 represents a phenyl or pyridinyl group optionally substituted, one or two times, each substituent independently selected from a halogen atom or a group selected from C_1-C_2-alkyl, C_1-C_2-fluoroalkyl, -OR^9, -N(R^{10})(R^{11}), -C(=O)-N(R^{12})(R^{13}) and -C(=O)-OR^{17};

R^7 represents a hydrogen atom or a C_1-C_2-alkyl group;

R^8 represents a -C(=O)-NH_2 group;

R^9 represents a hydrogen atom or a group selected from C_1-C_2-alkyl, benzyl, C_1-C_2-fluoroalkyl, (C_1-C_2-alkoxy)-C_2-alkyl-, ((C_1-C_2-alkyl)-C(=O)-O)-C_2-alkyl-, -C(R^{18})(R^{19})-C(=O)-N(R^{20})(R^{21}), -C(=O)-N(R^{20})(R^{21}) and phenyl,

wherein the phenyl group within said benzyl group and said phenyl group itself are optionally substituted one or two times, each substituent independently selected from a fluorine atom and a chlorine atom, or a group selected from cyano and methyl;

R^{10} and R^{11} represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_2-alkyl, (C_3-C_5-cycloalkyl)-(C_1-C_2-alkyl)-, C_3-C_7-cycloalkyl and (phenyl)-(C_1-C_2-alkyl)-O-C(=O)-,

wherein C_3-C_7-cycloalkyl, and the C_3-C_5-cycloalkyl within said (C_3-C_5-cycloalkyl)-(C_1-C_2-alkyl)- group are optionally substituted one or two times, each substituent independently selected from a fluorine atom or a group selected from cyano, methyl and C_1-fluoroalkyl,

and wherein the phenyl group within said (phenyl)-(C_1-C_2-alkyl)-O-C(=O)- group is optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a methyl group,

or

R^{10} and R^{11}, together with the nitrogen atom to which they are attached, represent a monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group which is optionally substituted one or two times, each substituent independently selected from a fluorine atom or a group selected from cyano, methyl and C_1-fluoroalkyl;

R^{12} and R^{13} represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_4-alkyl, C_1-C_2-fluoroalkyl, C_1-C_2-hydroxyalkyl, (C_1-C_4-alkoxy)-C_2-C_3-alkyl-, (C_1-C_2-fluoroalkoxy)-C_2-C_3-alkyl-, (phenoxy)-C_2-C_3-alkyl-, C_3-C_7-cycloalkyl and (phenyl)-(C_1-C_2-alkyl)-,

wherein C_3-C_7-cycloalkyl is optionally substituted one or two times, each substituent independently selected from a fluorine atom or a methyl group,

and wherein the phenyl groups within said (phenoxy)-C_2-C_3-alkyl- group and said (phenyl)-(C_1-C_2-alkyl)- group are optionally substituted one or two times, each substituent independently selected from a fluorine atom and a chlorine atom, or a group selected from methyl, trifluoromethyl and methoxy;

R^{17} represents a C_1-C_2-alkyl group;

R^{18} and R^{19} represent, independently from each occurrence, a hydrogen atom or a methyl group;

R^{20} represents a hydrogen atom or a group selected from C_1-C_3-alkyl and phenyl,

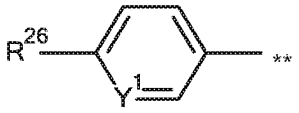
wherein said C_1-C_3-alkyl group is optionally substituted one or two times, each substituent independently selected from a fluorine atom or a group selected from hydroxy, C_1-C_3-alkoxy and phenyl, said phenyl itself being optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a methyl group,

and wherein said phenyl group is optionally substituted one, two or three times, each substituent independently selected from a fluorine atom and a chlorine atom or a group selected from methyl, trifluoromethyl, methoxy and trifluoromethoxy, and

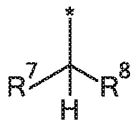
R^{21} represents a hydrogen atom or a C_1-C_2-alkyl group,

or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

6. The compound according to claim 1, 2 or 3, wherein:

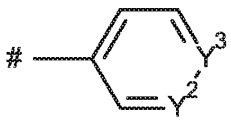
R^1 represents a group  ,

wherein "**" indicates the point of attachment to the nitrogen atom to which R^1 is attached;

R^2 represents a group  ,

wherein "*" indicates the point of attachment to the nitrogen atom to which R^2 is attached;

R^3 represents a group selected from methyl and $-NH_2$;

R^4 represents a group 

wherein "#" indicates the point of attachment to the carbonyl group to which R^4 is attached;

R^7 represents a hydrogen atom or a C_1-C_2-alkyl group;

R^8 represents a $-C(=O)-NH_2$ group;

R^9 represents a hydrogen atom or a group selected from C_1-C_2-alkyl, benzyl, C_1-C_2-fluoroalkyl, (C_1-C_2-alkoxy)-C_2-alkyl-, ((C_1-C_2-alkyl)-C(=O)-O)-C_2-alkyl-, -C(R^{18})(R^{19})-C(=O)-N(R^{20})(R^{21}), -C(=O)-N(R^{20})(R^{21}) and phenyl,

wherein the phenyl group within said benzyl group and said phenyl group itself are optionally substituted one or two times, each substituent independently selected from a fluorine atom and a chlorine atom, or a group selected from cyano and methyl;

R^{10} and R^{11} represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_2-alkyl, C_3-C_7-cycloalkyl and (benzyl)-O-C(=O)-,

wherein C_3-C_7-cycloalkyl is optionally substituted one or two times, each substituent independently selected from a fluorine atom or a group selected from methyl and trifluoromethyl,

and wherein the phenyl group within said (benzyl)-O-C(=O)- group is optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a methyl group,

or

R^{10} and R^{11}, together with the nitrogen atom to which they are attached, represent a monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group which is optionally substituted one or two times, each substituent independently selected from a fluorine atom or a group selected from cyano, methyl and trifluoromethyl;

R^{12} and R^{13} represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_4-alkyl, C_1-C_2-fluoroalkyl, C_1-C_2-hydroxyalkyl, (C_1-C_4-alkoxy)-C_2-alkyl-, (C_1-C_2-fluoroalkoxy)-C_2-alkyl-, (phenoxy)-C_2-alkyl-, C_3-C_7-cycloalkyl and (phenyl)-(C_1-C_2-alkyl)-,

wherein the phenyl groups within said (phenoxy)-C_2-alkyl- group and said (phenyl)-(C_1-C_2-alkyl)- group are optionally substituted one or two times, each substituent independently selected from fluorine atom and a chlorine atom, or a group selected from methyl, trifluoromethyl and methoxy;

R^{17} represents a C_1-C_2-alkyl group;

R^{18} and R^{19} represent, independently from each occurrence, a hydrogen atom or a methyl group;

R^{20} represents a group selected from benzyl and phenyl,

wherein said phenyl group, and the phenyl group within said benzyl group, is optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a methyl group,

R^{21} represents a hydrogen atom or a methyl group,

Y^1 represents -C(H)=, -C(F)=, -C(Cl)=, -C(CN)= or -N=;

Y^2 represents -C(H)= or -N=;

Y^3 represents -C(R^{27})= or -N=,

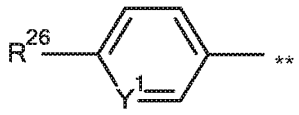
with the proviso that if Y^2 represents -N=, Y^3 represents -C(R^{27})=, and if Y^3 represents -N=, Y^2 represents -C(H)=;

R^{26} represents a fluorine atom, a chlorine atom or a bromine atom, or a group selected from methyl, difluoromethyl, trifluoromethyl, methoxy, benzyloxy, difluoromethoxy and trifluoromethoxy, and

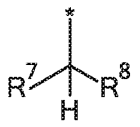
R^{27} represents a halogen atom or a group selected from C_1-C_2-alkyl, C_1-C_2-fluoroalkyl, -OR^9, -N(R^{10})(R^{11}), -C(=O)-N(R^{12})(R^{13}) and -C(=O)-OR^{17},

or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

7. The compound according to claim 1, 2, 3, 5 or 6, wherein:

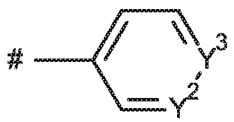
R^1 represents a group  ,

wherein "**" indicates the point of attachment to the nitrogen atom to which R^1 is attached;

R^2 represents a group  ,

wherein "*" indicates the point of attachment to the nitrogen atom to which R^2 is attached;

R^3 represents a group selected from methyl and -NH_2;

R^4 represents a group 

wherein "#" indicates the point of attachment to the carbonyl group to which R^4 is attached;

R^7 represents a hydrogen atom or a C_1-C_2-alkyl group;

R^8 represents a -C(=O)-NH_2 group;

R^9 represents a hydrogen atom or a group selected from C_1-C_2-alkyl, benzyl, C_1-C_2-fluoroalkyl and phenyl,

wherein the phenyl group within said benzyl group and said phenyl group itself are optionally substituted one or two times, each substituent independently selected from a fluorine atom and a chlorine atom, or a group selected from cyano and methyl;

R^{10} and R^{11} represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_2-alkyl and (benzyl)-O-C(=O)-,

and wherein the phenyl group within said (benzyl)-O-C(=O)- group is optionally substituted one or two times, each substituent independently selected from a fluorine atom, a chlorine atom and a methyl group,

or

R^{10} and R^{11}, together with the nitrogen atom to which they are attached, represent a monocyclic nitrogen containing 4- to 7-membered heterocycloalkyl group which is optionally substituted one or two times, each substituent independently selected from a fluorine atom or a group selected from cyano, methyl and trifluoromethyl;

R^{12} and R^{13} represent, independently from each occurrence, a hydrogen atom or a group selected from C_1-C_2-alkyl, (C_1-C_4-alkoxy)-C_2-alkyl-, (C_1-C_2-fluoroalkoxy)-C_2-alkyl-, (phenoxy)-C_2-alkyl-, C_3-C_7-cycloalkyl and (phenyl)-(C_1-C_2-alkyl)-;

Y^1 represents -C(H)=, -C(F)=, -C(Cl)= or -N=;

Y^2 represents -C(H)= or -N=;

Y^3 represents -C(R^{27})= or -N=,

with the proviso that if Y^2 represents -N=, Y^3 represents -C(R^{27})=, and if Y^3 represents -N=, Y^2 represents -C(H)=;

R^{26} represents a fluorine atom, a chlorine atom or a bromine atom, or a group selected from difluoromethyl, methoxy, benzyloxy, difluoromethoxy and trifluoromethoxy, and

R^{27} represents a halogen atom or a group selected from -OR^9, -N(R^{10})(R^{11}) and -C(=O)-N(R^{12})(R^{13}),

or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

8. The compound according to claim 1, which is selected from the group consisting of:

rac-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-4-methoxy-2-methyl-anilino)propanamide ,

rac-2-[N-(4-amino-5-benzoyl-thiazol-2-yl)-4-(dimethylamino)anilino]propanamide ,

rac-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-4-isopropoxy-anilino)propanamide ,

rac-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-2,4,6-trifluoro-anilino)propanamide ,

rac-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-2-bromo-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-(6-methylpyridine-3-carbonyl)thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-(pyridine-4-carbonyl)thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-(2-fluorobenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-4-cyano-anilino)propanamide ,

rac-2-(N-[4-amino-5-[4-chloro-3-(trifluoromethyl)benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide,

rac-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-2-chloro-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-(3-cyanobenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-[N-(4-amino-5-benzoyl-thiazol-2-yl)-3-chloro-4-(dimethylamino)anilino]propanamide ,

rac-2-(N-[4-amino-5-(6-methoxypyridine-3-carbonyl)thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-4-[4-amino-2-(N-[2-amino-1-methyl-2-oxo-ethyl]-4-fluoro-anilino)thiazole-5-carbonyl]-N-methyl-benzamide ,

rac-2-(N-[4-amino-5-(3-fluorobenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-3-chloro-4-methoxy-anilino)propanamide ,

rac-2-(N-[4-amino-5-(4-fluorobenzoyl)thiazol-2-yl]-4-methoxy-anilino)propanamide ,

rac-2-(N-[4-amino-5-(4-methylsulfonylbenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-(4-imidazol-1-ylbenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-(4-cyano-3-fluoro-benzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide ,

(R)-2-(N-[4-amino-5-(4-cyano-3-fluoro-benzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide ,

(S)-2-(N-[4-amino-5-(4-cyano-3-fluoro-benzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-(4-cyano-2-fluoro-benzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-(2-fluoro-4-methoxy-benzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-[N-(4-amino-5-benzoyl-thiazol-2-yl)-4-(trifluoromethoxy)anilino]propanamide ,

rac-2-(N-[4-amino-5-(3,4-difluorobenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-(3,4-dichlorobenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-[N-[4-amino-5-(4-fluorobenzoyl)thiazol-2-yl]-4-(trifluoromethoxy)anilino]propanamide ,

(R)-2-[N-[4-amino-5-(4-fluorobenzoyl)thiazol-2-yl]-4-(trifluoromethoxy)anilino]propanamide ,

(S)-2-[N-[4-amino-5-(4-fluorobenzoyl)thiazol-2-yl]-4-(trifluoromethoxy)anilino]propanamide ,

rac-2-[N-(4-amino-5-benzoyl-thiazol-2-yl)-4-(trifluoromethyl)anilino]propanamide ,

rac-2-(N-[4-amino-5-[6-(trifluoromethyl)pyridine-3-carbonyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

(R)-2-(N-[4-amino-5-[6-(trifluoromethyl)pyridine-3-carbonyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

(S)-2-(N-[4-amino-5-[6-(trifluoromethyl)pyridine-3-carbonyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-4-chloro-2-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-(indane-5-carbonyl)thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-3,4-difluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-(4-cyanobenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide ,

(R)-2-(N-[4-amino-5-(4-cyanobenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide ,

(S)-2-(N-[4-amino-5-(4-cyanobenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-4-chloro-anilino)propanamide ,

rac-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-3,4-dichloro-anilino)propanamide ,

rac-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-4-chloro-3-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-(4-fluorobenzoyl)thiazol-2-yl]-4-chloro-anilino)propanamide ,

(R)-2-(N-[4-amino-5-(4-fluorobenzoyl)thiazol-2-yl]-4-chloro-anilino)propanamide ,

(S)-2-(N-[4-amino-5-(4-fluorobenzoyl)thiazol-2-yl]-4-chloro-anilino)propanamide ,

rac-2-(N-[4-amino-5-(4-chlorobenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide ,

(R)-2-(N-[4-amino-5-(4-chlorobenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide ,

(S)-2-(N-[4-amino-5-(4-chlorobenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-ethyl 2-[4-[4-amino-2-(N-[2-amino-1-methyl-2-oxo-ethyl]-4-fluoro-anilino)thiazole-5-carbonyl]phenoxy]-2-methyl-propanoate ,

rac-2-(N-[4-amino-5-[4-(trifluoromethoxy)benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

(R)-2-(N-[4-amino-5-[4-(trifluoromethoxy)benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

(S)-2-(N-[4-amino-5-[4-(trifluoromethoxy)benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-(4-chlorobenzoyl)thiazol-2-yl]-4-chloro-anilino)propanamide ,

(R)-2-(N-[4-amino-5-(4-chlorobenzoyl)thiazol-2-yl]-4-chloro-anilino)propanamide ,

(S)-2-(N-[4-amino-5-(4-chlorobenzoyl)thiazol-2-yl]-4-chloro-anilino)propanamide ,

rac-2-(N-[4-amino-5-[4-(trifluoromethyl)benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-[N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-(trifluoromethyl)anilino]propanamide ,

R)-2-[N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-(trifluoromethyl)anilino]propanamide ,

(S)-2-[N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-(trifluoromethyl)anilino]propanamide ,

rac-2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

(R)-2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

(S)-2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

2-(N-[4-amino-5-[4-[2-amino-1-methyl-2-oxo-ethoxy]benzoyl]thiazol-2-yl]anilino)propanamide (mixture of stereoisomers) ,

(2R)-(N-[4-amino-5-[4-[2-amino-(1R)-methyl-2-oxo-ethoxy]benzoyl]thiazol-2-yl]anilino)propanamide ,

(2R)-(N-[4-amino-5-[4-[2-amino-(1S)-methyl-2-oxo-ethoxy]benzoyl]thiazol-2-yl]anilino)propanamide ,

(2S)-(N-[4-amino-5-[4-[2-amino-(1R)-methyl-2-oxo-ethoxy]benzoyl]thiazol-2-yl]anilino)propanamide ,

(2S)-(N-[4-amino-5-[4-[2-amino-(1S)-methyl-2-oxo-ethoxy]benzoyl]thiazol-2-yl]anilino)propanamide ,

rac-2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-chloro-2-fluoro-anilino)propanamide ,

(R)-2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-chloro-2-fluoro-anilino)propanamide ,

(S)-2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-chloro-2-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-chloro-anilino)propanamide ,

(R)-2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-chloro-anilino)propanamide ,

(S)-2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-chloro-anilino)propanamide ,

rac-2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-chloro-3-fluoro-anilino)propanamide ,

(R)-2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-chloro-3-fluoro-anilino)propanamide ,

(S)-2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-chloro-3-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-3,4-difluoro-anilino)propanamide,

(R)-2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-3,4-difluoro-anilino)propanamide,

(S)-2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-3,4-difluoro-anilino)propanamide,

rac-2-(N-[4-amino-5-(pyridine-4-carbonyl)thiazol-2-yl]-3,4-difluoro-anilino)propanamide ,

(R)-2-(N-[4-amino-5-(pyridine-4-carbonyl)thiazol-2-yl]-3,4-difluoro-anilino)propanamide ,

(S)-2-(N-[4-amino-5-(pyridine-4-carbonyl)thiazol-2-yl]-3,4-difluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-3,4-difluoro-anilino)propanamide ,

(R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-3,4-difluoro-anilino)propanamide ,

(S)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-3,4-difluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-(6-methoxypyridine-3-carbonyl)thiazol-2-yl]-3,4-difluoro-anilino)propanamide ,

(R)-2-(N-[4-amino-5-(6-methoxypyridine-3-carbonyl)thiazol-2-yl]-3,4-difluoro-anilino)propanamide ,

(S)-2-(N-[4-amino-5-(6-methoxypyridine-3-carbonyl)thiazol-2-yl]-3,4-difluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-[6-(trifluoromethyl)pyridine-3-carbonyl]thiazol-2-yl]-3,4-difluoro-anilino)propanamide ,

(R)-2-(N-[4-amino-5-[6-(trifluoromethyl)pyridine-3-carbonyl]thiazol-2-yl]-3,4-difluoro-anilino)propanamide ,

(S)-2-(N-[4-amino-5-[6-(trifluoromethyl)pyridine-3-carbonyl]thiazol-2-yl]-3,4-difluoro-anilino)propanamide ,

rac-2-(N-[5-[4-(difluoromethoxy)benzoyl]-4-methyl-thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[5-[4-(difluoromethoxy)benzoyl]-4-methyl-thiazol-2-yl]-3,4-difluoro-anilino)propanamide ,

(R)-2-(N-[5-[4-(difluoromethoxy)benzoyl]-4-methyl-thiazol-2-yl]-3,4-difluoro-anilino)propanamide ,

(S)-2-(N-[5-[4-(difluoromethoxy)benzoyl]-4-methyl-thiazol-2-yl]-3,4-difluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-(pyridine-4-carbonyl)thiazol-2-yl]-4-chloro-3-fluoro-anilino)propanamide ,

(R)-2-(N-[4-amino-5-(pyridine-4-carbonyl)thiazol-2-yl]-4-chloro-3-fluoro-anilino)propanamide ,

(S)-2-(N-[4-amino-5-(pyridine-4-carbonyl)thiazol-2-yl]-4-chloro-3-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-(pyridine-4-carbonyl)thiazol-2-yl]-4-chloro-anilino)propanamide ,

(R)-2-(N-[4-amino-5-(pyridine-4-carbonyl)thiazol-2-yl]-4-chloro-anilino)propanamide ,

(S)-2-(N-[4-amino-5-(pyridine-4-carbonyl)thiazol-2-yl]-4-chloro-anilino)propanamide ,

rac-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-chloro-anilino)propanamide ,

(R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-chloro-anilino)propanamide ,

(S)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-chloro-anilino)propanamide ,

rac-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-chloro-3-fluoro-anilino)propanamide ,

(R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-chloro-3-fluoro-anilino)propanamide ,

(S)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-chloro-3-fluoro-anilino)propanamide

rac-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)anilino)propanamide ,

rac-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-4-fluoro-anilino)propanamide ,

(R)-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-4-fluoro-anilino)propanamide ,

(S)-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide ,

(R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide ,

(S)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-(4-methylbenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide ,

(R)-2-(N-[4-amino-5-(4-methylbenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide ,

(S)-2-(N-[4-amino-5-(4-methylbenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-(4-fluorobenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-2,4-difluoro-anilino)propanamide ,

rac-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-4-methoxy-anilino)propanamide ,

rac-2-[(4-amino-5-benzoyl-1,3-thiazol-2-yl)(phenyl)amino]butanamide ,

rac-2-[(4-amino-5-benzoyl-1,3-thiazol-2-yl)(4-fluorophenyl)amino]butanamide ,

2-(N-[4-amino-5-[4-(2-amino-1-methyl-2-oxo-ethoxy)benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide (mixture of stereoisomers) ,

rac-2-{[4-amino-5-(4-methoxybenzoyl)-1,3-thiazol-2-yl](4-fluorophenyl)amino}butanamide ,

2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-4-fluoro-anilino)acetamide ,

2-(N-[4-amino-5-(4-methylbenzoyl)thiazol-2-yl]-4-fluoro-anilino)acetamide ,

rac-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-4-methyl-anilino)propanamide ,

(R)-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-4-methyl-anilino)propanamide ,

(S)-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-4-methyl-anilino)propanamide ,

rac-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-3-fluoro-anilino)propanamide ,

(R)-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-3-fluoro-anilino)propanamide ,

(S)-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-3-fluoro-anilino)propanamide ,

rac-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-2-fluoro-anilino)propanamide ,

(R)-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-2-fluoro-anilino)propanamide ,

(S)-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-2-fluoro-anilino)propanamide ,

rac-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-3-methyl-anilino)propanamide ,

(R)-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-3-methyl-anilino)propanamide ,

(S)-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-3-methyl-anilino)propanamide ,

rac-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-2-methyl-anilino)propanamide ,

(R)-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-2-methyl-anilino)propanamide ,

(S)-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-2-methyl-anilino)propanamide ,

rac-2-[(4-amino-5-benzoyl-thiazol-2-yl)-(1-methylpyrazol-4-yl)amino]propanamide ,

(R)-2-[(4-amino-5-benzoyl-thiazol-2-yl)-(1-methylpyrazol-4-yl)amino]propanamide ,

(S)-2-[(4-amino-5-benzoyl-thiazol-2-yl)-(1-methylpyrazol-4-yl)amino]propanamide ,

rac-2-[(4-amino-5-benzoyl-thiazol-2-yl)-(3-pyridyl)amino]propanamide ,

(R)-2-[(4-amino-5-benzoyl-thiazol-2-yl)-(3-pyridyl)amino]propanamide ,

(S)-2-[(4-amino-5-benzoyl-thiazol-2-yl)-(3-pyridyl)amino]propanamide ,

rac-2-(N-[4-amino-5-(4-bromobenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-ethyl 2-[4-[4-amino-2-(4-fluoro-N-[2-amino-1-methyl-2-oxo-ethyl]anilino)thiazole-5-carbonyl]phenoxy]acetate ,

(R)-ethyl 2-[4-[4-amino-2-(4-fluoro-N-[2-amino-1-methyl-2-oxo-ethyl]anilino)thiazole-5-carbonyl]phenoxy]acetate ,

(S)-ethyl 2-[4-[4-amino-2-(4-fluoro-N-[2-amino-1-methyl-2-oxo-ethyl]anilino)thiazole-5-carbonyl]phenoxy]acetate ,

rac-2-(N-[4-amino-5-[4-[2-(isopropylamino)-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-[4-[2-(m-tolylmethylamino)-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-[4-[2-(o-tolylmethylamino)-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-[4-[2-[(3-chlorophenyl)methylamino]-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-[4-[2-(4-methylpiperazin-1-yl)-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-[4-[2-(3-methylanilino)-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-[4-(2-morpholino-2-oxo-ethoxy)benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-[4-[2-oxo-2-[2-(1-piperidyl)ethylamino]ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-[4-[2-(4-benzyl-1-piperidyl)-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-[4-[2-(2-methoxyethylamino)-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-[4-[2-(4-cyanoanilino)-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-[4-[2-[methyl(prop-2-ynyl)amino]-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-[4-[2-[(2-methoxyphenyl)methylamino]-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-[4-[2-[(3-methoxyphenyl)methylamino]-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-[4-[2-[(2-fluorophenyl)methylamino]-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-[4-[2-[(4-fluorophenyl)methylamino]-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-[4-[2-(1H-benzimidazol-2-ylmethylamino)-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-[4-[2-oxo-2-(2,2,2-trifluoroethylamino)ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-[4-[2-[methyl(2-pyridyl)amino]-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-[4-[2-[methyl-(1-methyl-4-piperidyl)amino]-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-[4-[2-(methoxyamino)-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-[4-[2-[(5-methylisoxazol-3-yl)amino]-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-[4-[2-(ethylamino)-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-[4-[2-(4-methylanilino)-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-[4-[2-(cyclohexylamino)-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-3-[[2-[4-[4-amino-2-(N-[2-amino-1-methyl-2-oxo-ethyl]-4-fluoro-anilino)thiazole-5-carbonyl]phenoxy]acetyl]amino]benzamide ,

rac-2-(N-[4-amino-5-[4-[2-oxo-2-(6-quinolylamino)ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-4-[[2-[4-[4-amino-2-(N-[2-amino-1-methyl-2-oxo-ethyl]-4-fluoro-anilino)thiazole-5-carbonyl]phenoxy]acetyl]amino]benzamide ,

(2S)-1-[2-[4-[4-amino-2-(N-[2-amino-(1RS)-methyl-2-oxo-ethyl]-4-fluoro-anilino)thiazole-5-carbonyl]phenoxy]acetyl]pyrrolidine-2-carboxamide (mixture of two diastereomers) ,

rac-2-(N-[4-amino-5-[4-[2-[ethyl(methyl)amino]-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-[4-[2-[(3-methylisoxazol-5-yl)amino]-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-[4-[2-[3-(dimethylamino)propyl-methyl-amino]-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[5-[4-[2-(4-acetylpiperazin-1-yl)-2-oxo-ethoxy]benzoyl]-4-amino-thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-[4-[2-oxo-2-(3-pyridylmethylamino)ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

2-(N-[4-amino-5-[4-[2-(2,3-dihydroxypropylamino)-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide (mixture of stereoisomers) ,

rac-2-(N-[4-amino-5-[4-[2-(4-methoxyanilino)-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-[4-[2-[benzyl(methyl)amino]-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-[4-[2-(4-chloroanilino)-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-[4-[2-[(2-chlorophenyl)methylamino]-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-[4-[2-[(4-chlorophenyl)methylamino]-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-[4-[2-(4-fluoroanilino)-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-[4-[2-(azepan-1-yl)-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-[4-[2-[(4-methoxyphenyl)methylamino]-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

2-(N-[4-amino-5-[4-[2-oxo-2-(1-phenylethylamino)ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide (mixture of stereoisomers) ,

rac-2-(N-[4-amino-5-[4-[2-oxo-2-(p-tolylmethylamino)ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-[4-[2-[methyl(2-phenylethyl)amino]-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

2-(N-[4-amino-5-[4-[2-(3-methyl-1-piperidyl)-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide (mixture of stereoisomers) ,

rac-2-(N-[4-amino-5-[4-[2-(4-methyl-1-piperidyl)-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[5-[4-[2-(4-acetamidoanilino)-2-oxo-ethoxy]benzoyl]-4-amino-thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-[4-[2-oxo-2-(1H-pyrazolo[3,4-d]pyrimidin-4-ylamino)ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-[4-[2-(cyclopentylamino)-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-[4-[2-(3,4-dihydro-1H-isoquinolin-2-yl)-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-[4-(2-isoindolin-2-yl-2-oxo-ethoxy)benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-[4-[2-[2-furylmethyl(methyl)amino]-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-[4-[2-[4-(dimethylamino)-1-piperidyl]-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-[4-[2-[methyl(3-pyridylmethyl)amino]-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-[4-[2-(N,2-dimethylanilino)-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-[4-[2-(N,4-dimethylanilino)-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-[4-[2-(N,3-dimethylanilino)-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-[4-[2-(2,2-dimethylpropylamino)-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

2-(N-[5-[4-[2-(1-adamantylamino)-2-oxo-ethoxy]benzoyl]-4-amino-thiazol-2-yl]-4-fluoro-anilino)propanamide (single stereoisomer) ,

2-(N-[5-[4-[2-(1-adamantylmethylamino)-2-oxo-ethoxy]benzoyl]-4-amino-thiazol-2-yl]-4-fluoro-anilino)propanamide (single stereoisomer) ,

2-(N-[5-[4-[2-[2-(1-adamantyl)ethylamino]-2-oxo-ethoxy]benzoyl]-4-amino-thiazol-2-yl]-4-fluoro-anilino)propanamide (single stereoisomer) ,

2-(N-[4-amino-5-[4-[2-(4-chloroanilino)-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide (single stereoisomer) ,

4-[[2-[4-[4-amino-2-(4-fluoro-N-[2-amino-1-methyl-2-oxo-ethyl]anilino)thiazole-5-carbonyl]phenoxy]acetyl]amino]benzamide (single stereoisomer) ,

2-(N-[4-amino-5-[4-[2-((2RS),3-dihydroxypropylamino)-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide (mixture of two diastereomers) ,

2-(N-[4-amino-5-[4-[2-oxo-2-[2-(1-piperidyl)ethylamino]ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide (single stereoisomer) ,

2-(N-[4-amino-5-[4-(2-amino-2-oxo-ethoxy)benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide (single stereoisomer) ,

(R)-2-(N-[4-amino-5-[4-[2-(methylamino)-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

(S)-2-(N-[4-amino-5-[4-[2-(methylamino)-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

(R)-2-(N-[4-amino-5-[4-[2-(isopropylamino)-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

(S)-2-(N-[4-amino-5-[4-[2-(isopropylamino)-2-oxo-ethoxy]benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-[4-[4-amino-2-(N-(2-amino-1-methyl-2-oxo-ethyl)-4-fluoro-anilino)thiazole-5-carbonyl]phenoxy]-N-isopropyl-2-methyl-propanamide ,

rac-2-[4-[4-amino-2-(N-(2-amino-1-methyl-2-oxo-ethyl)-4-fluoro-anilino)thiazole-5-carbonyl]phenoxy]-2-methyl-propanamide ,

rac-2-(N-(5-benzoyl-4-methyl-thiazol-2-yl)-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-(4-hydroxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-(4-benzyloxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-[6-(difluoromethyl)pyridine-3-carbonyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-(pyridine-4-carbonyl)thiazol-2-yl]-3-chloro-4-fluoro-anilino)propanamide ,

(R)- 2-(N-[4-amino-5-(pyridine-4-carbonyl)thiazol-2-yl]-3-chloro-4-fluoro-anilino)propanamide ,

(S)- 2-(N-[4-amino-5-(pyridine-4-carbonyl)thiazol-2-yl]-3-chloro-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-3-chloro-4-fluoro-anilino)propanamide ,

(R)- 2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-3-chloro-4-fluoro-anilino)propanamide ,

(S)- 2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-3-chloro-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-[6-(difluoromethoxy)pyridine-3-carbonyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

(R)-2-(N-[4-amino-5-[6-(difluoromethoxy)pyridine-3-carbonyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

(S)-2-(N-[4-amino-5-[6-(difluoromethoxy)pyridine-3-carbonyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-[6-(difluoromethoxy)pyridine-3-carbonyl]thiazol-2-yl]-3,4-difluoro-anilino)propanamide ,

(R)-(N-[4-amino-5-[6-(difluoromethoxy)pyridine-3-carbonyl]thiazol-2-yl]-3,4-difluoro-anilino)propanamide ,

(S)-(N-[4-amino-5-[6-(difluoromethoxy)pyridine-3-carbonyl]thiazol-2-yl]-3,4-difluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-[6-(difluoromethoxy)pyridine-3-carbonyl]thiazol-2-yl]-4-chloro-3-fluoro-anilino)propanamide ,

(R)-2-(N-[4-amino-5-[6-(difluoromethoxy)pyridine-3-carbonyl]thiazol-2-yl]-4-chloro-3-fluoro-anilino)propanamide ,

(S)-2-(N-[4-amino-5-[6-(difluoromethoxy)pyridine-3-carbonyl]thiazol-2-yl]-4-chloro-3-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-(4-benzyloxybenzoyl)thiazol-2-yl]-3,4-difluoro-anilino)propanamide ,

(R)-2-(N-[4-amino-5-(4-benzyloxybenzoyl)thiazol-2-yl]-3,4-difluoro-anilino)propanamide ,

(S)-2-(N-[4-amino-5-(4-benzyloxybenzoyl)thiazol-2-yl]-3,4-difluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-(4-benzyloxybenzoyl)thiazol-2-yl]-4-chloro-3-fluoro-anilino)propanamide ,

(R)-2-(N-[4-amino-5-(4-benzyloxybenzoyl)thiazol-2-yl]-4-chloro-3-fluoro-anilino)propanamide ,

(S)-2-(N-[4-amino-5-(4-benzyloxybenzoyl)thiazol-2-yl]-4-chloro-3-fluoro-anilino)propanamide ,

rac-benzyl N-[4-[4-amino-2-(N-(2-amino-1-methyl-2-oxo-ethyl)-3,4-difluoro-anilino)thiazole-5-carbonyl]phenyl]carbamate ,

(R)-benzyl N-[4-[4-amino-2-(N-(2-amino-1-methyl-2-oxo-ethyl)-3,4-difluoro-anilino)thiazole-5-carbonyl]phenyl]carbamate ,

(S)-benzyl N-[4-[4-amino-2-(N-(2-amino-1-methyl-2-oxo-ethyl)-3,4-difluoro-anilino)thiazole-5-carbonyl]phenyl]carbamate ,

rac-2-[4-[4-amino-2-(N-(2-amino-1-methyl-2-oxo-ethyl)-4-fluoro-anilino)thiazole-5-carbonyl]phenoxy]ethyl acetate ,

rac-benzyl N-[4-[4-amino-2-(N-(2-amino-1-methyl-2-oxo-ethyl)-4-fluoro-anilino)thiazole-5-carbonyl]phenyl]carbamate ,

(R)-benzyl N-[4-[4-amino-2-(N-(2-amino-1-methyl-2-oxo-ethyl)-4-fluoro-anilino)thiazole-5-carbonyl]phenyl]carbamate ,

(S)-benzyl N-[4-[4-amino-2-(N-(2-amino-1-methyl-2-oxo-ethyl)-4-fluoro-anilino)thiazole-5-carbonyl]phenyl]carbamate ,

rac-2-(N-[4-amino-5-(4-benzyloxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide ,

(R)-2-(N-[4-amino-5-(4-benzyloxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide ,

(S)-2-(N-[4-amino-5-(4-benzyloxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-(4-iodobenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-(6-methoxypyridine-3-carbonyl)thiazol-2-yl]-4-chloro-3-fluoro-anilino)propanamide ,

(R)-2-(N-[4-amino-5-(6-methoxypyridine-3-carbonyl)thiazol-2-yl]-4-chloro-3-fluoro-anilino)propanamide ,

(S)-2-(N-[4-amino-5-(6-methoxypyridine-3-carbonyl)thiazol-2-yl]-4-chloro-3-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-(4-phenoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-methoxy-anilino)propanamide ,

(R)-2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-methoxy-anilino)propanamide ,

(S)-2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-methoxy-anilino)propanamide ,

rac-2-(N-[4-amino-5-(4-nitrobenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(4-fluoro-N-[5-(4-methoxybenzoyl)-4-methyl-thiazol-2-yl]anilino)propanamide ,

(R)-2-(4-fluoro-N-[5-(4-methoxybenzoyl)-4-methyl-thiazol-2-yl]anilino)propanamide ,

(S)-2-(4-fluoro-N-[5-(4-methoxybenzoyl)-4-methyl-thiazol-2-yl]anilino)propanamide ,

rac-4-[4-[4-amino-2-(N-(2-amino-1-methyl-2-oxo-ethyl)-4-fluoro-anilino)thiazole-5-carbonyl]phenyl]cyclopropanecarboxamide ,

rac-2-(N-[4-amino-5-(4-morpholinobenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-[4-(pyrazol-1-ylmethyl)benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-[4-(dimethylamino)benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-(4-pyrrolidin-1-ylbenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-benzyloxy-anilino)propanamide ,

(R)-2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-benzyloxy-anilino)propanamide ,

(S)-2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-benzyloxy-anilino)propanamide ,

rac-2-(N-[4-amino-5-[3-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-(pyridine-3-carbonyl)thiazol-2-yl]-3,4-difluoro-anilino)propanamide ,

(R)-2-(N-[4-amino-5-(pyridine-3-carbonyl)thiazol-2-yl]-3,4-difluoro-anilino)propanamide ,

(S)-2-(N-[4-amino-5-(pyridine-3-carbonyl)thiazol-2-yl]-3,4-difluoro-anilino)propanamide ,

rac-2-(N-[5-(4-acetamidobenzoyl)-4-amino-thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-(2-chloropyridine-4-carbonyl)thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-(2-methylpyridine-4-carbonyl)thiazol-2-yl]-4-fluoro-anilino)propanamide ,

(R)-2-(N-[4-amino-5-(2-methylpyridine-4-carbonyl)thiazol-2-yl]-4-fluoro-anilino)propanamide ,

(S)-2-(N-[4-amino-5-(2-methylpyridine-4-carbonyl)thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-[2-(difluoromethyl)pyridine-4-carbonyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-[(4-amino-5-benzoyl-thiazol-2-yl)-(4-pyridyl)amino]propanamide ,

rac-2-(N-[4-amino-5-(2-methoxypyridine-4-carbonyl)thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-3-fluoro-4-methoxy-anilino)propanamide ,

rac-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-4-cyano-3-fluoro-anilino)propanamide ,

rac-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-4-bromo-anilino)propanamide ,

rac-2-[N-(4-amino-5-benzoyl-thiazol-2-yl)-3-chloro-4-(difluoromethoxy)anilino]propanamide ,

rac-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-4-ethoxy-anilino)propanamide ,

rac-2-[(4-amino-5-benzoyl-thiazol-2-yl)-(1,3-benzodioxol-5-yl)amino]propanamide ,

rac-2-[(4-amino-5-benzoyl-thiazol-2-yl)-(2,2-difluoro-1,3-benzodioxol-5-yl)amino]propanamide ,

rac-2-[N-(4-amino-5-benzoyl-thiazol-2-yl)-4-(difluoromethoxy)-3-fluoro-anilino]propanamide ,

rac-2-(N-(4-amino-5-benzoyl-thiazol-2-yl)-4-benzyloxy-anilino)propanamide ,

rac-2-[N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-3-chloro-4-(difluoromethoxy)anilino]propanamide ,

rac-2-[N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-3-chloro-4-(difluoromethoxy)anilino]propanamide ,

rac-2-[N-[4-amino-5-(4-chlorobenzoyl)thiazol-2-yl]-3-chloro-4-(difluoromethoxy)anilino]propanamide ,

rac-2-[N-[4-amino-5-(pyridine-4-carbonyl)thiazol-2-yl]-3-chloro-4-(difluoromethoxy)anilino]propanamide ,

rac-2-[N-[4-amino-5-[6-(difluoromethoxy)pyridine-3-carbonyl]thiazol-2-yl]-3-chloro-4-(difluoromethoxy)anilino]propanamide ,

rac-2-[N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-(difluoromethoxy)-3-fluoro-anilino]propanamide ,

rac-2-[N-[4-amino-5-(4-chlorobenzoyl)thiazol-2-yl]-4-(difluoromethoxy)-3-fluoro-anilino]propanamide ,

rac-2-[N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-(difluoromethoxy)-3-fluoro-anilino]propanamide ,

rac-2-[N-[4-amino-5-(pyridine-4-carbonyl)thiazol-2-yl]-4-(difluoromethoxy)-3-fluoro-anilino]propanamide ,

rac-2-[N-[4-amino-5-[6-(difluoromethoxy)pyridine-3-carbonyl]thiazol-2-yl]-4-(difluoromethoxy)-3-fluoro-anilino]propanamide ,

rac-2-[N-(4-amino-5-benzoyl-thiazol-2-yl)-3-chloro-4-(trifluoromethoxy)anilino]propanamide ,

rac-2-[[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-(2,2-difluoro-1,3-benzodioxol-5-yl)amino]propanamide ,

rac-2-[[4-amino-5-(4-chlorobenzoyl)thiazol-2-yl]-(2,2-difluoro-1,3-benzodioxol-5-yl)amino]propanamide ,

rac-2-[[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-(2,2-difluoro-1,3-benzodioxol-5-yl)amino]propanamide ,

rac-2-[[4-amino-5-(pyridine-4-carbonyl)thiazol-2-yl]-(2,2-difluoro-1,3-benzodioxol-5-yl)amino]propanamide ,

rac-2-[[4-amino-5-[6-(difluoromethoxy)pyridine-3-carbonyl]thiazol-2-yl]-(2,2-difluoro-1,3-benzodioxol-5-yl)amino]propanamide ,

rac-2-[N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-3-fluoro-4-(trifluoromethoxy)anilino]propanamide ,

rac-2-[N-[4-amino-5-(4-chlorobenzoyl)thiazol-2-yl]-3-fluoro-4-(trifluoromethoxy)anilino]propanamide ,

rac-2-[N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-3-fluoro-4-(trifluoromethoxy)anilino]propanamide ,

rac-2-[N-[4-amino-5-(pyridine-4-carbonyl)thiazol-2-yl]-3-fluoro-4-(trifluoromethoxy)anilino]propanamide ,

rac-2-[N-[4-amino-5-[6-(difluoromethoxy)pyridine-3-carbonyl]thiazol-2-yl]-3-fluoro-4-(trifluoromethoxy)anilino]propanamide ,

rac-2-[N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-3-chloro-4-(trifluoromethoxy)anilino]propanamide ,

rac-2-[N-[4-amino-5-(4-chlorobenzoyl)thiazol-2-yl]-3-chloro-4-(trifluoromethoxy)anilino]propanamide ,

rac-2-[N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-3-chloro-4-(trifluoromethoxy)anilino]propanamide ,

rac-2-[N-[4-amino-5-(pyridine-4-carbonyl)thiazol-2-yl]-3-chloro-4-(trifluoromethoxy)anilino]propanamide ,

rac-2-[N-[4-amino-5-[6-(difluoromethoxy)pyridine-3-carbonyl]thiazol-2-yl]-3-chloro-4-(trifluoromethoxy)anilino]propanamide ,

rac-2-[(4-amino-5-benzoyl-thiazol-2-yl)-(6-methoxy-3-pyridyl)amino]propanamide ,

rac-2-[(4-amino-5-benzoyl-thiazol-2-yl)-[6-(trifluoromethoxy)-3-pyridyl]amino]propanamide ,

rac-2-[(4-amino-5-benzoyl-thiazol-2-yl)-[6-(difluoromethoxy)-3-pyridyl]amino]propanamide ,

rac-2-[(4-amino-5-benzoyl-thiazol-2-yl)-[6-(trifluoromethyl)-3-pyridyl]amino]propanamide ,

rac-2-[(4-amino-5-benzoyl-thiazol-2-yl)-[6-(difluoromethyl)-3-pyridyl]amino]propanamide ,

rac-2-[(4-amino-5-benzoyl-thiazol-2-yl)-(6-chloro-3-pyridyl)amino]propanamide ,

rac-2-[(4-amino-5-benzoyl-thiazol-2-yl)-(6-fluoro-3-pyridyl)amino]propanamide ,

rac-2-[(4-amino-5-benzoyl-thiazol-2-yl)-(6-methyl-3-pyridyl)amino]propanamide ,

rac-2-[N-(4-amino-5-benzoyl-thiazol-2-yl)-4-fluoro-3-(trifluoromethoxy)anilino]propanamide ,

rac-2-[N-(4-amino-5-benzoyl-thiazol-2-yl)-4-chloro-3-(trifluoromethoxy)anilino]propanamide ,

rac-2-[N-(4-amino-5-benzoyl-thiazol-2-yl)-3-(difluoromethoxy)-4-fluoro-anilino]propanamide ,

rac-2-[N-(4-amino-5-benzoyl-thiazol-2-yl)-4-chloro-3-(difluoromethoxy)anilino]propanamide ,

rac-2-[N-(4-amino-5-benzoyl-thiazol-2-yl)-2-fluoro-4-(trifluoromethoxy)anilino]propanamide ,

rac-2-[N-(4-amino-5-benzoyl-thiazol-2-yl)-2-chloro-4-(trifluoromethoxy)anilino]propanamide ,

rac-2-[N-(4-amino-5-benzoyl-thiazol-2-yl)-4-(difluoromethoxy)-2-fluoro-anilino]propanamide ,

rac-2-[N-(4-amino-5-benzoyl-thiazol-2-yl)-2-chloro-4-(difluoromethoxy)anilino]propanamide ,

rac-2-[N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-(difluoromethyl)anilino]propanamide ,

rac-2-[N-[4-amino-5-(4-chlorobenzoyl)thiazol-2-yl]-4-(difluoromethyl)anilino]propanamide ,

rac-2-[N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-(difluoromethyl)anilino]propanamide ,

rac-2-[N-[4-amino-5-(pyridine-4-carbonyl)thiazol-2-yl]-4-(difluoromethyl)anilino]propanamide ,

rac-2-[N-[4-amino-5-[6-(difluoromethoxy)pyridine-3-carbonyl]thiazol-2-yl]-4-(difluoromethyl)anilino]propanamide ,

rac-2-[[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-[6-(trifluoromethoxy)-3-pyridyl]amino]propanamide ,

rac-2-[[4-amino-5-(4-chlorobenzoyl)thiazol-2-yl]-[6-(trifluoromethoxy)-3-pyridyl]amino]propanamide ,

rac-2-[[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-[6-(trifluoromethoxy)-3-pyridyl]amino]propanamide ,

rac-2-[[4-amino-5-[6-(difluoromethoxy)pyridine-3-carbonyl]thiazol-2-yl]-[6-(trifluoromethoxy)-3-pyridyl]amino]propanamide ,

rac-2-[[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-[6-(difluoromethoxy)-3-pyridyl]amino]propanamide ,

rac-2-[[4-amino-5-(4-chlorobenzoyl)thiazol-2-yl]-[6-(difluoromethoxy)-3-pyridyl]amino]propanamide ,

rac-2-[[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-[6-(difluoromethoxy)-3-pyridyl]amino]propanamide ,

rac-2-[[4-amino-5-[6-(difluoromethoxy)pyridine-3-carbonyl]thiazol-2-yl]-[6-(difluoromethoxy)-3-pyridyl]amino]propanamide ,

rac-benzyl N-[5-[4-amino-2-(N-(2-amino-1-methyl-2-oxo-ethyl)-4-fluoro-anilino)thiazole-5-carbonyl]-2-pyridyl]carbamate ,

rac-Ethyl 4-[4-amino-2-(N-(2-amino-1-methyl-2-oxo-ethyl)-4-fluoro-anilino)thiazole-5-carbonyl]benzoate ,

rac-Ethyl 4-[4-amino-2-(N-(2-amino-1-methyl-2-oxo-ethyl)-4-chloro-3-fluoro-anilino)thiazole-5-carbonyl]benzoate ,

rac-Ethyl 2-[4-[4-amino-2-(N-(2-amino-1-methyl-2-oxo-ethyl)-4-fluoro-anilino)thiazole-5-carbonyl]phenoxy]-2-methyl-propanoate ,

rac-4-[4-amino-2-(N-(2-amino-1-methyl-2-oxo-ethyl)-4-fluoro-anilino)thiazole-5-carbonyl]-N-cyclohexyl-benzamide ,

rac-4-[4-amino-2-(N-(2-amino-1-methyl-2-oxo-ethyl)-4-fluoro-anilino)thiazole-5-carbonyl]-N-isopropyl-benzamide ,

rac-4-[4-amino-2-(N-(2-amino-1-methyl-2-oxo-ethyl)-4-fluoro-anilino)thiazole-5-carbonyl]-N-benzyl-benzamide ,

4-[4-amino-2-(N-(2-amino-1-methyl-2-oxo-ethyl)-4-fluoro-anilino)thiazole-5-carbonyl]-N-[(2S)-2-hydroxypropyl]benzamide (mixture of stereoisomers) ,

rac-4-[4-amino-2-(N-(2-amino-1-methyl-2-oxo-ethyl)-4-fluoro-anilino)thiazole-5-carbonyl]-N-(2-methoxyethyl)benzamide ,

4-[4-amino-2-(N-(2-amino-1-methyl-2-oxo-ethyl)-4-fluoro-anilino)thiazole-5-carbonyl]-N-[(2R)-2-hydroxypropyl]benzamide (mixture of stereoisomers) ,

rac-4-[4-amino-2-(N-(2-amino-1-methyl-2-oxo-ethyl)-4-fluoro-anilino)thiazole-5-carbonyl]-N-cyclopropyl-benzamide ,

rac-4-[4-amino-2-(N-(2-amino-1-methyl-2-oxo-ethyl)-4-fluoro-anilino)thiazole-5-carbonyl]-N-cyclopentyl-benzamide ,

rac-4-[4-amino-2-(N-(2-amino-1-methyl-2-oxo-ethyl)-4-chloro-3-fluoro-anilino)thiazole-5-carbonyl]-N-(2-phenoxyethyl)benzamide ,

rac-4-[4-amino-2-(N-(2-amino-1-methyl-2-oxo-ethyl)-4-chloro-3-fluoro-anilino)thiazole-5-carbonyl]-N-[2-(trifluoromethoxy)ethyl]benzamide ,

rac-4-[4-amino-2-(N-(2-amino-1-methyl-2-oxo-ethyl)-4-chloro-3-fluoro-anilino)thiazole-5-carbonyl]-N-[2-(difluoromethoxy)ethyl]benzamide ,

rac-4-[4-amino-2-(N-(2-amino-1-methyl-2-oxo-ethyl)-4-chloro-3-fluoro-anilino)thiazole-5-carbonyl]-N-(2-tert-butoxyethyl)benzamide ,

rac-4-[4-amino-2-(N-(2-amino-1-methyl-2-oxo-ethyl)-4-chloro-3-fluoro-anilino)thiazole-5-carbonyl]-N-(2-methoxyethyl)benzamide ,

rac-2-[4-[4-amino-2-(N-(2-amino-1-methyl-2-oxo-ethyl)-4-fluoro-anilino)thiazole-5-carbonyl]phenoxy]-N-[(4-chlorophenyl)methyl]-2-methyl-propanamide ,

rac-2-(N-[4-amino-5-(6-bromopyridine-3-carbonyl)thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-[6-[4-(trifluoromethyl)-1-piperidyl]pyridine-3-carbonyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-[6-(4-methyl-1-piperidyl)pyridine-3-carbonyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-[6-[4-(oxetan-3-yl)-1-piperidyl]pyridine-3-carbonyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-[6-(dimethylamino)pyridine-3-carbonyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-[6-(4,4-dimethyl-1-piperidyl)pyridine-3-carbonyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-[6-(3-azabicyclo[3.2.1]octan-3-yl)pyridine-3-carbonyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-[6-(3,5-dimethyl-1-piperidyl)pyridine-3-carbonyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-[6-(3-azabicyclo[3.1.0]hexan-3-yl)pyridine-3-carbonyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-[6-(1-piperidyl)pyridine-3-carbonyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-[6-(4,4-difluoro-1-piperidyl)pyridine-3-carbonyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

rac-2-(N-[4-amino-5-[6-(4-cyano-4-methyl-1-piperidyl)pyridine-3-carbonyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

(R)-2-(N-[4-amino-5-[6-(4-cyano-4-methyl-1-piperidyl)pyridine-3-carbonyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

(S)-2-(N-[4-amino-5-[6-(4-cyano-4-methyl-1-piperidyl)pyridine-3-carbonyl]thiazol-2-yl]-4-fluoro-anilino)propanamide ,

2-(N-[4-amino-5-(4-hydroxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide (single enantiomer) ,

(R)-2-(N-[4-amino-5-(4-hydroxybenzoyl)thiazol-2-yl]-3,4-difluoro-anilino)propanamide ,

(S)-2-(N-[4-amino-5-(4-hydroxybenzoyl)thiazol-2-yl]-3,4-difluoro-anilino)propanamide ,

2-(N-[4-amino-5-(4-hydroxybenzoyl)thiazol-2-yl]-4-chloro-3-fluoro-anilino)propanamide (enantiomer 1) ,

2-(N-[4-amino-5-(4-hydroxybenzoyl)thiazol-2-yl]-4-chloro-3-fluoro-anilino)propanamide (enantiomer 2) ,

2-(N-[4-amino-5-[4-(difluoromethoxy)benzoyl]thiazol-2-yl]-4-hydroxy-anilino)propanamide (single enantiomer) , and

rac-2-(N-[4-amino-5-[4-(2-hydroxyethoxy)benzoyl]thiazol-2-yl]-4-fluoro-anilino)propanamide,

or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

9. A compound of general formula (I) according to any one of claims 1 to 8 for use in the treatment or prophylaxis of a disease.

10. A pharmaceutical composition comprising a compound of general formula (I) according to any one of claims 1 to 8 and one or more pharmaceutically acceptable excipients.

11. A pharmaceutical combination comprising:

- one or more first active ingredients, in particular compounds of general formula (I) according to any one of claims 1 to 8, and
- one or more further active ingredients, in particular immune checkpoint inhibitors.

12. A pharmaceutical combination according to claim 11, wherein the immune checkpoint inhibitor is a aPD-1/-L1 axis antagonist.

13. A pharmaceutical combination according to claim 11, wherein the immune checkpoint inhibitor is a inhibitor of DGKα .

14. Use of a compound of general formula (I) according to any one of claims 1 to 8 for the treatment or prophylaxis of a disease.

15. Use of a compound of general formula (I) according to any one of claims 1 to 8 for the preparation of a medicament for the treatment or prophylaxis of a disease.

16. Use according to claim 9, 14 or 15, wherein the disease is cancer or a condition with dysregulated immune response or a disorder associated with aberrant DGKζ signalling, such as liquid and solid tumours, for example.